Cardiac and circulatory effects of
patent ductus arteriosus during
extracorporeal membrane oxygenation

**Cardiac and circulatory effects of patent
ductus arteriosus during extracorporeal membrane oxygenation**

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Contents

Abbreviations	x
Chapter 1: Introduction	1
Extracorporeal Membrane Oxygenation ECMO	
<i>History</i>	
<i>Definition and ECMO protocol</i>	
Clinical observations	
The aim of the study	
<i>Pulmonary Hypertension</i>	
<i>Persistent Ductus Arteriosus (PDA)</i>	
Entry diagnosis in relation to ECMO	
<i>Meconium Aspiration Syndrome (MAS)</i>	
<i>Congenital Diaphragmatic Hernia (CDH)</i>	
<i>Sepsis neonatorum</i>	
<i>Respiratory Distress Syndrome</i>	
Study Outline	
Objectives	
References	
Chapter 2: Neonatal pulmonary hypertension during extracorporeal membrane oxygenation	19
Abstract	
Introduction	
Materials and Methods	
<i>Echocardiographic measurements</i>	
<i>Management of patients</i>	
<i>Statistical Analysis</i>	
Results	
Discussion	
Acknowledgements	
References	

Chapter 3: The influence of ductal L-R shunting during extracorporeal membrane oxygenation 39

Abstract

Introduction

Materials and methods

Patient group

Statistical analysis

Results

Discussion

References

Chapter 4: Measurement of the ductal L-R shunt during extracorporeal membrane oxygenation in the lamb 51

Abstract

Introduction

Materials and Methods

Fetal animal preparations

Flow measurement and calculations

ECMO surgery and cannulation

Experimental protocol

Data analysis

Results

Discussion

References

Chapter 5: Ductal dependent changes in left ventricular dimensions and fractional shortening in neonates undergoing veno-arterial extracorporeal membrane oxygenation 63

Abstract

Conclusion

Introduction

Methods

Management of patients
Vascular access for ECMO
Statistical analysis

Results

Discussion

References

Chapter 6: Summary, conclusions and future perspectives 79

Summary and conclusions

Final conclusion

Future perspectives

Samenvatting en conclusies

Samenvattende eindconclusies

Aanbevelingen voor de toekomst

Dankwoord 93

Curriculum Vitae 97

Abbreviations

ACT	: activated clotting time
Ao	: aorta
CVP	: central venous pressure
ECMO	: extracorporeal membrane oxygenation
HR	: heart rate
LA	: left atrium
L-R	: left to right
LV	: left ventricle
MAP	: mean arterial pressure
MAS	: meconium aspiration syndrome
PEEP	: positive end-expiratory pressure
PIP	: positive inspiratory pressure
Qao	: flow across the aortic valve
Qduct L-R	: ductal left to right shunt
Qecmo	: flow in the ECMO circuit
Qpa	: flow across the pulmonary valve
PDA	: patent ductus arteriosus
R-L	: right to left

CHAPTER 1

Introduction

1 General introduction

Extracorporeal membrane oxygenation: ECMO

History

The development of extracorporeal circulation has had a tremendous effect on medicine. Now certain operations in the field of the cardiac and vascular surgery became possible and evolved to routine procedures, first in the US and later also in Europe (1). In Nijmegen the first cardiac operation assisted by extracorporeal circulation was performed in 1963, followed by the first coronary bypass operation in The Netherlands in 1968. Ever since the development of the mechanical ventilation in the newborn in the 1970's, the neonatal intensive care units were set up, giving treatment to critically ill neonates for acquired and congenital diseases. In 1976, the first neonatal Extracorporeal Membrane Oxygenation (ECMO) was performed by R. Bartlett, in the management of a neonate with respiratory failure (2). After this first neonatal procedure, the clinical use of ECMO therapy in neonates was facilitated between 1980 and 1990 and became established as an effective rescue-therapy. The results improved during the years and according to the Registry of the Extracorporeal Life Support Organization, the overall ECMO survival rate for neonatal respiratory failure is 86% and for neonatal cardiac failure 55%. Also other forms of extracorporeal membrane oxygenation were developed such as veno-venous ECMO with the great advantage of less vascular damage. Supported by a grant of the Ministry of Healthcare, ECMO was introduced in The Netherlands at the University Hospital Nijmegen in 1991. Between 1991 and 2001, 160 patients are treated in Nijmegen with an overall survival of 82.8% (range 71.1-95.7). Nowadays, ECMO is an indispensable rescue therapy for critically ill newborns. The use of ECMO for children after open-heart surgery, the so-called extracorporeal life support is increasing worldwide and also in our center since the first case in 1999. In 1987 the Registry of the Extracorporeal Life Support Organization started and documented the files of almost all ECMO patients from all over the world to collect the data leading to a better understanding of the ECMO related complications and providing a unique reference for study, results and quality control.

Definition and ECMO protocol

Extracorporeal membrane oxygenation is the application of temporary, but prolonged gas exchange outside the body and extracorporeal circulation in patients with reversible life-threatening situations of cardiac- or pulmonary failure (3,4,5,6). During veno-arterial ECMO, the venous blood flow in the right atrium is bypassed

through a venous cannula to the ECMO circuit in which a rollerpump supports the circulation and a membrane oxygenator will take care for the exchange of carbon dioxid and oxygen in the venous blood (see figure 1).

Figure 1. Scheme of the ECMO circuit

The fully saturated blood is guided back to the systemic circulation of the infant by way of a heat-exchanger to maintain normothermia, and next through the arterial cannula positioned on the crossing of the anonymous artery and aortic arch. In this way a pulmonary and cardiac support as well is performed. The bladderbox, a small collapsible reservoir with a sensitive microswitch, controls the rollerpump in case of decreased circulating volume by switching it off. For safety reasons, for example air bubbles in the arterial tubes, the bridge is the place to remove these air bubbles by clamping the arterial and venous canules and performing ECMO over the bridge. To support the circulation, usually an ECMO flow of 180-200 ml/min/kg bodyweight will be necessary for optimal cardiac output and oxygen saturation. This flow is reached after a gradually step up in ECMO flow during the first two hours approximately. Because of the risk of thrombosis and clotting problems in the extracorporeal circuit all patients are fully heparinized. This anticoagulation therapy is monitored using the activated clotting time (ACT).

Initially a loading dose of heparin 100-150 units/kg bodyweight is administered before cannulation, followed by 20-50 U/kg bodyweight based upon an ACT time of 220-250 seconds. The ACT is monitored every hour using an ACT-monitor (HemochronR).

During ECMO the patient is intubated and ventilated with minimal ventilator settings to prevent alveolar collapse (FiO_2 30%, respiration rate 16/min, PIP 20-24 mbar, PEEP 4 mbar) and barotrauma. On the contrary to open heart surgery, vascular access is usually reached by a cut down technique in the lateral side of the right neck region. The venous cannula is put through the right jugular vein and the arterial cannula is pushed up through the right common carotid artery. Both vessels are ligated at the cranial side. The cannula position is confirmed by X-ray and by ultrasound. All patients are sedated routinely using midazolam and fentanyl. Patients with congenital diaphragmatic hernia are also treated with pancuronium during the first 24 hours on bypass and after the surgical repair of the hernia. Standard antibiotic therapy is administered with ampicillin and gentamycin. Nutritional support is determined by fluid balance and established by the standard parenteral nutrition protocol. Patients are nursed in the neonatal intensive care unit on an Airshield II CS 90 table.

For the first 48 hours on ECMO in all patients an optimal condition is pursued, monitored by blood gases, heart rate, blood pressure and oxygen saturation. Arterial oxygen pressure is maintained between 10 to 13 kPa. After 48 hours, weaning attempts are undertaken when arterial oxygen pressure is above 13 kPa. In that case

ECMO flow will be diminished step by step (10-20 ml/hour) until a minimal ECMO flow is reached of 50 ml/min. When the clinical condition is stable for another 6-8 hour, decannulation is performed and the patient is taken off bypass.

Clinical observations

After our first experiences with ECMO in 1991 we observed some important clinical symptoms and signs in these patients. First, once on ECMO, a stabilisation of pulmonary- and cardiac function was observed leading to a better control of hypercapnia, hypoxaemia and oxygen saturation. Especially when pulmonary hypertension was “under control” there was a much better clinical condition of the patient. This usually happened after 24-48 hours after ECMO was started. However during the same first days on ECMO, a tendency to fluid retention was observed with severe subcutaneous edema all over the skull and on the backside of the patient together with oliguria. In the same time with these phenomena, the radiological pattern of the chest X-ray showed the development of pulmonary opacification known as the typical “white-out pattern” that will represent the severe pulmonary edema. In our ECMO center all patients were nursed in the neonatal intensive care unit where also treatment was performed to preterm neonates. In the observation of all these patients a certain overlap was noticed between the premature neonate suffering from an important ductal left to right (L-R) shunt on the one side and the ECMO patient on the otherside. Both had signs of general edema with or without prerenal failure and both had signs of pulmonary edema. When the duct was closed in the premature infant, usually polyuria will develop with improvement of the clinical condition as well as the radiological picture giving the possibility to wean the child from the ventilator. In the ECMO patient, usually there is an improvement in the initially worse lung compliance after the pulmonary edema has cleared up and weaning from bypass becomes possible. To illustrate our observations, figures 2a and 2b are showing the chest X-ray's during several days of patients from both groups. So, in conclusion, we hypothesized that perhaps an important ductal L-R shunt is created after the pulmonary hypertension is successfully treated with ECMO. Perhaps this ductal L-R shunt is on the one side the cause of the pulmonary edema related to the pulmonary hypercirculation, and on the other side this ductal shunt is “stealing” from the systemic circulation and so contributing to the onset of prerenal failure and general edema.

