FOR BETTER OR WORSE?

Long-term outcome of critical illness in childhood

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EEN GOEDE OF SLECHTE AFLOOP?

Lange-termijn gevolgen van kritische ziekte op de kinderleeftijd

Proefschrift

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Sterk door Genade

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Chapter 1

General Introduction

Introduction

Cardiac arrest (CA) is a life-threatening event which has a high impact on everyone involved, and requires immediate treatment. Without prompt and proper treatment the child with a CA will certainly die. CA is uncommon in children, but associated with high mortality (50-90%). [1-6]

The outcome after CA is determined by the duration of the lack of oxygen of the brain and the related ischemic injury, but also by delayed cell death up to 6 hours after the ischemic event, known as reperfusion injury. Immediate basic life support (BLS) or advance pediatric life support (APLS) will reduce the duration of the hypoxic-ischemic no-flow phase of the brain, and return of spontaneous circulation (ROSC) can hopefully be achieved not long after. Nevertheless, in spite of the interventions aiming to diminish the damage, there may be extra harm due to the lack of understanding of physiological processes and the influence of treatment on the long-term outcome.

The basic principles of resuscitation are similar throughout the world, which makes international collaboration possible and needed. The development of good resuscitation standards is not only a national concern, but an international concern as well. The care for children with a CA is evolving. The most recent guidelines propose a compression ventilation (CV) ratio of 30:2 when performed by lay persons, which is the same as for adults. Healthcare professionals should use the 15:2 CV ratio, preceded by five rescue breaths. [7] In addition, the compression technique for infants (age <1 year) includes two-finger compression for single rescuers and the two-thumb encircling technique for two or more rescuers. For older children, either a one- or two-hand technique can be used, according to rescuer preference. The emphasis is on achieving adequate depth of compression and complete release with minimal interruptions (no flow). APLS is always a continuum of BLS, rhythm assessment, and an intervention (shock/medication). After ROSC, the focus should be on treatment of the precipitating cause, and post-resuscitation care (e.g., controlled oxygenation and ventilation, temperature control, and start of therapeutic hypothermia).

The last two decades there has been increasing attention for outcome after CA. This has resulted in international guidelines on pediatric resuscitation by the

European Resuscitation Council in 1994, updated in 1998, 2000, 2005, and 2010. The first international pediatric guidelines were clearly different from the adult guidelines, but the most recent guidelines were changed for reasons of simplicity and consistency with adult guidelines. [7]

New guidelines are to be expected in October 2015. As there is variation in national and local emergency medical infrastructures, the international guidelines must be flexible, allowing application in different settings. [7] The resuscitation guidelines in our hospital are based on these ERC guidelines.

Outcome after CA in children can be categorized by rhythm (i.e., shockable and non-shockable), type of CPR (i.e., BLS and APLS), or location where it happened (i.e., in-hospital (IH) and out-of-hospital (OH)). The latter distinction (IH/OH) is an important determinant of outcome. We describe the national and international evidence on outcome after CA by location, trends in survival, overview of the short-term and long-term outcomes, and lastly the populations studied in this thesis.

In-hospital

Studies on the outcome after IH-CA in the Netherlands are scarce. In 1990, Hendrick et al. published a study of 91 CPRs on general wards over an 18 month period. [8] Forty-six children (49.5%) had ROSC. After the initial survival, 30 children (33%) died within hospital, and only 16.5% survived to hospital discharge. Bos et al. reported the outcome of CA (n=34) at our PICU over a 32-month period in 1992. [9] Only 4 patients (12%) had ROSC, one of whom died after 24 hours, resulting in an overall survival of 9%.

In international studies, around 60-70% percent of children with IH-CA achieve ROSC, the IH mortality rate varies around 50-60%. [3, 5, 10, 11]

Out-of-hospital

In the Netherlands, no more than two studies addressed mortality of OH pediatric CA. Bardai et al. reported an incidence of 9 per 100,000 with a mortality rate of 95%, the number of children with ROSC was not mentioned. [12] The study period was 4 years, in which 233 children had an OH-CA; 70% were boys, 19% were

younger than 1 year at time of CA, and 51% were at home. They included not only patients with CPR, but also patients who were found dead at arrival of the emergency medical services (EMS). Kieboom et al. evaluated the outcome of drowned children with CA and hypothermia in a Dutch nationwide retrospective cohort study. [13] Eighty-six percent had ROSC, and 29% survived to hospital discharge.

In international studies, around 30% of children had ROSC after OH-CA, but this is usually not reported. [1, 5] Survival to hospital discharge after OH-CA occurs in less than 10%, however there are large differences between studies. [1, 5] Michiels et al. found an overall mortality of 95% in a large retrospective cohort study. [14] On the other hand, in a multicenter cohort study by Moler et al. the overall mortality was 62%. [6] López-Herce et al. reported a mortality rate of 72%. [15]

Causes of death

Only a few other studies reported the cause of death after ROSC in children. As uniformity in reported causes of death is lacking, results are not completely comparable. In Europe, a Spanish group studying CA in children reported that 38% was brain death, 42% had multiple-organ failure, 12% did not respond to CPR attempts after a new CA, and that in 9% a not to be resuscitated decision was made in case of new CA. [16, 17] Unfortunately withdrawal of life-sustaining treatment was not reported.

In a study from the United States, the causes of death after CPR in childhood are very briefly described. The authors only reported the neurological causes of death (neurologic futility or brain death) and cardiovascular causes of death, without further description of the actual causes. [4] However, they reported that the causes of death were significantly different between OH-CA and IH-CA, with cardiovascular causes occurring more commonly in the IH cohort (50% versus 22%), and neurological causes more commonly in the OH cohort (69% versus 20%). This is in line with results from a Spanish group, i.e., 67% of children with OH-CA was brain death, 22% had multi-organ failure, and 11% had no ROSC after another CPR attempt in a new CA event. [15]

Trends in survival

In the last decade outcome after CA has improved. Meyer et al. described the survival trends of cardiovascular-related sudden OH-CA in children and young adults and found significant reduction in mortality from 87% in 1980-1989 to 60% in 2000-2009 ($p<0.001$). [18] Girotra et al. found that the risk-adjusted rate of survival to discharge of in-hospital resuscitated children significantly increased from 14% in 2000 to 43% in 2009. [19]

These improvements in OH-CA survival can most likely be ascribed to early BLS provided by lay persons, better availability of automated external defibrillators, and a greater use of air medical services on site. [20] The improvements in IH-CA survival are most likely due to better training of medical health care professionals. Overall, improvements in intensive care treatment have improved the survival of OH-CA and IH-CA as well.

With the reductions in mortality there is a rise in morbidity, as shown by Namachivayam et al. [21] This raises questions on the short-term and long-term outcomes of these survivors.

Short-term outcome

The short-term outcome after CA in children, which we considered as the outcome up to 12 months after PICU discharge, is mainly described in very general terms (as good or poor) or in terms of the pediatric cerebral performance categories (PCPC) scale/pediatric overall performance categories (POPC) scale. [8, 13-17, 22-25] These scales classify the pediatric outcome into six different categories ranging from good/ normal to death.

Few studies have investigated the short-term outcome (at discharge or during the first year) in more detail and reported some of the neurological and neuropsychological sequelae. [26-28]

Table 1. Literature data on the detailed outcome after cardiac arrest in children

Author *(Journal)*	Year	N	Inclusion	Follow-up Interval	Methods	Main Results
Morris *(Journal of Learning Disabilities)*	1993	25	80% Congenital heart disease	> 1 year	- Physical examination - Neuropsychological examination	Low scores on intelligence, visual-perceptual-motor functioning, academic achievement, and adaptive and behavioral functioning
Amicuzi *(Brain Injury)*	2005	1	Arrhythmic CA patient	5, 9, 12 months	Neuropsychological examination	Dysfunctions in functional outcome, visual recognition, and self-regulation
Maryniak *(Resuscitation)*	2008	10	Arrhythmic CA patients	6 months	Neuropsychological examination	Memory impairments
Suominen *(Resuscitation)*	2011	29	Drownings with CA	10 years (median)	HR-QoL	Only significant reduction in HR-QoL in patients aged ≥16 years at follow-up
Suominen *(Resuscitation)*	2014	21	Drownings with CA	8 years (median)	- Neurological examination - Neuropsychological examination	Neurological dysfunction: 57% - Coordination dysfunction: 52% - Fine motor skill dysfunction: 43% Full-scale IQ <80: 40%

Long-term outcome

Only few studies have investigated the long-term outcome (considered as more than 1 year after PICU discharge) of survivors of CA in childhood. (Table 1) Some studies used only very general scoring systems, such as the PCPC mentioned above. [14, 29]

One study reported the health-related quality of life (HR-QoL) after a drowning incident. [30] Significant reductions in HR-QoL were found only in patients aged 16 years or older at follow-up.

No study has reported parents' quality of life in this context.

Only one small study reported on emotional and behavioral outcome after CA, as part of a neuropsychological outcome study. [31] These researchers studied 25 children at least 1 year after CA and reported that few children (number unknown) scored at or lower than 1 standard deviation (SD) below the normative population mean of the Child Behavior Checklist (CBCL). They used 1 SD as criterion for a deficit score. Children showed internalizing problem behavior (e.g., anxiety, depression, withdrawn behavior), and more physically impaired children had worse scores on the hyperactivity scale. As detailed description is lacking and 80% of these children had a congenital heart disease, it is unknown whether these results can be generalized to all CA survivors.

Only two small studies investigated the long-term neuropsychological functioning of children who survived a CA. Morris et al. reported lower scores on tests measuring intelligence, visual-perceptual-motor functioning, academic achievement, and adaptive and behavioral functioning at least 1 year post-CA (n=25; mean age 67 months; median follow-up interval unknown; 80% had a congenital heart disease). [31] Suominen et al. found impairments in intelligence, verbal and/or visual memory, and executive functions after a drowning incident as a child (n=21; median age 12.5 years; median follow-up interval 8.5 years). [32] These studies, however, had methodological limitations (small sample size, short follow-up interval or only subgroups of CA studied). It is therefore unknown whether these results can be generalized to all CA survivors.

To determine whether long-term outcome in CA survivors are CA-specific, we compared our results with findings in children who survived meningococcal septic shock. These are the most critically ill children at our PICU, and can therefore be used as a comparison group. In addition, they form a well-defined, homogeneous study sample, for which the neuropsychological outcome was already known. In addition, severity of illness as such was not a predictor of long-term neuropsychological outcomes in these meningococcal septic shock survivors.

Hypothesizing that not only the disease itself has an influence on long-term outcome, but also treatment at the PICU, we now studied the impact of medical treatment on long-term neuropsychological outcome in this patient group. This subject deserves more attention and research, since current knowledge on this topic is mostly based on studies in adults.

Meningococcal septic shock

Septic shock with petechial and/or purpuric rash is a life-threatening clinical syndrome predominantly caused by *Neisseria meningitidis* and characterized by a sudden onset and rapid progression in previously healthy young children and adolescents. Meningococcal sepsis in children develops when the initial host response to the infection becomes inappropriately amplified and dysregulated. After the development of the first petechiae, the patient rapidly deteriorates and may subsequently develop shock, disseminated intravascular coagulation, and ultimately organ failure. The severity of these symptoms requires immediate therapy.

In the PhD thesis of Corinne Buysse, the long-term *medical* outcome of meningococcal septic shock was investigated. [33] Long-term neurological impairments were found, ranging from mild to severe and irreversible. Also long-term poorer health status and health-related quality of life were found. In the PhD thesis of Lindy Vermunt, the long-term *(neuro)psychological* outcome was studied. [34] The long-term emotional and behavioral functioning of survivors of meningococcal septic shock was comparable to those in the general population. Long-term neuropsychological investigation showed that meningococcal septic shock affects several domains, including neuropsychological functioning, verbal comprehension, visual motor integration, attention, and executive functioning.

Surprisingly, severity of illness was not a significant predictor of poorer long-term neuropsychological functioning. As mentioned above, we now hypothesized that medical treatment at the PICU (specifically the use of analgesia and sedatives) would have an important influence on long-term neuropsychological outcome. In young rodents, the use of a variety of analgesics and sedatives has been associated with adverse cognitive development in the presence of widespread neurodegeneration due to neuronal cell death. [35-40] The outcome in critically ill children, especially those with meningococcal septic shock who require high dosages of analgesia and sedation, is not known.

The next sections give an overview of the demographics of our PICU and of the study samples presented in this thesis. Our hospital is the referral hospital for all CAs in the southwest of the Netherlands and also the referral hospital for children with a meningococcal septic shock.

Setting

The setting for the studies in this thesis was a tertiary level pediatric ICU (PICU) with 27 beds. This PICU is part of a 250-bed pediatric university hospital, the Erasmus MC-Sophia Children's Hospital Rotterdam, with a referral population of 4 million and staffed full-time by intensive care specialist with basic training in pediatrics or anesthesiology.

A considerable number of patients is admitted each year (2012: 1855 and 2013: 1950) and this PICU is by far the largest in the Netherlands. [41] The median admission duration is 2 days and in 5% of admissions length of stay is 28 days or more. The median age at admission is 1.4 years, 43% are younger than 1 year. Approximately 25% of patients receive invasive mechanical ventilation. The PICU has several units with a specific focus (neurocritical care, cardiology and cardiac surgery, neonatal surgery) and also offers Extracorporeal Life Support (ECLS) and transitional care, including the Centre for Home Ventilation and Respiratory Disorders. Our PICU is the largest of two centers for neonatal and pediatric ECLS in the Netherlands. The mortality rate at the PICU is 2.7%.

Study population

Between 2002 and 2011, we have had 474 resuscitations in 401 children in our hospital. We included all children resuscitated IH (e.g., emergency department, ward, ICU), and OH and subsequently admitted to our ICU, and children resuscitated in a regional hospital or other university hospital and after ROSC consecutively admitted to our ICU. Neonates resuscitated at the hospital's neonatal intensive care unit (NICU), or in another hospital and subsequently admitted to the NICU of our hospital were excluded.

An overview of the characteristics of the first events of these patients is shown in Table 2.

Table 2. Cardiac arrest and patient characteristics

	n=401
Age at cardiac arrest (months)	20.4 (0 – 262.6)
Male gender	228 (57%)
Advanced Pediatric Life Support (APLS)	339 (85%)
Out-of-hospital cardiac arrest (OH-CA)	202 (50%)
Bystander CPR	324 (81%)
Initial Rhythm	
- Non-Shockable	332 (83%)
- Shockable	42 (11%)
- Unknown	27 (7%)
Etiology	
- Cardiac	138 (34%)
- Respiratory	172 (43%)
- Neurologic	42 (11%)
- SIDS/ALTE	27 (7%)
- Gastro-intestinal	6 (2%)
- Metabolic	3 (1%)
- Unknown	13 (3%)
Pre-existing medical condition	179 (45%)
- Cardiac	103 (58%)
- Respiratory	56 (31%)
- Other	20 (11%)
Mild therapeutic hypothermia	65 (16%)
Rescue ECMO	11 (3%)

All data are presented as "number of subject (%)", except age which is presented as "median (range)".

Of the 401 children, 121 (30%) had no ROSC. Of the 280 (70%) surviving children, 145 (36%) survived to hospital discharge. Thus, the overall mortality rate was 64%. (Figure 1)

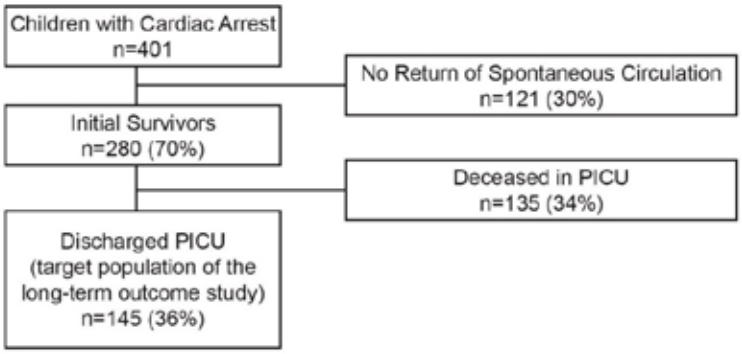

Figure 1. Overview of outcome to hospital discharge

An overview of the characteristics by location of arrest in our study population is shown in Table 3.

Table 3. Characteristics in-hospital and out-of-hospital cardiac arrest events

	IH-CA (n=199)	OH-CA (n=202)
N	50%	50%
Non-shockable rhythm	89%	76%
CA-related pre-existing condition	68%	22%
ROSC	79%	61%
Withdrawal	35%	44%
Brain death	9%	37%
Survival to hospital discharge	44%	28%

N = number of patients.

In-hospital

In the study period (2002-2011), we had a total of 199 in-hospital CAs (IH-CA) (50%). Twenty-two children (11%) were in a regional hospital or other tertiary hospital and subsequently admitted to our hospital, and 177 (89%) were in our hospital. The first monitored rhythm was non-shockable in 89%. Sixty-eight percent of the children had a CA-related pre-existing condition. ROSC was achieved in 79%, and the overall survival to hospital discharge rate was 44%. Of the children surviving to hospital discharge, 6% died within 1 year of hospital

discharge (2 due to discontinuation of another CPR event, 1 due to underlying disease, 2 unknown). In comparison with the results of Bos et al. and Hendrick et al., our results show that outcome after an IH-CA has dramatically improved over the last 2 decades, most probably due to the availability of rapid response teams, and training of professionals (i.e., APLS training). [8, 9] Our overall mortality of IH-CA is in line with the international studies, as mentioned earlier. [3, 5, 10, 11]

Out-of-hospital

Of all 401 patients, 202 (50%) were out-of-hospital (OH-CA). The most common location was at home (53%). In 154 cases the first monitored rhythm was a non-shockable rhythm, of which asystole was the most common rhythm (46%). In only 22% of all cases there was a CA-related pre-existing condition. ROSC was achieved in 61%, and the overall survival to hospital discharge was 28%. Of the children surviving to hospital discharge, 7% died within 1 year of hospital discharge (1 due to discontinuation of another CPR event, 1 due to sequelae of the CA, 2 unknown). In comparison with the results of Bardai et al. we have a better outcome after OH-CA, although it should be mentioned that their inclusion criteria were different. [12] Good comparison with Kieboom et al. is difficult as they only studied a subgroup of CA patients. [13]

Internationally, our outcome is better than in most studies, which could be due to differences in availability of EMS and differences in causes of CA. [1, 5, 6, 14, 15]

Causes of death

The most common causes of death after ROSC in our study population were withdrawal of life-sustaining treatment (poor physical and/or (neuro)psychological outcome based on repeated neurological examination, brain imaging, electroencephalography) (39%), followed by brain death (22%), cardiorespiratory failure/multiple-organ failure (19%), no ROSC after a new CA (13%), underlying disease (3%), and unknown (5%).

Trends in survival

At our PICU, survival of children after CA has significantly increased in the period 2002-2013 (OR 1.096 per year; 1.045-1.151 95% CI; p<.001). See Figure 2

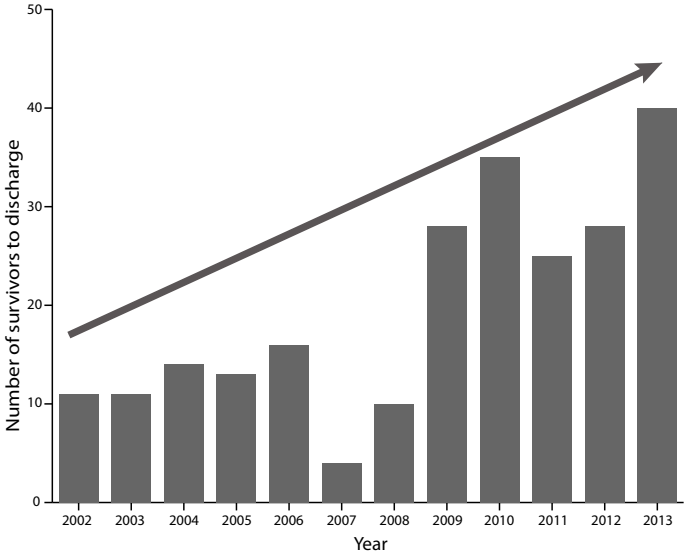

Figure 2. Overview CA-survival at our PICU: 2002-2013

Improved outcomes have also been found in other studies, as mentioned earlier. As mortality is decreasing, the short-term and long-term outcomes after CA are very important.

Long-term outcome

The long-term outcome contains several dimensions of functioning; that is, health status and health-related quality of life (HR-QoL), emotional and behavioral functioning, and neuropsychological functioning.

As little is known about the long-term outcome of CA survivors, our aim was to bridge this gap of knowledge. We therefore systematically investigated the above-mentioned dimensions in survivors of CA in childhood.

In addition, the study of predictors of long-term outcome in critically ill children is equally important. In this thesis we focused on predictors of long-term outcome after CA and the influence of PICU treatment in survivors of meningococcal septic shock.

Outline of this thesis

The aim of this thesis was to investigate the long-term health status, health-related quality of life, emotional and behavioral functioning, and neuropsychological outcome of children who survived a critical illness, specifically cardiac arrest. In addition, the influence of medical predictor variables, such as hyperoxia on mortality after cardiac arrest, and analgesia/sedation (specifically for meningococcal septic shock survivors) on long-term neuropsychological outcome after a critical illness, was examined.

Chapter 2 provides an overview of the influence of the partial pressure of arterial oxygen on the in-hospital mortality after cardiac arrest. In **chapter 3**, the long-term health status and health-related quality of life of survivors of cardiac arrest is presented. In **chapter 4**, the long-term emotional and behavioral problems (psychopathology) in survivors of cardiac arrest are presented. **Chapter 5** addresses the long-term neuropsychological functioning after cardiac arrest. **Chapter 6** investigates the association between analgesic and sedative drug use during PICU treatment and long-term neuropsychological outcome in children who survived meningococcal septic shock. In **chapter 7** (general discussion), we discuss the findings presented in this thesis, put them into perspective and propose recommendations for future studies.

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Chapter 2

High cumulative oxygen levels are associated with improved survival of children treated with mild therapeutic hypothermia after cardiac arrest

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Abstract

Aim: The aim of this study was to analyze the relationship between the partial pressure of arterial oxygen (PaO_2) and in-hospital (IH) mortality in children after cardiac arrest (CA) using the conventional cutoff analysis, which was compared with the cumulative analysis, a new method in PaO_2 analysis. Additionally, we analyzed this relationship for children with and without mild therapeutic hypothermia (MTH; 32-34 °C).

Methods: This observational cohort study included all children (aged > 28 days) with CA and return of spontaneous circulation (ROSC) between 2002 and 2011.

The first research question was the association between PaO_2 and IH mortality after ROSC. This was analyzed for three hyperoxia cutoff values, and for three time intervals using the cumulative PaO_2 determined with the area under the curve (AUC). For the second research question, these analyses were repeated for children with and without MTH.

Results: Of the 200 patients included (median age 2.6 years), 84 (42%) survived to hospital discharge. Fifty-eight children (29%) were treated with MTH.

With the cutoff analysis and the AUC analysis we found no relationship between PaO_2 and IH mortality. However, analysis of the MTH-group showed a lower IH mortality in children with high cumulative PaO_2 levels on two of the three time intervals. Multivariable analysis showed significantly higher odds of survival (0.643 (95% confidence interval (CI) 0.424-0.976), 0.554 (95% CI 0.335-0.916)).

Conclusions: Cumulative PaO_2 analysis showed that the IH mortality is significantly lower in MTH-treated children with high PaO_2 levels. The effects of cumulative PaO_2 on the outcome needs to be studied further, and this will help us to achieve individualized goal-directed therapy.

Introduction

Cardiac arrest (CA) in children is uncommon and associated with high mortality (50-90%). [1-6] Oxygen therapy has always been important in the treatment of CA. However, there is increasing evidence for the adverse effects of oxygen. Oxidative stress and reperfusion promotes free radical-generated injury contributing to neurologic injury and cardiac dysfunction, and they seem to be associated with increased mortality after CA. [7, 8] Furthermore, a meta-analysis of animal studies by Pilcher et al. showed that treatment with 100% oxygen after resuscitation resulted in significantly worse neurological deficit scores than oxygen administered at lower concentrations. [9]

Observational studies in humans examined the influence of arterial oxygen (PaO_2) on in-hospital (IH) mortality. They used different time intervals after return of spontaneous circulation (ROSC) and different definitions of hyperoxia, or included only patients treated with mild therapeutic hypothermia (MTH), which resulted in contradictory conclusions. [10-16] Most studies used an arbitrary cutoff value to describe the influence of PaO_2 on the IH mortality. Only two studies used an alternative method. Janz et al. used PaO_2 as a continuous value and Ferguson et al. modeled the first PaO_2 within the first hour after ROSC in a non-linear matter. [11, 13]

In contrast with previous studies, we hypothesized that not a single value above a previously set cutoff, but rather the cumulative PaO_2 during the first 24 h after ROSC (especially the first 6 h) is associated with worse survival of children with CA. Our first research question was the association between PaO_2 and the IH mortality, analyzed with the commonly used cutoff method and compared with a cumulative method. In addition, although the evidence for the protective effects of MTH is debatable, we hypothesized that MTH is protective against the effects of hyperoxia, as it is the only post-resuscitation intervention, introduced in our hospital in 2007, in accordance with international guidelines.

Methods

This observational cross-sectional cohort study was performed at the intensive care unit (ICU) of the Erasmus MC - Sophia Children's Hospital, a tertiary-care university hospital. Our hospital provides health care to children in the southwest of The Netherlands (total population of approximately 4.2 million people), and this population is a representative sample of the Dutch population.

Patient selection

This study concerned all patients aged >28 days and <18 years with documented CA between January 2002 and December 2011, and admitted to the ICU of the Erasmus MC - Sophia Children's Hospital. CA was defined as absent pulse rate or the need for cardiac compressions. Treatment of children with CA in our hospital has been in line with the European Resuscitation Council guidelines for pediatric life support. [17]

The inclusion criteria were as follows: (1) all children resuscitated in-hospital (e.g., emergency department, ward, or ICU) and out-of-hospital, and subsequently admitted to our ICU, and (2) children resuscitated in a regional hospital or other university hospital, and after ROSC subsequently admitted to our ICU. Neonatal resuscitations, children with cyanotic congenital heart disease, and children without an arterial line were excluded. In addition, only data of the first CA episode were included when a child had multiple arrests.

Hypothermia was introduced as treatment after CA in children with post-resuscitation coma in 2007. Hypothermia was started as soon as possible following ROSC. Hypothermia was achieved by administering a bolus of cold fluids and applying external cooling using a mattress with the Blanketrol® III (Cincinnati Sub-Zero Products, Inc., Sharonville, OH, USA). The target temperature is 32-34 °C for 24 h following ROSC, after which they were rewarmed passively at a rate of 0.5 degrees Celsius per 2 h. The target temperature must have been reached for MTH to be effective. Children in whom the target temperature range was not reached were classified as "without MTH".

Data collection

All CA data were retrospectively collected. CA data were derived from ambulance

registration forms, clinical medical records, electronic medical records, Patient Data Management System (PDMS) and CA registration forms. The starting point of the time interval of collected data (T=0) was defined as the actual time of ROSC or, if unknown, the time of ICU admission.

The following data were collected: (1) basic patient characteristics (e.g., gender, age, and medical history), (2) CA characteristics (e.g., type of resuscitation (basic life support (BLS)/advanced pediatric life support (APLS)), etiology of arrest, first monitored rhythm, bystander cardiopulmonary resuscitation (CPR), and location), and (3) outcome (IH mortality).

For all children, laboratory values (arterial pH, lactate, and PaO_2) and data regarding MTH (time period before MTH reached, lowest temperature if >34 °C) were retrospectively collected. The laboratory values of all children were automatically recalculated to the value at 37 °C, as this is a standard procedure in our hospital. [18]

Statistical analysis

The primary outcome measure was IH mortality. The first research question was the association between PaO_2 and IH mortality. The second question was the influence of MTH on this association.

In the first analysis of the first research question, we explored the association between PaO_2 and IH mortality for different cutoff values of hyperoxia (>200, >250, and >300 mmHg) as proposed in the literature. [13-16] Logistic regression analysis was applied to explore the influence of hyperoxia on IH mortality with the highest PaO_2 over the first 24 h. In the multivariable analysis, we calculated an adjusted odds ratio (OR) for pre-selected variables: age, gender, type of resuscitation (BLS/APLS), location, rhythm, lowest pH and highest lactate.

In the second analysis of the first research question, the "area under the curve" (AUC) of PaO_2 was calculated for each patient to determine the influence of the cumulative PaO_2 on IH mortality. The trapezoidal method was used. A minimum of four PaO_2 measurements and an overall time interval of at least 12 h were required to include the arterial measurements and their corresponding time points in the analysis. This resulted in a cumulative PaO_2 over the 0-6 h, 6-24 h, and 0-24 h interval after ROSC. The AUC was corrected for the time in which the PaO_2 was measured, as not all patients had a 24 h time period in which PaO_2 was measured. This resulted in a cumulative PaO_2 per hour which was converted into

the cumulative PaO_2 by multiplying with 6, 18, or 24, respectively.

In univariable logistic regression analyses the assumption that the AUC of PaO_2 had a linear effect on the logit of IH mortality was tested using the Box-Tidwell test (i.e., an interaction term between the covariate and its natural logarithm was added to the model). If any significant interaction between the covariate and its natural logarithm was present, the linearity assumption was violated. Univariable and multivariable logistic regression analysis (with the same preselected variables as in the cutoff analysis) was applied to evaluate the relationship between cumulative PaO_2 and IH mortality over the three time intervals after ROSC. In advance of the regression analysis the original AUC variables were rescaled by dividing by 100 to obtain more distinctive results out of the logistic regression analysis.

The same analyses were performed regarding the influence of MTH on the association between PaO_2 and IH mortality.

Univariable comparison of the distribution of patient characteristics and clinical data between survivors and non-survivors was performed by independent sample t-tests for normally distributed data, and Mann-Whitney U tests for non-normally distributed data. Normality was examined with the Kolmogorov-Smirnov test. Fisher's exact test was used for comparison of dichotomous data. Statistical significance was considered with two-tailed *p*-value of ≤ 0.05.

All analyses were performed with SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL, USA) or Graphpad Prism 5.00 for Windows (GraphPad Software, Inc.).

Results

Patient and CA characteristics

Between January 2002 and December 2011, a total of 474 CA events were documented. ROSC was achieved in 335 events (70%). An overview of the patient inclusion is given in Figure 1. The basic patient characteristics are presented in Table 1.

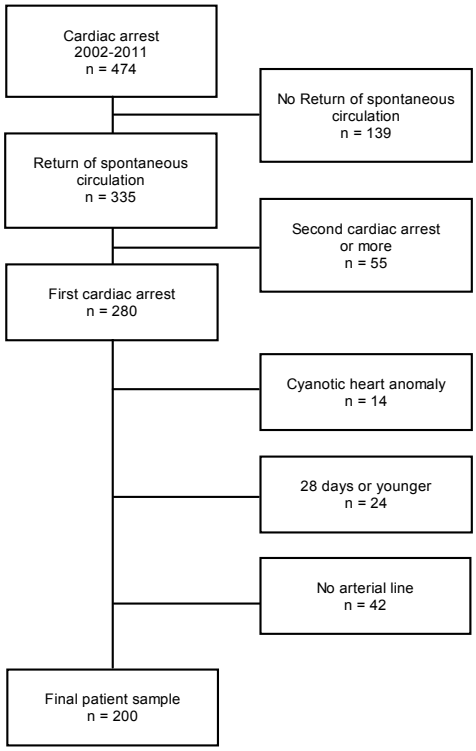

Figure 1. Overview of the patient inclusion

MTH was initiated in 63 (32%) children, 58 (92%) of whom reached the target temperature in a median time of 6.7 h (range, 0.8-21.3) for survivors and 6.3 h (range, 0.4-25.5) for non-survivors after ROSC.

Eventually, 116 of the 200 children (58%) died within a median of 2 days (range: 0-135; 40 died within the first 24 h) after ROSC. The major cause of death was withdrawal of life-sustaining treatment (poor physical and/or (neuro)psychological outcome based on repeated neurological examination, brain imaging, and electroencephalography) (n=52, 45%), followed by brain death based on the criteria of whole-brain death (n=31, 27%), cardiorespiratory failure/multiple-organ failure (n=31, 27%), and underlying disease (n=2, 2%).

Table 1. Patient characteristics and cardiac arrest characteristics

	Survivors (n = 84)			Non-survivors (n = 116)			*p*-value[d]
	n[a]			n[a]			
Age (months)[b]	84	20.4	(1.0 - 211.9)	116	37.6	(1.0 – 262.6)	.069
Male gender[c]	84	49	(58%)	116	61	(53%)	.472
Advanced Pediatric Life Support (APLS)[c]	84	64	(76%)	116	107	(92%)	**.002**
Out-of-hospital arrest[c]	84	37	(44%)	116	61	(53%)	.254
Bystander CPR[c]	79	74	(88%)	112	93	(80%)	**.044**
Initial Rhythm Non-shockable[c]	77	64	(76%)	107	99	(85%)	.060
Etiology	84			116			
- Cardiac[c]		27	(32%)		33	(39%)	.640
- Arrhythmia[c]	27	8	(30%)	33	3	(9%)	
- Cardiomyopathy[c]	27	8	(30%)	33	8	(24%)	
- Hypovolemic shock[c]	27	1	(4%)	33	5	(15%)	
- Obstructive shock[c]	27	2	(7%)	33	2	(6%)	
- Septic shock[c]	27	6	(22%)	33	14	(42%)	
- Other[c]	27	2	(7%)	33	1	(3%)	
- Respiratory[c]		49	(58%)		46	(40%)	**.010**
- Aspiration[c]	49	1	(2%)	46	6	(13%)	
- Bronchomalacia/ -spasm[c]	49	4	(8%)	46	1	(2%)	
- Congenital[c]	49	3	(6%)	46	3	(7%)	
- Drowning[c]	49	19	(39%)	46	12	(26%)	
- Hanging[c]	49	2	(4%)	46	2	(4%)	
- Insufficiency/ Infection[c]	49	8	(16%)	46	11	(24%)	
- Obstruction other[c]	49	9	(18%)	46	3	(7%)	
- Pulmonary hypertension[c]	49	2	(4%)	46	1	(2%)	
- Other[c]	49	1	(2%)	46	7	(15%)	
- Neurologic[c]		2	(2%)		26	(22%)	**<.001**
- Herniation[c]	2	0	(0%)	26	3	(12%)	
- Vascular accident[c]	2	0	(0%)	26	3	(12%)	
- Trauma[c]	2	0	(0%)	26	18	(69%)	
- Other[c]	2	2	(100%)	26	2	(8%)	
- ALTE / SIDS[c]		3	(4%)		6	(5%)	.737
- Other/Unkown[c]		3	(4%)		5	(4%)	1.000

Table 1. *Continued*

	Survivors (n = 84)			Non-survivors (n = 116)			*p*-value[d]
	n[a]			n[a]			
Pre-existing condition[c] *	83	36	(43%)	114	44	(38%)	.558
- Cardiac[c]		20	(56%)		23	(52%)	.824
- Respiratory[c]		13	(36%)		16	(36%)	1.000
- Neurologic[c]		2	(6%)		3	(7%)	1.000
- Other/Unkown[c]		1	(3%)		2	(5%)	1.000
Mild therapeutic hypothermia[c] **	84	26	(31%)	116	37	(31%)	1.000
- 32-34 °C reached[c]	26	22	(85%)	37	36	(97%)	.150
Lowest pH[b]	84	7.18	(6.47 – 7.53)	116	7.04	(6.36 – 7.46)	**<.001**
Highest lactate[b]	83	4.5	(1.1 – 24.0)	112	12.1	(.9 – 25.0)	**<.001**
Lowest PaO_2[b]	84	66.0	(18.8 - 171.8)	116	54.8	(12.8 - 240.0)	.154
Highest PaO_2[b]	84	229.9	(32.3 - 624.8)	116	273.4	(27.0 - 628.6)	.394
min. PaO_2 <60 mmHg[c]	84	31	(37%)	116	61	(53%)	**.032**
max. PaO_2 > 200 mmHg[c]	84	51	(61%)	116	76	(66%)	.551
max. PaO_2 > 250 mmHg[c]	84	37	(44%)	116	65	(56%)	.115
max. PaO_2 > 300 mmHg[c]	84	31	(37%)	116	52	(45%)	.309
AUC 0 - 24 hours mmHg[b]	69	2966.9	(1271.6 – 5785.5)	83	3157.2	(565.9 – 5405.5)	.585
- mmHg/hour[b]	69	123.6	(53.0 – 241.1)	83	131.5	(23.6 – 225.2)	
AUC 0-6 hours mmHg[b]	64	854.0	(297.8 – 2066.9)	78	870.7	(166.7 – 2290.2)	.925
- mmHg/hour[b]	64	142.3	(49.6 – 344.5)	78	145.1	(27.8 – 381.7)	
AUC 6-24 hours mmHg[b]	68	2063.0	(930.3 – 4645.2)	81	2199.6	(424.4 – 3911.5)	.424
- mmHg/hour[b]	68	114.6	(51.7 – 258.1)	81	122.2	(23.6 – 217.3)	

[a] Number of subjects in whom the variable was obtained.

[b] Median (range).

[c] Number of subjects (%).

[d] *p*-value: independent sample t-test for continuous data or Mann-Whitney dependent on normality; Fisher's Exact test for dichotomous data.

* Children with a pre-existing medical history which was the cause of CA, classified by the etiology of the CA.

** Children in whom mild therapeutic hypothermia was initiated (n=63).

Abbreviations: ALTE = Apparent Life Threatening Event, AUC = area under the curve, max. = maximum, n = number, PaO_2 = partial pressure of arterial oxygen, SIDS = sudden infant death syndrome.

PaO_2 Cutoff Analysis

All 200 patients were included in the cutoff analysis. No significant difference

between survivors and non-survivors was found. (Table 1)

The influence of the highest measured PaO_2 on the overall mortality is presented in Table 2.

Table 3 displays the influence of PaO_2 on IH mortality for patients with and without MTH. The univariable analysis of maximum PaO_2 values >250 mmHg showed a significantly lower survival rate of children without MTH treatment, which was no longer present in the multivariable analysis.

Table 2. Univariable and multivariable logistic regression analyses of all children with survival as dependent variable

Variable	Crude		*p*-value	Adjusted [a]		*p*-value
	OR	(95% CI)		OR	(95% CI)	
max. PaO_2 > 200 mmHg	1.230	(.687) – (2.198)	.813	.810	(.413) – (1.590)	.541
max. PaO_2 > 250 mmHg	1.618	(.920) – (2.849)	.095	1.107	(.581) – (2.114)	.756
max. PaO_2 > 300 mmHg	1.389	(.782) – (2.469)	.262	.905	(.465) – (1.761)	.770
AUC 0 - 24 hours mmHg [b]	.998	(.966) – (1.030)	.894	.984	(.949) – (1.021)	.403
AUC 0-6 hours mmHg [b]	.998	(.924) – (1.078)	.957	.971	(.892) – (1.057)	.497
AUC 6-24 hours mmHg [b]	.997	(.955) – (1.042)	.903	.980	(.933) – (1.031)	.447

[a] Adjusted for: age, gender, location of arrest, rhythm, basic life support/advanced pediatric life support, lowest pH, highest lactate.

[b] Value was rescaled by dividing by 100 in advance of the regression analysis.

Abbreviations: AUC = area under the curve, max. = maximum, OR = Odds Ratio, PaO_2 = partial pressure of arterial oxygen.

Cumulative PaO_2 Analysis

Forty-eight children (24%) were excluded from the AUC-calculation (less than four measurements and/or time interval <12 h). (Table 1)

Results of the Box-Tidwell tests showed no significant nonlinear effects of the AUC of PaO2 on the logit of IH mortality.

Univariable and multivariable regression analyses showed no significant relationship between the cumulative AUC of PaO_2 and IH mortality. (Table 2)

Multivariable regression analysis, evaluating the relationship between cumulative PaO_2 and IH mortality for patients with and without MTH, showed an overall significant difference (OR 0.916, 95% CI 0.843 -0.995; p = 0.038) towards a lower risk

of mortality over the 0-24 h interval in patients with MTH. This was also found on the 6-24 h interval (OR 0.882, 95% CI 0.792-0.981; p = 0.021) in patients with MTH. (Figure 2)

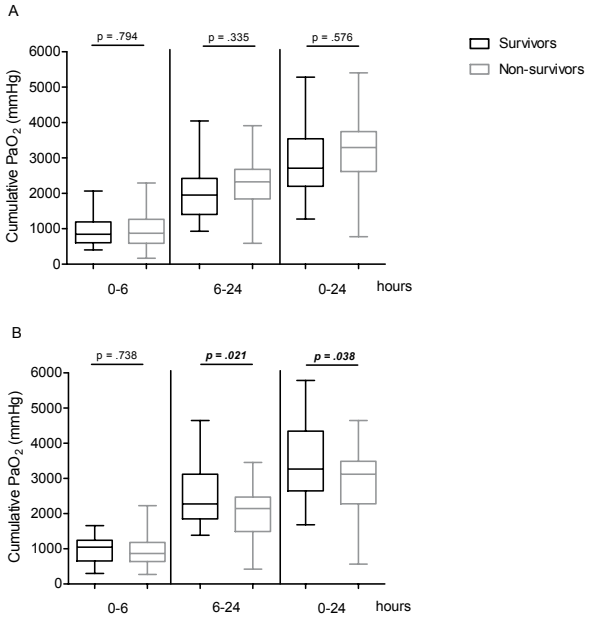

Figure 2. Cumulative PaO_2 of all children with and without MTH treatment

A. Cumulative PaO_2 in children without hypothermia.

B. Cumulative PaO_2 in children with hypothermia.

Each boxplot shows a minimum, 25th percentile, median, 75th percentile, and maximum value.

P-values of the multivariable regression analysis are shown.

Clinical relevance

As shown by five examples (Figure 3), both methods led to substantially different results. As to the cumulative PaO_2 in patients with MTH, the *mean* AUC of survivors with MTH was 502.7 points higher over the 0-24 h interval, and 469.9 points higher over the 6-24 h interval, than that of non-survivors. As the AUC was rescaled before being entered in the regression analysis, the mean difference had to be rescaled by dividing by 100. Ultimately, this resulted in a clinically relevant difference in OR of 0.643 (95% CI 0.424-0.976) and 0.554 (95% CI 0.335-0.916). The odds of survival are significantly increased in children with higher cumulative PaO_2 levels over the 6-24 h and 0-24 h interval.

Table 3. Univariable and multivariable logistic regression analyses of all children with and without mild therapeutic hypothermia treatment with survival as dependent variable

	Survivors			Non-survivors			*p*-value[d]	Crude			Adjusted		
Variable	n[a]			n[a]				OR (95% CI)		*p*-value	OR (95% CI)		*p*-value
No Hypothermia †													
max. PaO_2 > 200 mmHg [b]	62	37	(60%)	80	52	(65%)	.600	1.255	(.633) – (2.488)	.516	.899	(.394) – (2.053)	.801
max. PaO_2 > 250 mmHg [b]	62	23	(37%)	80	45	(56%)	**.028**	2.179	(1.106) – (4.310)	**.024**	1.912	(.866) – (4.237)	.109
max. PaO_2 > 300 mmHg [b]	62	19	(31%)	80	35	(44%)	.120	1.761	(.876) – (3.534)	.112	1.166	(.518) – (2.625)	.711
AUC 0 - 24 hours mmHg [c,f]	47	2712.2	(1271.6 - 5283.4)	48	3295.0	(778.2 - 5405.5)	.100	1.025	(.983) – (1.067)	.245	1.014	(.964) – (1.067)	.576
- mmHg/hour [c]	47	113.0	(53.0 – 220.1)	48	137.3	(32.4 – 225.2)							
AUC 0-6 hours mmHg [c,f]	45	844.6	(399.0 – 2066.9)	45	874.0	(166.7 – 2290.2)	.812	1.006	(.913) – (1.107)	.909	.985	(.881) – (1.101)	.794
- mmHg/hour [c]	45	140.8	(66.5 – 344.5)	45	145.7	(27.8 – 381.7)							
AUC 6-24 hours mmHg [c,f]	47	1954.8	(930.3 – 4045.5)	46	2326.7	(586.8 – 3911.5)	**.031**	1.047	(.986) – (1.111)	.131	1.037	(.963) – (1.116)	.335
- mmHg/hour [c]	47	108.6	(51.7 – 224.8)	46	129.3	(32.6 – 217.3)							

Table 3. *Continued*

	Survivors			Non-survivors			*p*-value[d]	Crude			Adjusted		
Variable	n[a]			n[a]				OR (95% CI)		*p*-value	OR (95% CI)		*p*-value
Hypothermia ††													
max. PaO_2 > 200 mmHg [b]	22	14	(64%)	36	24	(67%)	1.00	1.143	(.376) – (3.472)	.814	.435	(.076) – (2.488)	.349
max. PaO_2 > 250 mmHg [b]	22	14	(64%)	36	20	(56%)	.593	.714	(.240) – (2.123)	.545	.218	(.034) – (1.399)	.108
max. PaO_2 > 300 mmHg [b]	22	12	(55%)	36	17	(47%)	.787	.746	(.257) – (2.160)	.589	.398	(.087) – (1.818)	.235
AUC 0 - 24 hours mmHg [c,f]	22	3264.8	(1682.5 - 5785.5)	35	3119.9	(565.9 - 4643.3)	.159	.945	(.890) – (1.004)	.069	.916	(.843) – (.995)	**.038**
- mmHg/hour [c]	22	136.0	(70.1 – 241.1)	35	130.0	(23.6 – 193.5)							
AUC 0-6 hours mmHg [c,f]	19	1046.3	(297.8 – 1661.4)	33	867.5	(268.1 – 2221.8)	.549	.980	(.861) – (1.117)	.769	.975	(.839) – (1.133)	.738
- mmHg/hour [c]	19	174.4	(49.6 – 276.9)	33	144.6	(44.7 – 370.3)							
AUC 6-24 hours mmHg [c,f]	21	2278.1	(1384.3 – 4645.2)	35	2144.0	(424.4 – 3452.9)	.110	.923	(.854) – (.997)	**.041**	.882	(.792) – (.981)	**.021**
- mmHg/hour [c]	21	126.6	(76.9 – 258.1)	35	119.1	(23.6 – 191.8)							

[a] Number of subjects in whom the variable was obtained.

[b] Number of subjects (%).

[c] Median (range).

[d] *p*-value: independent sample t-test for continuous data or Mann-Whitney dependent on normality; Fisher's Exact test for dichotomous data.

[e] Adjusted for: age, gender, location of arrest, rhythm, basic life support/advanced pediatric life support, lowest pH, highest lactate.

[f] Value was rescaled by dividing by 100 in advance of the regression analysis.

† Children without mild therapeutic hypothermia treatment or where the target temperature of 32-34°C was not reached.

†† Children with mild therapeutic hypothermia treatment, where the target temperature of 32-34°C was reached.

Abbreviations: AUC = area under the curve, max. = maximum, n = number, OR = Odds Ratio, PaO_2 = partial pressure of arterial oxygen.

Discussion

The innovative aspect of this study is that it uses a novel and simple method to analyze cumulative PaO_2. We found that patients with MTH and higher cumulative PaO_2 had a lower mortality rate. With the cumulative PaO_2 measurement, we could not reproduce the relationship between higher PaO_2 and IH mortality in children after CA as found in various cutoff studies. It is important to note that, due to the retrospective nature, small sample size, and heterogeneous population, we did not determine causation in this study, this study is hypothesis generating.

Patient and CA Characteristics

The patient sample was heterogeneous in terms of location and etiologies, among other things, which was also the case in other studies. [10, 11, 13, 15] Half of the CAs were out-of-hospital CAs, the proportion of which was within the range reported in other studies (from 43-58%). [12, 13, 16] In our population, out-of-hospital CA was also more common (70%) in patients with MTH.

Only 32% underwent MTH after CA, because MTH was newly introduced in our clinical protocol in 2007 and it was only used in children with post-resuscitative coma after CPR. Similar to other studies our median time to reach the MTH target temperature was >6 h, most probably due to unfamiliarity with the new protocol and failure of the technique. [19, 20] The exact timing to start hypothermia after ROSC is controversial, as well as the duration and temperature. [21-23] There could be a therapeutic window in which hypothermia should be applied. [21, 23] Furthermore, controlling the effects of systemic inflammatory response syndrome (SIRS) with continued normothermia could be important. [22]

Method of PaO_2 Analysis

Most studies on hyperoxia and CA used a single cutoff value to describe PaO_2 over different time periods after ROSC. [10, 12, 14-16] Such cutoff analyses may be limited, however, in their ability to approximate the complex oxygen physiology as fluctuations of PaO_2 are common. Using AUC as a measure of cumulative exposure to oxygen, patients with MTH and high cumulative PaO_2 levels had a lower mortality rate, which was not found in the cutoff analyses. In addition, we did not find any harmful effects of the high cumulative arterial oxygen levels whatsoever.

This supports our hypothesis that the method of analysis is important in the approximation of oxygen physiology. A dichotomous cutoff value cannot account for the amount of oxygen and duration, an inherent problem of summarizing a continuous variable with an important time course as a dichotomous variable.

We chose to use different time periods in the AUC analysis, as both direct cell injury after an ischemic event and delayed cell death known as reperfusion injury have an important influence on the outcome. Therefore, it is difficult to compare our results with other studies, but these different methods extend our knowledge of these concepts.

The cumulative PaO_2 can be legitimately measured with the trapezoidal AUC method. [24] This method is commonly used in pharmacokinetic research to measure the total drug exposure, and it has also been used in other medical fields, for instance in metabolic research and pulmonary research.

Cumulative PaO_2 and Outcome

The analysis of patients without MTH showed no significant relationship between PaO_2 and IH mortality, regardless of the method used. This is similar to findings of Bellomo et al., who found no significant difference after Cox proportional-hazards modeling in a large retrospective cohort of 12,108 patients. [10]

In multivariable analysis, clinically relevant differences in OR were found. There are various explanations for our findings. One important new theory is that of a therapeutic window for oxygen. As suggested by Martin et al., precise control of arterial oxygenation may avoid harmful effects associated with unnecessary extremes of arterial oxygenation. [25] Based on physiological principles, they constructed a scheme with an optimal therapeutic oxygenation range. This optimal range will probably be dependent on factors such as age, clinical setting, underlying disease, and other comorbidities. In our retrospective cohort, the cumulative oxygen levels in survivors with MTH were higher than in the non-survivors with MTH. This suggests that MTH might shift the optimal therapeutic range wherein high cumulative oxygen levels could be favorable compared to lower cumulative oxygen levels.

An alternative explanation is the possibility of impairments in microcirculatory function. As shown by van Genderen et al. and Buijs et al., macrocirculatory parameters cannot estimate microcirculatory function and MTH causes

abnormalities in microcirculation and peripheral tissue perfusion. [26, 27] Buijs et al. found that the microcirculation was impaired during MTH and more severely impaired at the start of MTH in non-survivors. Despite impairments in microcirculatory function during MTH, increased amounts of dissolved oxygen could have maintained oxygen supply to the organs in the patients in the present study. Measurement of systemic and cerebral tissue oxygenation by near-infrared spectroscopy, Laser-Doppler spectroscopy, functional imaging, and perhaps even invasive methods, is necessary to study the interacting effects of hyperoxia and hypothermia on the outcome in children after CA.

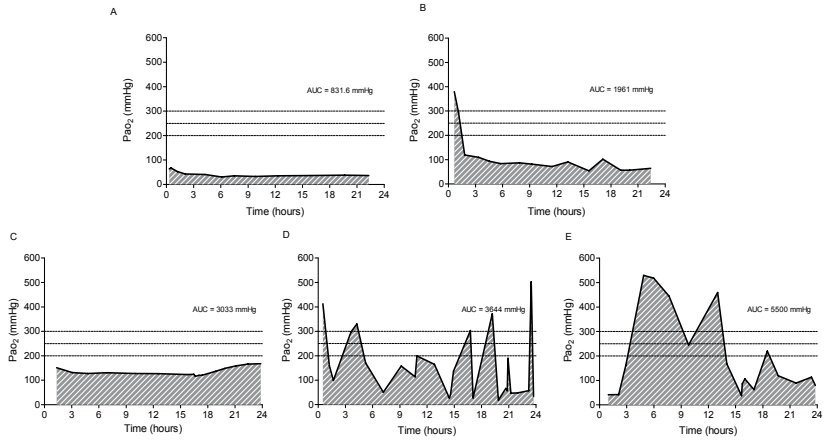

Figure 3. Observations of PaO_2 for 5 selected patients in the dataset, cutoff versus area under the curve (AUC)

A. Low AUC value, no PaO_2 above a cutoff value.

B. Low AUC value, PaO2 above cutoff values.

C. High AUC value, no PaO_2 above a cutoff value.

D. High AUC value, PaO_2 above cutoff values.

E. High AUC value, fluctuating PaO_2 above cutoff values.

Another explanation could be the synergistic effect of hypothermia and hyperoxia. It has been demonstrated that hypothermia attenuates oxidative stress after traumatic brain injury (TBI) in children. [28] Hyperoxia has been shown to improve organ function, and to attenuate tissue apoptosis and oxidative stress during early septic shock. [29] Even anti-inflammatory effects of hyperoxia are reported. [30]

Hyperoxia causes vasoconstriction. The mechanisms underlying this vasoconstriction are not well understood, but there are different theories as

mentioned by Sjoberg and Singer. [30]

Limitations

Several limitations of our study should be acknowledged. First, this is an observational, retrospective, single-center cohort study in a heterogeneous population without a control group over a relatively long study interval. Changes in clinical care during this study period will have improved the outcome after CA; however this probably did not change the impact of high oxygen levels on the outcome, as the attention was more focused on preventing hypoxia, rather than avoiding hyperoxia. Only recent international CA guidelines have recommended avoiding an arterial oxygen saturation of 100%. [17]

Another limitation is that the time intervals of PaO_2 measurements were not standardized. We would recommend measuring PaO_2 at least every hour, which permits a more precise measurement of the AUC and thus a better estimation of the influence of PaO_2 on mortality.

A third limitation is the small number of patients in which MTH was applied, as therapeutic hypothermia was introduced halfway through the study period. However, this number of patients was not smaller than that in other studies. [19, 31] As our findings stem from a small heterogeneous group of patients, we expect they will most probably be confirmed by larger, homogeneous groups of patients.

A fourth limitation is that some important variables are lacking, such as fluid administration during CPR, and time to ROSC.

Lastly, the information on temperature is limited. We recorded the time in which MTH was reached, but we did not document the course of the temperature during the following 24 h and during rewarming. In addition, we did not document the presence of fever.

Conclusions

Aware of the limitations of our study, we would recommend standardized prospective collection of all CA-related data in children in large multicenter networks. Retrospective analysis of a large set of prospective collected data will help us to answer such difficult questions in our very heterogeneous populations. Additionally, we need to study the effects of PaO_2 on physical outcome,

neuropsychological outcome and health-related quality of life. Combining this information will help us to achieve goal-directed therapy which can automatically adjust the fraction of inspired oxygen to the individual physical demands of a child. Until individualized therapy can be practiced, we must use oxygen carefully within the therapeutic window and avoid the harmful effects of extreme values of PaO_2.

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Supplementary Table 1. Patient characteristics and cardiac arrest characteristics of children with and without initiated mild therapeutic hypothermia *

	MTH + (n = 63)			MTH - (n = 137)			*p*-value[d]
	n[a]			n[a]			
Age (months)[b]	63	47.5	(1.1-212.0)	137	22.4	(.95 - 262.6)	**.008**
Male gender[c]	63	43	(68%)	137	67	(49%)	**.014**
Advanced Pediatric Life Support (APLS)[c]	63	59	(94%)	137	112	(82%)	**.030**
Out-of-hospital arrest[c]	63	44	(70%)	137	54	(39%)	**<.001**
Bystander CPR[c]	59	48	(81%)	132	119	(90%)	.102
Initial Rhythm Non-shockable[c]	61	50	(82%)	123	113	(92%)	.053
Etiology	63			137			
- Cardiac[c]		17	(27%)		43	(31%)	.619
- Arrhythmia[c]	17	5	(29%)	43	6	(14%)	
- Cardiomyopathy[c]	17	6	(35%)	43	10	(23%)	
- Hypovolemic shock[c]	17	1	(6%)	43	5	(12%)	
- Obstructive shock[c]	17	3	(18%)	43	1	(2%)	
- Septic shock[c]	17	2	(12%)	43	18	(42%)	
- Other[c]	17	0	(0%)	43	3	(7%)	
- Respiratory[c]		35	(56%)		60	(44%)	.130
- Aspiration	35	4	(11%)	60	3	(5%)	
- Bronchomalacia / -spasm[c]	35	1	(3%)	60	4	(7%)	
- Congenital[c]	35	0	(0%)	60	6	(10%)	
- Drowning[c]	35	11	(31%)	60	20	(33%)	
- Hanging[c]	35	4	(11%)	60	0	(0%)	
- Insufficiency/Infection[c]	35	6	(17%)	60	13	(22%)	
- Obstruction other[c]	35	1	(3%)	60	9	(15%)	
- Pulmonary hypertension[c]	35	2	(6%)	60	1	(2%)	
- Other[c]	35	6	(17%)	60	4	(7%)	
- Neurologic[c]		5	(8%)		23	(17%)	.124
- Herniation[c]	5	0	(0%)	23	3	(13%)	
- Vascular accident[c]	5	1	(20%)	23	2	(9%)	
- Trauma[c]	5	3	(60%)	23	15	(65%)	
- Other[c]	5	1	(20%)	23	3	(13%)	
- ALTE / SIDS[c]		5	(8%)		4	(3%)	.144
- Other/Unkown[c]		1	(2%)		7	(5%)	.439

Supplementary Table 1. *Continued*

	MTH + (n = 63)			MTH - (n = 137)			*p*-value[d]
	n[a]			n[a]			
Pre-existing condition[c] **	63	19	(30%)	134	61	(46%)	**.044**
- Cardiac[c]		10	(53%)		33	(54%)	1.000
- Respiratory[c]		8	(42%)		21	(34%)	.591
- Neurologic[c]		1	(5%)		4	(7%)	1.000
- Other/Unkown[c]		0	(0%)		3	(5%)	1.000
Lowest pH[b]	63	7.02	(6.37 - 7.43)	137	7.11	(6.36-7.53)	.106
Highest lactate[b]	63	10.6	(1.3 - 25.0)	132	8.6	(.90-23.0)	**.046**
Lowest PaO_2[b]	63	61.5	(17.3 - 132.0)	137	62.3	(12.8 - 240.0)	.649
Highest PaO_2[b]	63	291.0	(32.3 - 626.3)	137	241.5	(27.0 - 628.6)	**.016**
min. PaO_2 <60 mmHg[c]	63	29	(46%)	137	63	(46%)	1.000
max. PaO_2 > 200 mmHg[c]	63	43	(68%)	137	84	(61%)	.429
max. PaO_2 > 250 mmHg[c]	63	38	(60%)	137	64	(47%)	.094
max. PaO_2 > 300 mmHg[c]	63	31	(49%)	137	52	(38%)	.165
AUC 0 - 24 hours mmHg[b]	61	3227.9	(565.9 – 5785.5)	91	2986.7	(778.2 – 5405.5)	.497
- mmHg/hour[b]	61	134.5	(23.6 – 241.1)	91	124.4	(32.4 – 225.2)	
AUC 0-6 hours mmHg[b]	56	888.6	(268.1 – 2221.8)	86	862.8	(166.7 – 2290.2)	.828
- mmHg/hour[b]	56	148.1	(44.7 – 370.3)	86	143.8	(27.8 – 381.7)	
AUC 6-24 hours mmHg[b]	60	2155.4	(424.4 – 4645.2)	89	2199.6	(586.8 – 4045.5)	.591
- mmHg/hour[b]	60	119.7	(23.6 – 258.1)	89	122.2	(32.6 – 224.8)	

[a] Number of subjects in whom the variable was obtained.

[b] Median (range).

[c] Number of subjects (%).

[d] *p*-value: independent sample t-test for continuous data or Mann-Whitney dependent on normality; Fisher's Exact test for dichotomous data.

* Children in whom mild therapeutic hypothermia was initiated (n=63), 58 of whom reached target temperature.

* * Children with a pre-existing medical history which was the cause of CA, classified by the etiology of the CA.

Abbreviations: ALTE = Apparent Life Threatening Event, AUC = area under the curve, max. = maximum, n = number, PaO_2 = partial pressure of arterial oxygen, SIDS = sudden infant death syndrome.

Supplementary Table 2. Duration and number of measurement per time period

	n	Median time measured	Range time measured	Median number of measurements	Range number of measurements
AUC 0-24 hours	152	21.2	(12.3-24.0)	12	(4-33)
AUC 0-6 hours	142	4.3	(0.1-6.0)	5	(2-13)
AUC 6-24 hours	149	14.9	(4.3-17.8)	7	(2-22)

Abbreviations: AUC = area under the curve.

Editorial on our findings:

"Blowing hot or cold? Oxygenation and temperature after paediatric cardiac arrest"

Resuscitation. 2015 May; 90:A1-3

Blowing hot or cold? Oxygenation and temperature after paediatric cardiac arrest

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Chapter 3

Cardiac arrest in children: long-term health status and health related quality of life

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Pediatr Crit Care Med. 2015 Mar. In Press

Abstract

Objective: To assess long-term health status and health-related quality of life (HR-QoL) in survivors of cardiac arrest (CA) in childhood and their parents. In addition, to identify predictors of health status and HR-QoL.

Design: This medical follow-up study involved consecutive children surviving CA between January 2002 and December 2011, who had been admitted to the ICU. Health status was assessed with a medical interview, physical examination and the Health Utilities Index (HUI). HR-QoL was assessed with the Child Health Questionnaires and Short-Form 36.

Setting: A tertiary-care university children's hospital.

Patients: Of the eligible 107 children, 57 (53%) filled out online questionnaires and 47 visited the outpatient clinic (median age 8.7 years; median follow-up interval 5.6 years).

Interventions: None.

Measurements and Main Results: Of the participants, 60% had an in-hospital CA, 90% a non-shockable rhythm, and 50% a respiratory etiology of arrest. Mortality rate after hospital discharge was 10%. On health status, we found that 13% had long-term neurological deficits, 34% chronic symptoms (e.g., fatigue, headache), 19% at least one sign suggestive of chronic kidney injury, and 15% needed special education. HUI-scores were significantly decreased on most utility scores and the overall HUI3 score.

Compared with Dutch normative data, parent-reported HR-QoL of CA survivors was significantly worse on general health perception, physical role functioning, parental impact and overall physical summary. On patient-reports no significant differences with normative data were found. Parents reported better family cohesion and better HR-QoL for themselves on most scales.

Patients' health status, general health perceptions and physical summary scores were significantly associated with CA-related pre-existing condition.

Conclusions: Considering the impact of CA, the overall outcome after CA in childhood is reasonably good. Prospective long-term outcome research in large homogeneous groups is needed.

Introduction

Overall survival after cardiac arrest (CA) in children is low and dependent on the location of the arrest. [1] In-hospital (IH) CAs are associated with survival rates of 30-50%, and 60-80% has a generally good neurologic outcome. [1, 2] Out-of-hospital (OH) CAs generally have a low survival rate of 10% and high morbidity rates (>90%). [1, 3] While return of spontaneous circulation (ROSC) occurs in 30-50%, brain death or withdrawal from life-sustaining treatment on the grounds of adverse neurological prognosis is the cause of death in approximately 25-50% of these children in the intensive care unit (ICU). [1, 3] Physical health and health-related quality of life (HR-QoL) of surviving children, as well as those of their parents, can still be affected years after the event as the mortality rate in the years after hospital discharge is more than 10%. [4]

Few studies have investigated the long-term health status and HR-QoL of survivors of CA in childhood. Various neurological impairments, such as speech and praxis disturbances, visual impairments, quadriplegia, and locked-in syndrome, were reported. [5-7] Unfortunately, these studies had limitations, such as small sample size (n=10-29), short follow-up interval (<6 months), or specific patient groups based on etiology (drowning; trauma, including head injury). Although findings on long-term renal function are still lacking, acute tubular necrosis at time of CA could have a significant impact on the long-term physical outcome as well. Furthermore, HR-QoL was studied with very general scoring systems only, such as the Pediatric Cerebral Performance Category (PCPC), which ranges from normal functioning to brain death. [2, 8, 9] No study has reported parents' quality of life in this context.

In this study, health status and HR-QoL were assessed by internationally widely used, validated questionnaires: the Health Utility Index (HUI, covering age-range: 5-13 years) and Child Health Questionnaire (CHQ, covering age-range: 0-17 years)/ Short-Form 36 (SF-36 for patients ≥18 years and parents). Participants' scores were compared with those of healthy peers/parents from the general Dutch population (normative data). The HUI assesses multiple dimensions of health status: vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, sensation, emotion and cognition. Previously, the HUI showed unfavourable outcomes on long-term health status for childhood survivors of meningococcal septic shock (age 5-31 years at time of follow-up). [10] The CHQ (child version) and SF-36 (adult version) are both generic HR-QoL instruments, having a similar structure, and assessing

multiple physical and psychosocial areas related to health, during the 4 weeks prior to completing the questionnaire. Previously, the CHQ indicated unfavourable long-term HR-QoL outcomes for childhood survivors of meningococcal septic shock (aged 4-17 years at time of follow-up), but not for their parents themselves. [11]

The aim of this study was to systematically investigate the long-term health status and HR-QoL in a consecutive series of survivors of CA in childhood and their parents. A medical interview, physical examination, and validated questionnaires were used to assess health status and HR-QoL. The surplus value of this project and innovative aspects include the use of internationally validated, well-known questionnaires with a multi-informant approach covering the physical, mental, and social well-being of both children and parents. Additionally, predictors of health status and HR-QoL were assessed. We hypothesized that health status and HR-QOL in survivors of CA in childhood is significantly impaired.