Figure 2a

Radiological findings in the same premature neonate with patent ductus arteriosus before and after closure. a = day of birth; b = second day, day of diagnosis; c = third day, day of treatment with indomethacin; d = fourth day

Figure 2b

Radiological findings in a term neonate before, during and after ECMO. a = day o birth; b = after 1 day of ECMO treatment; c = during ECMO weaning; d = before decannulation

The observations above have lead to the hypothesis described in the next paragraph: ‘The aim of the study’.

The aim of the study

As mentioned before, there is a great overlap in the clinical picture and in the radiological signs of an important ductal L-R shunt in the premature infant and the critically ill neonate on ECMO. So what will be the contribution of the ductal L-R shunt in the clinical picture and is this shunt responsible for the signs of pulmonary overflow and edema during ECMO? When a ductal L-R shunt, on the one hand, leads to pulmonary hyperperfusion and pulmonary edema, there has to be an important shunt. On the other hand, the amount of blood that is guided through the duct to the pulmonary circulation must be “stealed” from the systemic circulation, or more appropriate from the bloodflow in the descending aorta and even from the cerebral circulation. This will lead to a decrease in the renal perfusion possibly leading to general edema as a symptom of prerenal failure. We know that ECMO reduces pulmonary hypertension and decreases pulmonary resistance. However, is ECMO capable to diminish pulmonary blood pressure so early after cannulation that the ductal shunt will reverse? To get a better insight in this ductal behaviour and ductal shunt in relation to the consequences for the pulmonary- and systemic circulation, we want to answer the following questions.

- What is the level of pulmonary hypertension initial to ECMO and how is the reaction of this hypertension on ECMO therapy?
- Is the ductus arteriosus patent before and during ECMO and will the shunt reverse into the L-R type after pulmonary blood pressure has decreased?
- In which way the ductal L-R shunt will lead to general and pulmonary edema. How is the interaction with ECMO weaning?
- How is the left ventricular performance during ECMO and what is the influence of volume loading parameters.
- Will it be possible to objectivate and quantify the ductal L-R shunt during ECMO to get a better insight into the haemodynamic involvement?

In the next paragraphs, comprehensive information is presented on the subjects who are essential in this manuscript for a better understanding.

Figure 3b.
The neonatal circulation

The medial layer is composed of smooth muscle in the smaller pulmonary arteries, and in the following branches a thick muscular layer surrounds the whole circumference (7). Only approximately 7 % of the cardiac output is determined by the pulmonary bloodflow (8). Because of the elevated pulmonary vascular resistance, the pulmonary circulation is bypassed by a large patent ductus arteriosus with R-L shunt. Now, a substantial amount of venous bloodflow will enter the systemic circulation and will join the blood flow from the systemic circulation coming from the left ventricle at the transition of the duct to the descending aorta. This ductal R-L shunt, will prohibit a raise in arterial oxygen tension. Systemic cardiac output is delivered by the right and the left ventricle and the fetus is capable in maintaining its normal functions under partial oxygen saturations of approximately 65% (8). At the other side, a patent foramen ovale will permitt the already saturated blood coming from the placenta by the umbilic

vein, entering the left atrium by an atrial R-L shunt and so contributing to the systemic circulation. The systemic vascular resistance in the fetus is low and also the resistance of the placental circulation. The ductus venosus is important in connecting the umbilic vein to the fetal heart. This circulatory equilibrium is maintained during pregnancy until the moment of birth. Then transition to the postnatal circulation will be essential for normal life. This is reached by a tremendous increase in the pulmonary circulation. First, after birth, the lungs are ventilated in a rhythmic way inducing a drop in the pulmonary vascular resistance. The pulmonary bloodflow will increase rapidly and contribute to the gas exchange in both lungs. A rise in arterial oxygen tension will decrease the pulmonary vascular resistance and the pulmonary blood pressure more and more. A remodeling of the pulmonary vascular structure will take place. The endothelium of the pulmonary vessels plays a crucial role in this process from fetal to postnatal circulation. Finally, the normal pulmonary circulation will be marked by a low vascular resistance (9). In this process morphological changes such as the expansion of the lung and stretching of the pulmonary vessels with remodeling of the vascular structure form the underlying basis for the drop in resistance together with important humoral factors derived from the pulmonary endothelium and local vaso-active substances (10,11). These substances, such as nitric oxid, bradykinin and prostaglandin I₂, will rise when the lung begins to ventilate. The changes above will lead to a tremendous increase in pulmonary bloodflow and subsequently an increase in preload for the left ventricle. When the ductus arteriosus is still patent and pulmonary resistance is low, the initial ductal R-L shunt will reverse into the L-R shunt. After birth, systemic resistance will increase after disappearance of the placental circulation. This again will increase the ductal L-R shunt and the pulmonary circulation. So, the ductal L-R shunt will play an important role in converting the fetal-transitional circulation into the normal circulation before it will finally close. The fetus usually will show a right ventricular dominant heart that gradually will change into a left ventricular dominant heart in the infant by way of the transitional circulation (12,13,14,15,16,17). In critically ill neonates in whom ECMO is performed, the conversion of the transitional circulation into the neonatal circulation is disturbed. Severe respiratory failure due to acquired or congenital disease will form the basis that will lead to hypoxia, hypoxaemia, hypercarbia and acidosis (18). These disturbances will interact with the changing processes in the pulmonary circulation and result in pulmonary vasoconstriction with contraction of the smooth muscle layer leading to sustained elevated pulmonary vascular resistance. Now the ductal L-R shunt is prohibited and the ductal R-L shunt will persist and develop further,

reinforcing hypoxaemia in the postductal circulation of the descending aorta. Besides a ductal R-L shunt, an atrial R-L shunt becomes possible during severe pulmonary hypertension also contributing to cyanosis and hypoxaemia. This atrial R-L shunt at the level of the foramen ovale will occur when the right atrial pressure is severely elevated because of high systolic and end-diastolic pressures in the right ventricle. Usually, tricuspid valve regurgitation is observed during these situations enforcing the atrial R-L shunt (19,20). Circulatory interactions will create a deteriorating situation known as persistent pulmonary hypertension of the neonate. Before ECMO or therapy with inhaled nitric oxid, the basic treatment consisted of administration of non-specific vasodilating drugs such as tolazoline or isoprenaline with a systemic hypotension as adverse reaction. Besides vasodilating drugs, other supportive treatment was used as oxygen therapy, inotropics or alkali therapy. More recently the availability in clinical use of inhaled nitric oxid has changed the strategy for treatment of persistent pulmonary hypertension of the neonate. The vasodilating effect of inhaled nitric oxid is more specific to the pulmonary vessels and has nowadays the highest priority in the strategy of pulmonary hypertension treatment (21). Despite the great beneficial effects of this treatment there still is the need for ECMO in those patients who are non- or bad-responders.

Before the era of ECMO and inhaled nitric oxid therapy, the prognosis of persistent pulmonary hypertension of the neonate was poor (22). Mortality was high, up to 70% and morbidity was even higher. The prognosis after ECMO treatment has shown a lot of changes until a very acceptable to good prognosis is reached for certain specific ECMO patients groups according the ELSO registry for neonatal veno-arterial ECMO (23).

Persistent ductus arteriosus

In the paragraph above special attention is given to the ductal R-L shunt during pulmonary hypertension. However, when pulmonary hypertensive treatment is succesfull, a L-R shunt will develop when the duct remains patent. Than, two changes in blood flow are important. First, an increase of pulmonary blood flow will occur, leading to pulmonary hyperperfusion. Signs of tachy-dyspnoea, fatigue and failure to thrive are observed in infants with persistant ductus arteriosus. In ECMO patients nursed on the intensive care we usually don't see the classical symptoms of an important cardiac L-R shunt. Radiological analysis however will show in these patients the signs of cardiac enlargement and pulmonary edema also known as the 'typical white-out pattern' (24,25). The lung compliance in these patients is low because of the vascular overfilling and tendency to pleural

effusions (26). The clinical picture will show signs of high output failure especially when the pulmonary bloodflow is twice the systemic bloodflow or more ($Q_p/Q_s > 2$). At the other side, an important L-R shunt at ductal level together with a low pulmonary vascular resistance will create ideal circumstances for a stealing circulation in which the blood in the descending aorta will show a diastolic run-off in the direction of the pulmonary artery through the patent duct. This will lead to a decrease in perfusion of the lower body in which the renal perfusion is most important (27,28,29,30). In summary a ductal L-R shunt will lead to pulmonary hyperperfusion, a volume-loading to the left atrium and left ventricle and a decrease into the perfusion to the body, especially to the descending aorta and its continuation (postductal steal).