Materials and Methods

This medical follow-up study was performed at the ICU of the Erasmus MC-Sophia Children's Hospital, a tertiary care university children's hospital, containing the only specialized pediatric ICU in this region. Our hospital provides health care to children in the southwest of the Netherlands with a total population of approximately 4.2 million people, which is a representative sample of the Dutch population.

The Erasmus MC Ethical Review Board approved the study protocol.

Patient Selection and Data Collection

This study concerned all consecutive surviving patients aged 0-18 years with CA between January 2002 and December 2011, who were admitted to the ICU of the Erasmus MC-Sophia Children's Hospital.

CA was defined as absent pulse rate or the need for cardiac compressions. Cardiopulmonary resuscitation (CPR) was defined as "basic life support" (BLS), in line with the European Resuscitation Council Guidelines for pediatric life support, and if needed, followed by "advanced pediatric life support" (APLS). [12]

All CA data were retrospectively collected. Data were derived from ambulance registration forms, clinical and electronic medical records, and CA registration forms. We collected: 1) basic patient characteristics, 2) CA characteristics (e.g., location, rhythm, etiology), and 3) outcome (mortality). Additionally, medical records were retrospectively analyzed if the health status prior to the CA was related to the cause of the arrest (i.e., cardiac, respiratory or other).

Eligible for this study were: 1) children resuscitated in-hospital (e.g., emergency department, ward, ICU), 2) children resuscitated in a regional hospital or other university hospital, and subsequently admitted to the ICU of our hospital, and 3) children resuscitated out-of-hospital, and subsequently admitted to our ICU.

Neonates resuscitated at the hospital's neonatal ICU (NICU), or in another hospital and subsequently admitted to the NICU of our hospital were excluded.

Surviving children and parents were invited to participate 2-11 years after ICU discharge. Informed consent was obtained from parents, and children (≥ 12 years). Participating families were invited to complete online health status and HR-QoL questionnaires. Choice of respondent (mother or father) was left to the parents

themselves. Parents also completed assessments. Subsequently, children were invited for a medical interview and physical examination.

Assessment at Follow-Up

Parents and children were interviewed by a medical doctor (L.v.Z.) in a semi structured format using a CPR-specific standardized questionnaire on health consequences and medical care since the CA. It included questions on family characteristics, healthcare consumption, current physical and behavioral functioning, and changes in this functioning since the CA. This allowed us to differentiate between pre-existing complaints, and physical and behavioral changes due to the CA. Somatic symptoms (such as fatigue, pain, headache, among other) were defined as *chronic* if they had developed in the first weeks *after* ICU discharge and were still present at the time of follow-up. Severity of these complaints was scored on a 5-point scale (very mild to very severe).

A general physical examination (including blood pressure (BP)) was performed by the same medical doctor (L.vZ.). BP was measured with an electronic device three times at 1-minute intervals, with the child in a seated position following 5 minutes of rest. Hypertension was defined as median systolic BP (SBP) or diastolic BP (DBP) above the 95th percentile corrected for age, sex, and height. [13]

Renal function was assessed by measuring serum creatinine (SCr), random urine protein sample, and random urine protein to creatinine ratio. An estimated glomerular filtration rate (eGFR) was calculated with the Schwarz formula eGFR (mL/min/1.73 m^2) = 36.5 x height (cm)/creatinine (µmol/L) for children younger than 16 years. [14] For children older than 16 years the MDRD formula was used: eGFR (mL/min/1.73 m^2) = 186 x (SCr/88.4)$^{-1.154}$ x Age$^{-0.203}$ x (0.742 if Female). [15] Renal function was staged using the chronic kidney disease (CKD) stages provided by the National Kidney Foundation. The stages were defined as stage 0, GFR ≥ 90 mL/min/1.73m^2; stage 1, proteinuria with GFR ≥ 90 mL/min/1.73m^2; stage 2, proteinuria with GFR 60-89 mL/min/1.73m^2; stage 3, GFR 30-59 mL/min/1.73m^2; stage 4, GFR 15-29 mL/min/1.73m^2; and stage 5, GFR <15 mL/min/1.73m^2. [16] A protein concentration in a randomly collected urine sample of >22 mg protein/mmol creatinine was classified as proteinuria. [12]

Questionnaires

Generic health status was assessed with validated classification systems, the Health Utilities Index mark 2 and 3 (HUI2 and HUI3), encompassing 6 to 8 health dimensions. [17, 18] As parent-report, the 15-item HUI was used (age-range 4-17 years). The complete dataset of representative normative data was available (1,435 Dutch schoolchildren aged 5-13 years). [17, 18]

HR-QoL in children was assessed with the Child Health Questionnaire (CHQ) and in parents with the SF-36. [18-22] The CHQ-IT97 (0-3 years) and CHQ-PF50 (4-17 years) were filled out by parents about their child, and the CHQ-CF87 (age 12-17) was filled out by children about themselves. [18, 19, 23] Normative data were derived from representative samples of the general Dutch population. [18, 19, 24] For the SF-36, Dutch normative data were available (1,742 participants, 16-94 years) of which a normative reference group (those aged 41-60 years) was used. [25]

Socioeconomic status

Socioeconomic status (SES) at time of follow-up was categorized as "low" (elementary occupations), "middle" ('middle' occupations), or "high" ('highest' professional occupations). [26] The highest occupation of both parents was used. SES of non-participants at time of follow-up was calculated based on a combined status score of the Netherlands Institute for Social Research based on home address. [27] This score consisted of average income in neighborhood, percentage of people with low income, percentage of less educated people, and percentage of people not working. A status score of 0 (±1.16 SD) was classified middle SES, <-1.16 was classified low SES, and >+1.16 was classified high SES.

Statistical analysis

Univariable comparison of the distribution of patient characteristics and clinical data between survivors and non-survivors was performed by independent sample t-tests for normally distributed data, and Mann-Whitney-U tests for non-normally distributed data. Fisher's exact test was used for comparison of dichotomous data.

Normality of our data was examined with the Kolmogorov-Smirnov test. If the HUI data were normally distributed, the Welch's t-test (for unequal variances) was performed to compare data of children with CA with normative data. Mann-

Whitney-U test was used for non-normally distributed data. If the HR-QoL data were normally distributed, one-sample t-test was performed to compare with normative data. One-sample Wilcoxon Signed Rank Test was used for non-normally distributed HR-QoL data. Effect sizes were reported with Cohen's d. [28]

Associations between putative predictor variables (age at ICU admission, BLS/APLS, pre-existing condition, location, SES) and the HUI and HR-QoL scores were explored with the Spearman's correlations for continuous variables, Mann-Whitney-U test for dichotomous variables, and Kruskal-Wallis test for ordinal variables.

Statistical significance was considered with 2-tailed *p*-values of <0.05. All analyses were performed with SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Patient sample

The target population consisted of 145 surviving patients who had survived to hospital discharge, of whom 13 (9%) had subsequently died and 25 (17%) who were lost to follow-up. (Figure 1) Causes of death after hospital discharge were another CA without ROSC (n=3), underlying disease (n=2), severe cerebral damage (n=1), or unknown (n=7).

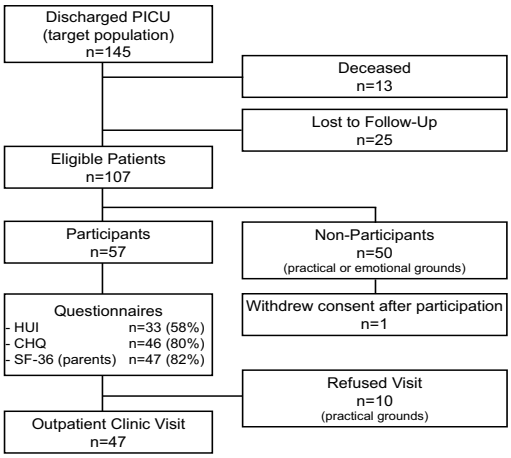

Figure 1. Flowchart of patient inclusion

The overall response rate was 53% (57/107).

Lost to Follow-up: moved abroad n=7, untraceable n=18.

Abbreviations: CHQ = Child Health Questionnaire; HUI = Health Utility Index; SF-36 = Short Form-36.

The median follow-up interval of children visiting the outpatient clinic was 5.6 years (1.8 – 11.9 years) with a median age at follow-up of 8.7 years (2.4-18.3 years). Participants and non-participants differed significantly on SES. (Table 1)

Table 1. Characteristics of participants and non-participants

	Participants (n=57)			Non-participants (n=50)			*p*-value
	n [a]			n [a]			
Age at ICU admission (months)	57	4.9	(0 – 193.3)	50	9.1	(0 – 204.2)	.137
Male gender	57	29	(51%)	50	35	(70%)	.050
Advanced Pediatric Life Support (APLS)	57	33	(58%)	50	35	(70%)	.230
Out-of-hospital arrest	57	22	(39%)	50	17	(34%)	.689
Bystander CPR	57	56	(98%)	47	46	(98%)	1.00
Initial Rhythm Non-shockable	46	40	(87%)	46	39	(85%)	1.00
Etiology							
- Cardiac	57	20	(35%)	50	18	(36%)	1.00
- Respiratory	57	29	(51%)	50	29	(58%)	.560
- Other	57	8	(14%)	50	3	(6%)	.213
CA-related pre-existing condition [b]	57	32	(56%)	50	23	(46%)	.336
- Cardiac	32	16	(50%)	23	14	(61%)	.584
- Respiratory	32	13	(41%)	23	7	(30%)	.572
- Other	32	3	(9%)	23	2	(9%)	1.00
Mild therapeutic hypothermia [c]	57	8	(14%)	50	14	(28%)	.095
Socioeconomic status at follow-up							
- Level 1: "Low"	57	4	(7%)	50	14	(28%)	**.005**
- Level 2: "Middle"	57	25	(44%)	50	27	(54%)	.336
- Level 3: "High"	57	28	(49%)	50	9	(18%)	**.001**

[a] Number of subjects for whom the variable was obtained.

[b] Medical records were retrospectively analyzed if the health status prior to the CA was related to the cause of the arrest.

[c] Children treated with mild therapeutic hypothermia (32-34 °C).

All data are presented as "number of subject (%)", except age which is presented as "median (range)".

Health status at follow-up

Neurological impairments had developed in six of the 47 children (13%) after CA: n=2 severe mental and physical retardation (n=1 with epilepsy, n=1 with visual impairments); n=2 motor skill deficit; n=1 quadriplegia with mental disability; and n=1 epilepsy. Fourteen children (30%) still needed follow-up care by a rehabilitation physician, physiotherapist, speech therapist, and/or occupational therapist for physical impairments starting after the CA. One patient (2%) lived in a healthcare facility due to severe physical impairments. Chronic symptoms with

onset after the CA were reported for 16 children (34%): n=7 (15%) fatigue (mild – severe); n=10 (21%) headache (mild – severe); n=3 (6%) abdominal pain (moderate – severe). Permanent change in the child's behavior was reported in 15% (n=7) of the children after CA, for example changes from normal to more childlike, quieter, difficulties in emotional regulation, or severe mental and physical retardation. For 21 children, this was unknown, as they were very young at time of CA. Ten children (21%) had had professional assistance for emotional/behavioral problems. In total, seven children (15%) needed special education after CA, mostly due to behavioral problems or cognitive impairments. One child is not able to go to school due to severe mental and physical impairments.

Renal function was measured in 43 children (91%), in whom median eGFR was 122.0 mL/min/1.73 m^2 (IQR 109.1-134.5). Nine children (19%) had at least one symptom suggestive of CKD: n=4 proteinuria (median 36.0 mg/mmol, IQR 29.4 – 60.9), n=5 DBP and/or SBP above 95th percentile (n=1 with proteinuria), n=1 eGFR < 90 mL/min/1.73m^2 (86 mL/min/1.73m^2). (see Supplemental Table 2 for long-term outcome and related CA characteristics)

Questionnaires: children's outcome

On HUI2, HUI3 attributes, and the overall HUI3 multi-attribute, scores were significantly lower (medium and large effect sizes) compared with normative data, indicating poorer health status. (Table 2)

Parent-reported HR-QoL scores were significantly lower on role functioning (physical), general health perceptions, parental impact (emotion), and overall physical summary; and significantly higher on family cohesion, when compared with normative data (small to large effect sizes). (Table 3) Self-reports of children aged 12 to 17 years (CHQ-CF87) showed no significant differences with normative data. (Table 4)

Subanalysis directly comparing parents' results and children's results *within* the CPR population, showed no differences. Subanalysis to test differences between IH CA versus OH CA on HR-QoL outcomes is shown in Supplemental Table 3.

Table 2. HUI2 and HUI3 scores in patients: results of parent-reports

	Patients	Norm	*p*-value	Cohen's d
	Mean (SD)	Mean (SD)		
*HUI3 single-attribute utility score**	*n=33*	*n=1,435*		
Vision	0.94 (0.20)	0.99 (0.04)	**.014**	**1.01**
Hearing	1.00 (0.00)	1.00 (0.04)	.464	0.00
Speech	0.88 (0.26)	0.97 (0.08)	**.005**	**1.02**
Ambulation	0.93 (0.24)	1.00 (0.04)	**<.001**	**1.32**
Dexterity	0.93 (0.24)	1.00 (0.02)	**<.001**	**1.72**
Emotion	0.98 (0.04)	0.98 (0.07)	.459	0.00
Cognition	0.83 (0.28)	0.97 (0.09)	**<.001**	**1.43**
Pain	0.90 (0.22)	0.98 (0.08)	.116	0.94
HUI3 multi-attribute utility score	0.77 (0.35)	0.93 (0.12)	**.002**	**1.31**
*HUI2 single-attribute utility score**				
Sensation	0.87 (0.25)	0.95 (0.12)	**.016**	.64
Mobility	0.94 (0.24)	1.00 (0.03)	**<.001**	**1.30**
Emotion	0.96 (0.08)	0.97 (0.08)	.866	.13
Cognitive	0.87 (0.24)	0.98 (0.06)	**<.001**	**1.59**
Self-care	0.89 (0.30)	0.99 (0.06)	**<.001**	**1.35**
Pain	0.97 (0.11)	0.99 (0.05)	.549	.38
HUI2 multi-attribute utility score	0.86 (0.23)	0.94 (0.09)	.073	.84

* Normative data only available for patients aged 5-13 years. Supplemental Table 1 shows the analysis of patients within the age-specific range, which had similar results.

Low scores imply worse functioning.

Cohen's d's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. [28]

Table 3. Health-related quality of life in patients: results of parent-reports

	Patients Mean (SD)	Norm Mean (SD)	*p*-value	Cohen's d
CHQ-IT97 (0-3 years)	*n=12*	*n=410*		
Physical functioning (PF)	76.4 (35.9)	97.2 (9.8)	.133	1.84
Growth and development (GD)	81.5 (15.6)	86.5 (10.6)	.271	.46
Bodily pain/discomfort (BP)	83.3 (23.3)	83.8 (16.8)	.874	.03
Temperament and moods (TM)	79.5 (11.7)	77.2 (10.5)	.638	.22
General behavior (GB)	71.5 (15.5)	72.8 (12.7)	.695	.10
Getting along (GA)	73.6 (13.4)	71.4 (8.8)	.529	.25
General health perceptions (GH)	57.8 (18.8)	79.0 (14.5)	**.005**	**1.45**
Parental impact: Emotional (PE)	90.5 (12.6)	92.1 (10.5)	.693	.15
Parental impact: Time (PT)	92.5 (11.0)	93.0 (11.0)	.874	.05
Family cohesion (FC)	87.9 (11.4)	75.3 (18.8)	**.013**	.68
Change in health (CH)	66.7 (24.6)	56.1 (18.4)	.807	.57
CHQ-PF50 (4-17 years)	*n=33*	*n=353*		
Physical functioning (PF)	89.9 (24.9)	99.1 (4.3)	.610	1.11
Role functioning: Emotional/behavior (REB)	87.9 (30.7)	97.9 (7.2)	.062	.89
Role functioning: Physical (RP)	87.9 (31.0)	95.8 (15.6)	**.015**	.45
Bodily pain (BP)	79.1 (27.0)	85.7 (17.2)	.222	.36
General behavior (GB)	75.4 (15.9)	78.5 (13.1)	.514	.23
Mental health (MH)	82.3 (13.4)	81.4 (12.1)	.320	.07
Self-esteem (SE)	78.0 (13.5)	79.2 (11.0)	.355	.11
General health perceptions (GH)	57.9 (27.6)	82.9 (13.4)	**<.001**	**1.66**
Parental impact: Emotional (PE)	74.5 (26.0)	86.3 (15.2)	**.027**	.72
Parental impact: Time (PT)	81.8 (28.4)	94.0 (13.0)	.119	.82
Family activities (FA)	84.7 (24.7)	91.5 (11.9)	.935	.51
Family cohesion (FC)	76.2 (20.0)	72.2 (19.4)	**.013**	.21
Physical summary (PHS)	47.3 (17.3)	56.4 (5.7)	**.003**	**1.23**
Psychosocial summary (PSS)	51.3 (8.2)	53.2 (6.4)	.367	.29

Low scores imply worse functioning.

Scores on the CHQ-PF50 scale "change in health" are not presented since individual normative data were not available for this scale.

Cohen's d's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. [28]

Health status and HR-QoL in parents

The median age of parents was 40 years (range, 22-60). On semi-structured questions during the interview at the outpatient clinic, nine of 47 parents (19%) reported limitations in their daily activities (e.g., job, holidays, hobbies, social visits) after the CA.

On HR-QoL, parents showed a better physical functioning, general mental health, social functioning, physical and emotional role functioning, and less bodily pain, when compared with normative data (small and medium effect sizes). (Table 5)

Predictors of health status and HR-QoL in children and parents

Univariate analysis of the neurological impairments, renal impairments, and CA-induced behavioral changes showed no significant relationship with predictor variables. Children with chronic symptoms had BLS (no APLS) more often (χ^2=4.691, p=.037).

On the HUI, males scored worse than females on both cognition scores (HUI3: Z=-2.320, p=.033; HUI2 Z=-2.468, p=.024) and the HUI3 multi-attribute score (Z=-2.418, p=.016). On the CHQ-PF50, CA-related pre-existing condition was associated with worse patients' general health perceptions (Z=-2.443, p=.015) and physical summary (Z=-2.003, p=.045). Family cohesion was significantly worse in children with an out-of-hospital CA (Z=-2.264, p=.024). On the SF-36, parents' physical functioning was significantly worse when their child had an out-of-hospital CA (Z=-2.049, p=.040). Social functioning was significantly higher in parents with a high SES compared with those with a middle SES (χ^2=7.024, p=.030).

Table 4. Health-related quality of life in patients: results of self-reports

	Patients Mean (SD)	Norm Mean (SD)	p-value	Cohen's d
CHQ-CF87 (12-17 years)	*n=8*	*n=457*		
Physical functioning (PF)	95.8 (5.0)	96.0 (6.9)	.256	.03
Role functioning: Emotional/ Behavior (REB)	92.4 (11.1)	89.4 (17.2)	1.00	.18
Role functioning: Physical (RP)	91.7 (12.9)	95.0 (12.9)	.667	.26
Bodily pain (BP)	83.8 (20.0)	73.5 (22.7)	.888	.45
General behavior (GB)	80.2 (10.3)	80.9 (10.6)	.575	.07
Mental health (MH)	72.7 (13.4)	76.5 (15.4)	.123	.25
Self-esteem (SE)	74.3 (10.1)	74.7 (12.2)	.160	.03
General health perceptions (GH)	70.3 (18.2)	73.5 (16.5)	.050	.19
Family activities (FA)	77.6 (22.0)	80.0 (17.7)	.161	.14
Family cohesion (FC)	72.5 (24.2)	70.6 (23.5)	.573	.08

Low scores imply worse functioning.

Cohen's d's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. [28]

Note: The CHQ-CF87 scales "role functioning-emotional" and "role functioning-behavioral" were merged into a single scale, like the reference group [24]. Scores on the CHQ-CF87 scale "change in health" are not presented since individual normative data were not available for this scale.

Table 5. Health-related quality of life in parents

	Parents Mean (SD)	Norm Mean (SD)	*p*-value	Cohen's d
SF-36	*n=47*	*n= 1.742*		
Physical functioning (PF)	91.1 (19.2)	84.0 (19.6)	**<.001**	.36
Role limitations due to physical functioning (RP)	85.6 (33.7)	74.5 (36.8)	**.004**	.30
Social functioning (SF)	88.6 (23.7)	83.5 (22.1)	**.048**	.23
Bodily pain (BP)	85.3 (22.0)	71.8 (24.1)	**<.001**	.56
General mental health (MH)	78.2 (17.3)	75.6 (18.5)	**.044**	.14
Role limitations due to emotional problems (RE)	88.7 (28.9)	81.6 (33.2)	**.001**	.21
Vitality (VI)	64.9 (21.5)	68.6 (20.2)	.611	.18
General health perceptions (GH)	72.6 (25.9)	69.7 (20.6)	.280	.14

Low scores imply worse functioning.

Cohen's d's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. [28]

Note: Scores on the SF-36 scale "change in health" and summary scores are not presented since individual normative data were not available for these scales.

Discussion

Our study provides a detailed overview of the long-term medical outcome and health-related quality of life (HR-QoL) after CA in childhood. After the initial survival another 9% died following ICU discharge. A minority of CA survivors showed long-term neurological impairments, chronic symptoms, and renal impairments. On HUI and HR-QoL, parent-reports of CA survivors showed significantly worse outcomes on physical scales and parental impact compared with normative data. Surprisingly, parents reported better scores towards their own functioning.

We had a heterogeneous patient sample regarding location of CA, rhythm, and etiology, which was not the case in other studies in terms of etiology and rhythm. [5-7, 29] The response rate was satisfactory, considering the long follow-up interval, number of tests, and aim of the project (research, not patient care). Only SES significantly differed between participants and non-participants. Although SES was measured differently, it suggests that our results might be too positive, as SES is an important predictor of outcome. [30]

In line with other studies, various significant neurological impairments were found. [5, 31] The low number of children with these neurological impairments is reasonably similar to previous studies describing long-term outcome in very general terms. These studies reported that 60-85% had a PCPC score of one, two, or no change from pre-arrest score at hospital discharge, dependent on CA location. [2, 8, 32]

Acute tubular necrosis can develop following an ischemic attack to the kidneys, and reduces the number of functioning nephrons. While a child grows in height and weight, the demand for clearance may exceed the number of nephrons, and loss of renal function may follow. We found that only 19% of our population had at least one sign of CKD and/or hypertension. Long-term kidney function in children after extracorporeal membrane oxygenation has shown that 32% has at least one sign of CKD and/or hypertension. [33] As long-term kidney function has only been studied in other groups of critically ill children, further research is needed and should be focusing on identifying risk factors of CKD (e.g., pre-existing condition, CA characteristics, use of nephrotoxic drugs after CA).

Concerning HUI outcomes, in line with our outcomes, children after meningococcal septic shock also showed significant long-term impairments on most HUI scales. [10]

The HUI is a reliable and valid measure for outcome assessment (i.e., morbidity) in heterogeneous populations of children and performs well in a pediatric intensive care setting. [34, 35] It has shown to have a very good inter-rater reliability and a very good parent-child agreement, and is therefore suitable for assessment by proxies. [34, 35]

As postanoxic encephalopathy after CA causes significant impairments in physical and cognitive functioning, outcome is dependent on the degree of global ischemia during CA, but also on delayed cell death up to six hours after CA (reperfusion injury). [36] While severe impairments are usually adequately recognized, milder forms of physical and cognitive problems may receive less attention in school and social environments or even be denied by child or parents. Consequently, the child's abilities may be overestimated, resulting in fatigue, stress, tension headache, or other physical complaints. Since the HUI has proven sensitivity to change, it can be used for early identification of physical and cognitive problems, so that (neuro) rehabilitation can be started as soon as possible. [35]

We used well-known, internationally validated questionnaires with a multi-informant approach. Although for both age-ranges (0-3, and 4-17 years) parents reported a significantly lower perceived general health in all children compared with normative parents, children reported no impairments compared with normative peers. It should be noted that these results were found when comparing with different normative groups (for parents and children separately). As described by Raat et al., it is common to find differences between proxy reports and self-reports, and both views provide a picture on the influence of a disease on the HR-QoL. [20] The scores on the self-reports might be explained by the small number of children completing this questionnaire, denial or impairments by the child, or the inability of children with physical or mental impairments to fill out questionnaire themselves. In contrast, the parents' questionnaires were filled out by parents both with and without children with physical and mental impairments. Elliot et al. showed that previous studies have used different and small control groups. [9] We used large representative Dutch population samples to compare with, thus reducing the risk of chance findings and selection bias. [17-19, 24, 25] However, as Elliot confirm, the most appropriate reference group has not been defined yet. [9]

Nineteen percent of the parents reported limitations in their daily activities, which is reflected by the parental impact scale (CHQ-PF50). Parents have more emotional

concerns as a result of their child's physical functioning or psychosocial health.

While usually the impact of a CA and ICU stay is enormous, parents' long-term HR-QoL scores were surprisingly more favorable than normative data. [37, 38] This might be explained by concepts such as 'response shift' or 'posttraumatic growth'. Response shift is "the change of the internal standards and values after a life-threatening or traumatic event". [39] Parents may compare their problems with those of their child, which puts their own problems into another perspective. Posttraumatic growth is "the experience of positive change as a result of the struggle with highly challenging life crises". [40] After CA parents may worry less about futilities in life. Nevertheless, favorable scores could also have been influenced by social desirability, denial, or overcompensation, which has also been described in parents of children surviving surgery for congenital heart disease. [41]

Univariate analysis of health status was limited by the small number of children with health problems, therefore no strong conclusions can be drawn. BLS alone (no APLS) was significantly related to the presence of chronic symptoms. As BLS alone is considered to have less impact than APLS, there might be less attention for the impact of the CA on the child's health.

Neuropsychological functioning after CA may be mediated by the child's overall disease severity, as suggested by Bloom et al. regarding patients with congenital heart disease. [29] We believe that similar effects of other pre-existing diseases explain our findings on general health perception, and physical summary.

Although overall parents reported better physical functioning than the normative group, parents of out-of-hospital resuscitated children reported limitations in their physical activities. Family presence during resuscitation might be beneficial on psychological functioning and anxiety of parents. The initiation of an out-of-hospital resuscitation of your own child without the presence of health care professionals can negatively influence later parental functioning. [42]

The better social functioning of parents with a high SES might be explained by the financial and practical facilities they have to manage and cope with the impact of their child's CA (e.g., hiring day-care, nanny).

Prospective investigation on predictors of long-term prognosis is urgently needed. As half of our patients had a CA-related pre-existing condition, it could be an important determinant of outcome.

Limitations

First, this is a single-center cohort study with a relatively small number of participating children, which however still seems satisfactory compared with other studies in this field of research. A second limitation is that data obtained at follow-up are subject to recall bias, wherein parents may not remember minor problems from years back. Parents may minimize medical problems experienced prior to the CA given the overwhelming effect of CA on their lives. A third limitation is the heterogeneity of our patient sample. This is inherent to studying CA in children. A fourth limitation is the different way in which the SES was obtained in participants and non-participants, and the underrepresentation of children with a low SES. As mentioned, our results might give a too positive impression of the long-term outcome of CA in childhood. As fifth limitation, we have to mention that correction for multiple testing was not applied as this is an explorative study. We did not want to miss any influences on long-term outcome. Finally, some important variables are lacking, such as time to ROSC, severity of underlying illness, and a severity of illness score at ICU admission.

Conclusions

This follow-up study showed that long-term outcome of pediatric CPR is reasonably good. A minority of children surviving CA have long-term impairments on health status and HR-QoL. Prospective long-term outcome research in large homogeneous groups is needed. Further research should also be focusing on long-term psychosocial and neurocognitive functioning and predictors of outcome, since these factors influence the long-term health status and HR-QoL.

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Supplemental Table 1. Health Utility Index: results of parent-reports with age-specific norms

	Patients	Norm	*p*-value	Cohen's d
	Mean (SD)	Mean (SD)		
HUI3 single-attribute utility score*	*n=24*	*n=1,435*		
Vision	0.93 (0.23)	0.99 (0.04)	**.009**	**1.22**
Hearing	1.00 (0.00)	1.00 (0.04)	.532	.00
Speech	0.87 (0.29)	0.97 (0.08)	**.008**	**1.15**
Ambulation	0.91 (0.28)	1.00 (0.04)	**<.001**	**1.51**
Dexterity	0.90 (0.28)	1.00 (0.02)	**<.001**	**2.48**
Emotion	0.98 (0.04)	0.98 (0.07)	.468	.00
Cognition	0.80 (0.31)	0.97 (0.09)	**<.001**	**1.75**
Pain	0.89 (0.24)	0.98 (0.08)	.103	1.06
HUI3 multi-attribute utility score	0.72 (0.39)	0.93 (0.12)	**.002**	**1.63**
HUI2 single-attribute utility score*				
Sensation	0.86 (0.28)	0.95 (0.12)	**.029**	.72
Mobility	0.91 (0.28)	1.00 (0.03)	**<.001**	**1.95**
Emotion	0.97 (0.06)	0.97 (0.08)	.604	.00
Cognitive	0.84 (0.28)	0.98 (0.06)	**<.001**	**2.02**
Self-care	0.87 (0.34)	0.99 (0.06)	**<.001**	**1.64**
Pain	0.97 (0.12)	0.99 (0.05)	.946	.39
HUI2 multi-attribute utility score	0.85 (0.26)	0.94 (0.09)	.071	.95

* Normative data available for patients aged 5-13 years (n=1,435).

Low scores imply worse functioning.

Cohen's D's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. [28]

Supplemental Table 2. Overview of the long-term medical outcome and related cardiac arrest characteristics

	Neurological impairments	Chronic symptoms	Follow-up care by physician or therapist	Parent reported change in behavior	Special education	Renal function: at least one symptom suggestive of CKD	Parents: Limitations in daily activities.
Number of patients	6 (13%)	16 (34%)	14 (30%)	7 (15%)	7 (15%)	9 (19%)	9 (19%)
Age at ICU admission (months)	8.3 (1.7-34.6)	5.5 (0-157.1)	5.5 (0.1-118.4)	34.6 (6.2-118.4)	8.5 (1.7-118.4)	1.3 (0-88.9)	8.0 (0-145.2)
Male gender	3 (50%)	8 (50%)	9 (64%)	4 (57%)	3 (43%)	5 (56%)	6 (67%)
Advanced Pediatric Life Support (APLS)	4 (67%)	5 (31%)	6 (43%)	2 (29%)	4 (57%)	3 (33%)	6 (67%)
Out-of-hospital arrest	1 (17%)	7 (44%)	4 (29%)	4 (57%)	2 (29%)	6 (67%)	4 (44%
Initial Rhythm Non-shockable	5 (83%)	11 (69%)	12 (86%)	4 (57%)	5 (71%)	6 (67%)	7 (78%)
Bystander CPR	6 (100%)	15 (94%)	14 (100%)	7 (100%)	7 (100%)	9 (100%)	8 (89%)
Etiology							
- Cardiac	4 (67%)	6 (38%)	5 (36%)	4 (57%)	6 (86%)	1 (11%)	7 (78%)
- Respiratory	1 (17%)	9 (56%)	7 (50%)	2 (29%)	1 (14%)	6 (67%)	0 (0%)
- Other	1 (17%)	1 (6%)	2 (14%)	1 (14%)	0 (0%)	2 (22%)	1 (11%)
CA-related pre-existing condition *	3 (50%)	10 (63%)	9 (64%)	3 (43%)	5 (71%)	3 (33%)	6 (67%)
Mild therapeutic hypothermia **	0 (0%)	2 (13%)	3 (21%)	1 (14%)	1 (14%)	1 (11%)	3 (33%)

All data are presented as "number of subject (%)", except age which is presented as "median (range)".

* Medical records were retrospectively analyzed if the health status prior to the CA was related to the cause of the arrest.

** Children treated with mild therapeutic hypothermia (32-34 °C).

Supplemental Table 3. Health-related quality of life in patients: results of parent-reports

	In-hospital Mean (SD)	Out-of-Hospital Mean (SD)	*p*-value
CHQ-PF50 (4-17 years)	*n=19*	*n=14*	
Physical functioning (PF)	90.6 (23.8)	88.9 (27.3)	.761
Role functioning: Emotional/behavior (REB)	84.2 (33.6)	92.9 (26.7)	.193
Role functioning: Physical (RP)	86.0 (33.9)	90.5 (27.5)	.861
Bodily pain (BP)	80.0 (26.5)	77.9 (28.6)	.833
General behavior (GB)	73.8 (18.3)	77.5 (12.1)	.596
Mental health (MH)	82.6 (12.3)	81.8 (15.3)	.985
Self-esteem (SE)	78.9 (12.5)	76.8 (15.1)	.766
General health perceptions (GH)	56.1 (26.1)	60.3 (30.5)	.523
Parental impact: Emotional (PE)	79.8 (17.2)	67.3 (34.0)	.337
Parental impact: Time (PT)	81.3 (32.1)	82.5 (23.8)	.715
Family activities (FA)	81.1 (29.6)	89.6 (15.6)	.641
Family cohesion (FC)	82.4 (19.7)	67.9 (17.8)	**.024**
Physical summary (PHS)	47.2 (16.9)	47.5 (18.4)	.884
Psychosocial summary (PSS)	51.3 (8.0)	51.2 (8.6)	1.000

Low scores imply worse functioning.
Scores on the CHQ-PF50 scale "change in health" are not presented since individual normative data were not available for this scale.