Entry diagnosis in relation to ECMO

Meconium aspiration syndrome (MAS)

MAS forms with 35-40% the most frequent indication to ECMO (31,23). The clinical picture of MAS is characterized by aspiration of meconium-stained-amniotic-fluid in the perinatal period. The meconium is spread into the periphery of the lung by the first breathings of the newborn. In the lung, small airway obstruction with atelectasis, hyperinflation and inflammatory pneumonitis will develop with respiratory depression, respiratory distress, hypoxia and hypercarbia. This situation often is associated with a certain degree of pulmonary hypertension and sustained elevation of pulmonary vascular resistance. So the “fetal” circulation will persist with signs of cardiac R-L shunting at atrial or ductal level also known as persistent pulmonary hypertension in the neonate. In earlier days therapy consisted of conventional artificial ventilation with a high percentage of oxygen in combination with vasodilating drugs. Nowadays inhaled NO is the first treatment of choice in combination with advanced ventilatory strategies such as high frequency ventilation. In the patients who are unresponsive to the various therapeutic strategies, ECMO will be indicated with a mean ECMO survival of 94% (23).

Congenital Diaphragmatic Hernia (CDH)

With the term CDH usually a posterolateral hernia, type Bochdalek, is pointed out. Patients with CDH are characterized by a closing defect of the diaphragm that is present with still unknown cause. During the fetal period the “abdominal” viscera are present in the pleural cavity attended with a certain degree of pulmonary hypoplasia. Both the malformations will soon after birth lead to the respiratory

distress and hypoxaemia resulting in persistent pulmonary hypertension of the neonate, depending on the gravity of the clinical picture. Similar to the therapy for MAS, the therapy for CDH has changed enormously. In the past, CDH was treated surgically as soon as possible after birth. Then the strategy was changed somewhere between 1980 and 1990. Pre-operative stabilization and delayed surgery has become the general approach. In the preoperative period nowadays, inhaled NO and ECMO are frequently used to manage the pulmonary hypertension and hypoxaemia. A demonstrated $\text{PaO}_2 > 10 \text{ kPa}$ in CDH patients prior to ECMO is used in our center to select those CDH patients with minimal acceptable lungfunction for ECMO. When ECMO is indicated, in our center the surgical correction will be performed during the ECMO course after pretreatment of the pulmonary hypertension. According to the ELSO registry, the diagnosis CDH represents about 22% of ECMO runs with an improving prognosis up to 55% survival (23).

Sepsis neonatorum

According to the latest ELSO data the diagnosis sepsis is responsible for about 14% of all neonatal ECMO runs. The survival rate is 76% (23). Usually the patient is infected during birth. Mostly group B streptococcus and E.Coli are involved. The clinical picture of a neonatal sepsis is that of multi-organ failure. Free bacterial toxins will paralyse the systemic circulation with hypoxaemia and severe metabolic acidosis. In this way the cascade of pulmonary hypertension is activated. Also direct infectious effects to the pulmonary circulation will lead to vasoconstriction of the pulmonary vasculature.

Respiratory Distress Syndrome

Respiratory Distress Syndrome is caused by a surfactant deficiency leading to the clinical picture of tachy-dyspnoea, grunting expiration and in-drawings at the sternum and intercostal space. Usually, these patients are artificial ventilated with extra oxygen. Surfactant therapy has changed the impact of this disease but sometimes patients are exposed to severe respiratory acidosis and hypoxaemia. This situation can lead to elevation of the pulmonary blood pressure and persistent pulmonary hypertension of the neonate. In about 8% this diagnosis will form the ECMO indication with a fair prognosis concerning survival of 84% (23).

Study Outline

This study was designed to achieve more insight in the circulatory aspects of the several ductal shunt types before, during and after ECMO. The consequences of these circulatory changes to the left ventricle, the ECMO run and the pulmonary circulation are studied.

Objectives

- Timing of the responsiveness of the pre-existing pulmonary hypertension to ECMO therapy.
- Determination in time of the turnover of the ductal R-L shunt into the L-R shunt in connection to the changes in pulmonary hypertension during ECMO.
- Measurement of the duration of ductal L-R shunting and observation of the spontaneous ductal closure.
- Determination of the clinical impact of a ductal L-R shunt during ECMO.
- Invasive measurement of the ductal L-R shunt during ECMO and the relation to cardiac output and ECMO flow in the animal model.
- Left ventricular performance during ECMO under several loading conditions.

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CHAPTER 2

Neonatal pulmonary hypertension during extracorporeal membrane oxygenation

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2 Neonatal pulmonary hypertension during extracorporeal membrane oxygenation

Abstract

Objectives

This prospective study was designed to monitor severe pulmonary hypertension during extracorporeal membrane oxygenation using echo Doppler variables

Background

All neonates treated with extracorporeal membrane oxygenation also have severe pulmonary hypertension. A study which monitors the reaction of the pre-existing pulmonary hypertension during extracorporeal oxygenation by frequent sampling of those variables related to pulmonary pressure is still lacking. Such a study is necessary to analyze the complex haemodynamic changes in patients undergoing extracorporeal membrane oxygenation.

Method

In 29 neonates, we estimated pulmonary arterial pressure using peakflow velocity of regurgitation across the tricuspid- and pulmonary valve, peakflow velocity of shunting across persistent arterial ductus, and systolic time intervals of the right ventricle. Correlation between the several estimations of pulmonary arterial pressure were analysed with the Spearman correlation coefficient.

Results

Systolic pulmonary arterial pressure measured by the velocity of tricuspid regurgitation illustrated severe pulmonary hypertension prior to extracorporeal membrane oxygenation (mean 63 mmHg, sd 20). Similar levels for the systolic pulmonary arterial pressure could be derived (mean 73 mmHg, sd 17) from ductal shunting. A fair correlation of 0.76 ($P < 0.002$) could be demonstrated. Pulmonary hypertension responded well and quickly to treatment by extracorporeal membrane oxygenation, with reductions within 24 hours to mean systolic levels of 35 mmHg, sd 23. This very early reaction has not previously been demonstrated and could be of importance in defining parameters for weaning from cardiopulmonary bypass. Diastolic pulmonary arterial pressure was investigated because of its relation to vascular resistance. It proved more difficult to measure because of the low incidence of pulmonary regurgitation. Derived diastolic pressures did not show any good correlations.

Conclusion

Pulmonary hypertension is well documented prior to extracorporeal membrane oxygenation and responds very quickly to the institution of treatment. Ultra sound techniques are indicated at the bedside, and prove useful in monitoring pulmonary

blood pressure during the procedure.

Key words

Extra Corporeal Membrane Oxygenation, pulmonary hypertension, neonates

Introduction

Severe neonatal pulmonary hypertension due to several causes such as aspiration of meconium, congenital diaphragmatic hernia, respiratory distress syndrome or neonatal septicaemia is a frequent common pathway for critically ill neonates. This clinical situation often fails to respond to standard intensive care, including artificial ventilation and pharmacological manipulation of pulmonary vascular resistance. Extracorporeal membrane oxygenation has now been used for more than 20 years to treat this complication, with good results. According to the registry from the Extracorporeal Life Support Organization, overall survival was 79% (1) or even higher in selected subgroups (2). Extracorporeal Membrane Oxygenation treatment will usually last about one week, during which there are several potentially hazardous complications, such as disorders of coagulation, hemolysis, renal failure and intracerebral bleeding (3). This study was designed to observe the degree of pulmonary hypertension before and during extracorporeal membrane oxygenation, using the predicted pressures calculated from echo-Doppler-derived parameters. Furthermore, we studied the time necessary for recovery from pulmonary hypertension. The results provide details about the changes in the pulmonary circulation in these neonates, and could be useful developing more objective criteria for weaning from cardiac bypass where, among other parameters such as pulmonary mechanics and fluid accumulation, changes in pulmonary hypertension are equally important.

Materials and methods

We studied prospectively 29 critically ill neonates admitted consecutively between September 1995 and September 1997. Mean birthweight was 3306 gram (sd 574). The group consisted of 10 girls and 19 boys. Mean age at time of cannulation was 1.8 days (sd 1.3). Extracorporeal oxygenation was indicated because of one of the following diagnoses: Aspiration of meconium 16 (55%), congenital diaphragmatic hernia 8 (28%), respiratory distress syndrome 1 (3%), neonatal sepsis 4 (14%). All patients met the criteria for inclusion and exclusion as shown in Table 1.

Because of possible rapid changes in the hypertensive pulmonary circulation after the initiation of oxygenation, the first ultrasound study was started just prior to cannulation and repeated within every 12 hours during the first 60 hours on

Table 1. Inclusion and exclusion criteria for veno-arterial extracorporeal membrane oxygenation

Inclusion criteria:

Alveolar-arterial oxygen difference (AaDO₂) of more than 600 mmHg during 8 hours.

AaDO₂ of more than 605 mmHg during four hours together with positive inspiration pressure of more than 38 mbar.

Oxygenation-index of more than > 40 in 3 to 5 consecutive bloodgas analysis.

Acute deterioration during 2 hours (pH < 7.15 and PaO₂ < 40 mmHg).

No improvement despite maximal therapy during 3 hours.

Exclusion criteria:

Birth weight less than 2000 gram.

Gestational age less than 34 weeks.

Severe congenital malformations.

Intracerebral bleeding more than grade 2 according to Papile.

Coagulation disorders interacting with heparin therapy.

bypass, and for all following days including the last investigation made within 24 hours after decannulation. All echocardiographic measurements were made with a Toshiba SSH 140 echocardiograph using M-mode-, Doppler- and color-Doppler techniques. Interpretation of all echo Doppler variables took place without any knowledge of the clinical course of the patient to the observer.

The following data were collected during this study:

Echocardiographic measurements

Systolic time-intervals for left and right ventricles, peak flow velocity of tricuspid and pulmonary regurgitation and, systolic peak flow velocity in the pulmonary arteries. Ductal shunting was expressed as right-to-left, left-to-right, or bidirectional, and peak flow velocity of shunting was obtained.

Pulmonary arterial pressure (systolic and diastolic) was approximated in three ways, using the simplified Bernouilli equation (4,5) or the right ventricular systolic time interval according to Hirschfeld and colleagues (6).

- From peak velocity of tricuspid regurgitation according to the equation: Systolic pressure right ventricle = $4 \times (\text{tricuspid insufficiency peak flow velocity})^2 + \text{central venous pressure in mmHg}$.

Pulmonary valvar stenosis was excluded so systolic pulmonary arterial pressure was assumed to be equal to systolic right ventricular pressure. Diastolic pulmonary arterial pressure was estimated as diastolic pressure = $4 \times (\text{pulmonary insufficiency peak flow velocity})^2 + \text{central venous pressure in mmHg}$.

- From ductal shunting from right-to-left according to the equation $\text{systolic pulmonary arterial pressure} = 4x(\text{systolic ductal peak flow velocity})^2 + \text{systolic blood pressure}$ and systolic left-to-right shunting to the equation $\text{systolic pulmonary arterial pressure} = \text{systolic blood pressure} - 4x(\text{ductal peak flow velocity})^2$ Bidirectional ductal shunting also permitted estimation of diastolic pulmonary arterial pressure using the equation $\text{diastolic pulmonary arterial pressure} = \text{diastolic blood pressure} - 4(\text{diastolic peak flow velocity})^2$ In bidirectional shunting, the shunt from right-to left occurs in systole, and left-to-right shunting is in diastole
- In addition to the pressure calculations derived using the simplified Bernoulli equation, right ventricular systolic time intervals were also measured and related to pulmonary pressures The pre-ejection phase was defined as the time from the onset of the QRS-complex to the initial of valvar opening in milliseconds The time between initial valvar opening and the end of valvar closure was defined as the right ventricular ejection time The ratio of these two variables was used as the right ventricular systolic time interval According to Hirschfeld et al (6), diastolic pulmonary arterial pressure may be estimated from this interval as $\text{diastolic pulmonary arterial pressure} = 153.9(\text{systolic time interval}) - 20.88$ The impact of the observed pulmonary hypertension is best interpreted clinically when related to systemic blood pressure Supra-systemic pressure in the pulmonary arteries is the worst situation with right-to-left shunting and desaturation On the other hand, a pressure less than half systemic blood pressure is reassuring

Management of patients

All patients were nursed in a special intensive care room on an AirShield IICS 90 table Body temperature was maintained between 36.8-37.5 degrees Celsius Bloodpressure was obtained from an umbilical arterial line placed with the tip in the descending aorta and recorded by a Siemens monitor Central venous pressure was measured by an umbilical line with the tip in the right atrium, and recorded by the same monitor in addition to heart rate Pre- and postductal oxygen saturation were monitored with a Nellcor pulsoximeter Depending on age, weight gain and fluidbalance, minimal prescribed fluid intake was 50 ml/kg, and maximal 150 ml/kg Standard diuretic therapy was administered using furosemide 8 mg/kg/day or 4 mg/kg/day when fluid balance is negative and urinary production was above 3 ml/kg body weight Mannitol was administered only on indication when oliguria was present (mannitol 2 g/kg/day intravenously Antibiotics were routinely prescribed, amoxicillin 100 mg/kg/day and gentamycin 5-7 mg/kg/day Prior to

cardio-pulmonary bypass, heart failure or hypotension not due to hypovolaemia was treated with intravenous administration of dopamine or dobutamine (5-10 mcg/kg/min). Pulmonary hypertension was treated with tolazoline, prostacycline, magnesiumsulphate, or with inhalation of nitric oxide if necessary. Before the extracorporeal oxygenation was started, ventilatory support ranged from standard mechanical positive pressure ventilation to high frequency oscillation. During bypass, basic mechanical ventilation was supported with minimal ventilator settings. Surgical intervention for correction of congenital diaphragmatic hernia was performed only after several days of pre-treatment with extracorporeal oxygenation, including a weaning period. All patients were sedated during bypass using midazolam 0.1-0.3 mg/kg/h and fentanyl 2-10 mcg/kg/h. Pancuronium 0.01-0.02 mg/kg/h was used in all patients with diaphragmatic hernia 24 hour prior to extracorporeal oxygenation, and also for 24 hours after the surgical correction. Parental consent was obtained for each patient. The study was approved by the local committee on human experimental research.

Statistical Analysis

Observations were arranged in intervals before, during and after extracorporeal oxygenation. These intervals were 12 hours for the first three days, and 24 hours thereafter. The Spearman correlation coefficient was used. P-values of 0.05 or less were considered significant.

Results

Treatment using extracorporeal membrane oxygenation therapy was successful in all our 29 neonates. The mean duration of extracorporeal oxygenation was 169.7 hours (sd 45.6). Of the patients, two died after they had been dismissed from the hospital (7% mortality). Because of the rapid changes in the echocardiographic parameters during the course of treatment, it is important to distinguish these observed changes from possible influences produced by changes in bypass. During the first 48 hours on bypass, no changes were observed in flow. The mean flow was 571ml/min. Attempts to wean were undertaken after 48 hours, with a gradual decrease of flow until it was possible to decannulate.

Systolic echo parameters and approximations of systolic pulmonary arterial pressure

Before attempting to predict pressure from the echo-Doppler parameters, the incidence of tricuspid insufficiency, pulmonary insufficiency, ductal shunting and related Doppler velocities of peak flow were studied before and during

extracorporeal oxygenation. In Table 2, we have listed the incidence of tricuspid insufficiency and peak flow velocity before and during bypass.

During the first 96 hours on bypass, tricuspid insufficiency was found to be maximal in 50-60% of all investigated patients. From these values for tricuspid insufficiency, we calculated the predicted systolic pulmonary arterial pressure. After 96 hours of bypass, tricuspid insufficiency was less representative for this population. Figure 1 shows the derived values for systolic pulmonary arterial pressure calculated from the peak velocity of the regurgitant flow in comparison to systemic systolic blood pressure. Because of significant changes occurring almost immediately after commencement of bypass, only the first 120 hours are presented in the figures. Prior to bypass ($t=0$) all patients with tricuspid insufficiency demonstrate pulmonary hypertension (mean 63 mmHg (sd 20). A sharp decline was observed even within the first 24 hours on bypass. Values for the systolic pulmonary arterial pressure decreased within 24 hours to a mean of 35 mmHg (sd 23). Looking at the relation to systemic blood pressure, 94% of the patients with

Table 2. *The incidence of tricuspid insufficiency and the related peak velocities before and during extracorporeal membrane oxygenation*

Number of -patients Time (h)	Peak velocity from the with tricuspid insufficiency present	regurgant tricuspid flow (m/s (sd))
Prior to oxygenation	16	3.59 (0.67)
0-12	16	2.93 (0.26)
12-24	13	2.45 (0.97)
24-36	12	2.31 (1.35)
36-48	10	2.52 (1.28)
48-60	10	1.95 (0.67)
60-72	09	2.53 (0.84)
72-96	14	2.42 (1.12)
96-120	09	2.09 (0.55)
120-144	05	2.01 (0.52)
144-168	04	2.67 (0.90)
168-192	02	2.10 (0.43)
192-216	02	3.12 (0.08)
216-240	02	2.00 (0.08)
240-264	0	-
264-288	0	-

Figure 1.

Comparison of mean systolic pulmonary arterial blood pressure with mean systolic systemic blood pressure before and during extra corporeal membrane oxygenation treatment. Indicated is the mean, continuous line, and $\pm$ SD.

tricuspid insufficiency showed a predicted systolic pulmonary arterial pressure of more than half the systemic blood pressure before extracorporeal oxygenation, which fall to 33% after 36 hours, illustrating the important drop in pulmonary blood pressure very early during bypass. This early and beneficial reaction from the pulmonary circulation was achieved within one fifth of the total time spent on bypass. Only in one patient (not in the figure) did we observe a rebound pulmonary hypertension due to septicaemia occurring after 168 hours on bypass, with a predicted systolic pulmonary arterial pressure of 70 mmHg which responded well to an increase of bypass flow and administration of antibiotics. In all other patients, pulmonary hypertension disappeared without rebound. Looking in the subgroup of patients with congenital diaphragmatic hernia, it is remarkable that the course of pulmonary hypertension is not essentially different from the rest of the investigated patients. After 48 hours on bypass, there is a slight difference, with lower values in those with diaphragmatic hernia. Because of small numbers (only 8 patients with a hernia), and a wide range in predicted pressures, we

Figure 2.
Comparison of mean systolic pulmonary arterial pressure in patients with congenital diaphragmatic hernia to the other patients of the investigated group. Indicated is the mean, continuous line, and $\pm$ SD.

performed no statistical analysis. The data for the patients with diaphragmatic hernia are presented in Figure 2.