Cohen's D's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. [28]

Chapter 4

Cardiac arrest in children and adolescents: long-term emotional and behavioral functioning

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Abstract

Objective: Very little is known about psychological consequences of a cardiac arrest (CA) during childhood. Aim: to assess long-term emotional and behavioral functioning, and its predictors, in survivors of CA in childhood.

Methods: This long-term follow-up study involved all consecutive children and adolescents surviving CA between January 2002 and December 2011. Emotional and behavioral functioning was assessed with the Child Behavior Checklist (CBCL), Teacher's Report Form (TRF), and Youth Self Report (YSR).

Results: Of the eligible 107 CA-survivors, 52 patients, parents, and/or teachers filled out online questionnaires measuring emotional and behavioral functioning (median age at PICU 0.5 years; median age at follow-up 8.6 years). Fifty-eight percent had an in-hospital CA, 85% a non-shockable rhythm, and 46% a respiratory related etiology.

Compared with normative data, parents and teachers reported significantly more attention and somatic problems (age-range: 6-18 years). Parents also reported more attention problems for age-range 1.5-5 years. Twenty-eight percent of the children (n=14) scored in the psychopathological range (i.e., for age-range: 1.5-18 years; $p<0.001$) according to parent-reports. On teachers' and self-reports, percentages scoring in the psychopathological range were normal ($p>0.05$).

Boys, older children, and basic life support were significantly related to worse scores on the scales Internalizing problems, Externalizing problems, Total problems, and subscale Attention problems.

Conclusions: Long-term deficits in attention and somatic complaints were reported. Attention problems after childhood CA can interfere with school performance. Long-term follow-up with neuropsychological assessment should be organized.

Introduction

Survival after cardiac arrest (CA) in children is low and dependent on the location of the arrest. [1-3] Due to hypoxic-ischemic brain injury, CA survivors show long-term physical and neuropsychological impairments. [4, 5] Additionally, these survivors may suffer from the impact of neuropsychological sequelae of the hypoxic-ischemic event on emotional and behavioral functioning. Moreover, the CA itself and the hospital related experiences (including their pre-existing condition) may have an overwhelming emotional impact, as children and parents may realize that they/ their child would have died if no resuscitation was applied.

Little is known about the long-term psychological consequences of CA during childhood, especially regarding emotions and behavior. Emotional and behavioral problems can be classified into internalizing problems (intrapsychic problems, such as anxiety, depression, withdrawn behavior, and somatic complaints), externalizing problems (conflicts with rules or others), and social, attention, and thought problems. [6] Long-term emotional and behavioral problems have been described for various groups of critically ill children. For example, in children with congenital heart disease (ConHD), attention problems, anxiety and depression, among other problems have been reported. [7] In survivors of meningococcal septic shock, long-term assessment showed more parent-reported somatic complaints. [8] After neonatal asphyxia long-term elevated levels of hyperactivity and the presence of autism have been found. [9]

Only one small study by Morris et al. reported on emotional and behavioral outcome after CA, as part of a neuropsychological outcome study. [4] These researchers studied 25 children at least 1 year after CA and reported that few children (number unknown) scored at or lower than 1 SD below the normative population mean of the CBCL, a criterion they used as a deficit score. Children showed internalizing problem behavior, and more physically impaired children had worse scores on the hyperactivity scale. As detailed description is lacking and 80% of these children had a ConHD, it is unknown whether these results can be generalized to all CA survivors.

To bridge this gap in knowledge, the aim of present study was to systematically investigate long-term emotional and behavioral outcomes, and their predictors, in a consecutive series of survivors of CA in childhood. A multi-informant approach (parents', teachers', self-report) was used, comprising internationally validated, and

well-known psychological questionnaires. We hypothesized that survivors of CA in childhood have long-term emotional and behavioral problems.

Patients and Methods

This study was performed at the Intensive Care Unit (ICU) of the Erasmus MC-Sophia Children's Hospital in Rotterdam. This is the only university specialized pediatric ICU in this region with approximately 4.2 million inhabitants, representative of the Dutch population.

The Erasmus MC Ethical Review Board approved the study protocol (NL 39084.078.12).

Patient sample

The target population consisted of all consecutive surviving patients aged 0-18 years with a CA between January 2002 and December 2011, who were admitted to the ICU of the Erasmus MC-Sophia Children's Hospital.

CA was defined as absent pulse rate or the need for cardiac compressions. Cardiopulmonary resuscitation (CPR) was defined as "basic life support" (BLS), in line with the European Resuscitation Council Guidelines for pediatric life support, and if needed, followed by "advanced pediatric life support" (APLS). [10]

All CA data were retrospectively collected. Data were derived from ambulance registration forms, clinical and electronic medical records, and CA registration forms. We collected: 1) basic patient characteristics, 2) CA characteristics (e.g., location, rhythm, etiology), and 3) outcome (mortality). Additionally, medical records were retrospectively analyzed if the health status prior to the CA was related to the cause of the arrest (i.e., cardiac, respiratory or other).

Eligible for this study were: 1) children resuscitated in-hospital (e.g., emergency department, ward, ICU), 2) children resuscitated in a regional hospital or other university hospital, and after return of spontaneous circulation (ROSC) subsequently admitted to the ICU of our hospital, and 3) children resuscitated out-of-hospital, and subsequently admitted to our ICU. Neonates resuscitated at the hospital's neonatal intensive care unit (NICU), or in another hospital and subsequently admitted to the NICU of our hospital were excluded.

Procedure: In May 2013, children and parents (including one caregiver) were invited to participate 2 to 11 years after ICU discharge. Informed consent was obtained from parents, and children (if ≥ 12 years). Families were invited to complete online questionnaires on emotional and behavioral functioning. Choice

of respondent (mother, father or caregiver) was left to the parents themselves. Parents and children were explicitly instructed to complete questionnaires separately. Parents were asked to deliver an invitation to their child's teacher to fill out an online questionnaire.

Emotional and behavioral functioning

Emotional and behavioral problems were assessed with Dutch versions of the Child Behavior Checklist (CBCL), Teacher's Report Form (TRF) and Youth Self-Report (YSR). [6] These questionnaires were used to obtain parent, teacher, and self-reports, using parallel standardized questionnaires with overlapping items. For preschool children (1.5-5 years), the CBCL 1.5-5 and Caregiver-TRF (C-TRF) were used. For school aged children (6-18 years), the CBCL 6-18 and TRF 6-18 were used. The YSR was completed by adolescents aged 11-18 years.

Items of these questionnaires were rated on a three-point scale (0=not true; 1=somewhat or sometimes true; 2=very true/often true). The preschool forms consists of six subscales and the school age forms of eight subscales. These subscales can be combined in an Internalizing problem scale, Externalizing problem scale, and an overall Total problem scale. Higher scores indicate higher problem levels. Complete datasets with corresponding age ranges of representative normative data were available and consisted of the following large representative samples of the general Dutch population: 1) CBCL 1.5-5 years: 532 children; 2) CBCL 6-18 years: 1,451 children; 3) C-TRF: 346 children; 4) TRF 6-18 years: 1,016 children; 5) YSR 11-18 years: 731 children. [11]

All psychological questionnaires have adequate psychometric properties. [6]

Predictors

The following predictors were tested: gender, age at ICU admission, age at follow-up, type of CPR (BLS/APLS), location (in-hospital/out-of-hospital), CA-related pre-existing medical condition, present health status and socioeconomic status (SES) at follow-up.

Present health status was defined as suffering from co-morbidity at follow-up, not related to the CA.

SES at time of follow-up was based on parents' occupation, and categorized as

"low" (elementary occupations), "middle" ('middle' occupations), or "high" ('highest' scientific occupations) conform Dutch standard classification. [12] The highest occupation of both parents was used.

Statistical analysis

Patient and CA characteristics of participants and non-participants were examined with independent sample t-tests for normally distributed continuous data, and Mann-Whitney-U test for non-normally distributed data. Fisher's exact test was used for comparison of dichotomous data.

Normality of data was examined with the Kolmogorov-Smirnov test. To compare CA survivors with normative data, the Welch's t-test (for unequal variances) was performed for normally distributed data, or the Mann-Whitney-U test for non-normally distributed data. Cohen's *d* effect sizes (ES) were also reported and presented as absolute numbers. [13] According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large.

The Kruskal-Wallis test served to test differences in responses between caregivers (mother, father, and caregiver) on the individual emotional and behavioral problem scores.

To distinguish problem children (i.e., scoring in the psychopathological range) from non-problem children, 90th percentiles of the cumulative frequency distributions of Total Problem Scores obtained from the reference groups (gender and age specific) were chosen as the cut-offs. Proportions of children scoring in the psychopathological range in the CA group were compared with the normative group using the Binomial Test. Predictors of outcome were examined with Spearman correlations for continuous variables, Mann-Whitney-U test for dichotomous variables, and the Kruskal-Wallis test for ordinal variables. The influence of putative predictor variables was only tested for Internalizing, Externalizing and Total problem scores, and subscales for which mean scores were significantly different from the normative population.

All analyses were performed with SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL). Statistical significance was considered with 2-tailed *p*-values of <0.05.

Results

Our target population consisted of 145 surviving patients, 38 (26%) of whom were deceased or lost lost to follow-up (13 died after hospital discharge, 7 moved abroad, 18 untraceable). (Figure 1) Causes of death after hospital discharge were another CA without ROSC (n=3), underlying disease (n=2), severe cerebral damage (n=1), or unknown (n=7).

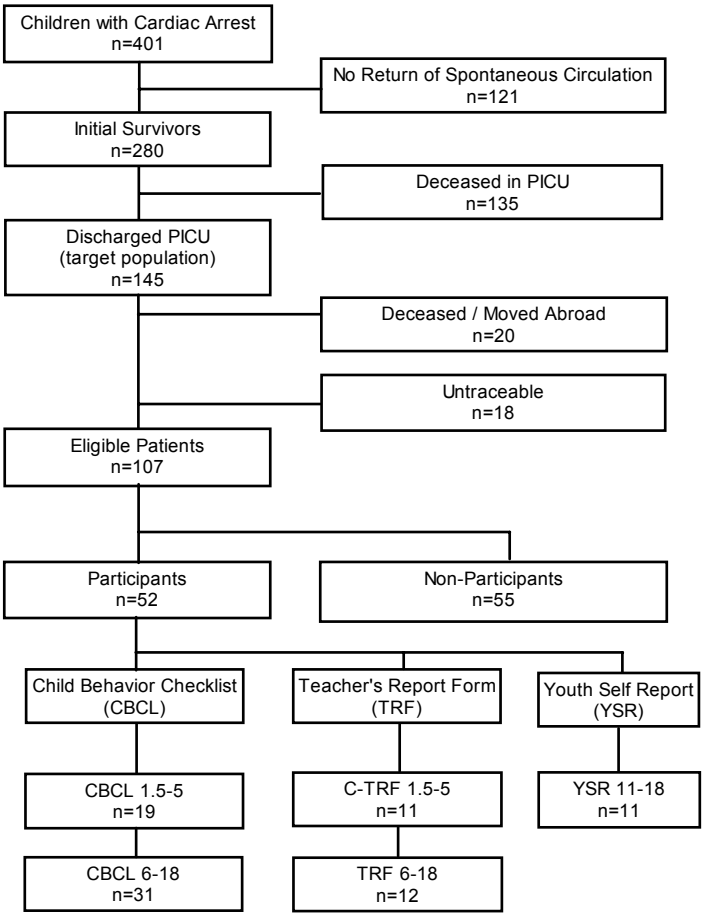

Figure 1. Flowchart of patient inclusion

Note: Two parents did not complete the CBCL, but their child completed the YSR.

Of 107 eligible patients, 52 (49%) participated. Non-participants refused participation due to practical reasons (n=20), or emotional reasons (n=14, e.g., too anxious/confronting). Reasons for non-participation were unknown for 21 eligible patients.

Patient characteristics of participants versus non-participants differed significantly on SES. (Table 1)

Emotional and behavioral functioning

The Kolmogorov-Smirnoff test indicated that the data were non-normally distributed, therefore the Mann-Whitney-U test was used for comparisons with normative data.

Compared with normative data, parents' reports (CBCL) showed significantly more attention problems (1.5-5 years and 6-18 years; medium ES) and more somatic complaints (6-18 years; large ES). (Table 2 and 3) Teachers also reported significantly more somatic complaints and attention problems (inattention) in children aged 6-18 years (medium/large ES). (Table 3) On item-level, the somatic problems most frequently reported were headache and abdominal pain. On self-reports, children reported significantly less social problems than the healthy peers (medium ES).

According to parent-reports, the percentages of patients scoring in the psychopathological range was 28% (n=14; $p<.001$) when combining both age-groups (i.e., for age-range: 1.5-18 years). Sub-analyses of the different age-ranges showed that the percentages in the deviant range was specifically elevated for the children aged 1.5-5 years (42%, $p<0.001$), whereas for the older age-range (6-18 years) a non-significant trend ($p=.083$) was found. When combining both age groups of the teacher-reports, no significant differences were found (psychopathological range 4% (n=1); $p=.315$). (Table 2 and 3)

Table 1. Characteristics of participating participants and non-participants

	Participants (n=52)		Non-participants (n=55)		*p*-value
	n [a]		n [a]		
Age at ICU admission (months)	52	6.3 (0 – 193.3)	55	6.5 (0 – 204.2)	.267
Male gender	52	28 (54%)	55	36 (65%)	.242
Advanced Pediatric Life Support (APLS)	52	30 (58%)	55	38 (69%)	.235
Out-of-hospital arrest	52	22 (42%)	55	17 (31%)	.235
Bystander CPR	52	51 (98%)	52	51 (98%)	1.00
Initial Rhythm Non-shockable	41	35 (85%)	51	44 (86%)	1.00
Etiology					
- Cardiac	52	20 (38%)	55	18 (33%)	.552
- Respiratory	52	24 (46%)	55	34 (62%)	.123
- Other	52	8 (15%)	55	3 (5%)	.117
Pre-existing medical condition [b]	52	28 (54%)	55	27 (49%)	.700
- Cardiac	28	16 (57%)	27	14 (52%)	.552
- Respiratory	28	9 (32%)	27	11 (41%)	.123
- Other	28	3 (11%)	27	2 (7%)	.117
Present health status					
- Actual comorbidity	52	30 (58%)	-	-	-
Mild therapeutic hypothermia [c]	52	8 (15%)	55	12 (22%)	.462
Socioeconomic status at follow-up					
- Level 1: "Low"	52	4 (8%)	55	14 (25%)	**.019**
- Level 2: "Middle"	52	23 (44%)	55	29 (53%)	.441
- Level 3: "High"	52	25 (48%)	55	12 (22%)	**.005**
Age at follow-up (months)	52	103.3 (28.5 – 220.7)	-	-	-

[a] Number of subjects for which the variable was obtained.

[b] Children with a pre-existing medical history which was the cause of the CA.

[c] Children treated with mild therapeutic hypothermia.

All data are presented as "number of subject (%)", except age which is presented as "median (range)".

Socioeconomic status (SES) of non-participants at time of follow up was calculated based on a combined status score of the Netherlands Institute for Social Research based on home address. (26) This score consisted of average income in neighborhood, percentage of people with low income, percentage of less educated people, and percentage of people not working. A status score of 0 (±1.16 SD) was classified middle SES, <-1.16 was classified low SES, and >+1.16 was classified high SES.

Abbreviations: CPR = cardiopulmonary resuscitation; ICU = intensive care unit; n = number.

Table 2. Parent and teacher-reported emotional and behavioral functioning: age-range 1,5-5 years

	Patients Mean (SD)	Norm Mean (SD)	*p*-value	Cohens' D
CBCL (1,5-5 years)	*n=19*	*N=532*		
Internalizing	9.68 (8.0)	7.86 (5.9)	.560	.30
- Emotionally Reactive	3.05 (3.2)	2.80 (2.5)	.811	.10
- Anxious/Depressed	1.84 (2.1)	1.81 (1.8)	.859	.02
- Somatic Complaints	2.58 (2.9)	1.98 (2.0)	.604	.30
- Withdrawn	2.21 (2.7)	1.27 (1.4)	.116	.64
Sleep Problems	2.32 (2.5)	2.18 (2.1)	.946	.07
Externalizing	15.37 (12.0)	12.51 (7.2)	.566	.38
- Attention Problems	3.68 (2.9)	2.29 (1.8)	**.038**	.74
- Aggressive Behavior	11.68 (9.3)	10.22 (6.1)	.835	.23
Posttraumatic Stress Problems	2.58 (2.3)	1.99 (1.6)	.356	.36
Total Problem Score	36.37 (25.9)	30.58 (17.1)	.504	.33
- Deviant range (%)*	42%	10%	**<.001**	
C-TRF (1,5-5 years)	*n=11*	*n=346*		
Internalizing	4.55 (3.3)	5.54 (5.8)	.954	.17
- Emotionally reactive	0.82 (1.5)	1.51 (2.0)	.153	.35
- Anxious/Depressed	1.18 (1.1)	1.60 (2.0)	.872	.21
- Somatic Complaints	0.45 (0.8)	0.41 (0.9)	.778	.04
- Withdrawn	2.09 (2.1)	2.03 (2.4)	.667	.02
Externalizing	9.09 (10.7)	7.69 (9.5)	.610	.15
- Attention Problems	4.18 (5.1)	2.87 (3.5)	.478	.36
- Aggressive Behavior	4.91 (6.5)	4.82 (6.7)	.768	.01
Posttraumatic Stress Problems	1.55 (1.1)	1.26 (1.5)	.222	.19
Total Problem Score	18.55 (16.5)	17.36 (17.5)	.662	.07
- Deviant range (%)*	9%	10%	.697	

* Age and gender specific 90th percentile cut-off scores of the reference group were used.

Internalizing problem scale: reflecting intrapsychic problems. Externalizing problem scale: reflecting conflicts with other people or rules.

Cohen's d's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. [13]

Higher scores implicate more psychological problems.

Mean scale scores were not significantly different between respondents on the CBCL 1.5-5 (mothers n=16, fathers n=3, p>0.05).

Abbreviations: CBCL = Child Behavior Checklist; C-TRF = Caregiver-TRF.

Table 3. Parent, teacher and self-reported emotional and behavioral functioning: age-range 6-18 years

	Patients Mean (SD)	Norm Mean (SD)	*p*-value	Cohens' D
CBCL (6-18 years)	*n=31*	*n=1,451*		
Internalizing	8.16 (8.8)	6.64 (5.7)	.918	.26
- Anxious/Depressed	2.55 (3.6)	3.02 (3.0)	.083	.16
- Withdrawn/Depressed	2.23 (2.6)	2.11 (2.2)	.801	.05
- Somatic Complaints	3.39 (4.1)	1.51 (2.0)	**.003**	**.90**
Social Problems	2.84 (3.6)	2.06 (2.3)	.530	.34
Thought Problems	2.23 (3.1)	1.83 (2.1)	.988	.19
Attention Problems	6.03 (5.0)	3.77 (3.2)	**.015**	.70
Externalizing	6.00 (6.6)	6.32 (5.9)	.446	.05
- Rule-Breaking Behavior	1.29 (1.6)	2.01 (2.3)	.092	.31
- Aggressive Behavior	4.71 (5.6)	4.32 (4.2)	.789	.09
Posttraumatic Stress Problems	4.77 (4.6)	3.90 (3.3)	.473	.26
Total Problem Score	28.87 (25.5)	23.91 (16.7)	.651	.29
- Deviant range (%)*	19%	10%	.083	
TRF (6-18 years)	*n=12*	*n=1,016*		
Internalizing	5.83 (8.5)	5.21 (5.7)	.870	.11
- Anxious/Depressed	2.33 (4.1)	2.77 (3.3)	.194	.13
- Withdrawn/Depressed	2.08 (3.2)	1.98 (2.5)	.684	.04
- Somatic Complaints	1.42 (2.3)	0.46 (1.2)	**.010**	.78
Social Problems	1.17 (1.2)	1.58 (2.4)	.860	.17
Thought Problems	0.33 (0.7)	0.45 (1.1)	.958	.11
Attention Problems	13.00 (8.8)	8.21 (8.6)	**.036**	.56
- Attention Problems - Inattention	9.17 (6.0)	4.86 (5.2)	**.007**	**.83**
- Attention Problems - Hyperactivity-Impulsivity	3.83 (4.2)	3.35 (4.4)	.466	.11
Externalizing	4.08 (5.8)	4.22 (6.7)	.683	.02
- Rule-Breaking Behavior	1.42 (2.9)	1.27 (2.2)	.900	.07
- Aggressive Behavior	2.67 (3.7)	2.94 (4.9)	.635	.05
Posttraumatic Stress Problems	3.00 (3.6)	2.92 (3.0)	.904	.03
Total Problem Score	24.75 (16.1)	20.36 (19.5)	.195	.23
- Deviant range (%)*	0%	10%	.282	

Table 3. *Continued*

	Patients Mean (SD)	Norm Mean (SD)	*p*-value	Cohens' D
YSR (11-18 years)	*n=11*	*n=731*		
Internalizing	11.73 (8.4)	10.25 (7.0)	.640	.21
- Anxious/Depressed	3.82 (4.3)	4.22 (3.7)	.423	.11
- Withdrawn/Depressed	3.18 (2.7)	3.00 (2.3)	.997	.08
- Somatic Complaints	4.73 (3.7)	3.03 (2.6)	.083	.64
Social Problems	1.82 (2.4)	3.27 (2.4)	**.027**	.60
Thought Problems	2.09 (1.7)	3.12 (2.7)	.279	.38
Attention Problems	4.36 (2.7)	5.12 (3.7)	.471	.25
Externalizing	7.64 (4.3)	9.21 (6.4)	.518	.25
- Rule-Breaking Behavior	2.82 (1.2)	3.88 (3.1)	.389	.35
- Aggressive Behavior	4.82 (3.7)	5.34 (3.9)	.659	.13
Posttraumatic Stress Problems	5.91 (4.3)	5.99 (3.7)	.835	.02
Total Problem Score	31.00 (14.4)	35.06 (18.2)	.461	.22
- Deviant range (%)*	0%	10%	.314	

* Age and gender specific 90th percentile cut-off scores of the reference group were used.

Internalizing problem scale: reflecting intrapsychic problems. Externalizing problem scale: reflecting conflicts with other people or rules.

Cohen's d's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. [13]

Higher scores implicate more psychological problems.

Mean scale scores were not significantly different between respondents on the CBCL6-18 (mothers n=22, fathers n=8, p>0.05; (including caregiver n=1, p>0.05)).

Abbreviations: CBCL = Child Behavior Checklist; TRF = Teacher's Report Form; YSR = Youth Self-Report.

Predictors of outcome

Univariate analysis showed that, on parent reports for 1.5-5 years old children, older age at ICU admission was a significant predictor of more externalizing problems and total problem scores, on parent reports for 1.5-5 years old children. (Table 4) This was also found on the subscale Attention problems (ρ=.523, p=.022).

BLS/APLS was a significant predictor of internalizing, externalizing and total problem scores, on parent reports (CBCL) for 6-18 years old children. (Table 4) This was also found on the subscale Somatic complaints (Z=-2.923, p=.003). Children with only BLS had significant higher problems scores, implying worse psychological functioning. Seventy-two percent of these children had an out-of-

hospital CA.

Gender was significantly related with psychopathology; boys (1.5-5 years) showed more internalizing, externalizing, and total problems than girls. On self-reports (YSR), girls reported significantly more internalizing problems than boys.

Age at follow-up was a significant predictor of somatic complaints (ρ=.588, p=.044) on the TRF.

For none of the questionnaires or age categories, a significant relation was found between emotional and behavioral problems and location of arrest, CA-related pre-existing condition, present health status or SES.

Discussion

This is the first study that addresses long-term emotional and behavioral problems in a relatively large consecutive series of children and adolescents surviving CA. Compared to normative data, CA survivors showed significantly more long-term attention problems and somatic complaints, on parents' and teachers' reports. On self-reports, significantly less social problems were found. According to parents, children showed more often psychopathological problem behavior. Gender, age, and BLS showed significant associations with long-term outcome, but remarkably, less social problems (self-reports) and no long-term significantly higher levels on anxiety, depression or posttraumatic stress problems, or associations with location of arrest or present health status were found.

Emotions and behavior

Elevated levels on the subscale Somatic complaints were found in 6-18 years old children, according to parents and teachers. It is unknown whether these complaints were also found by Morris et al. [4] In other groups of critically ill children, such as children after neonatal extracorporeal membrane oxygenation (ECMO) or after meningococcal septic shock, long-term somatic complaints (parent- or self-reported) are well-known. [8, 14] These results are also found in children with a chronical illness, like ConHD, and seems to be a more generic finding for chronic diseases in childhood. [15] However, we did not find elevated somatic complaints in preschool children.

For a broad age-range (preschoolers, school children and adolescents) parents and teachers reported significantly more attention problems in CA survivors. In contrast to our findings, Morris et al. described more hyperactivity related problems. [4] Evidence for long-term attention problems after hypoxic-ischemic brain injury is mainly limited to children with ConHD and neonatal asphyxia. Long-term follow-up of children with ConHD showed overall attention problems, and both inattention and hyperactivity problems 5 to 10 years after cardiac surgery. [15, 16] Studies into neonatal encephalopathy reported significantly more attention problems, or increased risk of attention deficit/hyperactivity disorder-related diagnoses at school age, compared with normative data. [14, 17, 18] Hyperactivity and inattention were found to co-exist or causally related as described by Marlow et al. in children without physical disabilities 7 years after severe neonatal hypoxic

encephalopathy.[19] However, it is difficult to generalize these findings to our patient population, as age at which hypoxia occurred is different, and comorbid underlying condition in our population is heterogeneous. As inattentional problems could be an expression of sustained attentional problems, these outcomes also suggest more neuropsychological problems.

Sustained attention is related to multiple areas in the brain, e.g., frontal lobe, prefrontal region, subcortical region and the parietal lobe. As sustained attention is one of the basic functions of the brain, damage to the brain could lead to the failure of this function. Neuropsychological assessment is needed in order to establish a specific neurocognitive profile.

According to parents, childhood CA survivors showed more often psychopathological problem behavior in comparison with the general population. In contrast, teachers and self-reports of CA-survivors did not show elevated percentages of problem behavior. Due to the small number of respondents it is difficult to draw strong conclusions. Limited awareness of own emotional and behavioral functioning due to frontal lobe lesions might contribute to a potential underreporting of emotional and behavioral problems and to the positive finding on the social problem scale. This has also been suggested in children after traumatic brain injury (TBI) where adolescents display less insight into executive functioning difficulties. [20, 21] On the other hand, concepts as posttraumatic growth could also have influenced these positive outcomes on social functioning. [22] Posttraumatic growth is "the experience of positive change that occurs as a result of the struggle with highly challenging life crises". [22] Children may worry less about futilities and may appreciate their capabilities more.

Remarkably, no elevated levels of anxiety and depression were reported, which is in contrast with long-term survivors of TBI or ConHD. [23, 24] However, long-term follow-up of other groups of critically ill children (e.g., neonatal ECMO, meningococcal septic shock) showed similar results as the present study. [8, 14] Posttraumatic growth or emotional resilience could contribute to these outcomes. One could also hypothesize that a long follow-up interval could decrease complaints as anxiety and depression. However no association was found.

Predictors of outcome

Univariable analyses were limited by the small number of respondents, therefore

no strong conclusions can be drawn. However, there are some hypothesis-generating findings.

Overall, age could be an important determinant of outcome. Anderson states that "early brain damage may have a cumulative effect on ongoing development, with increasing deficits emerging through childhood as more functions are expected to mature and need to be subsumed within the undamaged tissues". [25] This "growing into deficits" phenomenon may have an important influence on future psychological functioning. [26] As the median age at follow-up was relatively young, more problems on higher cognitive functions, such as executive functioning which includes emotional regulation, may emerge later in life, as these functions mature in adolescence.

Additionally, in the 1.5-5 year group, older age at ICU admission gave significantly more externalizing problems and total problems. Children may work through traumatic experiences at this non-verbal age-range by more externalizing behavior (screaming, shouting).

Present health status was not associated with any of the outcome measurements. Although more somatic complaints were found, they were not associated with the presence of actual comorbidities at time of assessment, as the subscale Somatic complaints contains mostly questions on physical disabilities without known medical cause.

Further, children with BLS had significantly more internalizing, externalizing, and total problems. As BLS is considered to have less impact than APLS, there might be less attention for its impact on the child's psychological functioning. As the problems are so widespread, multidisciplinary outpatient follow-up should be organized as standard of care.

Lastly, gender was significantly related to emotional and behavioral functioning. The pattern that boys show more externalizing problems is also well-known in the general community. [6] However, in contrast to the general community, boys with CA had more internalizing problems than girls.

<u>Limitations</u>

First, this is a single center cohort study in a heterogeneous patient group. Second, since participants with high SES are relatively overrepresented, and some non-

participants refused participation for emotional reasons, our results might be too positive. [27, 28] Third, correction for multiple testing was not applied since this is an explorative and descriptive study. We did not want to miss any influences on long-term outcomes. Finally, some important variables are lacking, such as time to ROSC, severity of underlying illness, and treatment/course after ROSC during ICU admission.

Conclusion

This is the first systematic study on long-term emotional and behavioral outcome in survivors of CA in childhood. Overall, the psychological outcomes of CA are remarkably well, as specific problems such as anxiety, depression or posttraumatic problems are absent. However, compared with normative data, significantly more long-term somatic complaints were found, which seems to be a common finding in children after hospitalization, regardless of the illness. Also significantly more attention problems were found, which suggest also neuropsychological problems.

As deficits in emotion and behavior have a significant impact on the child, their family and society as a whole, structured (neuro)psychological follow-up is warranted.

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Table 4. Univariate predictors of emotional and behavioral functioning

Risk factor variables	Gender	Age at ICU	BLS/APLS	Location	CA-related Pre-existing condition	SES	Age at follow-up	Present health status: Actual comorbidity
	Z	ρ	Z	Z	Z	χ^2	ρ	Z
CBCL 1.5-5 yrs.								
Internalizing problems	-	-	-	-	-	-	-	-
Externalizing problems	-	.505*	-	-	-	-	-	-
Total problems	-	.509*	-	-	-	-	-	-
CBCL 6-18 yrs.								
Internalizing problems	-	-	-2.451*	-	-	-	-	-
Externalizing problems	-	-	-2.598**	-	-	-	-	-
Total problems	-	-	-2.463*	-	-	-	-	-
C-TRF 1.5-5 yrs.								
Internalizing problems	-2.018*	-	-	-	-	-	-	-
Externalizing problems	-2.580*	-	-	-	-	-	-	-
Total problems	-2.745**	-	-	-	-	-	-	-
TRF 6-18 yrs.								
Internalizing problems	-	-	-	-	-	-	-	-
Externalizing problems	-	-	-	-	-	-	-	-
Total problems	-	-	-	-	-	-	-	-
YSR 11-18 yrs.								
Internalizing problems	-2.196*	-	-	-	-	-	-	-
Externalizing problems	-	-	-	-	-	-	-	-
Total problems	-	-	-	-	-	-	-	-

* p<0.05, ** p <0.01; - = not significant; Abbreviations: APLS = Advanced Pediatric Life Support; BLS = Basic Life Support; CBCL = Child Behavior Checklist; ICU = intensive care unit; SES = Socioeconomic status; (C-)TRF = (Caregiver)-Teacher's Report Form; yrs. = years; YSR = Youth Self-Report.

Chapter 5

Long-term neuropsychological outcomes in children and adolescents after cardiac arrest

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Abstract

Purpose: Research into neuropsychological functioning of survivors of cardiac arrest (CA) in childhood is scarce. We sought to assess long-term neuropsychological functioning in children and adolescents surviving CA.

Methods: Neuropsychological follow-up study involving all consecutive children surviving CA between January 2002 and December 2011. Intelligence (IQ), language, attention, memory, visual-spatial, and executive functioning were assessed with internationally validated, neuropsychological tests and questionnaires. Scores were compared with Dutch normative data.

Results: Of 107 eligible children, 47 who visited the outpatient clinic (median follow-up interval: 5.6 years) were analyzed. Fifty-five percent had an in-hospital CA, 86% a non-shockable rhythm, and 49% a respiratory-related etiology.