Together with the approximated systolic pulmonary arterial pressure predicted from the peak velocity of the regurgitant tricuspid flow, the systolic pulmonary arterial pressure was also calculated from the systolic shunting from right-to-left across the arterial duct, using the equation described before. Before looking at the calculated values, we studied the incidence of right-to-left shunting before and during bypass. These data are presented in Figure 3. Complete or partial shunting from right-to-left was seen in 82% of patients before bypass. In 18%, no ductal shunt could be detected. During bypass, this leftward shunting disappeared very early in the course, mostly within 24 hours. In most patients a period of shunting was found from left to right before closure took place. In about half the patients, this rightward shunt was already detected within the first 12 hours on bypass.

Figure 3.

Incidence of ductal shunt before and during extracorporeal membrane oxygenation

Results for the approximated systolic pulmonary arterial pressure calculated from ductal shunting are presented in Table 3. Predicted pressures were slightly higher when calculated from ductal shunting in comparison to those derived from the

Table 3. *Values for derived systolic pulmonary arterial pressure calculated from the leftward ductal shunting peak velocities*

Time (h)	mean pressure (mmHg)	Sd	N
Before	74	17	23
0-12	75	18	10
12-24	61	5	2
24-36	-	-	-
36-48	107	9	2
48-60	86	7	2

peak velocity of regurgitant tricuspid flow. Statistical analysis showed a fair correlation between predicted systolic pulmonary arterial pressure calculated from tricuspid insufficiency and from systolic ductal shunting, with a correlation coefficient of 0.76 (Figure 4- $P < 0.002$).

Figure 4.

Comparison between predicted systolic pulmonary arterial pressure from tricuspid insufficiency and ductal shunt peak velocities ($r = 0.76$).

● = predictions from ductal shunt

○ = predictions from tricuspid insufficiency

Diastolic variables and approximations of diastolic pulmonary arterial pressure

The peak velocity of pulmonary insufficiency, diastolic shunting from left to right in those with a bidirectional shunt across the arterial duct, and the right ventricular systolic time intervals were used as parameters to approximate diastolic pulmonary arterial pressure. Pulmonary insufficiency was, in contrast to tricuspid insufficiency, observed in so few patients that a derived diastolic pulmonary arterial pressure could be calculated only rarely. This was possible in only 3 patients between 24 and 36 hours after commencement of bypass. Thus the results for diastolic pulmonary arterial pressure are limited, especially when compared to those derived from tricuspid insufficiency. The individual predictions in the few

patients studied during the first 36 hours on bypass showed no signs of severely elevated diastolic pulmonary blood pressure. Before extracorporeal oxygenation, pulmonary insufficiency was present in only one patient with a peak velocity of 2.66 m/s predicting an elevated diastolic pulmonary arterial pressure of at least 38 mmHg.

Diastolic shunting from left to right across the duct was often seen, especially during the first 48 hours on bypass. Between 10 and 67% of all patients showed this type of shunt before and during bypass. Data are presented in Table 4. Predictions for diastolic pulmonary arterial pressure from these values were much higher compared to predictions from the peak velocity of pulmonary insufficiency. Statistical analysis is not possible between these predictions because of the very

Table 4. Values for derived diastolic pulmonary arterial pressure calculated from the rightward ductal shunting peak velocities

Time (h)	mean pressure (mmHg)	SD	N
Before	38	6	11
0-12	40	1	17
12-24	43	13	8
24-36	36	15	3
36-48	38	19	6

low incidence of pulmonary insufficiency.

The right ventricular systolic time interval is the third source for calculation of diastolic pulmonary arterial pressure. (Figure 5). The standard deviation was high, especially when the systolic time interval was elevated, producing extremely high predictions for diastolic pulmonary arterial pressure. Prior to extracorporeal oxygenation, the mean interval is only slightly elevated, with a mean value of 0.34 (sd 0.17). A marked increase is seen during the first 24 hours on bypass, with a maximum after 12 hours of oxygenation (mean value of 0.73, sd 0.56). After the first 12 hours on bypass, there is then a marked decrease leading to normal values (0.30/sd 0.12) after 120 hours.

Comparisons could be made between the predicted diastolic pulmonary arterial pressure calculated from ductal left to right shunting and systolic time intervals, (Figure 6), but they showed no good correlation before or during extracorporeal oxygenation (Spearman correlation coefficient 0.25).

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Figure 5

Mean right ventricular systolic time interval before and during extracorporeal membrane oxygenation. Indicated is the mean, continuous line, and $\pm$ SD

Diastolic Pressure (

mmHg)

Figure 6

Values for approximated diastolic pulmonary arterial pressure from the right ventricular systolic time interval before and during extracorporeal membrane oxygenation. Indicated is the mean, continuous line, and $\pm$ SD)

Discussion

This study informs us about the beneficial effect of extracorporeal membrane oxygenation on severe pulmonary hypertension in critically ill neonates monitored by non-invasive echo-doppler cardiography in the intensive care unit. The non-invasive estimation of the pulmonary arterial pressure in children, as well as in adults, is well documented. (6-14). In critically ill neonates, the incidence of tricuspid insufficiency is high (14) providing the opportunity for longitudinal monitoring of pulmonary arterial pressure in special clinical circumstances such as extracorporeal membrane oxygenation.(15,16) In particular, estimations of pressure from the speed of tricuspid insufficiency and ductal shunting have been shown to be reasonably reliable (10,12,17). During the first 24 hours on bypass, we found a very remarkable and early decrease in systolic pulmonary arterial pressure. Other authors (15,16) have described this drop in pulmonary hypertension but much later during the course of bypass. They used intervals of sampling much greater than 12 hours. Sometimes a counter current echo-contrast method was used (18) rather than Doppler, which is likely to interfere with the pressure equilibrium around the persistent arterial duct. According to the registry of the Extracorporeal Life Support Organization, the characteristics of the studied population could also influence the later decrease in pulmonary hypertension when there is a high percentage of patients with diaphragmatic hernia. In our study, we could not demonstrate a longer bypass time in patients with such hernias. Because of its comfort, and high incidence before and during extracorporeal oxygenation, calculations using tricuspid insufficiency are preferable means of predicting systolic pulmonary pressure, which is clinically most important. Predictions of pressure derived from ductal shunting correlate reasonable well with those obtained from tricuspid insufficiency but, in practice, measurements of velocity in a patent duct are not always easy to obtain in contrast to the color-doppler ductal shunt. Because of the temporary nature of the rightward ductal shunting, only limited interpretations and comparisons were possible. Our study reveals a very high percentage of partial shunting in this direction (82%) where others (15,16) found 67% and 74%. This high percentage of 82% in our study is most likely also the result from frequent sampling during the first days on bypass. Estimations of diastolic pressure were investigated because of their tighter relation to pulmonary vascular resistance. Unfortunately, the incidence of pulmonary insufficiency, and ductal diastolic rightward shunting, was very low. During the highest incidence of rightward ductal shunting between 12-24 hours on bypass, predictions of pressure made from right ventricular systolic time intervals showed markedly increased values for diastolic pulmonary arterial pressure. On one hand, rightward ductal

shunting can become possible when pulmonary resistance is decreasing but still elevated compared to body resistance. On the other hand, accurate measurement of right ventricular systolic time intervals can be very difficult during extracorporeal oxygenation because of the poor opening of the pulmonary valve in systole under maximal cardio-pulmonary bypass which involves the measured pre-ejection phase, leading to extremely high predictions of pressure. During such bypass, there is also the possible risk of cardiac stun and myocardial dysfunction, as reported by other studies (15,19). Perhaps, therefore, certain restrictions must be made in measuring right ventricular systolic time intervals during this situation.

Furthermore a worse ultrasound window in patients with diaphragmatic hernia interferes with reliable M-mode echocardiography. Moreover, the gradual decrease in pulmonary resistance even in normal neonates could be of influence (20,21), and fits with the more gradual decrease in pulmonary vascular resistance monitored by right ventricular systolic time intervals during extracorporeal oxygenation. Nevertheless, the poor correlation with predicted diastolic pulmonary arterial pressures, makes difficult the clinical application of the systolic time intervals. In contrast, the systolic pulmonary arterial pressure predicted from echo parameters such as tricuspid insufficiency and ductal shunting shows fair correlations. This could be used clinically, together with other important clinical conditions, to determine the optimal moment for weaning. Together with a favourable clinical course, the observed very early reaction of systolic pulmonary arterial pressure within 24 hours of oxygenation could, perhaps, allow earlier weaning to reduce morbidity and mortality and shorten total time of extracorporeal circulation in a substantial number of patients. In a certain, way every neonate on extracorporeal oxygenation has to overcome the severe pulmonary hypertension prior to and early during the treatment, a period during which the neonate will experience a circulatory 'renaissance' with cardio-pulmonary improvement leading to the ability to wean from extracorporeal oxygenation and producing better conditions for normal life. This so-called circulatory renaissance is best observed using serial Doppler echocardiography, with monitoring of the variables which permit predictions of pulmonary pressure.