CA survivors scored significantly worse on full-scale IQ ($\bar{x}$=87.3), verbal IQ ($\bar{x}$=92.7), performance IQ ($\bar{x}$=85.6), verbal comprehension index ($\bar{x}$=93.4), perceptual organization index ($\bar{x}$=83.8), and processing speed index ($\bar{x}$=91.1), than the norm population (mean IQ=100).

On neuropsychological tests, compared with norms, respectively adjusted for IQ, significantly worse scores were found on visual memory, significantly better on verbal memory (recognition), and comparable outcomes on visual-motor integration, attention, other measures of verbal memory, and executive functioning.

On questionnaires, parents reported better executive functioning than the norm, but teachers reported more problems in planning/organizing skills

Conclusions: Long-term neuropsychological assessment of CA survivors showed significant weaknesses, but also relatively intact functioning. As deficits in IQ, memory, and executive functioning have significant impact on the child, long-term follow-up and neuropsychological support of CA survivors is warranted.

Introduction

Survival after cardiac arrest (CA) in children is low and dependent on the location of the arrest. [1] In-hospital (IH) CAs are associated with relatively high survival rates of 30-50 and 60-90% have a generally good neurologic outcome. [1, 2] Out-of-hospital (OH) CAs generally have a low survival rate of 10% and high morbidity rates (>90%). [1, 3] Long-term prognosis in survivors seems to be associated with location, age, rhythm, witnessing of the arrest and Pediatric Cerebral Performance Category (PCPC) score at discharge. [4] Until now, a detailed overview of the long-term neuropsychological consequences is lacking.

Neuropsychological functioning refers to, e.g., memory, language, attention, and executive functioning. Executive functioning refers to several higher-order and interrelated cognitive functions (e.g., cognitive flexibility, task initiation, planning, working memory, self-regulation, and response inhibition). Considering the adverse impact of a lack of oxygen to the brain, neuropsychological deficits are to be expected. Problems with attention, executive functioning and deficits in visual-motor integration have been reported in children with complex congenital heart disease and survivors of meningococcal septic shock. [5, 6] Also in neonates with severe respiratory failure treated with ECMO, deficits in attention and behavior were found. [7]

Only three small studies and one case report have investigated the neuropsychological functioning of children who survived a CA. Maryniak et al. found visual and verbal memory impairments six months after the arrhythmic CA (n=10; mean age 15.7 years). [8] Amicuzi et al. reported a detailed long-term case study of a 9 year old girl recovering from an anoxic encephalopathy after CA and reported dysfunctions in gnosis, praxis and self-regulation. [9] Morris et al. reported lower scores on tests measuring intelligence, visual-perceptual-motor, achievement, and adaptive functioning in CA survivors at least 1-year post-CA (n=25; mean age 67 months; median follow-up interval unknown; 80% had a congenital heart disease). [10] Suominen et al. found impairments in intelligence, verbal and/or visual memory, and executive functions in resuscitated drowned children (n=21; median age 12.5 years; median follow-up interval 8.5 years). [11] However, these studies had methodological limitations (small sample size, short follow-up interval or only subgroups of CA studied). It is therefore unknown whether these results can be generalized to all CA survivors.

We sought to systematically investigate the long-term neuropsychological outcomes and predictors of those outcomes in a relatively large cohort of consecutive survivors of CA in childhood. We used internationally validated, well-known neuropsychological assessment instruments.

We hypothesized that survivors of CA in childhood have significant impairments in neuropsychological outcome.

Methods

This study was performed at the intensive care unit (ICU) of the Erasmus MC-Sophia Children's Hospital in Rotterdam, the only university specialized pediatric ICU in this region with approximately 4.2 million inhabitants, representative of the Dutch population.

The Erasmus MC Ethical Review Board approved the study protocol (NL 39084.078.12) in accordance with Dutch laws and regulations, and international conventions, such as the Declaration of Helsinki.

Patient sample

This study concerned all consecutive surviving patients aged 0-18 years with CA between January 2002 and December 2011, admitted to the ICU of the Erasmus MC-Sophia Children's Hospital.

CA was defined as absent pulse rate or the need for cardiac compressions. Treatment of children with CA in our hospital was in line with the European Resuscitation Council guidelines for pediatric life support.

All CA data were retrospectively collected from ambulance registration forms, clinical and electronic medical records, and CA registration forms. We collected: 1) basic patient characteristics (e.g., gender, age, medical history), 2) CA characteristics (e.g., type of resuscitation (BLS/APLS), etiology of arrest, first monitored rhythm, bystander CPR, location), and 3) outcome (mortality).

Eligible for this study were children resuscitated: (1) in-hospital (e.g.,emergency department, ward, ICU), (2) in a regional hospital or other university hospital, and after return of spontaneous circulation (ROSC) subsequently admitted to our ICU, and (3) out-of-hospital, and subsequently admitted to our ICU. Neonates resuscitated at the hospital's neonatal intensive care unit (NICU), or in another hospital and subsequently admitted to the NICU of our hospital, were excluded.

Procedure: informed consent was obtained from parents, and children (if ≥ 12 years). In May 2013, participating children (and parents) were invited for an extensive neuropsychological examination, in-hospital, by a pediatric psychologist (MM), 2-11 years after ICU-discharge.

Neuropsychological functioning

Intelligence tests and neuropsychological tests

Dutch versions of the intelligence tests and neuropsychological tests were used to assess the variables below:

1. Intellectual functioning: the age-appropriate versions of the Wechsler Scales (WPPSI-III, WISC-III, WAIS-IV). [12-14]
2. Language: Peabody Picture Vocabulary Test – 3th Edition (PPVT-III). [15]
3. (Verbal) Memory: Rey's Auditory Verbal Learning Test (RAVLT) [16, 17]; Rey-Osterrieth Complex Figure test (ROCF). [18]
4. Visual-spatial functioning: Rey-Osterrieth Complex Figure test (ROCF) [18]; Beery Developmental Test of Visual Motor Integration - 5th edition (Beery VMI-5th edition). [19]
5. Attention: Test of Everyday Attention for Children (TEA-Ch). [20]
6. Executive functions: Stroop Color Word Test (Stroop) [21]; Trail Making Test (TMT). [22]

Scores on neuropsychological tests were compared with normative data from representative Dutch general population samples, for corresponding age-categories (see Supplementary Table 1).

Neuropsychological questionnaire

Behaviour Rating Inventory of Executive Function questionnaires (BRIEF; parent version (5-18 years), teacher version (5-12 years), and self-report version (12-18 years)). [23]

Putative predictors

The following predictors were tested: age at time of CA and follow-up, gender, type of CPR (BLS/APLS), location (in-hospital/out-of-hospital), CA-related pre-existing medical condition, participation in a standardized multidisciplinary follow-up program, and socioeconomic status (SES) at follow-up. In our hospital, a multi-disciplinary follow-up program for children with congenital anatomical malformations and children treated with ECMO was started as standard of care in 1999. SES at time of follow-up was based on parents' occupation, and categorized

as "low" (elementary occupations), "middle" ('middle' occupations), or "high" ('highest' scientific occupations) conforming to Dutch classification. [24] The highest occupation of both parents was used.

Statistical analysis

Patient and CA characteristics of participants and non-participants were examined with independent sample t-tests for normally distributed continuous data, and Mann-Whitney U tests for non-normally distributed data. Normality of all data was examined with the Kolmogorov-Smirnov test. Fisher's exact test was used for comparison of dichotomous data.

One-sample statistical tests were performed to compare CA survivors with normative data regarding the BRIEF and intelligence. One-sample t-test was performed for normally distributed data (t-scores presented; means of the normative data presented in Supplementary Table 1), or one-sample Wilcoxon signed rank test for non-normally distributed data. Data of the neuropsychological assessment were compared with normative data, corrected for age, gender, or intelligence. In order to compare the performances of all children, scores were converted into Z-scores. These Z-scores were compared with the Z-score of the overall performance of CA-children on full-scale intelligence, as this reflects the overall capacity of the functioning of CA survivors; children with a lower IQ will have a lower neuropsychological functioning. To compare this neuropsychological outcome of CA survivors with normative data, the one-sample t-test was performed for normally distributed data, or the one-sample Wilcoxon Signed Rank Test for non-normally distributed data.

Predictors of neuropsychological outcomes were examined with Spearman correlations for continuous variables (age at time of CA, age at follow-up), Mann-Whitney U test for dichotomous variables (gender, location, BLS/APLS, CA-related pre-existing condition, participation in a follow-up program), and the Kruskal-Wallis test for ordinal variables (SES).

All analyses were performed with SPSS 21.0 for Windows (SPSS, Chicago, IL, USA). Statistical significance was considered with 2-tailed *p*-values of <0.05.

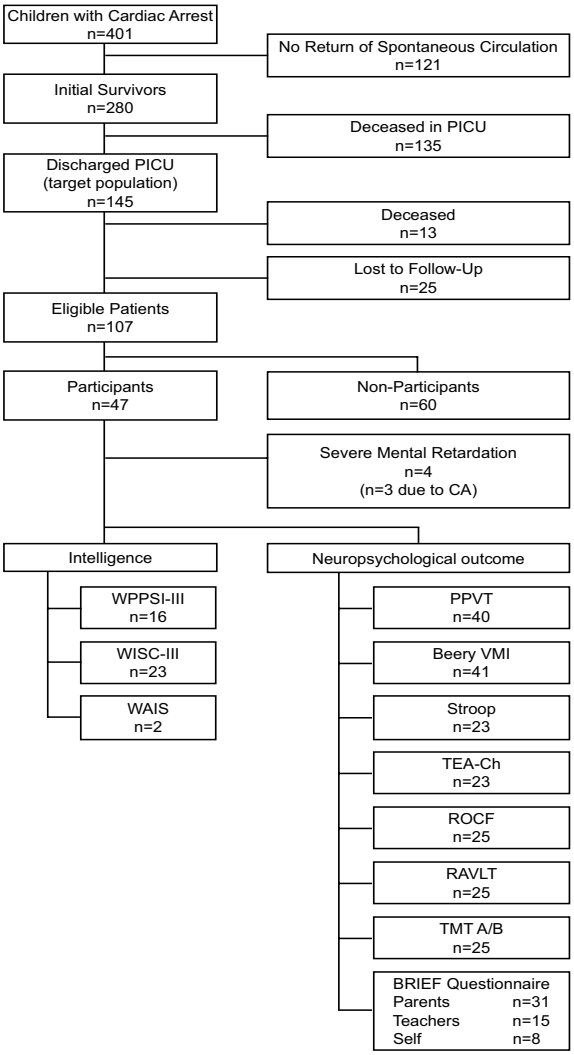

Figure 1. Flowchart of patient inclusion

Lost to Follow-up: moved abroad n=7, untraceable n=18.

n is the actual number of children tested, or the number of respondents to the questionnaire (BRIEF). Numbers of patients may differ for neuropsychological tests due to different age ranges covered by the different tests (and availability of norm data).

Abbreviations: Beery VMI = Beery Developmental Test of Visual Motor Integration; BRIEF = Behaviour Rating Inventory of Executive Function questionnaires; PICU = Pediatric Intensive Care Unit; PPVT = Peabody Picture Vocabulary Test; RAVLT = Rey's Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure Test; Stroop = Stroop Color Word Test; TEA-Ch = Test of Everyday Attention for Children; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

Results

Our target population consisted of 145 surviving patients, 38 of whom were deceased or lost to follow-up. (Figure 1) Causes of death after hospital discharge were another CA without ROSC (n=3), underlying disease (n=2), severe cerebral damage (n=1), or unknown (n=7).

Of 107 eligible patients, 47 (44%) participated. Median follow-up interval was 5.6 years (range 1.8 – 11.9). Intellectual functioning of one patient was recently tested (<1 year) and therefore not repeated at our hospital. His test results were used in this study. Twelve of 47 patients participated in the multidisciplinary follow-up program. Four participants could not be tested due to severe mental retardation (n=3 due to CA).

Non-participants refused participation due to practical reasons (n=23, e.g., distance to hospital/work of parents), or emotional reasons (n=16, e.g., too anxious/ confronting). For 21 non-participants, the reasons were unknown.

Medical characteristics of participants and non-participants were compared, and differed significantly on high SES. (Table 1)

Table 1. Characteristics of participants and non-participants

	Participants (n=47)		Non-participants (n=60)		*p*-value
	n [a]		n [a]		
Age at cardiac arrest (years)	47	0.4 (0 – 16.1)	60	0.6 (0 – 17.0)	.220
Male gender	47	25 (53%)	60	39 (65%)	.238
Advanced Pediatric Life Support (APLS)	47	25 (53%)	60	43 (72%)	.068
Out-of-hospital arrest	47	21 (47%)	60	18 (30%)	.157
Bystander CPR	47	46 (98%)	57	56 (98%)	1.00
Initial Rhythm Non-shockable	36	31 (86%)	56	48 (86%)	1.00
Etiology					
- Cardiac	47	16 (34%)	60	22 (37%)	.840
- Respiratory	47	23 (49%)	60	35 (58%)	.434
- Other	47	8 (17%)	60	3 (5%)	.056
Pre-existing medical condition *	47	26 (55%)	60	29 (48%)	.560
- Cardiac	26	13 (50%)	29	17 (59%)	.840
- Respiratory	26	10 (39%)	29	10 (35%)	.434
- Other	26	3 (12%)	29	2 (7%)	.056
Mild therapeutic hypothermia **	47	7 (15%)	60	15 (25%)	.235
Socioeconomic status at follow-up †					
- Level 1: "Low"	47	4 (9%)	60	14 (23%)	.066
- Level 2: "Middle"	47	21 (45%)	60	31 (52%)	.560
- Level 3: "High"	47	22 (47%)	60	15 (25%)	**.024**
Age at follow-up (years)	47	8.7 (2.4 – 18.3)	-	-	-

All data are presented as "number of subject (%)", except age which is presented as "median (range)".

[a] Number of subjects from which the variable was obtained.

* Children with a pre-existing medical history which was the cause of the CA.

** Children treated with mild therapeutic hypothermia.

† SES for non-participants at time of follow up was calculated on the basis of a combined status score of the Netherlands Institute for Social Research based on home address. [24] This score consisted of four variables: average income in neighborhood, percentage of people with low income, percentage of less educated people, and percentage of people not working. A status score of 0 (±1.16 SD) was classified as middle SES, a status score of <-1.16 was classified as low SES, and a status score of >+1.16 was classified as high SES.

Abbreviations: CPR = cardiopulmonary resuscitation; ICU = intensive care unit; n = number; - = not available.

Neuropsychological functioning

Intelligence tests

CA survivors scored significantly worse on full-scale IQ (87.3, t=-6.01), verbal IQ (92.7, t=-3.32), performance IQ (85.6, t=-7.07), verbal comprehension index (93.4, t=-2.26), perceptual organization index (83.8, t=-5.81), and processing speed index (91.1, t=-3.16), than the normal population. (Table 2)

Neuropsychological tests

After adjustment for (taking into account) their intellectual functioning (mean IQ Z-score: -0.84), CA survivors performed significantly better on receptive vocabulary (PPVT), attentional switching (TEA-Ch attentional switching), and verbal memory recognition (RAVLT recognition). (Figure 2, 3; Table 2) Significantly worse scores were found on short- and long-term visual-spatial memory (Rey immediate and delayed recall). No significant differences were found on visual-motor integration, attention, verbal memory (RAVLT 1-5, delayed recall), and executive functions.

Questionnaire

Parents reported significantly better functioning on the executive composite score and behavior regulation index, and subtests organization of materials, and monitoring. (Table 3; Supplementary Table 3) Teachers reported better scores on subtest inhibition, but worse on subtest planning/organizing compared to normative data. On self-reports, no significant differences were found.

Table 2. Overview of intelligence and neuropsychological outcome adjusted for participants' IQ

Intelligence	Cardiac arrest patients		Normative data			
	n	Mean (SD)		Mean (SD)		*p*-value
- Full scale IQ [a]	41	87.3	13.4	100	15	**.002**
- Verbal IQ [b]	39	92.7	13.7	100	15	**<.001**
- Performance IQ [b]	39	85.6	12.7	100	15	**<.001**
- Processing Speed Index [a, c]	31	91.1	15.6	100	15	**.004**
- Verbal Comprehension Index [d]	25	93.4	14.7	100	15	**.033**
- Perceptual organization index [d]	25	83.8	13.9	100	15	**<.001**
- Intelligence Subtest: Digit Span	25	8.0	3.1	10	3	**.009**

Neuropsychological tests [e]	n [f]	Mean (SD)		Mean (SD)		*p*-value	*p*-value adjusted for IQ [e]
Peabody Picture Vocabulary Test (PPVT)	40	-0.12	1.2	0	1	.451	**.002**
Beery Visual-Motor Integration (Beery VMI)	41	-0.85	0.9	0	1	**<.001**	.841
Stroop Color Word test	23	-1.14	2.4	0	1	.059	.692
Test of Everyday Attention for Children (TEA-Ch)							
- Sky Search time per target	22	-0.76	1.1	0	1	**.004**	.235
- Sky Search attention score *(selective attention)*	23	-0.96	1.3	0	1	**.003**	.646
- Score! *(sustained attention)*	23	-0.59	1.3	0	1	.052	.502
- Creature counting accuracy *(attentional switching)*	23	-0.29	1.0	0	1	.173	**.010**
- Creature counting timing score	23	-0.68	1.2	0	1	**.017**	.204
- Sky search Double Task decrement *(divided attention)*	23	-1.51	1.3	0	1	**<.001**	.059

Table 2. *Continued*

Neuropsychological tests [e]	n [f]	Mean (SD)	Mean (SD)	*p*-value	*p*-value adjusted for IQ [e]
Rey Complex Figure Test (ROCF)					
- ROCF copy	23	-0.42 1.3	0 1	.338	.181
- ROCF immediate recall	25	-1.89 1.0	0 1	**<.001**	**<.001**
- ROCF delayed recall	25	-1.87 1.0	0 1	**<.001**	**<.001**
- ROCF recognition	25	-0.66 1.0	0 1	**.022**	.510
Rey's Auditory Verbal Learning Test (RAVLT)					
- RAVLT 1-5	25	-0.66 1.0	0 1	**.005**	.339
- RAVLT delayed recall	25	-0.79 1.2	0 1	**.003**	.716
- RAVLT recognition	24	-0.27 1.1	0 1	.373	**.010**
Trail Making Test part A and B (TMT A/B)					
- TMT A	25	-0.43 1.0	0 1	**.042**	.109
- TMT B	25	-0.65 1.0	0 1	**.003**	.158

[a] Intelligence scores of different age-groups were combined for the total sample by combining scores on, respectively: 1) Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III; n=16), 2) Wechsler Intelligence Scale for Children (WISC-III; n=23), and 3) Wechsler Adult Intelligence Scale (WAIS-IV; n=2). One child was too young to be tested with the WPPSI-III(<2.6 years), and for one child the testing of intellectual functioning had to be stopped prematurely due to substantial attentional problem behavior, which made accurate testing of the intellectual functioning impossible.

[b] Intelligence scores combined for the total group of 1) Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), and 2)Wechsler Intelligence Scale for Children (WISC-III). WAIS-IV does not include the PIQ and VIQ.

[c] Procession Speed Index is not available for children < 4,5 years (n=10), on the WPPSI-III.

[d] Perceptual Organization Index and Verbal Comprehension Index are not available on the WPPSI-III (n=16).

[e] All neuropsychological test were converted into Z-scores and compared with the Z-score (-0.84) of the mean IQ of CA survivors, as significant difference in intelligence were found and developmental delay (lower IQ) worsens their abilities on neuropsychological tests.

[f] Numbers of patients differ for neuropsychological tests due to different age ranges and diversity in availability of normative data. The n is the actual number of patients tested.

Predictors of outcome

Males scored significantly worse than females on performance IQ (Z=-2.522, p=0.012), visual-motor integration (Z=-1.999, p=0.046), selective attention (TEA-Ch: Z=-1.999, p=0.046)), cognitive shifting and inhibition (Stroop: Z=-2.050, p=0.040). (Supplementary Table 2) Older age at time of CA and follow-up were associated with worse outcomes on language (ρ=-0.414, p=0.008; ρ=-0.408, p=0.009). Older age at follow-up was also associated with worse outcomes on visual-motor-integration (ρ=-0.312, p=0.047). Children with a CA-related pre-existing medical condition scored worse on attentional switching than children without (Z=-2.716, p=0.007). Children with BLS scored worse than children with APLS on the TMT part A (Z=-2.522, p=0.012). Children without follow-up scored significantly worse on divided attention (Z=-2.116, p=0.034) and TMT part B (Z=-2.000, p=0.046) than children participating in the follow-up program. Predictors of outcome on the BRIEF questionnaires are shown in Supplementary Table 4.

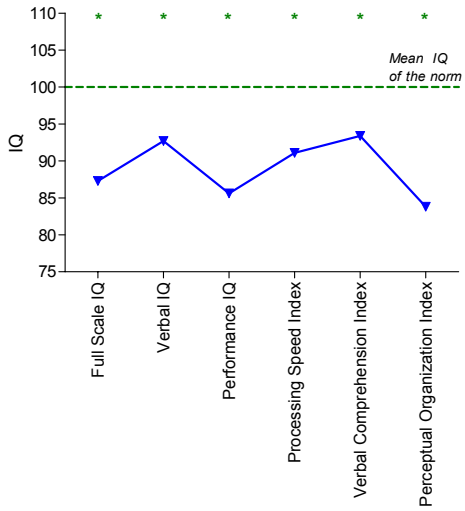

Figure 2. Results on intelligent tests compared with normative data

*) Significantly different from the norm.

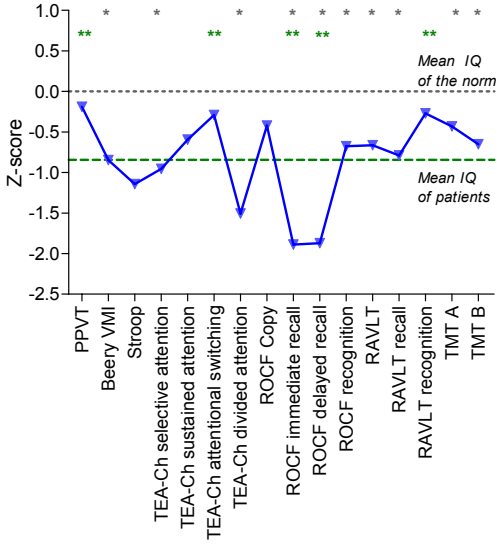

Figure 3. Results on neuropsychological tests, adjusted for mean full-scale IQ of CA survivors

*) Significantly different from the norm.

**) Significantly different from what would be expected based on the mean full-scale IQ of CA survivors.

Table 3. Parent, teacher, and self-reported executive functioning [a]

	Patients	Norm	*p*-value
	Mean (SD)	Mean (SD)	
BRIEF Parents-report	*n=31* [b]	*n=770*	
Behavioral Regulation Index	39.52 (12.0)	45.22 (11.3)	**.003**
- Inhibit	13.81 (4.3)	15.78 (4.5)	**.003**
- Shift	10.97 (3.5)	12.62 (3.5)	**.004**
- Emotional Control	14.74 (5.2)	16.79 (5.0)	**.016**
Metacognition Index	72.52 (21.6)	78.60 (17.5)	.108
- Organization of Materials	10.68 (3.9)	12.14 (3.3)	**.031**
- Monitor	12.77 (4.3)	14.81 (3.7)	**.017**
Global Executive Composite	112.03 (31.4)	124.13 (26.0)	**.024**
BRIEF Teacher-report	*n=15* [b]	*n=778*	
Behavioral Regulation Index	39.73 (12.9)	42.89 (13.3)	.099
- Inhibit	13.33 (3.9)	15.54 (6.0)	**.020**
Metacognition Index	75.27 (23.8)	70.00 (21.0)	.589
- Plan/Organize	16.73 (4.7)	13.84 (4.2)	**.041**
Global Executive Composite	115.00 (34.7)	112.88 (31.6)	.910
BRIEF Self-report	*n=8* [b]	*n=379*	
Behavioral Regulation Index	48.25 (8.9)	52.02 (11.2)	.207
Metacognition Index	52.75 (15.7)	56.60 (12.8)	.574
Global Executive Composite	101.00 (22.5)	108.62 (21.8)	.327

[a] Only the index scores and composite scores, and subscales on which significant differences were found when compared with normative data, are presented. A complete overview of all results on the BRIEF is presented in Supplementary Table 3.

[b] The actual number of respondents to the questionnaire.

Higher scores implicate worse executive functioning.

Abbreviations: BRIEF = Parent, teacher, and self-reported executive functioning.

Discussion

This is one of the first studies that has systematically examined the long-term neuropsychological outcomes in children surviving cardiac arrest (CA). As a result of the CA, 6% sustained such serious brain damage that they could not be tested. CA survivors scored significantly worse on intelligence. On neuropsychological tests, significantly worse scores were found on visual memory, significant better scores on verbal memory (recognition), and no differences on visual-motor integration, attention, verbal memory (RAVLT 1-5, delayed recall), and executive functioning. On questionnaires, parents reported better executive functioning, but teachers reported more problems in planning/organizing skills.

Neuropsychological functioning

Intelligence tests

Conform former research, lower scores were found on all intelligence scales. [10, 11] In general, intellectual outcome is highly dependent on the age at which brain injury was acquired. Acquired brain injury (ABI) at a young age results in more diffuse deficits in cognitive functioning, rather than specific deficits. [25] This can be explained by the vulnerability theory, since children with ABI at young age have to learn new skills with impaired basal functions. [26] The most susceptible areas to ischemic injury within the brain are vascular end zones, hippocampus, insular cortex, and basal ganglia. [27] With an increasing severity of hypoxic ischemia, more extensive and global neocortical injury will occur and could lead to global cerebral atrophy, as shown in adults. [27, 28] Moreover, ABI at young age has long-lasting effects on intelligence. [29]

Neuropsychological tests

Long-term neuropsychological functioning has mainly been assessed in subgroups of CA patients, i.e., congenital heart disease or drowned children. [10, 11] Besides impairments in intelligence, impairments in verbal and/or visual memory, visual-perceptual-motor functioning, and executive functions were also found. [10, 11]

A discrepancy between visual and verbal information processing is not only found on our results on the intelligence profile but also on our memory results, as only visual memory problems (Rey) were found, not verbal memory problems

(RAVLT). In addition, the PPVT and TEA-Ch attentional switching are both verbal tasks. Since the children's verbal functions are relatively good, this may result in an overestimation and better reported executive functioning by parents, as instructions by parents are mainly verbal. Academic achievement tasks at school are both visual-spatial and verbal orientated, which is reflected by the lower executive functioning reported by teachers. As these children have visual weaknesses and relatively intact verbal functioning, the visual-spatial deficits could be supported by verbal instructions at school, to improve their academic achievements.

Various pathological mechanisms may explain our findings on the neuropsychological tests. The hippocampus, playing an important role in memory, is sensitive to cerebral hypoperfusion. While neuronal injury is mostly observed within 3 h after ROSC, delayed neuronal death, especially in the hippocampus, can be present up to 48-72 h after ROSC. [30]

Furthermore, the watershed areas in the brain are particularly vulnerable to effects of hypoperfusion and hypoxia resulting in cognitive deficits and prefrontal lesions. [31] Cognitive deficits could be explained by periventricular leukomalacia (white matter injury), which is believed to arise from several factors including ischemia to the watershed areas. [5] As the integrity of the white matter is correlated with full-scale IQ and performance IQ, and not with verbal IQ, white matter injury could be an important explanation for our findings in CA survivors. [32] Damage to the prefrontal region could result in various types of frontal syndromes, which manifest themselves in deficits in executive functions, information processing and attention. The relatively high scores on the BRIEF do not necessarily mean better functioning, but could be an expression of a dorsolateral prefrontal syndrome. This syndrome is characterized by lack of initiative, personality changes, blunted affect, or problems with executive functions such as working memory and planning. Children with a lack of initiative are more dependent on external stimulation; rapid emotional changes and high distractibility are less common. This would also explain the positive results on the teacher-reported inhibition scale. Unfortunately, no imaging was performed, which could have provided valuable information on the neuropsychological outcome and CA-related brain damage. [33]

Questionnaire

Parents reported significantly better executive functions, particularly in behavior regulation, as compared to parents of healthy children. These results are in contrast to the negative outcomes, in e.g., patients with TBI or neonatal encephalopathy. [34, 35] Teachers reported deficits in planning/organizing skills and only favorable scores on inhibition.

Parental results on questionnaires are not supported by test results on executive functioning; on the TMT and STROOP lower outcomes found compared to normative data. Possibly the favorable scores were influenced by "response shift". [36] Due to the CPR, and the often traumatic and emotional experiences related to the critical illness of their child, parents have expected a worse outcome and may be happy with their child's present functioning. [37] They therefore may overestimate the capacities of their child. Favorable outcome may also be explained by social desirability, or denial.

Furthermore, the BRIEF questionnaire may not measure executive functions to the extent that is commonly believed. [38] A recent study in critical cyanotic congenital heart disease also showed significant impairments on neuropsychological testing, but remarkably the scores on the BRIEF were average. [39]

Noteworthy, executive functions are part of the higher cognitive functions. Increasing deficits may emerge later in childhood when these functions are expected to mature; this phenomenon is called "growing into deficits". [40]

Predictors of outcome

Univariable analyses were limited by the small number of patients, and therefore no strong conclusions can be drawn. However, there are some hypothesis-generating findings.

Overall, it is to be expected that males have a higher chance on worse neuropsychological functioning as to anatomical differences between the male and female brain. The right hemisphere of males is larger and contains more white matter than the right hemisphere of females. The impairments are found on visual-orientated tasks, which are functions more related to the right hemisphere. These results support the hypothesis of white matter injury.

In addition, older age at time of CA leads to more specific deficits, rather than

global deficits, which could be explained by the vulnerability theory. Also, increasing deficits may emerge later in childhood when functions are expected to mature (growing into deficits phenomenon).

Further, our findings that children with a CA-related pre-existing medical condition scored worse on attentional switching than those without, indicated that neuropsychological impairments can be related to the pre-existing condition. For example, children with a congenital heart disease and children treated with ECMO, both without CA, also have attentional problems. [5, 7]

Lastly, significantly better scores were found on divided attention and TMT part B in children participating in the follow-up program. Due to the multidisciplinary follow-up, children may have been referred to a professional (mental) healthcare provider in a more timely manner.

Limitation

First, this is a single center cohort study in a heterogeneous population. Second, since participants with a high SES are relatively overrepresented, our results may be too positive, since SES is an important predictor of outcome. Third, correction for multiple testing was not applied since this is an explorative and descriptive study. We did not want to miss any influences on long-term neuropsychological outcomes. Fourth, although we assessed the executive functions with the BRIEF questionnaire, the executive functions were not extensively tested with neuropsychological tests. Finally, some important variables are lacking, such as time to ROSC, severity of underlying illness, and treatment/course after ROSC during ICU admission.

Conclusion

Long-term neuropsychological testing of CA survivors showed significant weaknesses, but also relatively intact functioning. A structural neuropsychological follow-up screening is warranted, since cognitive deficits can be expected later in life ("grown into deficit"). Considering academic achievement, verbal support could improve these children's visual-spatial tasks.

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Supplementary Table 1. Overview neuropsychological measures

Measurements	Test	Age (yrs.)	Normative data	Notes
Intelligence	Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)	2.6-6	Mean 100, SD 15 [13]	IQ standard scores, and subscale standard scores. Overlapping results are shown (FSIQ, VIQ, PIQ, PSI, POI, VCI)
	Wechsler Intelligence Scale for Children (WISC-III)	7-15	Mean 100, SD 15 Subtest: Mean 10, SD 3 [14]	
	Wechsler Adult Intelligence Scale (WAIS-IV)	16-18	Mean 100, SD 15 Subtest: Mean 10, SD 3 [12]	
Language	Peabody Picture Vocabulary Test (PPVT-III)	2.3-18	Mean 100, SD 15 [15]	Standard norm score
Visual-Motor Integration	Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI-V)	2 -18	Mean 100, SD 15 [19]	Standard norm score
Visuospatial ability, Visual spatial memory	Rey-Osterrieth Complex Figure test	6-18	Mean 50, SD 10 [18]	T-score
Attention	Test of Everyday Attention for Children (TEA-Ch)	6-18	Mean 10, SD 3 [20]	Standard norm score
Executive functions	Behaviour Rating Inventory of Executive Function: parent, teacher, and self-report (12-18)	5-18	Normative data technical manual [23]	Screening tool
	Trail Making Test part A and B	6-18	Age dependent norms [22]	Z-score based on age appropriate scores
	Stroop Color Word test (Stroop)	8-18	Age dependent norms [21]	Z-score based on age appropriate scores
Verbal Memory	Rey's Auditory Verbal Learning Test (RAVLT)	7-18	Age dependent norms [16, 17]	Z-score based on age appropriate scores

Supplementary Table 2. Univariate predictors of neuropsychology

Risk factor variables	Gender	Age at ICU	BLS/APLS	Location	CA-related Pre-existing condition	SES	Age at follow-up	Participation in follow-up assessment
	Z	ρ	Z	Z	Z	χ^2	ρ	Z
Intelligence								
Full scale IQ †	-	-	-	-	-	-	-	-
Verbal IQ ††	-	-	-	-	-	-	-	-
Performance IQ ††	-2.522*	-	-	-	-	-	-	-
Processing Speed Index †	-	-	-	-	-	-	-	-
Neuropsychological tests								
Peabody Picture Vocabulary Test (PPVT)	-	-0.414**	-	-	-	-	-0.408**	-
Beery Visual-Motor Integration (Beery VMI)	-1.999*	-	-	-	-	-	-0.312*	-
Stroop Color Word test	-2.050*	-	-	-	-	-	-	-
Test of Everyday Attention for Children (TEA-Ch)								
- TEA-Ch selective attention	-1.999*	-	-	-	-	-	-	-
- TEA-Ch sustained attention	-	-	-	-	-	-	-	-
- TEA-Ch attentional switching	-	-	-	-	-2.716**	-	-	-
- TEA-Ch divided attention	-	-	-	-	-	-	-	-2.116*
Rey Complex Figure Test (Rey)								
- Rey copy	-	-	-	-	-	-	-	-
- Rey immediate recall	-	-	-	-	-	-	-	-
- Rey delayed recall	-	-	-	-	-	-	-	-
- Rey recognition	-	-	-	-	-	-	-	-

Supplementary Table 2. *Continued*

Risk factor variables	Gender	Age at ICU	BLS/APLS	Location	CA-related Pre-existing condition	SES	Age at follow-up	Participation in follow-up assessment
	Z	ρ	Z	Z	Z	χ^2	ρ	Z
Rey's Auditory Verbal Learning Test (RAVLT)								
- RAVLT	-	-	-	-	-	-	-	-
- RAVLT recall	-	-	-	-	-	-	-	-
- RAVLT recognition	-	-	-	-	-	-	-	-
Trail Making Test part A and B (TMT A/B)								
- TMT A	-	-	-2.522*	-	-	-	-	-
- TMT B	-	-	-	-	-	-	-	-2.000*

* p<0.05, ** p <0.01; - = not significant Abbreviations: APLS = Advanced Pediatric Life Support; BLS = Basic Life Support; ICU = intensive care unit; n = number; SES = Socioeconomic status; yrs. = years.

† Combined intelligence scores of Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), Wechsler Intelligence Scale for Children (WISC-III), and Wechsler Adult Intelligence Scale (WAIS).

†† Combined intelligence scores of Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), and Wechsler Intelligence Scale for Children (WISC-III).

Supplemental Table 3. Parent, teacher, and self-reported executive functioning

	Patients Mean (SD)	Norm Mean (SD)	*p*-value	Cohens' d
BRIEF Parents-report	*n=31*	*n=770*		
Behavioral Regulation Index	39.52 (12.0)	45.22 (11.3)	**.003**	.50
- Inhibit	13.81 (4.3)	15.78 (4.5)	**.003**	.44
- Shift	10.97 (3.5)	12.62 (3.5)	**.004**	.47
- Emotional Control	14.74 (5.2)	16.79 (5.0)	**.016**	.41
Metacognition Index	72.52 (21.6)	78.60 (17.5)	.108	.34
- Initiate	13.00 (4.2)	14.12 (3.4)	.131	.32
- Working Memory	17.81 (5.9)	17.32 (5.1)	.784	.09
- Plan/Organize	18.26 (6.1)	19.97 (5.2)	.147	.32
- Organization of Materials	10.68 (3.9)	12.14 (3.3)	**.031**	.44
- Monitor	12.77 (4.3)	14.81 (3.7)	**.017**	.55
- Task Completion	-	-	-	-
Global Executive Composite	112.03 (31.4)	124.13 (26.0)	**.024**	.46
BRIEF Teacher-report	*n=15*	*n=778*		
Behavioral Regulation Index	39.73 (12.9)	42.89 (13.3)	.099	.24
- Inhibit	13.33 (3.9)	15.54 (6.0)	**.020**	.37
- Shift	14.27 (5.7)	14.57 (4.6)	.278	.07
- Emotional Control	12.13 (4.4)	12.77 (4.6)	.527	.14
Metacognition Index	75.27 (23.8)	70.00 (21.0)	.589	.25
- Initiate	12.67 (4.9)	11.52 (3.9)	.690	.30
- Working Memory	19.07 (6.2)	16.65 (6.0)	.172	.40
- Plan/Organize	16.73 (4.7)	13.84 (4.2)	**.041**	.69
- Organization of Materials	10.60 (4.7)	10.51 (4.1)	.567	.02
- Monitor	16.20 (5.3)	17.48 (5.7)	.333	.23
- Task Completion	-	-	-	-
Global Executive Composite	115.00 (34.7)	112.88 (31.6)	.910	.07

Supplemental Table 3. *Continued*

	Patients Mean (SD)	Norm Mean (SD)	*p*-value	Cohens' d
BRIEF Self-report	*n=8*	*n=379*		
Behavioral Regulation Index	48.25 (8.9)	52.02 (11.2)	.207	.34
- Inhibit	17.13 (3.0)	19.35 (4.5)	.090	.50
- Shift	11.25 (3.2)	11.71 (3.0)	.779	.15
- Emotional Control	13.88 (3.4)	14.60 (4.2)	.483	.17
Metacognition Index	52.75 (15.7)	56.60 (12.8)	.574	.30
- Initiate	-	-	-	-
- Working Memory	15.00 (4.5)	16.45 (4.0)	.398	.36
- Plan/Organize	13.38 (3.7)	15.01 (4.0)	.206	.41
- Organization of Materials	9.25 (2.9)	10.59 (2.9)	.160	.46
- Monitor	6.00 (2.0)	6.36 (2.0)	.888	.18
- Task Completion	15.13 (5.2)	14.54 (4.0)	1.000	.15
Global Executive Composite	101.00 (22.5)	108.62 (21.8)	.327	.35

Cohen's d's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large. Higher scores implicate worse executive functioning.

Abbreviations: BRIEF = Parent, teacher, and self-reported executive functioning.

Supplemental Table 4. Univariate predictors of BRIEF

Risk factor variables	Gender	Age at ICU	BLS/APLS	Location	CA-related Pre-existing Condition	SES	Age at follow-up	Participation in follow-up assessment
	Z	ρ	Z	Z	Z	χ^2	ρ	Z
BRIEF Parents-report								
Behavioral Regulation	-	-	-2.168*	-	-	-	-	-
Metacognition	-	-	-	-	-	6.149*	.427*	-2.003*
Global Executive Composite	-	-	-	-	-	-	-	-
BRIEF Teacher-report								
Behavioral Regulation	-2.280*	-	-	-	-	-	-	-
Metacognition	-2.883**	-	-	-	-	-	-	-2.435*
Global Executive Composite	-2.822**	-	-	-	-	-	-	-2.319*
BRIEF Self-report								
Behavioral Regulation	-	-	-	-	-	-	-.883**	-
Metacognition	-	-	-	-	-	-	-	-
Global Executive Composite	-	-	-	-	-	-	-	-

* p<0.05, ** p <0.01, *** p <0.001 - = not significant.

Abbreviations: APLS = Advanced Pediatric Life Support; BLS = Basic Life Support; BRIEF = Behaviour Rating Inventory of Executive Function; SES = Socioeconomic status.

Chapter 6

Analgesia-sedation in PICU and neurological outcome: a secondary analysis of long-term neuropsychological follow-up in meningococcal septic shock survivors

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Abstract

Objectives: To investigate whether analgesic and sedative drug use during PICU treatment is associated with long-term neurodevelopmental outcome in children who survived meningococcal septic shock.

Design: This study concerned a secondary analysis of data from medical and psychological follow-up of a cross-sectional cohort of all consecutive surviving patients with septic shock and purpura requiring intensive care treatment between 1988 and 2001 at the Erasmus MC - Sophia Children's Hospital. At least 4 years after PICU admission, these children showed impairments on several domains of neuropsychological functioning. In the present study, type, number, and dose of sedatives and analgesics were retrospectively evaluated.

Setting: Tertiary care university hospital.

Patients: Seventy-seven meningococcal septic shock survivors (median age, 2.1 years).

Interventions: None.

Measurements and Main Results: Forty-five patients (58%) received one or more analgesic and/or sedative drugs during PICU admission, most commonly benzodiazepines (n = 39; 51%), followed by opioids (n = 23; 30%). In total, 12 different kinds of analgesic or sedative drugs were given.
The use and dose of opioids were significantly associated with poor test outcome on full-scale intelligence quotient (P = 0.02; Z = -2.28), verbal intelligence quotient (p = 0.02; Z = -2.32), verbal intelligence quotient subtests (verbal comprehension [p = 0.01; Z = -2.56] and vocabulary [p = 0.01; Z = -2.45]) and visual attention/ executive functioning (Trail Making Test part B) (p = 0.03; Z = -2.17). In multivariate analysis adjusting for patient and disease characteristics, the use of opioids remained significant on most neuropsychological tests.

Conclusions: The use of opioids during PICU admission was significantly associated with long-term adverse neuropsychological outcome independent of severity of illness scores in meningococcal septic shock survivors.

Introduction

Meningococcal septic shock (MSS) is characterized by sudden onset and fulminant course in previously healthy children. Despite better knowledge of pathophysiology and treatment, it is still associated with high short- and long-term morbidity. [1-7] Fortunately, the prevalence has significantly decreased since the start of vaccination programs in different countries.

We previously showed that MSS affects several medical and psychological domains, including neuropsychological functioning, notably verbal comprehension, visual-motor integration, attention and executive functioning. [2-6, 8] Surprisingly, severity of illness was not a significant predictor of poorer long-term neuropsychological functioning.

The use of a variety of analgesics and sedatives has been associated with adverse cognitive development in young rodents, in the presence of widespread neurodegeneration due to neuronal cell death. [9-14] However, the data in animals are conflicting. The few studies on the influence of analgesics and sedatives on neurodevelopmental outcome in children also showed contradictory results. Guerra et al. found that perioperative sedation or analgesia were not associated with adverse neurodevelopmental outcome two years after cardiac surgery before the age of 7 weeks. [15] De Graaf et al. did find a significant relation in 5 year-old children who as preterm neonates on mechanical ventilation had received morphine. Their overall intelligence quotient was lower, but this effect had disappeared 3 to 4 years later. [16, 17]

Currently, the influence of analgesics and sedatives on neurodevelopmental outcome in critically ill children is not known, particularly in MSS survivors. We hypothesized that the use of sedative or analgesic agents during Pediatric Intensive Care Unit (PICU) admission is a significant predictor of poorer long-term neuropsychological functioning in MSS survivors.

The aim of the study was to investigate the relationship between the use of analgesic and sedative drugs and the neurodevelopmental outcome in MSS survivors.

Materials and Methods

Patient Selection

This study concerned a secondary analysis of data from medical and psychological follow-up of a cross-sectional cohort of all consecutive surviving patients with septic shock and purpura requiring intensive care treatment between 1988 and 2001. [2-6, 8] Eligible for this study were all consecutive surviving patients 1 month to 18 years old with a clinical picture of MSS, defined as septic shock (i.e., sepsis-induced hypotension or the requirement for vasopressors/inotropes to maintain blood pressure despite adequate fluid resuscitation along with perfusion abnormalities) with petechiae and/or purpura. [18] Patients were recruited from the PICU of the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital. Those with insufficient command of the Dutch language or unable to undergo the psychological assessment due to severe mental handicap were previously excluded. Neuropsychological assessment was only available for children 6-17 years old at follow-up due to the specific age ranges in the different neuropsychological tests. A detailed description can be found in the original article. [6]

The original study protocol was approved by the Erasmus MC Medical Ethical Review Board.

Neuropsychological outcome variables

Patients were previously interviewed and examined by one psychologist using standard assessment procedures and the following neuropsychological tests - child and adolescent versions:

1. The Wechsler Intelligence Scale for Children-Third Edition (WISC-III): full-scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), verbal comprehension Index (VCI), perceptual organization Index, verbal subtests, and performance subtests. [19]
2. The Stroop Color Word Test (Stroop), assessing selective attention. [20]
3. The Trail Making Test (TMT) part A and part B, assessing visual attention and executive functioning. [20]
4. The subtest "Score!" of the Test of Everyday Attention for Children, a test for

sustained attention. [21]

5. The Beery Developmental Test of Visual Motor Integration (fifth edition). [22]
6. The 15-Word Test, consisting of 15-Word Test 1-5 and long-term 15-Word Test, a Dutch adaptation of Rey's Auditory Verbal Learning Test, a test for memory and learning. [23, 24]

Medical Predictor Variables at the Time of PICU Admission

Clinical and Demographic Characteristics

Information on age, sex, socioeconomic status (SES), weight, length of stay in PICU, severity of illness, and follow-up interval was available from the original study.[6]

SES was assessed at follow-up on a three-point scale of parental occupation, with SES-level 1 indicating elementary and "lower" occupations; SES-level 2 indicating "middle" occupations; and SES-level 3 indicating "higher" and scientific occupations. This scale is based on a national Dutch classification system for occupations. [25]

Severity of illness was assessed with the Pediatric Risk of Mortality (PRISM) score, vasopressor (VAS) score, disseminated intravascular coagulation (DIC) score, and predicted death rate (PDR) score based on the Rotterdam score. [26-29] The PRISM is a generic scoring system based on the worst physiological and laboratory variables in the first 24 hours after PICU admission. The VAS is an inotropic score: dopamine dose (µg/kg/min) x1 + dobutamine (µg/kg/min) x1 + epinephrine (µg/kg/min) x100 + norepinephrine (µg/kg/min) x100 + phenylephrine (µg/kg/min) x100. The DIC measures disseminated intravascular coagulation based on platelet count, fibrine dimers, prothrombin time, and fibrinogen. The PDR, which is based on the Rotterdam score, is a prognostic score based on four laboratory features (serum C-reactive protein level, base excess, serum potassium level, and platelet count) independently associated with mortality in children with MSS.

Analgesic and Sedative Drug Use

Data on analgesic and sedative drug use during PICU admission of patients admitted from 2001 onwards (n=6) were retrieved from electronic medical records. Before 2001, all medication was manually registered on the appropriate medical charts, and the relevant data were extracted from these charts. Pain or sedation

scores were not available. Pain management or the use of sedatives and analgesics did not change during the study period. All drugs had to be exclusively given for analgesia and/or sedation, not for treatment of seizures.

For all drugs the route of administration, the dose in mg/kg and the date and time the drug was started, changed, and/or stopped were extracted from the files. If the drugs were given per infusion pump: the dose, volume, and infusion rate were also recorded. Cumulative doses were calculated from both IV injection and continuous IV infusion; duration only concerned continuous IV infusion .

Based on pharmacological characteristics, agents were classified into: opioids, barbiturates, benzodiazepines, ketamine, and alimemazine. Only fentanyl could be calculated in an equivalent morphine dose (fentanyl dose x 10 = equal morphine dose), which is similar to the conversion factor used at our PICU. All drug groups were dichotomized as "used" or "not used", independent of the dose.

Statistical Analysis

Data are presented as mean +/- SD or median (interquartile range) dependent on the normality of data.

To be able to compare the performances on all neuropsychological tests, scores were compared with normative data and converted into Z-scores. Z-scores less than -2 were considered indicative of clinically important neuropsychological impairments and unusual poor functioning.

The neuropsychological outcome scores and pharmacological data were used in the analyses both as continuous and dichotomous variables. Associations between dichotomous variables were tested with the chi square test. The Mann-Whitney test was used to compare dichotomous variables with continuous variables. The Spearman correlation was used to test the association between putative predictor variables for continuous variables when the data were not normally distributed. If mean scores on the WISC-III VIQ or PIQ differed statistically significantly from normative data, then the corresponding individual (verbal/performance) subtests were further analyzed.

Univariate analysis was applied to evaluate the predictive value of patient characteristics (SES, age at PICU admission, and age at follow-up), disease characteristics (severity of illness scores), and the pharmacological characteristics

on long-term neuropsychological outcome scores. The univariate analysis of the patient and disease characteristics was published in the original article. [6] p values of predictor-scores were set to a level of 0.10 in the univariate analysis for entry in the multivariate analysis.

Multivariate analysis was applied to evaluate the relationship between neuropsychological outcome and pharmacological characteristics, with adjustment for preselected variables including patient characteristics (SES, age at PICU admission, age at follow-up, and follow-up interval) and disease characteristics (severity of illness scores). A *p*-value of less than or equal to 0.05 was considered statistically significant.

Statistical analysis was performed with SPSS 18.0 for Windows (SPSS, Chicago, IL).

Results

Patient Sample

The original study sample numbered 136 children. One hundred and six, now 6-17 years old, fitted the inclusion criteria for present study. Twenty-seven patients declined participation on practical or emotional grounds; two patients had a severe mental and motor handicap and were therefore unable to participate in the psychological assessment. (Figure 1) The final study sample consisted of 77 patients (73%). (Table 1)

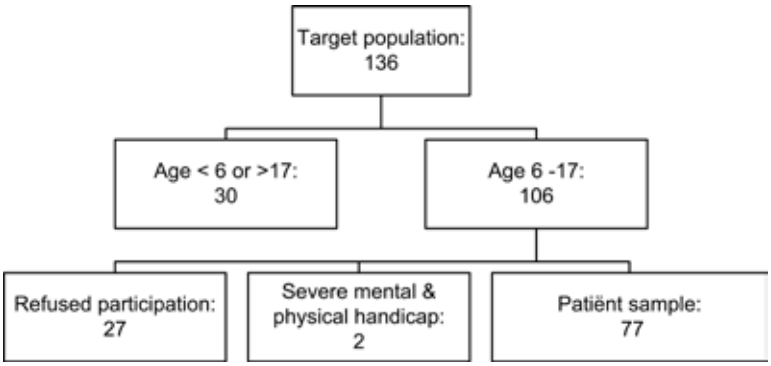

Figure 1. An overview of the patient inclusion

Previously, statistical analyses showed a significant difference in the distribution of age at follow-up between participating patients and non-participants (mean age, yr: 11 +/- 3.5 vs. 13 +/- 3.4; p = 0.01). Neither group differed with regard to gender, age at time of PICU admission, length of stay in PICU and severity of illness.

Table 1. Patient characteristics and disease characteristics

	Median (IQR)	Range
Sex	40 male (52%) / 37 female (48%)	
Socioeconomic status		
- Level 1: "lower" occupations	27 (35%)	
- Level 2: "middle" occupations	36 (47%)	
- Level 3: "higher" occupations	14 (18%)	
Age at time of ICU admission (years)	2.1 (1.3 - 3.5)	0.1 - 11.4
Length of ICU stay (days)	3.4 (1.8 - 6.5)	0.4 - 45
Mechanical ventilation	29 (37%)	
PRISM-score	16 (11 - 24)	1 - 36
VAS-score	15.0 (0.0 - 43.1)	0 - 310
DIC-score	6 (5 - 7)	3 - 8
PDR-score	2.8 (0.5 - 16.1)	0.0 - 99.6
Age at follow-up (years)	11.3 (8.4 - 14.6)	5.9 - 17.8
Follow-up interval (years)	8.0 (5.0 - 10.0)	4.0 - 16.0

ICU = Intensive Care Unit; PRISM = Pediatric Risk of Mortality Score; VAS = Vasopressor score, dopamine dose; DIC = Disseminated Intravascular Coagulation score; PDR = Predicted Death Rate score based on the Rotterdam score.

Analgesic and Sedative Drugs During PICU Admission

Forty-five of the 77 patients (58%) were given analgesic and/or sedative drugs during PICU admission. (Table 2) The median number of drugs was 2 (range, 1 – 8) (Figure 2). Midazolam was the most commonly used sedative drug (n=39, 51%) followed by alimemazine (n=22, 29%). Morphine was the most commonly used analgesic drug (n=19; 25%). In total, 12 different drugs were given (including the above three drugs): clonazepam (n=1), temazepam (n=1), ketamine (n=8), pentobarbital (n=1), phenobarbital (n=4), diazepam (n=3), paracetamol/codeine (n=1), codeine (n=1) and fentanyl (n=8). Table 2 presents the drugs sorted by their corresponding categories including cumulative dose and duration of the infusion.

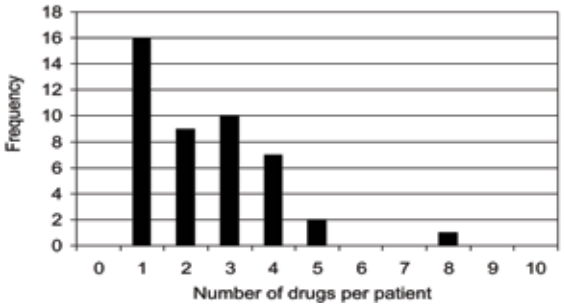

Figure 2. Number of sedative and analgesic drugs during PICU admission

Table 2. Sedative and analgesic drug use during pediatric intensive care unit admission

	Number (%)	Cumulative dose (mg/kg) Median (IQR)	Duration infusion pumps (days) Median (IQR)
Benzodiazepine	39 (51)	-	-
- Midazolam	39 (51)	7.48 (2.73-19.07)	4,5 (2,2 - 9,0)
Opioids	23 (30)	-	-
- Morphine	19 (25)	2.08 (0.77-3.50)	6.5 (3.4 - 13.9)
- Fentanyl	8 (10)	.00397 (0.0012-0.051)	3.0[b]
- Fentanyl(10)[a] + Morphine	22(29)	2.12 (0.78-4.01)	6.0 (3.0 - 12.8)
Alimemazine	22 (29)	1.80 (.88-8.26)	-
Barbiturates	5 (7)	-	-
Ketamine	8 (10)	1.77 (0.99-17.59)	1.5[b]

[a] The dose of fentanyl was calculated in an equal morphine dose, a tenfold of the original dose.

[b] Infusion pumps were only applied in a small group of children, therefore calculation of the interquartile range (IQR) was not possible: Fentanyl: n=1; Ketamine: n=3 (range (days): 0.5 - 18.6).

- = not available / calculation not possible.

Predictors of Long-Term Neuropsychological Outcome

The use of morphine, and the combination of morphine and fentanyl, and opioids showed significant negative associations with FSIQ, VIQ (and two out of five verbal subtests), and VCI. (Table 3)

In addition, fentanyl and opioids (as a group) were significantly negatively associated with TMT part B (visual attention and executive functioning).

The use of barbiturates was significantly associated with VIQ, verbal subtest comprehension, and TMT part B.

The use and cumulative dose of other sedative agents and benzodiazepines as a group showed no significant associations with any neuropsychological test.

Final Prediction Model: Multivariate Analysis.

After adjusting for SES, age at follow-up, length of stay in ICU, and severity of illness scores, significant associations remained between the use of opioids and poor test outcome on VIQ, verbal subtest comprehension, verbal subtest vocabulary, and TMT part B. (Table 4)

The use of barbiturates only showed significant difference on VIQ when corrected for SES, verbal comprehension subtest when corrected for four individual factors (SES, age at follow-up, length of stay in ICU, or severity of illness scores), and did not show a significant difference on TMT part B.

Table 3. Associations between drug use and long-term neuropsychological outcome *

	Morphine (mg/kg)		Morphine (yes/no)		Fentanyl (mg/kg)		Fentanyl (yes/no)		Morphine / Fentanyl (mg/kg)		Opioids (yes/no)		Barbiturates (yes/no)	
	p	R^2	*p*	Z	*p*	R^2	*p*	Z	*p*	R^2	*p*	Z	*p*	Z
FSIQ	-	-	.034	-2.12	.031	-.266	.029	-2.16	.043	-.250	.022	-2.28	-	-
VIQ	.024	-.278	.013	-2.47	-	-	-	-	.031	-.266	.020	-2.32	.043	-2.01
VCI	.028	-.271	.015	-2.41	-	-	-	-	.031	-.266	.019	-2.34	-	-
V-C	.037	-.257	.020	-2.31	-	-	-	-	.021	-.285	.010	-2.56	.008	-2.51
V-V	.028	-.271	.013	-2.47	-	-	-	-	.029	-.270	.013	-2.45	-	-
TMT B	-	-	-	-	.034	-.277	.028	-2.17	-	-	.029	-2.17	.045	-1.99

FSIQ = full-scale intelligence quotient; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; VCI = verbal comprehension index; V-C = verbal subtest comprehension; V-V = verbal subtest vocabulary; TMT B = Trail Making Test (TMT) part B; - = not significant ($p \geq .05$).

* No associations have been found between drug use and the following neuropsychological tests: Performance IQ, Perceptual Organization Index, Stroop Color Word Test, Trail Making test part A, Test of Everyday Attention for Children, Beery Developmental Test of Visual Motor Integration, 15-Word Test, 15-Word Test Recall. In addition, benzodiazepines showed no significant association on any neuropsychological test. These variables are therefore not shown in this table.

Table 4. Multivariate analysis[a] of the effect of drug use on the long-term neuropsychological outcome

	Opioids (no/yes)		
	β	Standard Error	*p*-value
FSIQ	-	-	-
VIQ	9.44	4.28	.032
PIQ	-	-	-
VCI	-	-	-
V-C	2.31	0.77	.004[b]
V-V	2.12	0.90	.022
POI	-	-	-
Stroop	-	-	-
TMT A	-	-	-
TMT B	1.01	0.45	.031
TEA-Ch	-	-	-
Beery VMI	-	-	-
15 WT	-	-	-
15WT RC	-	-	-

FSIQ = full-scale intelligence quotient; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; VCI = verbal comprehension index; V-C = verbal subtest comprehension; V-V = verbal subtest vocabulary; POI = perceptual organization index; Stroop = Stroop Color Word Test; TMT A/B = Trail Making Test (TMT) part A or part B; TEA-CH = Test of Everyday Attention for Children; Beery VMI = Beery Developmental Test of Visual Motor Integration ; 15 WT (RC) = 15-Word Test (Recall); - = not significant ($p \geq .05$).

[a] Corrected for: socioeconomic status, severity of illness (PRISM, VAS, DIC and PDR), age at follow-up, and length of ICU stay.

[b] Remained significant ($p < 0.05$) after additional adjustments for age at ICU-admission, and follow-up interval.

Discussion

The use and dose of opioids were significantly associated with poor test outcome on VIQ and verbal subtests (verbal comprehension and vocabulary) and visual attention/executive functioning (TMT part B). After correcting for patient and disease characteristics (in particular severity of illness), associations remained significant.

The use and dose of benzodiazepines were not significantly associated with any neuropsychological test.

Sedative and Analgesic Drugs Use During PICU Admission

Half of the children had received midazolam, which was the first sedative drug of choice in children on mechanical ventilation. Only one quarter had received morphine because at that time there was less attention to pain and pain management (no validated pain assessment tools were used). Pain was often not considered a primary problem in the acute phase, but became more prominent in a later stadium, as a result of severe skin lesions due to purpura. In addition, pediatric intensivists feared possible negative side effects on myocardial function and systemic vascular resistance, which might cause hypotension in a patient already in shock.

During the study period, in the absence of an adequate pain or sedation protocol, a variety of analgesic and sedative drugs were used. A first-generation antihistamine called "alimemazine" (administered orally) was given more frequently (29%) as it has good sedative effects and only few side effects.

Predictors of Long-Term Neuropsychological Outcome

To the best of our knowledge, we are the first to show a relationship between opioid use and poor long-term neuropsychological outcome after critical illness (e.g., MSS) in childhood. The innovative aspect of this study is that it shows multiple cognitive impairments, especially on the domains of verbal functioning, executive functioning and attention, in critically ill children who received opioids while treated for MSS. This has not been published before.

Animal studies have found histopathologic (apoptotic) changes in various parts of the rat brain due to morphine use or neurotoxicity by opioid-induced tolerance.

[12, 30-33] Also an in vitro study by Hu et al. showed apoptosis of microglia cells and neurons in human fetal cells. [34] Whether these models can be transposed and applied to humans is a matter of ongoing debate.

In line with our study, human studies reported long-term medical and psychological impairments in preterm neonates associated with morphine use. [16, 35, 36] However, in two of these studies, the impairments were not present at later follow-up. Other studies in critically ill (preterm) neonates reported no significant differences in outcome. [15, 17, 37, 38] A study in adults reported transient impairments on cognitive functioning when an immediate-release opioid was taken next to a sustained-release opioid, suggesting that opioids affect neurocognitive functioning. [39]

Most of our knowledge is based on studies in preterm infants. Differences between findings from the present study and other studies may be explained by the type of illness, pain and narcotics during hospitalization, the related sequelae, and age at time of illness. The inflammatory response in critically ill children may change pharmacokinetics. The release of proinflammatory cytokines seems to down-regulate the expression of drug metabolizing enzymes and drug transporters. As reviewed by Vet et al., this may result in reduced plasma clearance. [40] In addition, down-regulation of drug efflux transporters at the blood-brain barrier may result in higher intracerebral concentrations. This could apply to morphine as well, which is an ABCB1 efflux transporter substrate.

MSS is characterized by cutaneous lesions caused by hemorrhagic skin necrosis. [2] Our results may very well be related to opioids being used in patients who were importantly different and perhaps more severely ill than those who did not receive opioids (despite controlling for other indicators of illness severity), as they had worse purpura and more severe wounds. Our clinical experience is that children with MSS receive extra analgesic drugs during wound care after PICU discharge, which we did not account for. These, however, might also have contributed to overall neuropsychological functioning. Additionally, if pain itself can lead to neuronal death, then pain may be the reason that the children receiving narcotic did worse and the narcotics they received may have mitigated that long-term adverse neurological effects of the pain itself. [36]

The median age at the time of illness in our study was higher than that in other studies. Thus, age-related developmental changes may contribute to

pharmacokinetic and pharmacodynamic variability in children.

Pathophysiology

Previously, poor long-term verbal comprehension (social and practical understanding), executive functioning, visual–motor integration and attention were shown in the same sample. [6] These functions are assumed to be located in the frontal cortical region and parietal cortical region. A rat study by Atici et al. reported apoptosis after opioid use in the parietal, frontal, temporal, occipital, entorhinal, pyriform, and hippocampal CA1, CA2, CA3 regions of the brain, which was not found in the control group. [31] Other studies on the effects of (acute and chronic) use of opioids in rats showed histopathologic changes in rat brain as well. [31-33] However, it seems unlikely that these histopathologic changes are visible on MRI.

Current evidence for adverse (neuro)psychologic effects of opioids in humans is mainly limited to cross-sectional studies in preterm neonates. Neuropsychological problems of MSS children may also be due to immaturity of the frontal lobe at the onset MSS (before 4 years old in 78 % of the children). Early brain damage may possibly result in a cumulative effect on ongoing development, and increasing deficits may emerge later when more functions are expected to mature. This is called the "growing into deficits" phenomenon, which in combination with morphine-induced apoptosis may have an important influence on future cognitive functioning. [41] Unfortunately, these explanations could not be shown in this study because MRI data were unavailable. Ideally, neuropsychological tests and functional MRIs would have been performed shortly after PICU discharge and later at follow-up to objectify the neuropsychological functioning (and the 'growing into deficit' phenomenon). Then we would be able to see if more damage to the brain is associated with poorer neuropsychological functioning. This is a subject for future research.

In conclusion, despite our results, our findings may not be strong enough to warrant an urge for caution in the use of morphine. Adequate analgesia remains crucial in critically ill children, in particular in case of MSS because necrotic skin lesions can be very severe in these patients.

Benzodiazepines, Barbiturates

In the present study, the use of benzodiazepines was not associated with long-term neuropsychological outcome, like in a review study by Loepke and Soriano, which reported only transient neurological abnormalities and no long-term neurological effects. [11] Nevertheless, as many animal studies have reported long-term neurological effects, there is every reason to remain alert.

On the other hand, the use of barbiturates was statistically significantly associated with poor long-term neuropsychological outcome. Animal studies have shown widespread apoptotic neurodegeneration in young rats at barbiturates plasma levels similar to therapeutic plasma levels in children. [11, 42] Future research should further explore the clinical implications of these findings as adverse effects of barbiturates in humans have been reported only in small case series. [11]

Limitations

Several limitations of our study should be acknowledged. First, this is an observational, retrospective, single center, cohort study without control group. Second, as for all but six patients relevant data were extracted from manually completed medical charts, we cannot exclude that registration may have been incomplete and that number, dose, and duration of drugs therefore was underestimated. In addition, we only included analgesic drugs administered at the PICU. A large proportion of children receive extra opioids during wound care after PICU discharge. The analgesic drugs given in the ward were not included in our study.

Finally, neuropsychological assessment was only available for children 6-17 years old at follow-up, due to the specific age ranges of the different neuropsychological tests used. This removes a relative large number of patients from the analysis.

The generalizability of our results is debatable. Studies with larger groups of patients and longitudinal standardized assessments are necessary to draw strong conclusions on possible negative effects of opioids on the neuropsychological outcome in critically ill children.