Doppler echocardiography is therefore an excellent diagnostic tool when used at the bedside in the intensive care unit to monitor severely ill neonates undergoing extracorporeal membrane oxygenation. Serial examinations give the opportunity to monitor haemodynamic changes notably pulmonary hypertension. Our study has demonstrated a very early decrease in pulmonary hypertension during oxygenation. The results also give a better understanding of changes in one of several complex parameters. Improvement of pulmonary hypertension, in

combination with pulmonary recovery, will lead to the possibility to wean from cardiopulmonary bypass. The results could provide more objective criteria for weaning. More studies will be necessary to analyze these various factors and their interrelations in determine the course of extracorporeal membrane oxygenation.

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CHAPTER 3

**The influence of ductal L-R shunting
during extracorporeal
membrane oxygenation (ECMO)**

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3 The influence of ductal L-R shunting during extracorporeal membrane oxygenation (ECMO)

Abstract

Background/Purpose: To analyze, whether a ductal L-R shunt will prolong ECMO in neonates with severe pulmonary hypertension. This study will inform us about the onset and termination of a ductal L-R shunt and its potential influences on ECMO when pulmonary hypertension decreases during veno-arterial bypass.

Methods: 29 neonates were monitored during veno-arterial ECMO, using bedside echocardiography with 12 hours interval observations.

Results: Up to 43% of the patients showed this type of shunt already after 12 hours on bypass. In total, this type of ductal shunt was found between 12-72 hours on ECMO in 62% of the patients. After 72 hours the ductal L-R shunt was no longer detected. In 38% of the patients no ductal L-R shunt was found during ECMO.

Comparisons between these two patient groups revealed a significant longer ECMO duration in patients with ductal L-R shunt ($p < 0.007$). The mean prolongation time was 46 hours. Also a significant decrease of LA/Ao ratio ($p < 0.01$) was observed during ECMO in the ductus group after closure of the duct, illustrating the decrease in volume load for the left heart and lungs.

Conclusions: We conclude that ductal L-R shunting is related with a substantial prolongation of the ECMO course (mean prolongation of almost two days). We suggest that on the one side the ductal L-R shunt will lead to pulmonary hypercirculation and on the other side, post-ductal stealing from the descending aortic circulation will lead to prerenal failure. Possibly because of interactions with pulmonary- and renal function, a ductal L-R shunt will, among other factors, interfere with weaning from ECMO, resulting in a prolonged bypass time.

Introduction

In critically ill neonates, veno-arterial ECMO may be indicated usually because of severe pulmonary hypertension and hypoxaemia due to R-L shunting at ductal or atrial level. Already 12-24 hours after the start of ECMO, an important drop in pulmonary hypertension is observed in almost all patients (1,2). As a consequence of these changes in pulmonary blood pressure, the pressure-equilibrium around a patent ductus arteriosus will change and the pre-existing R-L shunt will reverse into a L-R shunt. This ductal L-R shunt will lead to an increase in pulmonary blood flow with volume load for the left atrium and left ventricle. The ductal L-R shunt will be reinforced during bypass, by the blood flow returning from the aortic cannula. Usually the aortic cannula is positioned in the arcus aortae opposite the

patent duct. As a result from this ductal L-R shunt, pulmonary hypercirculation with pulmonary edema and poor lung compliance will possibly develop on the one side established by other authors (3-6). On the other side renal perfusion will decrease because of postductal stealing from the blood flow in the descending aorta described by others (4,7,8). This stealing could lead to prerenal failure with general edema. Depression in renal- and pulmonary function will possibly interfere with weaning from cardiopulmonary bypass and will lead to a prolongation of ECMO. The aim of this study was to determine the onset and disappearance (closure) of ductal L-R shunting during ECMO and to study its clinical impact on weaning difficulties. The results of this study will illustrate our hypothesis that ductal L-R shunting induced by a drop in pulmonary hypertension, interferes with the total bypass time leading to a prolongation on ECMO.

Methods

Patient group

Between September 1995 and September 1997 this study was performed prospectively in 29 consecutive critically ill neonates with a mean birth weight of 3306 gram (sd.574). The observed group consisted of 10 girls and 19 boys. Mean age at the time of cannulation was 1.8 day's (sd.1.3). Treatment with ECMO was indicated because of the following diagnoses: Meconium Aspiration Syndrome in 16 patients (55%), Congenital Diaphragmatic Hernia in eight patients (28%), Respiratory Distress Syndrome in one patient (3%) and Neonatal Sepsis in four patients (14%). All patients followed the in - or exclusion criteria used in our ECMO centre regarding the ELSO standards for ECMO (9). Each patient was studied with serial echo Doppler cardiography using a Toshiba SSH 140 echo Doppler machine. Because of rapid changes in the pulmonary circulation early after initiation of ECMO, the first ultrasound examination was started just prior to cannulation and repeated every 12 hours during the first 60 hours on ECMO. There-after the ultrasound study was repeated every 24 hours including the last examination made within 24 hours after decannulation. Special attention was given to the ductal shunt using colour echocardiography to determine the shunt direction in suprasternal and parasternal views. Ductal shunt was qualified as R-L, L-R or bidirectional. In bidirectional shunt, R-L shunt is in systole and L-R shunt in diastole. All ductal shunts were checked using Doppler cardiography where the suprasternal window gives the opportunity to measure the blood flow velocity in the ductus itself. Ductal L-R shunt was defined as a continuous inflow from the aorta into the pulmonary artery together with the matched colour Doppler pattern of ductal L-R shunt. To analyse the volume load to the left atrium, we measured

the diameter of the aorta and the left atrium to calculate the LA/Ao ratio (10) in parasternal long axis view. All patients were nursed in a supine position on a Airshield IICS 90 table. Body temperature was maintained between 36.8-37.5 degrees Celsius. Cannulation for veno-arterial ECMO was performed in the right neck region with positioning of the venous canula in the right atrium and the arterial canula in the aortic arch. After cannulation, ECMO flow was initiated using 180 ml flow/kg/min. Standard sedation and analgesia was given using midazolam 0.1-0.3 mg/kg/h and fentanyl 2-10 mcg/kg/h. Antibiotics were routinely prescribed, amoxicilline 100 mg/kg and gentamycine 5 mg/kg. Conservative treatment of pulmonary hypertension prior to cannulation was discontinued during ECMO. In case of hypotension dopamin or dobutamine 5-10 mcg/kg/min was used after fluid replacement in case of hypovolaemia. Standard fluid therapy was administered intravenously. Patients received, depending on age, weight gain and fluid balance, between 50-150 ml/kg. Diuretics were given routinely with furosemide 8 mg/kg. In case of oliguria, mannitol 2 g/kg. was prescribed. Pancuronium 0.01-0.02 mg/kg/h was used in all patients with Congenital Diaphragmatic Hernia before ECMO was started and also 24 hours after the surgical correction. During ECMO all patients were mechanically ventilated using a Babylog 8000 with 'rest' settings of 24 mbar inspiration pressure and 4 mbar end-expiratory pressure. Total ECMO duration was defined from the onset of cardiopulmonary bypass just after cannulation up to decannulation and measured in hours. Weaning attempts were not undertaken within the first 48 hours on ECMO. After this period weaning was attempted by lowering cardiopulmonary bypass with steps of 20 ml until an ECMO flow of 300 ml/ min was reached followed by steps of 10 ml until decannulation at an bypass flow of 50 ml/min.

Statistical analysis

The incidence of the several types of ductal shunt is presented in absolute and relative numbers. Comparisons between patients groups with and without a ductal L-R shunt were made with the two-sample Wilcoxon test. Differences with a p-value of 0.05 or less were considered significant. The 95% confidence interval was calculated. Within group comparisons in LA/Ao ratio before and directly after ductal closure were assessed with the one-sample Wilcoxon test.

Results

First, we observed the incidence of the several types of ductal shunting as reaction on ECMO treatment. It is important to distinguish the observed changes from possible influences produced by changes in bypass flow. During the first 48 hours,

bypass flow was unchanged with a mean flow of 173 ml/kg/min. After 48 hours on ECMO weaning attempts were undertaken as described before. The results are presented in Figure 1. Before ECMO is initiated, 43% of the patients showed a ductal R-L shunt and 39% a bidirectional type of ductal shunting. So, 82% showed the type of ductal shunt that corresponds with the initial existing pulmonary hypertension. In this pre-ECMO period, no ductal shunt was detected in 18% of the patients. After 12 hours of ECMO treatment we observed a remarkable increase in ductal L-R shunt up to 43% of patients. This ductal L-R shunt showed a gradually decrease during the following observation periods and was not longer detectable after 96 hours on ECMO. On the contrary, the initially observed ductal R-L shunt showed a decrease after 12 hours on bypass and reached its lowest percentage after 24 hours. The bidirectional type is observed longer, up to 60 hours in only few patients and its initial course is the same as for the ductal R-L shunt. With the disappearance of the several types of ductal shunting, an increase is observed in patients up to 62% after 24 hours on bypass, in which no longer a ductal shunt is detectable because of spontaneous ductal closure. Finally after 120 hours on ECMO, spontaneous closure of the duct was found in almost all patients. Because the remarkable changes are only present during the first 96 hours of ECMO, the figure represents only this interval on ECMO and not the total ECMO run. Observations from 96 hours on ECMO showed no interesting changes in ductal shunting.