Conclusions

MSS children who were given opioids at the time of PICU admission showed long-term impairments on several domains of intelligence and neuropsychological functioning. Our data suggest that long-term follow-up of drug effects and drug safety is important to minimize the risk of any unintended harm caused by the use of analgesic or sedative drugs. It is important to note that we did not determine causation in this study; this study is hypothesis-generating (not proving).

As to clinical implications, one should be careful not misinterpreting the results by assuming that opioids should be avoided in children with sepsis, since this might lead to undertreatment of pain and pain itself can have detrimental neurologic effect. [43] Before drawing too firm conclusions and changing clinical care, there is an urgent need to conduct additional research on the neurocognitive effects of critical illness and critical care.

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Editorial on our findings:

"No pain, no gain in pediatric sepsis?"

Pediatr Crit Care Med. 2014 Mar;15(3):264-6

No pain, no gain in pediatric sepsis?

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Chapter 7

General Discussion

The aim of the thesis was to investigate the long-term health status and health-related quality of life (HR-QoL), emotional and behavioral functioning, and neuropsychological functioning of children who survived a critical illness, specifically cardiac arrest (CA). In addition, the influence of medical predictor variables was examined, such as the impact of hyperoxia on mortality after CA, and that of analgesia-sedation on long-term neuropsychological outcome after a specific critical illness, meningococcal septic shock.

Changes in PICU treatment: decreased mortality, increased morbidity

The balance between mortality and morbidity in the PICU setting has shifted over the last three decades.

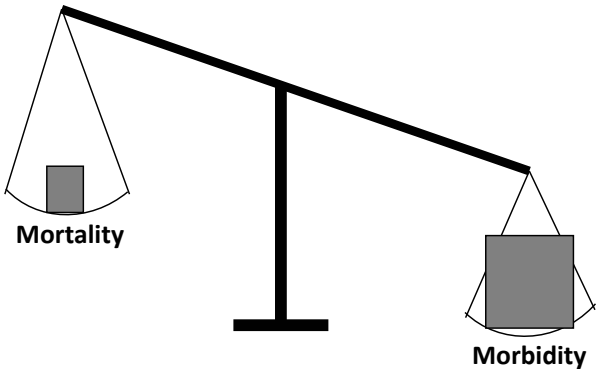

Figure 1. Balance between mortality and morbidity

Namachivayam et al. described the characteristics of children admitted in 1982, 1995 and 2005-2006 to the PICU at the Royal Children's Hospital in Melbourne. They found that the number of readmissions had increased significantly over the years, from 11% to 31% (P<.001). The proportion of children with a moderate or severe disability at follow-up had increased from 8.4% to 17.9% (p<.001). On the other hand, the mortality rate had decreased from 11% to 4.8% (p<.001). [1]

In our PICU, the overall mortality rate has decreased as well, from 5.5% in 2003 to 2.7% in 2011. [2] The lower mortality rates in our PICU can be explained by some crucial differences with the Australian situation, in particular the case mix. First, the

PICU in Melbourne mainly admits children with a very complex congenital heart disease. Second, the severity of illnesses may differ, as the PICU in Melbourne is a designated center for PICU services (including major pediatric trauma, extra-corporeal life support, pediatric heart and liver transplantations) for a much larger area covering Tasmania, Victoria and southern New South Wales.

As a result of improvements in medical treatment, and better understanding of critical illness, most children who would previously have died, nowadays survive. As a consequence, the proportion of survivors with moderate or severe physical and/or (neuro)psychological sequelae has increased significantly. Pollack et al. found that the prevalence of 'new morbidity' – i.e., that incurred by critical illness and therapy – was 4.8%, twice the mortality rate. [3] This was seen in essentially all types of pediatric patients, in relatively equal proportions, and involved all aspects of questioned functions (mental status, sensory, communication, motor function, feeding, and respiratory). When they compared their data with historical data they also found that the field of pediatric critical care has exchanged decreased mortality rates for increased morbidity rates. Whereas the number of children with acute or traumatic injury is declining nowadays, the number of children with a chronic illness is rising. [1]

Bed occupancy can be considered as an indication of the changes in the ICU population described above. In our PICU there was a slight increase in bed occupancy of long-stay patients (admitted more than 28 days, three times the mean length of stay) from 41% in 2003 to 46% in 2011. [2] Naghib et al. found that between 2003 and 2005 mortality of long-stay patients in our PICU was five times higher than the average PICU mortality rate (22.0% versus 4.6%). [4] Most of them (70%) died because of withdrawal or limitations of therapy. Namachivayam et al. reported a significant increase in bed occupancy by long-stay patients from 8% in 1989 to 21% in 2008. [5] Fifty percent of these long-stay patients died, 53% of whom in the PICU and 47% after PICU discharge.

Changing characteristics over time of critically ill children who undergo CPR?

Between 2002 and 2011, the study period of this thesis, 474 children were resuscitated in our hospital. Neonates resuscitated at the hospital's neonatal ICU, or in another hospital and subsequently admitted to the neonatal ICU of our hospital were excluded from analysis. An overview of the characteristics of these patients is

shown in the introductory chapter (table 1).

Over time, the proportion of patients with a pre-existing medical condition related to the CA had increased significantly (Spearman correlation coefficient=0.133, p=0.001). This incidence has increased from 31% in 2002 to 60% in 2011. (Figure 2)

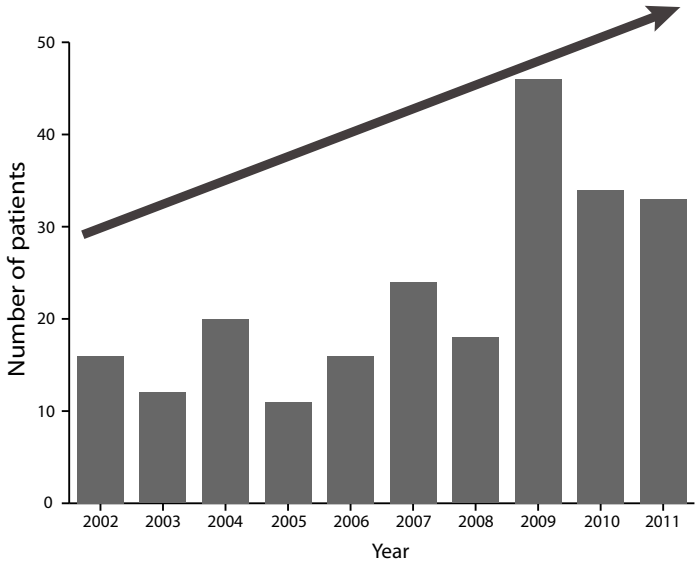

Figure 2. Incidence of pre-existing medical condition in CA patients

Due to prevention and changes in the PICU population a shift has occurred from CA related to accidental injury (e.g., trauma, drowning) to CA related with a pre-existing medical condition. [1, 6] This could have consequences for the outcome after CA.

An example of a change in the CA population is the increasing incidence of ventricular fibrillation (VF)/ ventricular tachycardia (VT), which can partially be explained by the decreased mortality of children with a congenital heart disease and better recognition of this rhythm. [1] In our evaluation there is a non-significant trend (at the 5% level of significance) towards a higher incidence of VT/VF from 2002-2013. VT/VF was mainly related to cardiac disease (86%), either primary arrhythmia (41%) or cardiomyopathy (29%). In addition, a non-significant trend towards a higher survival was seen in patients with VT/VF, most likely due to early

basic life support provided by lay persons, better availability of automated external defibrillators, and improved intensive care treatment.

Since the population of children with CA may be slowly changing, this may have consequences for the long-term outcome after CA and the outcome-based decisions. As Namachivayam et al. states: "*The increasing number of survivors from pediatric intensive care who have a moderate or severe long-term disability has major emotional, practical, and financial implications for the individual and the family, and has important resource implications for the whole community.*". [1] It is therefore important to learn more about the long-term health status and HR-QoL, emotional and behavioral functioning, and neuropsychological functioning, and its predictors, of children surviving CA or another critical illness (e.g., meningococcal septic shock). This consideration formed the rationale for the studies described in this thesis.

"What is my child's outcome after cardiac arrest?" A simple question with a complex answer

A. Mortality; when?

The increasing attention for outcome after CA has also resulted in the formulation of guidelines for uniformity in reporting outcome after resuscitation in children in 1995, which were updated and simplified in 2004. [7] These guidelines have already stressed the importance of uniformity in reporting outcome after CA in children. The most important outcome measure after CA is mortality. Mortality can be measured at different moments. The first assessment moment is the immediate survival of the CA event. The second assessment moment is survival to PICU discharge. The following moments are survival to hospital discharge and in the weeks/months after hospital discharge. Also 30-day or 1-month survival is a commonly used definition. [8, 9]

B. Mortality; numbers and causes

Outcome after CA cannot be generalized with respect to numbers and causes of mortality. For clear understanding of numbers and causes of mortality after CA, several determinants need to be investigated, from different perspectives. Such

determinants are: etiology, rhythm (i.e., shockable and non-shockable), type of CPR (i.e., BLS and APLS), or location of CA (i.e., IH (medium care versus PICU) and OH). There is also a difference between children who died due to failure of CPR and children who survived the CA, but died in following days. In children achieving ROSC, four main categories of mortality after ROSC can be distinguished: 1) withdrawal of life-sustaining treatment, 2) brain death, 3) multi-organ failure, and 4) no ROSC after next event of CA. As shown in the introductory chapter 1, the commonest causes of death after ROSC in our hospital were withdrawal of life-sustaining treatment (41%), brain death (22%), cardiorespiratory failure/multiple-organ failure (19%), no ROSC after a new CA (14%), and underlying disease (4%). [10]

C. Prediction of mortality

Outcome after CA in children is predicted by various medical variables, which can be classified into three different groups: 1) pre-arrest, 2) arrest, and 3) post-arrest. (Table 1)

Table 1. Overview of the medical predictors of mortality

Pre-arrest	Pre-existing medical condition
Arrest	Etiology
	Location (IH-CA/OH-CA)
	(Un)witnessed
	Rhythm (shockable/non-shockable)
	Interval between CA and CPR (e.g., availability of rapid response team)
	Bystander BLS
	Duration and quality of CPR
Post-arrest /	Blood pressure
Post-resuscitation care	Glucose control
	Hypocapnia/hypercapnia
	Hypoxia/hyperoxia
	Hypothermia/hyperthermia

The ultimate goal of post-resuscitation care is cerebral resuscitation aimed at minimizing the cerebral damage. Until now, evidence-based interventions to improve outcomes have had limited success. [11] The Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trial is expected to provide more information on the evidence-based use of hypothermia in children beyond neonatal age. [12]

Oxygen

Oxygen administration is still considered essential in treatment during and after resuscitation. Despite the lack of evidence, current guidelines recommend resuscitating with 100% oxygen and targeting SaO_2 94-98% after ROSC with the aim of avoiding hyperoxia. [13] For decades the role of oxygen has been debated as a potential cellular poison and the evidence for adverse effects of oxygen is accumulating. Oxidative stress and reperfusion promote free-radical generated injury contributing to neurologic injury and cardiac dysfunction, and seem to be associated with increased mortality after CA. [14, 15] Two recent reviews have suggested that hyperoxia exposure is associated with poor outcome in terms of increased mortality. [16, 17] Damiani et al. reported that hyperoxia may be associated with increase mortality in patients with stroke, traumatic brain injury, and CA. [16] Wang et al. reported that hyperoxia appears to be correlated with increased IH mortality. [17] However, both studies conclude that these results must be interpreted cautiously because of the high heterogeneity of the patient samples, the use of different time intervals after CA, and different cutoff levels.

A common key feature of most studies – both in children and adults – is the use of a single cutoff value to describe PaO_2 over different time periods after ROSC. [18-22] (Table 2) However, such cutoff analyses have limited ability to approximate the complex oxygen physiology, since fluctuations of PaO_2 are common, and a dichotomous cutoff value cannot estimate the amount of oxygen and duration.

Table 2. Overview of studies on PaO_2 and outcomes after CA in children

Author	Year	Cutoff values (mmHg)	Hypothermia	Characteristics	Outcome
Castillo *(Resuscitation)*	2012	PaO_2 *(<60 & ≥300)* $PaCO_2$ *(<30 & ≥50)*	No	- 223 children (0 - 18 years) - IH-CA - First PaO_2/$PaCO_2$ after ROSC and at 24 hours - Classification in 3 groups (hypo, normo, hyper) based on first PaO_2	- Hyperoxia: no relationship with mortality - Hypercapnia (OR 3.27; 95%CI 1.62 - 6.61) and hypocapnia (OR 2.71; 95% CI 1.04 -7.05) associated with higher mortality
Ferguson *(Circulation)*	2012	PaO_2 *(<60 & ≥300)*	No	- 1875 children (<16 years) - IH-CA & OH-CA - First PaO_2 within 1 hour after ROSC - Classification in 3 groups (hypo, normo, hyper) based on first PaO_2	Hypoxia (OR 1.9; 95% CI 1.8 -2.2) and hyperoxia (OR 1,3; 95% CI 1.2 - 1.4) increase the risk on mortality
Bennett *(Critical Care Medicine)*	2013	PaO_2 *(<50 & ≥200)* $PaCO_2$ *(<30 & >50)*	No	- 195 children (0 - 18 years) - IH-CA & OH-CA - Lowest/highest PaO_2 within 6 hours after ROSC - Classification in 4 groups (hypo, normo, hyper, hyper & hypo) based on PaO2 first 6 hour	No relationship with mortality
Guerra-Wallace *(Pediatric Critical Care Medicine)*	2013	PaO_2 *(<60 & >200/>300)*	No	- 74 children (0 – 18 years) - IH-CA & OH-CA - Lowest/highest PaO_2 within 24 hours after ROSC - Used the exact PaO_2 values	No relationship with mortality in first 6 months

Instead of using a single value above a previously set cutoff, we used the cumulative PaO_2 during the first 24 hours after ROSC. [10] (see Chapter 2) The cumulative PaO_2 was calculated with a new, simple method in PaO_2 analysis: the area under the curve (AUC), based on *at least* 4 measurements in at least 12 hours. The cumulative PaO_2 can be legitimately measured with the trapezoidal AUC method. [23] This method is commonly used in pharmacokinetic research to measure total drug exposure and has also been used in other medical fields, for instance in metabolic research and pulmonary research. Although PaO_2 can vary quite markedly and in a matter of minutes, our method (Chapter 2) is superior to the previously used cutoff, as the time course of PaO_2 is taken into account. [11] In our study, patients with mild therapeutic hypothermia (MTH) and higher cumulative PaO_2 had a lower IH mortality rate. (Chapter 2) With the cumulative PaO_2 measurement, we could not reproduce the relationship between higher PaO_2 and IH mortality in children after CA as found in various other studies using the cutoff values.

Several theories can explain our findings. One important new theory suggests there is a therapeutic window for oxygen. [24] A scheme was constructed, based on physiological principles, in which there is an optimal therapeutic oxygenation range. An alternative explanation can be the impairments in microcirculatory function. Buijs et al. have found that MTH causes abnormalities in microcirculation and peripheral tissue perfusion. [25] They found that microcirculation was impaired during MTH and more severely impaired at start of MTH in non-survivors. Despite potential impairments in microcirculatory function during MTH, increased amounts of dissolved oxygen could have maintained oxygen supply to the organs in the patients in our study. However, as microcirculatory function in the brain has not been studied, it is unknown whether the results of Buijs et al. can be translated to the brain as well.

The synergistic effect of hypothermia and hyperoxia can provide another explanation. While hypothermia attenuates oxidative stress after TBI in children [26], hyperoxia improves organ function and attenuates both tissue apoptosis and oxidative stress, at least during early septic shock. [27] Even anti-inflammatory effects of hyperoxia have been reported. [28]

As stressed by Martin et al. the aim should be to avoid the harms associated with excessive and inadequate oxygenation. [24] However, the balance between hypoxia

and hyperoxia is unknown; for example, there is no clinical evidence for permissive hypoxia, a method to minimize the possible harms caused by restoration of normoxia while avoiding tissue hypoxia. This balance is most probably dependent on a combination of patient characteristics, disease characteristics, timing, and treatment (e.g., hypothermia).

Future research should focus on prospective data collection in large multicenter networks. We should focus on the optimization of oxygen therapy, not only for CA-patients, but for critically ill children in general. The balance between hypoxia and hyperoxia should not be studied in relation to duration of mechanical ventilation, PICU mortality and short term outcome only, but also considering long-term medical and (neuro)psychological outcome . Oxygen supplementation is still the most used therapy in critically ill children worldwide, but much is still unknown about the effects of oxygen at the cellular level in different organs. [29] A first step is an observational study with standardized PaO_2 and $PaCO_2$ measurements using a standard interval. In addition, the relation between arterial PaO_2 and $PaCO_2$, saturation and transcutaneous PO_2 and PCO_2 should be studied, to make less-invasive transcutaneous measurement of PO_2 and PCO_2 feasible. The second step will be an intervention study in which goal directed therapy with saturation and PO_2 within a lower range (e.g., target SaO_2 of 90-92% with the lowest FiO_2%, "conservative" oxygen therapy) will be compared with standard of care ("conventional" oxygen therapy) in mechanically ventilated PICU patients. [30] As the measurement of the intracellular oxygen tension is the ultimate goal, non-invasive strategies to monitor of the mitochondrial function have to be explored. [31]

D. Prognostication of CA; mortality, short-term and long-term outcome

Prognostication after CA is one of the most challenging tasks that intensivists have to face. A good estimation of the chances of survival and the impact of the hypoxic-ischemic injury of the brain on the physical and (neuro)psychological outcome, both short-term and long-term, is essential to deliver good quality care for child and parents. [32] A multimodal prognostication model for children is not yet available, and recently multimodal prognostication models for adults have been proposed. [33] Variables proposed in the literature to predict outcome are listed in Table 3.

Table 3. Overview of variables for prognostication

Pre-arrest condition	Age Gender Pre-existing medical condition Socio-economic status
Arrest characteristics	See Table 1
Post-Resuscitation Care	See Table 1
Diagnostics in the post-arrest phase *	Clinical neurological examination Electroencephalography (EEG) Somatosensory evoked potentials (SSEPs) Biomarkers (e.g., serum neurone-specific enolase, serum astroglial protein S-100, creatine kinase isoenzyme, neurofilament light protein, protein tau, inflammatory protein YKL-40, amyloid beta) Neuroimaging

* Timing of the diagnostics in the post-arrest phase could also be crucial.

Long-term outcome after cardiac arrest

The main focus of this thesis was the long-term follow-up of children who had a CA and were admitted to the ICU of the Erasmus MC-Sophia Children's Hospital between January 2002 and December 2011. Of the eligible 107 children, 57 (53%) filled out online questionnaires, and 47 (43%) of them also visited the outpatient clinic.

At long-term follow-up, at least 2 years after PICU discharge, participants were between 2-18 years of age. A broad range of medical and (neuro)psychological outcome variables was investigated in this relatively large patient sample using standardized assessment procedures. Long-term health status, health-related quality of life (HR-QoL), emotional and behavioral functioning, and neuropsychological functioning are described in this thesis. (see Chapters 3, 4, 5)

First of all, this long-term outcome study encompasses long-term mortality: i.e., what was the survival of CA after discharge form the PICU? Of the 145 initial survivors to hospital discharge (31%), 13 died (9%; 9 children within 1 year of discharge). Causes of death were another CA without ROSC (n=3), underlying disease (n=2), severe cerebral damage (n=1), or unknown (n=7). In a retrospective cohort study, Michiels et al. showed that even after 10 years of follow-up a proportion of children died: survival after hospital discharge was 92% at 1 year,

86% at 5 years, and 77% at 20 years. Causes of death were primarily anoxic brain damage (33%) and sequelae due to accidents (33%). [34] However these sequelae are not further specified, which makes interpretation difficult. Furthermore, in the study by Michiels et al., the survivors to discharge with a poor outcome on the Pediatric Cerebral Performance Category score had a five-fold higher risk of subsequent death than those with a favorable PCPC.

Health status and health-related quality of life

Health status

Thirteen percent of the CA survivors in the present study had long-term neurological deficits after CA. (Chapter 3) This proportion is in line with findings from previous studies describing long-term outcome in very general terms, reporting that 60-85% of the CA survivors had a favorable PCPC score of 1 or 2, or no change from pre-arrest score at hospital discharge, dependent on CA location. [34-37] However, the PCPC score measures overall functional morbidity and cognitive impairment only in a very limited way.

Thirty percent still needed follow-up care by a rehabilitation physician, physiotherapist, speech therapist and/or occupational therapist for physical impairments developing after the CA.

Chronic symptoms with onset after the CA were reported for 34%. These symptoms included, fatigue, headache, and abdominal pain, all ranging from mild to severe. While severe impairments are usually adequately recognized, milder forms of physical problems may receive less attention in school and social environments or even be denied by child or parents. However, also these milder problems deserve attention, as the child's capacities may be overestimated, and chronic symptoms (i.e., fatigue, stress, tension headache, or other physical or (neuro)psychological complaints) may develop. [38]

In the general Dutch population, 5% of children in the age-range 4-14 years follow special education. [39] In our population, this percentage was significantly higher, i.e., 15% ($p<0.008$). It must be noted, however, that the age-range in our study was not the same as that in the Dutch normative sample. On the other hand, our results are more favorable than the results of Suominen et al. to the effect that 52%

of children with CPR after a drowning incident had received special education. [40] However, as they studied only a subgroup of CA patients, these results are not comparable. With regard to other groups of critically ill children, 10% of survivors of meningococcal septic shock were found to receive special education as well as 9% of children treated with neonatal extracorporeal membrane oxygenation (ECMO). [41, 42] This seems to indicate that not only CA survivors, but critically ill children in general have a higher need for special education.

Nineteen percent of our population had at least one sign of chronic kidney disease (CKD) and/or hypertension. Acute tubular necrosis can develop following an ischemic attack to the kidneys, and reduces the number of functioning nephrons. While a child grows in height and weight, the demand for clearance may exceed the number of nephrons, and loss of renal function may follow. Long-term follow-up of kidney function in children after ECMO has shown that 32% has at least one sign of CKD and/or hypertension. [43] The authors recommended screening for CKD development in early adulthood . In summary, long-term renal functioning after CA in childhood is also an area of concern, which needs further attention, both in research and clinical practice. Additional screening of renal function during follow-up in childhood is recommended.

Subjective health status and HR-QoL

Intensive care treatment aims to reduce mortality and morbidity, and to conserve health status and functional capacity. Traditionally, outcome research has focused on mortality and health status in terms of objective, physical measurements. It has become increasingly clear that improved long-term survival after critical illness may result in long-term morbidity, which is associated with impaired HR-QoL. [44] Thus, HR-QoL also has become a key outcome. The subjective nature of HR-QoL is not a shortcoming, but an essential component of it. However, we should also measure HR-QoL directly from the perspective of the patient. Routine collection of patient reported outcomes (PROMS) is therefore regarded essential nowadays. [45]

Sometimes the terms health status and HR-QoL seem to be used as equivalents. [44] They are not equivalent, however, because health status refers to assessment of the patient's actual, more objective problems and limitations in functioning, whereas HR-QoL includes the person's subjective, emotional evaluation and reaction to such problems and limitations. Until now, long-term health status and

HR-QoL have not been thoroughly investigated in CA survivors. [40, 46, 47] Therefore an important aim of this thesis was to study these outcome measures using validated questionnaires. (see Chapter 3)

Compared with Dutch normative data, parents of CA survivors reported significantly worse HR-QoL outcomes regarding their child as to general health perception, physical role functioning, parental impact, and overall physical summary. In a study of Suominen et al., children and adolescents who were resuscitated after drowning also reported a significant loss in HR-QoL, compared to normative data of the general population. In addition, they scored significantly lower on the dimensions vitality and usual activities. [40] In line with our study, Buysse et al., using the same questionnaire as in our study, found that parents of survivors of meningococcal septic shock reported worse HR-QoL scores regarding the children. [48] In addition, parents reported significantly worse HR-QoL outcomes for the children regarding general health perception, physical role functioning, overall physical summary, and also on self-esteem and role-emotional/behavioral functioning. The findings above indicate that outcome after critical illness seems to be related with a worse HR-QoL, especially on the physical domains.

Self-reported HR-QoL of the adolescent survivors of CA in our study was not significantly different from normative data. (Chapter 3) Perhaps this is explained by the small number of adolescents completing the HR-QoL questionnaire, denial of impairments, or the inability of adolescents with physical or mental impairments to fill out questionnaire themselves. For that matter, the parents' questionnaires were filled out by parents of children with and children without physical and mental impairments.

Parents reported better family cohesion and better HR-QoL for themselves on most scales. While the impact of a CA and PICU stay is known to be overwhelming, parents' long-term HR-QoL scores regarding themselves were surprisingly more favorable than normative data. [49-52] Similar results were found in the long-term follow-up of parents of children with a meningococcal septic shock and with a congenital heart disease. [48, 53] This phenomenon can be explained by concepts such as 'response shift' or 'posttraumatic growth'. "Response shift encompasses the change of the internal standards and values after a life-threatening or traumatic event". [54] In other words, parents may put their own problems into another perspective when comparing these with those of their child. Posttraumatic

growth reflects the experience of positive change, due to struggle with highly challenging life crises. [55] After their child's CA, parents may worry less about futilities in life. However, our favorable results could also have been influenced by social desirability, denial, or overcompensation. These phenomena have also been described in parents of children surviving surgery for congenital heart disease. [53]

In this thesis the generic health status was also assessed with the Health Utility Index (HUI). On most utility scores and the overall HUI3 score, parents reported poorer health status of their child. Long-term impairments on most HUI scales have also been reported in children after meningococcal septic shock. [56] The HUI is suitable for assessment by proxies as it has shown to have a very good inter-rater reliability and a very good parent-child agreement. [57, 58] In addition, it can be used for early identification of changes in HR-QoL, as it has proven sensitivity to change. [58] In this way, rehabilitation can be started as soon as possible if any impairments or disabilities are reported.

Emotional and behavioral functioning

Parents and teachers of CA survivors reported significantly more long-term attention problems and somatic complaints for the children in the study, compared to normative data. (Chapter 4) Parents' reports often seemed to indicate problem behavior within the psychopathological range when compared with the general population. In contrast, more problem behavior was not apparent from the teachers' and CA-survivors self-reports. Our findings are in line with a study in children treated with neonatal ECMO, in which also a significantly higher proportion of total problems within the psychopathological range was found [42] and a study in children with congenital heart disease, which also found that the proportion of children scoring in the psychopathological range was significantly higher than the norm. [59]

For a broad age-range, parents and teachers reported significantly more attention problems, mainly of the inattentional type as reflected in the teacher-reports. Morris et al., however, reported more hyperactivity related problems. [60] There are only few long-term outcome studies on attentional problems in critically ill children. Long-term overall attention problems, both of the inattention and hyperactivity type, have been reported for children with a congenital heart disease 5 to 10 years after cardiac surgery. [59, 61] Long-term follow-up of children

with neonatal encephalopathy showed significantly more attention problems, or increased risk of attention deficit/hyperactivity disorder-related diagnoses at school age, compared with normative data. [42, 62, 63] As described by Marlow et al. in children without physical disabilities, hyperactivity and inattention were found to co-exist seven years after severe neonatal hypoxic encephalopathy. [64] Inattentional problems could be an expression of sustained attention problems. Sustained attention is related to multiple areas in the brain, e.g., frontal lobe, prefrontal region, subcortical region and the parietal lobe. As sustained attention is one of the basic functions of the brain, damage to the brain could lead to the failure of this function. Thus, these outcomes also suggest more neuropsychological problems. Unfortunately, no magnetic resonance imaging was performed at follow-up. This could have given more insight into CA-related brain damage and the findings presented in our study.

Elevated levels on the subscale Somatic complaints were reported by parents and teachers for 6-18-year-old children. The results on this subscale are supported by our findings regarding health status, i.e., chronic symptoms in 34% of children and follow-up care for physical problems in 30%. It is unknown whether these somatic complaints were also found by Morris et al. [60] In other groups of critically ill children, such as children after neonatal ECMO, after meningococcal septic shock, or after invasive treatment for congenital heart disease, long-term somatic complaints (parent- or self-reported) are well-known. [42, 59, 65]

Neuropsychology

Regarding intellectual functioning, CA survivors scored significantly worse on full-scale IQ, verbal IQ, performance IQ, verbal comprehension index, perceptual organization index, and processing speed index, than the norm population. (see Chapter 5) Previous research shows that, in general, intellectual outcome is highly dependent on the age at which brain injury was acquired. Brain injury acquired at an older age results in more specific deficits in cognitive function, rather than the diffuse deficits observed in young children. [93] According to the vulnerability theory, children with acquired brain injury at a young age have to learn new skills with impaired basal functions. This has a more dramatic effect at a young age, and moreover long-lasting effects on intelligence. [66, 67] Our results regarding health status also showed neurological deficits (in 13%), and, moreover, significantly more

children surviving CA needed special education (15%) than the general Dutch population. Our findings regarding impaired intellectual functioning are in line with those of Morris et al., who also reported intellectual deficits in CA survivors (aged 2- 15 years). [60] Impaired intellectual functioning could have influenced our findings on self-reported HR-QoL. Children with impaired cognitive functioning did not fill-out the HR-QOL questionnaires, and, moreover, limited self-insight may have resulted in a too positive impression.

After adjustment for their intellectual functioning, CA survivors scored significantly worse regarding visual memory, but significantly better on verbal memory (recognition). Furthermore, no significant differences compared to normative data were found on visual-motor integration, attention, other measures of verbal memory and executive functioning. So far, long-term neuropsychological outcome in survivors of CA during childhood has been assessed only in subgroups of CA patients, i.e., congenital heart disease or drownings. Those studies showed impairments in verbal and/or visual memory, visual-perceptual-motor functioning, and executive functions, in addition to intellectual deficits. [60, 68] Overall, white matter injury (more specifically periventricular leukomalacia) might also explain these cognitive deficits, as white matter injury is believed to arise from several factors including ischemia to the watershed areas. [69] The integrity of the white matter is correlated with full scale IQ and performance IQ, and not with verbal IQ. This might also be an important explanation for our findings on intellectual functioning and memory. [70] And in this perspective, the outcomes regarding cognition on the HUI cognition scales and multi-attribute score could also be associated with white matter injury.

Our study showed a discrepancy between visual and verbal information processing on the intelligence profile. This discrepancy was also found on neuropsychological tests assessing memory, since we found problems on visual memory (Rey), but a relatively strong verbal memory (RAVLT recognition). The verbal functioning of CA survivors in our study appears to be relatively better than their visual functioning. This is supported by our results on other verbal tasks (i.e., PPVT and TEA-Ch attentional switching, which are both verbal tasks). The pitfall of relatively good verbal functioning is that parents may tend to overestimate the child's abilities. Considering that parents mainly give verbal instructions to their children, this

tendency could also explain the better results on parent-reported executive functions. Due to the problems in the visual processing domain, children may not be able to function on a normal level in school. Since school tasks consist of both visual-spatial and verbal orientated tasks, impairments can be expected to be noticed at school. This was reflected by the lower executive functioning reported by teachers. Since the verbal functions of the CA survivors have been relatively preserved, clear verbal instructions at school may help these children in completing visual-spatial orientated tasks, thus improving their academic achievements. In line with the findings on the intelligence and neuropsychological tests, parents reported problems in cognitive functioning as reflected by the lower scores on the HUI cognition scales.

Despite the attention problems reported by parents and teachers on questionnaires assessing emotional and behavioral functioning, no significant differences with normative data were found on neuropsychological tests assessing attention, as we would have expected. As attention and executive functions are interrelated, and mature during adolescence, more problems might be expected when these CA survivors grow older. This phenomenon is called the "growing into deficit" phenomenon, reflecting that problems may become more salient at an older age, when more complex tasks are required.

The parent-reported executive functions for CA survivors on the BRIEF questionnaire were significantly better than the norm. This is in contrast to the negative results found in patients with traumatic brain injury or patients after neonatal encephalopathy. [64, 71] As stated above, the relatively favorable verbal functioning of the CA survivors may contribute to the positive outcomes on parent-reported executive functioning. In addition, "response shift" may (partially) explain these outcomes. After the often traumatic CA of their child, parents could have expected a worse outcome and may have other internal standards now for evaluating their child's functioning.

In contrast to parents, teachers reported favorable scores on inhibition only. Moreover, teachers reported impairments of the planning/organizing skills. This supports our previous statement, i.e., that problems in neuropsychological domains can be expected to be noticed at school.