Next, we analysed the clinical impact of the ductal L-R shunt on the total ECMO duration. In 18 patients (62%) a ductal L-R shunt was found during the ECMO course while in 11 patients (38%) this shunt was not observed. In this so-called ductus group a total ECMO duration was measured of 179 hours (s.d. 46). Patients without a ductal L-R shunt showed a total ECMO duration of 133 hours (s.d. 37). The mean difference of 46 hours in ECMO duration was statistically significant with a p-value <0.007, and a 95% confidence interval of 12-80 hours. So, apparently a ductal L-R shunt goes hand in hand with a longer ECMO course.

Figure 1.
The incidence of the different ductal shunt types before and after ECMO.

In Table 1 we present the several diagnostic sub-groups and their ECMO duration.

Table 1. Diagnostic subgroups and matched ECMO duration

Diagnosis	ductal l-r shunt presence	number	ECMO duration (mean/ s.d.)	p-value
RDS	yes	1	157 (--)	ns
	no	0	--	
CDH	yes	6	170 (36)	p<0.045
	no	2	101 (32)	
MAS	yes	9	184 (55)	ns
	no	7	144 (40)	
SEPSIS	yes	2	200 (59)	ns
	no	2	125 (10)	
Total	yes	18	179 (46)	p<0.007
	no	11	133 (37)	

Comparisons between patients with and without a ductal L-R shunt were possible in all subgroups except for Respiratory Distress Syndrome where only one patient was diagnosed. All subgroups showed a longer ECMO duration when a ductal L-R shunt was observed although time differences were only significant in patients with Congenital Diaphragmatic Hernia. In this subgroup a difference of 69 hours in ECMO duration was found. Comparisons in ECMO duration in the group of all other diagnosis except Congenital Diaphragmatic Hernia showed a longer ECMO run in the “ductal” group with a significant difference of 44 hours. This difference, with a p-value < 0.03 , is even more significant when compared to the significance level of $p < 0.045$ in the hernia group. It is also important to mention that in our study, patients with Congenital Diaphragmatic Hernia, in general, did not show the longest ECMO duration. Finally, we analysed the volume load from a ductal L-R shunt for the left atrium during ECMO. Within the patient group with a ductal L-R shunt, comparisons were made between the LA/Ao ratio before and after ductal closure in 17 patients. These observations are presented in Figure 2. During ECMO there is a decrease observed in the mean LA/Ao ratio after ductal closure from 1.2 to 1.0. The difference is statistically significant with a p-value < 0.01 .

Figure 2.

The LA/Ao ratio during ECMO in patients with ductal L-R shunt , before and after spontaneous closure

Discussion

This study reveals that a ductal L-R shunt is present in a considerable amount of neonates on ECMO. This ductal shunt becomes possible when pulmonary hypertension falls down during ECMO (1). During this process of circulatory changes around a patent ductus arteriosus, the flow from the aortic cannula will possibly reinforce the L-R shunt at ductus level. This ductal L-R shunt also potentially interferes with renal perfusion (4,7-8) by postductal stealing from the descending aortic blood flow leading to prerenal failure with oliguria and general edema. Besides that, Lotze et al. demonstrated that the ductal L-R shunt will create a situation with pulmonary hyperperfusion and pulmonary edema with great impact on lung compliance (3). A lot has been published about the typical radiological 'white-out' pattern of the chest X-ray as an expression of pulmonary edema, which is present in a high proportion of patients (11-14). Also other factors are important in the genesis of pulmonary- and general edema and fluid retention during ECMO such as reoxygenation injury (15). In the way described above a ductal L-R shunt can reinforce several causes of edema and worsen the ECMO course by interfering with weaning from cardiopulmonary bypass because of a bad lung compliance. Other authors also found ductal L-R shunts during ECMO but in a lower incidence and later in the course (2). Possibly our 12 hours examination interval is more sensitive in detecting ductal shunts. However, this study reveals the prolonging effect from a ductal L-R shunt on ECMO with almost 48 hours. To our opinion this ductus-associated prolongation is of clinical importance because of the risks associated with ECMO to which a patient is exposed. Only few studies report the reversal in ductal shunting but without granting great clinical impact (2). Although the numbers of the various diagnostic subsets are small, it is remarkable that patients with Congenital Diaphragmatic Hernia did not show the longest ECMO duration, which is usually the case according to the ELSO data (9). To our opinion a longer ECMO course is more likely to be the effect of ductal L-R shunting than a result from the diagnosis Congenital Diaphragmatic Hernia. Unfortunately, there are no other publications about this specific issue. Concerning the volume loading to the left heart by a ductal L-R shunt, it is documented (10) that LA/Ao is influenced by a ductal L-R shunt. However, during ECMO it is not earlier demonstrated. During cardiopulmonary bypass for ECMO, antegrade pulmonary blood flow is diminished so, preload to the left heart is also diminished and therefore the LA diameter. The reinfused blood flow into the ascending aorta from the aortic cannula could alter the aortic diameter. So during bypass LA diameter is probably smaller and aortic diameter larger. Therefore the LA/Ao ratio will not be much increased but is useful in monitoring changes in the left atrial

diameter especially when bypass flow is unchanged. When ECMO creates a drop in pulmonary hypertension and subsequently a ductal L-R shunt, pulmonary blood flow is likely to be increased by the continuous ductal inflow. During ECMO it is therefore possible that the LA/Ao ratio will increase and subsequently will decrease again after spontaneous closure of the ductus. The observed changes in LA/Ao are mostly detected very early in the ECMO course when bypass flow is still unchanged or will show only very small changes. Other authors measured also diameters of the left atrium and aorta before during and after ECMO. They observed no significant changes in LA/Ao ratio. However, observation intervals in their study were much larger compared to our study. Besides that, they made no difference between patients with and without a ductal L-R shunt (2). The results of our study indicate that the ductal shunt deserves much more attention during ECMO and more studies are necessary to analyze the effect from the ductal L-R shunt and its relevance among other factors, on weaning variables. If we were able to control the ductal L-R shunt during ECMO after pulmonary hypertension is treated efficaciously, possible reduction in ECMO duration could be realizable with lowering risk for mortality and morbidity.

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CHAPTER 4

**Measurement of the ductal L-R shunt during
extracorporeal membrane oxygenation in the lamb**

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4 Measurement of the ductal L-R shunt during extracorporeal membrane oxygenation in the lamb

Abstract

In neonates, initially a ductal shunt is often observed during ECMO. Depending to the degree of pulmonary hypertension in these patients the ductal shunt will be R-L, L-R or bidirectional. A ductal L-R shunt will possibly lead to pulmonary hyperperfusion and interact with ECMO weaning. The aim of this study was to give more insight in this ductal L-R shunting during ECMO.

In seven lambs, closure of the duct was prohibited by infiltration of the ductal wall with formaline 10%. Secondary, this patent duct could be closed using a vesselloop around the duct. Ultrasound flowprobes were installed around the pulmonary artery, ascending aorta and around the ECMO circulation tube. Right and left ventricular output and ECMO circulating volume were measured. Ductus flow was defined as $Q_{\text{duct L-R}} = Q_{\text{ao}} - Q_{\text{pa}}$ and $Q_{\text{duct R-L}} = Q_{\text{pa}} - Q_{\text{ao}}$.

In 6 of 7 lambs a ductal L-R shunt was observed with a mean shunt of 44% (range 11-79) of left ventricular output ($Q_{\text{duct L-R}}/Q_{\text{ao}}$). Comparison to ECMO flow ($Q_{\text{duct L-R}}/Q_{\text{ecmo}}$) revealed a mean shunt of 91% (range 15-230). When compared to the total circulating volume ($Q_{\text{pa}} + Q_{\text{ecmo}}$), the mean ductal L-R shunt showed a percentage of 51% (range 7-142%).

During veno-arterial ECMO mostly a ductal L-R shunt is observed in the lamb. This ductal shunt is haemodynamically important with a mean shunt of 44% of left ventricular output. When the ductal L-R shunt is compared to the total circulating volume a mean shunt of 51% is calculated. Because of this important L-R shunt, interference with pulmonary- and systemic perfusion such as renal perfusion is to be expected.

Introduction

Extracorporeal membrane oxygenation is used for many years (1) in critically ill neonates with severe pulmonary hypertension due to cardiorespiratory failure secondary to meconium aspiration syndrome, congenital diaphragmatic hernia, neonatal sepsis or persistent pulmonary hypertension of the neonate. In the clinical situation prior to ECMO, the duct is mostly patent with R-L shunting due to pulmonary hypertension (2,3). During ECMO, a drop in pulmonary hypertension is observed, usually early in the course (2,3).