The watershed areas in the brain are particularly vulnerable to effects of

hypoperfusion and hypoxia resulting in cognitive deficits and prefrontal lesions. [72] Damage to the prefrontal region can result in deficits in executive functions, information processing and attention. The favorable results on teacher-reports regarding inhibition and the impairments on planning/organizing could be a reflection of a dorsolateral prefrontal syndrome. This syndrome is characterized by lack of initiative, personality changes, blunted affect, or problems with executive functions. Children with a lack of initiative are more dependent on external stimulation, whereas rapid emotional changes and high distractibility are less common in these children. This might be an explanation why attention problems of the inattentive type were found on the emotional and behavioral questionnaires. The favorable findings on parents' questionnaires regarding children's executive functions are in contrast to outcomes on actual neuropsychological testing, since on the TMT and STROOP lower outcomes were found compared to normative data. As reported by McAuley et al., the BRIEF questionnaire may not measure the executive functions to the extent as commonly believed. [73] A recent study by Cassidy et al. in children with critical cyanotic congenital heart disease supports this statement. In this study also significant impairments on neuropsychological testing were found, whereas the results on the BRIEF were average. [74] This indicates that actual standardized neuropsychological testing is needed to get a complete picture of impairments, since respondents give subjective answers on questionnaires. In addition, imaging of the brain would give good insight into the relationship of neuropsychological deficits and structural brain damage.

Predictors of long-term outcome after CA

In this section, several hypothesis-generating findings regarding prediction of long-term outcome on health status, HR-QOL, emotional, behavioral and neuropsychological function will be discussed.

The univariate analyses performed in this thesis regarding putative predictors of long-term outcome after CA were limited by the small number of children. Therefore, we should be careful of drawing firm conclusions. The significant predictors identified were: age, gender, socio-economic status, pre-existing medical condition, location (in or out-of-hospital CA) and type of CPR (BLS/APLS). (Chapters 3, 4, 5)

- ***Age:*** age predicted several outcomes regarding emotional and behavioral problems and on neuropsychological domains. On the questionnaires assessing *emotional and behavioral problems*, older age at PICU admission predicted significantly more externalizing problems and total problems for children in the age-range 1.5-5 years. During this non-verbal age-range children may work through traumatic experiences by, e.g., acting out through more externalizing behavior (screaming, shouting). The median age of our CA survivors at follow-up was relatively young, namely 4.9 months. Therefore, more problems on higher cognitive functions, such as executive functioning (also including emotional regulation) may emerge later in life, as these functions mature in adolescence ("growing into deficits" phenomenon). Furthermore, older age at PICU admission was significantly associated with worse outcome on *verbal functioning*. Older age at follow-up was significantly associated with worse outcome on visual-motor-integration and verbal functioning. As these neuropsychological functions (e.g., verbal functioning) develop early in life, impairments in these functions at a younger age will harm adequate development of later neuropsychological functions (vulnerability theory). Anderson et al. found that younger age at time of traumatic brain injury was related to a lower white matter volume. [67] Considering these outcomes and later school perspectives of these children, it is important to keep in mind that increasing deficits may emerge later in life, when functions are expected to mature.
- ***Gender****:* gender predicted several outcomes on the *HUI scales* and on the instruments assessing *emotional, behavioral and neuropsychological problems*. Boys scored significantly worse on the HUI cognition scales and multi-attribute score. Regarding emotional and behavioral functioning, boys in the age-range 1.5-5 years showed significantly more internalizing, externalizing and total problems than girls in this age-range. The pattern that boys show more problems on externalizing problems is well-known in the general community. [94]

  Boys surviving CA scored also worse than girls on *performance IQ, visual-motor integration, selective attention, cognitive shifting and inhibition*. Overall, it is to be expected that boys are at elevated risk for worse (neuro)psychological functioning considering the anatomical differences between the male and female brain. The right hemisphere of males is bigger and contains more

white matter than the right hemisphere of females. Since impairments were found on visual orientated tasks, which are functions more related to the right hemisphere, our results support the hypothesis of white matter injury.

- ***Socio-economic status***: our results showed that regarding HR-QOL, parents with a high socio-economic status (SES) showed a better social functioning. As shown by Anderson et al. in children with traumatic brain injury, SES is an important predictor of outcome. [67] The finding of better social functioning may be explained by the enriched facilities of parents with a high SES (intellectual, financial and practical facilities) to cope with the outcome of their child's CA.
- ***Pre-existing medical condition*** was related to several *HR-QoL outcomes and a neuropsychological outcome* (attentional switching).
  Pre-existing medical condition was related to the HR-QoL subscales: general health perception, and physical summary. In contrast, pre-existing medical condition was not associated with emotional and behavioral functioning as assessed by the CBCL. However, the items on the CBCL subscale Somatic complaints are somewhat different from those on the HR-QoL scales, since they assess physical complaints *without* known medical cause. On this subscale, more parent-reported somatic complaints were found than in the norm. This is in line with our findings on the health status, since 34% of children had chronic symptoms, such as headache, fatigue and abdominal pain. These complaints are also assessed by the subscale Somatic complaints. Moreover, pre-existing medical condition was associated with the neuropsychological outcome on attentional switching. As suggested by Bloom et al. regarding patients with congenital heart disease, functioning after CA may be mediated by the child's overall disease severity. [75] At long-term follow-up of children with congenital heart disease and children after ECMO, attentional problems were found as well. [42, 69]
  Considering these findings, we believe that there is a more complex relationship between pre-existing diseases and the outcome after CA and critical illness in general.
- ***Location of cardiac arrest:*** Our results showed that parents of out-of-hospital resuscitated children reported long-term limitations in their own physical activities.

- ***Type of CPR (BLS/APLS):*** Regarding health status, treatment with only BLS was significantly related to the presence of chronic symptoms. As BLS is considered to have less impact than APLS, its impact on the child's health might be underestimated. Sanghavi et al. suggested that adult patients who received BLS might have more pre-existing comorbidities than adult patients who received APLS, and thus worse physical/psychological, functioning at time of CA. [76] In our study, however, no relationship between BLS and pre-existing medical condition was found ($p>0.05$).
  Surprisingly, as to emotional/behavioral functioning, children who received BLS had significantly more internalizing, externalizing, and total problems. Similarly, as described above regarding the relationship between BLS and the presence of chronic symptoms (health status), there might also be less attention for the impact of BLS (compared to APLS) on the child's emotional and behavioral functioning.

Analgesics and sedatives during PICU admission as predictors of long-term outcome of critical illness in childhood

Importantly, treatment at the PICU per se can also have an important influence on long-term outcome. However, further putative predictors of long-term outcome, such as treatment at the PICU, specifically use of analgesics and sedatives, was not investigated in our CA-sample. (Chapter 6)

In another sample of critical ill children (i.e., survivors of meningococcal septic shock) several medical and psychological domains were found to be affected, including neuropsychological functioning, notably verbal comprehension, visual-motor integration, attention and executive functioning. [41, 56, 77-79]

Surprisingly, severity of illness was not a significant predictor of poorer long-term neuropsychological functioning. The use of a variety of analgesics and sedatives was found associated with adverse cognitive development in young rodents, in the presence of widespread neurodegeneration due to neuronal cell death. [80-85] However, the data in animals were conflicting. And what is more, as in many animal experiments the dosages of drugs were abnormally high, it is debatable whether they have any relationship with the consequences in humans. The few studies on the influence of analgesics and sedatives on neurodevelopmental outcome in

children showed contradictory results. Garcia Guerra et al. found that perioperative sedation or analgesia were not associated with adverse neurodevelopmental outcome two years after cardiac surgery before the age of 7 weeks. [86] However, future research is needed to further investigate the influence of perioperative sedation or analgesia on neuropsychological outcomes in children who underwent cardiac surgery for a congenital heart defect, since the type of the cardiac defect was related to outcome. [87] E.g., children with hypoplastic left heart syndrome are known to have poorer intellectual functioning. [87] De Graaf et al. found a significant relation in 5-year-old children who as preterm neonates on mechanical ventilation had received morphine. Their overall intelligence quotient was lower, but this effect had disappeared 3 to 4 years later. [88, 89] Currently the influence of analgesics and sedatives on neurodevelopmental outcome in critically ill children is not known.

Therefore, we performed a secondary analysis of the long-term outcomes in 77 survivors of meningococcal septic shock during childhood, admitted to our PICU in 1998-2001. (see chapter 6) Analgesia and sedation during PICU stay appeared to be significant predictors of long-term neuropsychological outcomes (at least 4 years after PICU admission). Multivariate analyses showed that the use and dose of opioids were significantly associated with poor long-term test outcome on full scale intelligence, verbal intelligence, verbal intelligence subtests vocabulary and verbal comprehension, and visual attention/executive functioning.

Differences between findings from our study and other studies (mainly in preterm infants) may be explained by the type of illness, pain related to purpuric skin wounds, the related sequelae (e.g., orthopedic and neurologic), and age at time of illness. The inflammatory response in critically ill children may change pharmacokinetics. [90] The release of proinflammatory cytokines seems to down-regulate the expression of drug metabolizing enzymes and drug transporters.

Although an influence of benzodiazepines was expected, the use of benzodiazepines was not associated with long-term neuropsychological outcome in our sample of meningococcal septic shock survivors. Similarly, a review study by Loepke et al. found only transient neurological impairments and no long-term effects of the use of benzodiazepines. [82]

Knowledge of drug effects is important to minimize the risk of any unintended

harm. However, we must take care not to interpret the results of our study as a rationale to withhold or underutilize opioids or other sedatives and analgesics for critically ill children requiring life sustaining technological support. [91] If our findings should be confirmed in larger prospective studies, this would provide additional support for interventions avoiding excessive use of analgesics and sedatives and for modification of pain management regimens. [91, 92]

Clinical implications

This thesis provides an overview of the long-term health status, health-related quality of life (HR-QoL), emotional, behavioral, and neuropsychological outcome of CA in childhood. This information can be used to guide adequate counseling following the initial crisis. This thesis provides several clinical implications:

- As the overall outcome of CA survivors is reasonably good, this should have implications for the prognostications and end-of-life decisions following CA.
- There is room for improvement with respect to resuscitations and post-resuscitation care. Our studies on oxygen-treatment following CA and the influence of analgesia and sedation on neuropsychological outcome in meningococcal septic shock survivors concluded that many aspects deserve future research.
- In spite of the reasonably good overall outcome of CA survivors, the critical illness had nevertheless a significant negative impact on their long-term physical and (neuro)psychological functioning. Early diagnosis and treatment of impairments could reduce negative consequences. Follow-up by a multidisciplinary team, including a pediatric intensivist, neurologist, physiotherapist and psychologist, should therefore be organized as standard of care in the Netherlands. The follow-up program should provide fixed moments of assessment with multiple tools for a comprehensive evaluation of physical and (neuro)psychological outcome. Brain imaging should be an essential part of such a follow-up program. In the Erasmus MC – Sophia Children's hospital a structured multidisciplinary follow-up program for children with congenital anatomical malformations and children treated with ECMO became standard of care in 1999, for meningococcal septic shock survivors in 2008, and for survivors of CA and severe traumatic brain injury in 2012. The Dutch Pediatric Association (Dutch: Nederlandse Vereniging voor

Kindergeneeskunde; (NVK)) is currently working on a national guideline for follow-up after critical illness, which is expected to be released at the end of 2016.

- In addition, structured information regarding long-term medical and (neuro) psychological outcome should be provided, by means of a brochure or website, not only aimed at parents and patients, but also at healthcare workers.
- The child's health status (severity of co-morbidities) and (neuro)psychological functioning prior to the CA should be taken into account as well, including school results (in the Netherlands for example: *CITO toets*). We advise to organize the collection of this data at PICU discharge or hospital discharge, as at that time parents are probably less stressed than at PICU admission. It is essential to obtain this information from teachers as well.

Future directions

More research should be done to replicate our findings on long-term medical and (neuro)psychological outcome after CA and critical illness in general.

The following aspects should be studied:

1) Health status before CA (premorbid "baseline" assessment), both physical and (neuro)psychological. As this is subject to recall bias, timing to obtain this information is important.
2) Standardized prospective collection of CA-related data. (see Table 1)
3) Standardized prospective collection of post-resuscitation care-related data (see Table 3), to investigate putative predictor variables such as PO_2 and $PaCO_2$.
4) A standardized protocol for prognostication after CA. (see Table 3) This should contain multimodal (neuro)monitoring and diagnostics, including MRI to detect and locate areas in the brain where damage may have occurred.
5) Standardized prospective collection of medical and (neuro)psychological outcome data. This should be the concern of all PICUs, not only nationwide. Large organizations, such as the European Society of Paediatric and Neonatal Intensive Care (ESPNIC), should take the lead in setting up an

outcome project (e.g., mortality, outcome at 3 and 12 months measured with general instruments, such as the PCPC score).

6) Intervention studies with physical and cognitive rehabilitation during PICU admission, at the ward and after hospital discharge.

Conclusion

While it is important to be able to predict the likelihood of survival in critical illness, the long-term medical and (neuro)psychological outcome is of paramount interest. Evaluating long-term outcome can improve the provided care with fewer complications. Furthermore, information on the expected long-term medical and (neuro)psychological outcome should be shared with parents, teachers and other healthcare providers. The majority of patients in most PICUs are less than five years old, thus experience critical illness during crucial periods of development. Early diagnosis and treatment of impairments could reduce short and long-term impairments in functioning, as the crucial periods for the development of certain essential skills are short. Children with impairments should benefit from these periods, especially regarding neuropsychological outcomes, in which early interventions should focus on intelligence, visual memory and executive functions.

Further, we recommend standardized prospective collection of critical illness data in children in large multicenter international networks. Outcome measures, both from a medical and (neuro)psychological perspective, are important for benchmarking of PICU practice.

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Summary

Summary

The aim of this thesis was to investigate the long-term outcome of critically ill children admitted to the pediatric intensive care unit (PICU) of the Erasmus MC – Sophia Children's' Hospital in Rotterdam, the Netherlands. Our main focus was to investigate the long-term health status, health-related quality of life (HR-QoL), emotional and behavioral functioning, and neuropsychological functioning in survivors of cardiac arrest (CA) in childhood. This included a semi-structured interview, physical and neuropsychological examination, and the use of validated, internationally well-known questionnaires with a multi-informant approach. Further, the influence of medical predictor variables, such as the impact of hyperoxia on mortality after CA, and analgesia-sedation on the long-term neuropsychological outcome after a critical illness (specifically meningococcal septic shock) was examined.

In the study described in **chapter 2** we analyzed the relationship between the partial pressure of arterial oxygen (PaO_2) and in-hospital (IH) mortality in children after CA. We compared the conventional cut-off analysis, with the cumulative analysis, a new method in PaO_2 analysis.

The innovative aspect of this study is that it uses a novel and simple method (area under the curve) to analyze this cumulative PaO_2. We found that patients with mild therapeutic hypothermia (MTH) and higher cumulative PaO_2 had a lower mortality rate. With the cumulative PaO_2 measurement, we could not reproduce the relationship between higher PaO_2 and IH-mortality in children after CA as found in various cut-off studies.

In **chapter 3** we provided a detailed overview of the long-term health status and health-related quality of life (HR-QoL) in survivors of CA in childhood and their parents. After the initial survival another 9% died following PICU discharge. A minority of CA survivors showed long-term neurological impairments, chronic symptoms, and renal impairments. On health status and HR-QoL, parent-reports of CA survivors showed significantly worse outcomes on physical scales and parental impact compared to normative data. On self-reports no significant differences with normative data were found. Surprisingly, parents reported better scores towards their own functioning. Patients' health status, general health perceptions and physical summary scores were significantly associated with CA-related pre-existing condition.

In **chapter 4** the results of the long-term emotional and behavioral functioning of CA survivors are presented. Compared to normative data, CA survivors showed significantly more long-term attention problems and somatic complaints, on parents' and teachers' reports. On self-reports, significantly less social problems were found. According to parents, children showed more often psychopathological problem behavior. Remarkably, less social problems (self-reports) and no higher levels on anxiety, depression or posttraumatic stress problems were found. Boys, older children, and basic life support were significantly related to worse scores on the scales Internalizing problems, Externalizing problems, Total problems, and subscale Attention problems.

In **chapter 5** we described the long-term neuropsychological outcomes in children surviving cardiac arrest (CA). CA survivors scored significantly worse on intelligence. On neuropsychological tests, compared with norms, respectively adjusted for IQ, significantly worse scores were found on visual memory, significantly better on verbal memory recognition, and comparable outcomes on visual-motor integration, attention, and executive functioning. On questionnaires, parents reported better executive functioning, but teachers reported more problems in planning/organizing skills. Boys and older age at time of cardiac arrest were significantly related with worse neuropsychological functioning.

The study presented in **chapter 6** investigates the association between analgesic and sedative drug use during PICU treatment and long-term neuropsychological outcome in children who survived meningococcal septic shock. The use and dose of opioids were significantly associated with poor outcome on full-scale IQ, verbal IQ and verbal IQ subtests (verbal comprehension and vocabulary) and visual attention/executive functioning (Trail Making Test B). After adjusting for patient and disease characteristics (in particular severity of illness), the use of opioids remained a significant predictor on most neuropsychological tests. The use and dose of benzodiazepines were not significantly associated with any neuropsychological test.

In **chapter 7** we discussed the findings presented in this thesis, put them into perspective and propose recommendations for future studies.

Samenvatting

Samenvatting

Het doel van dit proefschrift was het onderzoeken van de lange-termijn gevolgen van een levensbedreigende ziekte op de kinderleeftijd. Dit onderzoek is uitgevoerd op de Intensive Care voor Kinderen (ICK) in het Erasmus MC - Sophia in Rotterdam. Ons voornaamste doel was het onderzoeken van de lange-termijn effecten van een reanimatie op de fysieke gezondheid, gezondheid-gerelateerde kwaliteit van leven, emotioneel en gedragsmatig functioneren, en neuropsychologisch functioneren. Dit onderzoek bestond uit een semi-gestructureerd interview, lichamelijk onderzoek en neuropsychologisch onderzoek. Daarnaast werden er internationaal bekende, gevalideerde vragenlijsten gebruikt, waarbij gebruik werd gemaakt van meerdere informanten (ouders, leraren, en het kind zelf). Verder hebben we de invloed van medische variabelen op de uiteindelijke uitkomst onderzocht, zoals bijvoorbeeld de effecten van een teveel aan zuurstof (hyperoxie) op de sterfte na hartstilstand en pijnstilling en sedatie op het lange termijn neuropsychologische functioneren na een levensbedreigende ziekte (m.n. meningokokken septische shock).

In **hoofdstuk 2** hebben we de relatie onderzocht tussen de arteriële partiële druk van zuurstof (PaO_2) en de sterfte in het ziekenhuis bij kinderen na hartstilstand. We hebben de veelgebruikte cutoff analyse (door middel van een grens aangeven of er teveel zuurstof is gegeven of niet) vergeleken met de cumulatieve analyse (de totale hoeveelheid binnen een bepaalde tijdsperiode). Dit is een nieuwe methode voor PaO_2 analyse. Het vernieuwende aspect van dit onderzoek is dat het gebruik maakt van een nieuwe en eenvoudige methode om deze cumulatieve PaO_2 te analyseren. We vonden dat patiënten met milde therapeutische hypothermie (koeling tot 32-34 graden Celcius) en hogere cumulatieve PaO_2 een lagere mortaliteit hadden. Met de cumulatieve PaO_2 analyse was het niet mogelijk om de relatie tussen hogere PaO_2 en sterfte in het ziekenhuis te reproduceren, zoals verschillende cutoff studies hadden geconstateerd.

In **hoofdstuk 3** geven we een gedetailleerd overzicht van de lange-termijn gevolgen voor de fysieke gezondheid en de gezondheid-gerelateerde kwaliteit van leven van overlevenden van een hartstilstand op de kinderleeftijd. Daarnaast hebben we ook gekeken naar de kwaliteit van leven van hun ouders. Negen procent van de kinderen is na ontslag van de ICK overleden. Bij anamnese en lichamelijk onderzoek bleek slechts een minderheid van de kinderen

langdurige neurologische gevolgen, chronische symptomen (zoals moeheid en hoofdpijn) en renale schade te hebben. Op de vragenlijsten over de beleefde gezondheidstoestand en kwaliteit van leven rapporteerden ouders aanmerkelijk slechtere resultaten op de fysieke schalen en impact van de ziekte op ouders, in vergelijking met normatieve gegevens. Op de door het kind zelf beantwoordde vragenlijsten vonden we echter geen verschil met de norm. Verrassend genoeg rapporteerden ouders betere scores over hun eigen dagelijkse functioneren. De medisch voorgeschiedenis was voorspellend voor de huidige fysieke gezondheid, en beleving van de eigen gezondheid van het kind.

Hoofdstuk 4 beschrijft de resultaten van de lange-termijn gevolgen van een reanimatie op het emotioneel en gedragsmatig functioneren. Dit is de eerste studie naar lange-termijn emotionele en gedragsmatige gevolgen van een hartstilstand in een relatief groot cohort kinderen en adolescenten. In vergelijking met normatieve gegevens bleken overlevenden van een hartstilstand aanzienlijk meer langdurige aandachtsproblemen en somatische klachten te hebben in zowel de rapportages van de ouders als van de leraren. Volgens ouders bleken kinderen vaker probleemgedrag te hebben die in de psychopathologische range vallen. Zelfrapportages van de adolescenten lieten aanzienlijk minder sociale problemen zien. Opmerkelijk genoeg werden er geen hogere niveaus van angst, depressie of posttraumatische stress gevonden. Voorspellers van uitkomst waren geslacht, leeftijd en type reanimatie. Jongens, oudere leeftijd bij reanimatie, en basic life support waren voorspellers van significant meer aandachtsproblemen, internaliserende problemen, externaliserende problemen en totaal problemen.

In **hoofdstuk 5** beschrijven we één van de eerste studies naar de lange-termijn resultaten van neuropsychologisch onderzoek in kinderen na een hartstilstand. Deze resultaten hebben we vergeleken met gezonde kinderen van de algemene Nederlandse bevolking. Overlevenden van een hartstilstand scoorden significant slechter op intelligentie en intelligentie gerelateerde testen. Op neuropsychologische testen, gecorrigeerd voor IQ, scoorden kinderen slechter op visueel geheugen, beter op verbaal geheugen (subtest herkenning) en vergelijkbare resultaten op visueel motorische integratie, aandacht, andere onderdelen van het verbale geheugen en executief functioneren in vergelijking met de norm. Op vragenlijsten rapporteerden ouders beter executief functioneren,

maar leraren rapporteerden meer problemen bij plannen en organiseren. Jongens en oudere leeftijd bij reanimatie waren significante voorspellers van slechter neuropsychologisch functioneren.

Het onderzoek gepresenteerd in **hoofdstuk 6** kijkt naar de associatie tussen pijnstilling en sedatie gebruikt tijdens behandeling op de ICK en de langdurige neuropsychologisch gevolgen in overlevenden van een meningokokken septische shock. Het gebruik en de dosis van opioïden waren significant geassocieerd met slechte testresultaten op totaal IQ, verbaal IQ, verbaal subtesten (begrijpen en woordkennis), visuele aandacht en executief functioneren (Trail Making Test B). Na correctie voor patiëntkenmerken en ziektekenmerken (m.n. ernst van ziekte) bleef de relatie tussen opioïden en de meeste bevindingen op de neuropsychologische testen bestaan. Het gebruik en de dosis van benzodiazepines waren niet significant geassocieerd met één van de neuropsychologische testen.

In **hoofdstuk 7** bespreken we de bevindingen van dit proefschrift, plaatsen deze bevindingen in perspectief en doen we aanbevelingen voor toekomstige studies.

Dankwoord

Dankwoord

Allereerst wil ik de ouders en kinderen bedanken die aan dit onderzoek hebben meegewerkt. Bedankt voor jullie bereidheid om jaren later, geheel belangeloos, opnieuw naar het ziekenhuis te komen. Jullie hebben een belangrijke bijdrage geleverd aan de kennis over de gevolgen van een reanimatie op de kinderleeftijd.

Prof. dr. Tibboel, hartelijk dank voor uw steun en vertrouwen de afgelopen jaren. Zonder uw support was dit proefschrift er nooit gekomen. Uw kritisch denken en harde werken zijn inspirerend geweest!

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Ik wil de leden van de kleine commissie, Prof. dr. J. Bakker, Prof. dr. M.A. Grootenhuis, Prof. dr. E.H.H.M. Rings, hartelijk danken voor het kritisch lezen van mijn manuscript. Ook de overige leden dank ik hartelijk voor hun bereidheid zitting te nemen in de grote commissie. Dr. B.R. Scholefield, thank you for attending my thesis defense ceremony.

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"Sterk door Genade" is de betekenis van mijn naam en waar ik in geloof. Het is de Hemelse Vader die me hiervoor kracht en doorzettingsvermogen heeft gegeven. Zonder Zijn Genade was dit doelloos, zonder Zijn Leiding, Wijsheid en Inspiratie was dit nooit geworden wat het nu is.

Ik had dit niet willen missen.

Lennart

PhD Portfolio

PhD Portfolio

Name PhD student:	Lennart van Zellem
Erasmus MC Department:	Intensive Care (Erasmus MC-Sophia)
PhD-period:	January 2012 - June 2015
Promotor:	Prof. dr. D. Tibboel
Copromotors:	dr. C.M.P. Buysse, dr. E.M.W.J. Utens

	Core courses & seminars	ECTS
2013	Basic Rules & Regulations for Clinical Research (BROK) course, EMWO, Amersfoort	1,0
2014	English Biomedical Writing and Communication	3,0
2014	Research Integrity	0,3
2014	Research management	1,0
2014	Endnote course	0,1
2014	Indesign course	0,2
2014	Photoshop & Illustrator course	0,3
2014	Systematisch Literatuuronderzoek	1,0
2014	Neuropsychological assessment in children and adolescents (Rino groep)	2,0
2015	Erasmus Winter Programme	
	Biostatistics for Clinicians	0,7
	Diagnostic Research	0,9
	Regression Analysis for Clinicians	1,4
	Survival Analysis	1,4
2015	Biostatistical Methods I: Basic Principles Part A	2,0
2015	Quality of life measurement	0,9
2015	Mediacontact for researchers	0,3
	Attended Symposia and conferences	
2013	Congress "Sophia 150 jaar", Rotterdam	0,3
2013	Symposium "Kinderneurologische alarmsymptomen in de algemene praktijk", Rotterdam	0,5
2014	Erasmus MC – Sophia: Research Day 2014, Rotterdam	0,3
2014	ISICEM International Symposium on Intensive Care and Emergency Medicine, Brussels	0,3
2014	Second International Paediatric Psychology Conference in Europe, Amsterdam	0,3
2014	Pediatric emergency care: how research and practice interact	0,1
2015	ISICEM - International Symposium on Intensive Care and Emergency Medicine – Brussels	1,0

	(Conference) presentations & posters	ECTS
2012	ISICEM - International Symposium on Intensive Care and Emergency Medicine – Brussels (poster)	1,0
2013	Erasmus MC – Sophia: Research Day 2013, Rotterdam (poster)	0,5
2013	Erasmus MC - Sophia: Research Meeting ICK, ICN & Obstetrics , Rotterdam (oral presentation)	1,0
2013	Erasmus MC - Sophia: Pediatric Pharmacology Meeting, Rotterdam (oral presentation)	1,0
2013	ESPNIC - European Society of Paediatric Neonatal Intensive Care (poster)	1,0
2014	Erasmus MC – Sophia: Research Meeting dept. Child and Adolescent Psychiatry/Psychology (oral presentation)	1,0
2015	Rino groep: course "Neuropsychological assessment in children and adolescents" (oral presentation)	1,0
	Teaching	
2014	Supervision Bachelor students	1,0
2015	Teaching psychologist "Long-term outcome of cardiac arrest in children"	1,0
	Other	
2012	Pediatric Pharmacology meetings 2012-2015 (14x)	1,0
2012	Personal Coaching/Development	2,0
2013	Health related Quality-of-Life meetings 2012-2013 (8x)	0,3
2012	Grand Round 2012-2015 (15x)	1,0
2013	Colloquia Child and Adolescent Psychiatry/Psychology 2013-2015 (7x)	0,3
2013	Treatment and Researchmeeting Pediatric Psychology 2013-2015	0,6

ECTS = European Credit Transfer and Accumulation System

List of Publications

List of Publications

1. **van Zellem L**, Buysse C, Madderom M, Legerstee JS, Aarsen F, Tibboel D, Utens EM: Long-term neuropsychological outcomes in children and adolescents after cardiac arrest. Intensive Care Med, 2015 Apr 18. [Epub ahead of print]
2. **van Zellem L**, Utens EM, Legerstee JS, Cransberg K, Hulst J, Tibboel D, Buysse C: Cardiac arrest in children: long-term health status and health related quality of life. Pediatr Crit Care Med, 2015 Mar 12 (In press)
3. **van Zellem L**, de Jonge R, van Rosmalen J, Reiss I, Tibboel D, Buysse C: High cumulative oxygen levels are associated with improved survival of children treated with mild therapeutic hypothermia after cardiac arrest. Resuscitation, 2015 May; 90:150-7
4. **van Zellem L**, Utens EM, de Wildt SN, Vet NJ, Tibboel D, Buysse C: Analgesia-Sedation in PICU and Neurological Outcome: A Secondary Analysis of Long-Term Neuropsychological Follow-Up in Meningococcal Septic Shock Survivors*. Pediatr Crit Care Med, 2014 Mar; 15(3):189-96.

About the author

About the author

Lennart van Zellem was born on the 6th of April 1984 in Rotterdam. He grew up in Rotterdam and Oud-Beijerland, and received his Atheneum degree at the Christelijke Scholengemeenschap Willem van Oranje in Oud-Beijerland in 2003. Before starting his medical training, he studied nursing for two years at the Hogeschool Rotterdam. In 2005 he applied for the study Medicine at the Erasmus University in Rotterdam. From the third year onwards, Lennart combined his study with research at the intensive care unit of the Erasmus MC-Sophia Children's Hospital in Rotterdam, under supervision of dr. C.M.P. Buysse. He was involved in projects on cardiac arrest in children and the long-term effects of meningococcal septic shock in children. In 2011 he obtained his medical degree and worked for two months as resident (ANIOS) at the department of pediatric surgery in the Erasmus MC-Sophia Children's Hospital. In 2012 he started his PhD project studying the long-term outcome of cardiac arrest in children under supervision of prof. dr. D. Tibboel, dr. C.M.P. Buysse, and dr. E.M.W.J. Utens. The results of this research are presented in this thesis.

Lennart lives in Aalsmeer and is married with Patricia Mari Couton.

List of Abbreviations

List of Abbreviations

ABI = Acquired Brain Injury

ALTE = Apparent Life Threatening Event

APLS = Advanced Pediatric Life Support

AUC = Area Under the Curve

Beery VMI = Beery Developmental Test of Visual Motor Integration

BLS = Basic Life Support

BP = Blood Pressure

BRIEF = Behaviour Rating Inventory of Executive Function

C-TRF = Caregiver-TRF

CA = Cardiac Arrest

CBCL = Child Behavior Checklist

CHQ-CF87/IT97/PF50 = Child Health Questionnaire - Child Form 87/Infant Toddler 97/Parent Form 50

CI = Confidence Interval

ConHD = Congenital Heart Disease

CPR = Cardiopulmonary Resuscitation

CV = Compression Ventilation

DBP = Diastolic Blood Pressure

DIC = Disseminated Intravascular Coagulation

ECLS = Extracorporeal Life Support

ECMO = Extracorporeal Membrane Oxygenation

eGFR = Estimated Glomerular Filtration Rate

EMS = Emergency Medical Services

ES = Effect size

FiO_2 = Fraction of inspired oxygen

HR-QoL = Health Related Quality of Life

HUI = Health Utility Index

ICU = Intensive Care Unit

IH = In-Hospital

IH-CA = In-Hospital Cardiac Arrest

IQ = Intelligence Quotient

IQR = Interquartile Range

MSS = Meningococcal Septic Shock

MTH = Mild Therapeutic Hypothermia

N = Number

NICU = Neonatal Intensive Care Unit

OH = Out-of-Hospital

OH-CA = Out-of-Hospital Cardiac Arrest

OR = Odds Ratio

$PaCO_2$ = Partial Pressure of Arterial Carbon Dioxide

PaO_2 = Partial Pressure of Arterial Oxygen

PCPC = Pediatric Cerebral Performance Categories

PDR = Predicted Death Rate

PICU = Pediatric Intensive Care Unit

POPC = Pediatric Overall Performance Categories

PPVT = Peabody Picture Vocabulary Test

PRISM = Pediatric Risk of Mortality Score

RAVLT = Rey's Auditory Verbal Learning Test

ROCF = Rey-Osterrieth Complex Figure Test

ROSC = Return Of Spontaneous Circulation

SaO_2 = Arterial Oxygen Saturation

SBP = Systolic Blood Pressure

SCr = Serum Creatinine

SES = Socioeconomic Status

SF-36 = Short Form 36

SIDS = Sudden Infant Death Syndrome

SIRS = Systemic Inflammatory Response Syndrome

Stroop = Stroop Color Word Test

TBI = Traumatic Brain Injury

TEA-Ch = Test of Everyday Attention for Children

TMT = Trail Making Test

TRF = Teacher's Report Form

VAS = Vasopressor Score

VF = Ventricular Fibrillation

VT = Ventricular Tachycardia

WAIS = Wechsler Adult Intelligence Scale

WISC = Wechsler Intelligence Scale for Children

WPPSI = Wechsler Preschool and Primary Scale of Intelligence

YSR = Youth Self Report