The decrease in pulmonary blood pressure and pulmonary resistance will create ideal circumstances for a significant ductal L-R shunt in case the duct is still patent. From the clinical picture, there are characteristic signs and symptoms in the

neonate during the ECMO course such as general edema, pulmonary edema, decreased lung compliance and a typical white-out pattern on the chest X-ray (4,5). The question is whether a ductal L-R shunt plays, among other factors (6), an important role in this clinical picture. Therefore it is important to quantify this ductal L-R shunt during ECMO and observe its relation to cardiac output and ECMO flow.

Materials and methods

Fetal animal preparations

In this study, all animals were taken care of according to the rules of Good Laboratory Practice including water- and food supply. Surgical and experimental procedures were approved by the Ethical Committee on Animal Research of the University of Nijmegen. The lamb was selected for this study because of its close relation to physiological aspects of the circulation in the human infant (7), and also because of experience with the ECMO model in the lamb. Seven mixed breed ewes were operated under general anaesthesia around 140 days of gestation (term 147 days). Anaesthesia was induced with pentobarbital 30 mg/kg intravenously and maintained with 2 % enflurane in a 1:1 mixture of nitrous oxide and oxygen administered by mechanical ventilation (Engstrom ER 300 respirator, Stockholm, Sweden). Body temperature was maintained by means of a thermostatic pad. Heart rate was monitored by an ECG monitor. After shaving and disinfecting the abdominal skin, a laparotomy was performed by paramedian incision. The peritoneum was opened and the uterus was mobilized and covered with warm soaked gauzes. By palpating the fetal lamb and under accurate haemostasis, hysterotomy was performed around the fetal left shoulder followed by partial delivery of the upper part of the fetal lamb. After positioning for a left lateral thoracotomy in the fourth intercostal space, the fetal lamb was covered with warm soaked gauzes. Using a spatula, the left lung was kept aside and the great vessels including the duct were identified and bridled using vessel loops. Now the ascending aorta, pulmonary artery and the duct were trimmed from their adjacent tissue. The ductal wall was infiltrated without entering the ductal lumen to provide patency, with formaline 10 %, colored with a few drops of sterile methylene blue, according to the technique described by Rudolph et al (8).

Approximately the total length of the duct was infiltrated. This was checked by the blue colored ductal wall. The subadventitial infiltration was performed circular as much as was possible with special attention for the posterior part. Next a vessel loop was positioned around the duct without narrowing its lumen. The ends of the vessel loops were put into a sheath and fixed with a clamp. After this preparation,

the patent duct could easily be closed from outside the thorax by pulling the vesselloops out of the sheath. Flow probes (Transonic cardiac output A probes / Transonic Systems Inc. Ithaca NY, USA) were installed around the ascending aorta and pulmonary artery both just above the arterial valves. Probes ten or twelve millimeters of diameter were used depending of the artery diameter. Both the leads of the probes and the sheath containing the vessel loop around the duct were exteriorized from the thorax. The leads of the flow probes were connected with a Transonic Medical flowmeter HT 207 (Transonic Systems Inc. Ithaca NY, USA.). The thorax was closed in layers.

Flow measurement and calculations

To measure the ductal bloodflow we defined the total systemic circulation (Q_{tot}) as the summation of ECMO flow (Q_{ecmo}) and pulmonary artery flow (Q_{pa}). In formula, $Q_{tot} = Q_{ecmo} + Q_{pa}$. In case of ductal L-R shunting, the total systemic circulation is also defined as ECMO flow together with ascending aorta flow minus the flow in the ductal shunt (Q_{duct}). In formula, $Q_{tot} = Q_{ecmo} + Q_{ao} - Q_{duct}$. Both equations now define the total systemic circulating volume: $Q_{tot} = Q_{ecmo} + Q_{pa} = Q_{ecmo} + Q_{ao} - Q_{duct}$. Thus, $Q_{duct} = Q_{ao} - Q_{pa}$ in case of a ductal L-R shunt and $Q_{duct} = Q_{pa} - Q_{ao}$ in case of R-L shunt. Both blood flows in the pulmonary artery and in the ascending aorta are measured simultaneously and together with the ECMO flow, so the ductal L-R shunt is easily calculated from the equations above in ml/min. In this calculation, coronary perfusion and possible atrial shunting is left out of consideration. Comparison of the ductal L-R shunt to aortic flow (Q_{ao}), ECMO flow (Q_{ecmo}) or total systemic circulation ($Q_{pa} + Q_{ecmo}$) will provide the possibility to determine the haemodynamic importance.

ECMO surgery and cannulation

After the fetal preparations as described above, the fetal lamb was orotracheal intubated and mechanically ventilated using a Babylog 8000 (Draeger, Lubeck, Germany). The umbilical cord was ligated and the lamb was placed over to the ECMO table. Catheters were inserted through the femoral artery and vein and the tips were placed respectively in the abdominal aorta for bloodsampling and monitoring of the systemic blood pressure, and in the inferior caval vein for administration of fluids and medication. Anesthesia was induced using midazolam 0.2 mg/kg, fentanyl 10 µg/kg and pancuronium 0.1 mg/kg and maintained with midazolam 0.2 mg/kg/h, fentanyl 2-5 mg/kg/h and pancuronium 0.02 mg/kg/h. Standard veno-arterial ECMO was performed by cannulating the right common

carotid artery and the jugular vein using a 10 and 12 french cannula respectively. The tip of the arterial cannula was positioned in the brachiocephalic trunk and that of the venous cannula in the right atrium. During ECMO heparin was administered intravenously and monitored using the activated clotting time (ACT: 200-250 sec.). ECMO flow was measured by a Transonic flow probe around the arterial ECMO tube connected with a Transonic Medical volume flowmeter HT 107. ECG was monitored during the experiment using needle electrodes connected to a Hewlett Packard 78330A monitor (Hewlett Packard, Boeblingen Germany). Rectal temperature was kept between 38.5-39 degrees Celsius with a servo controlled heating mattress.

Experimental protocol

After all preparations, the lambs were stabilized. Ventilator settings were adjusted to maintain normoxemia: arterial oxygen saturation > 90%, arterial partial pressure of oxygen > 10 kPa and arterial partial pressure of carbon dioxide at 3.6-6.4 kPa. Priming of the ECMO system was carried out by using sheep's donor blood in combination with gelofusine. After starting ECMO, the flow rate was increased gradually over several minutes until further increase was impossible due to limitations of the backflow in the venous cannula. The mean ECMO flow obtained was 90 ml/kg/min (range 73-118 ml/kg/min). Mean bodyweight of the lambs was 4.3 kg (range 3.1-5.1). Once stabilized, ECMO was continued for two hours during which flows were measured according to our protocol. Then the duct was closed using the mechanism described before. Figure 1 is demonstrating an overview of all measured flows and calculated ductal L-R flow during an experiment. All flows were recorded in a data acquisition system (personal computer with data acquisition software, POLY (R), Inspector Research System, Amsterdam, The Netherlands) together with heart rate and blood pressure. After finishing the experiment, the lamb was terminated by an overdose of pentobarbital. Autopsy was performed with special attention for the patency of the duct and its mechanical closure system. The heart was inspected using the sequential analysis for detecting congenital heart disease.

Ductus flow

Figure 1. Overview of measured flows during an experiment and calculated ductal L-R flow
 →: closure of ductus arteriosus

Data analysis

All data were recorded with a frequency of 100 Hz. Mean flow data were calculated over the interval one hour before closing the duct and presented as the mean and its range. Data analysis

Mean ductal L-R shunt was calculated and also expressed as part of the left ventricular cardiac output, ECMO flow and total systemic circulating volume.

Results

Table 1 presents the flow data observed during all the experiments. A ductal L-R shunt could be calculated in 6 of 7 experiments. In one case a ductal R-L shunt was observed and calculated as 324 ml/min. In all lambs with a ductal L-R shunt,

Table 1. Measured flow in ascending aorta, pulmonary artery and ECMO-circuit with calculated ductal shunt

	R-L			L-R					
experiment no:	1	2	3	4	5	6	7	Mean	Range
Qao (ml/min)	582	1145	468	1047	1354	615	328	791	328-1354
Qpa ml/min	906	620	410	223	1201	215	166	534	166-1201
Qecmo ml/min	415	506	400	359	365	392	312	393	312-506
Q L-R ml/min	---	525	58	824	153	400	162	354	58-824
Q R-L ml/min	324							---	---

a mean shunt was calculated of 354 ml/min (58-824 ml.) corresponding to 82 ml/min/kg bodyweight. In Tabel 2, the flowratio of the ductal L-R shunt in comparison to the several output volumes, namely left ventricular cardiac output (Qao), ECMO flow (Qecmo) and total circulating volume (Qtot) is showed.

Table 2. Flow ratio between ductal L-R shunt and respectively left ventricular output, ECMO flow and total systemic circulation

	R-L				L-R					
experiment no:	1	2	3	4	5	6	7	Mean	Range	
Q L-R/Qao (%)	---	46	12	79	11	65	49	44	11-79	
Q L-R/Qecmo (%)	---	104	15	230	42	102	52	91	15-230	
Q L-R/Qtot (%)	---	47	7	142	10	66	34	51	7-142	
(= Qpa + Qecmo)										

Fortyfour percent of the left ventricular cardiac output is presented by the ductal L-R shunt. In comparison to the ECMO flow, a flowratio of 91% was demonstrated when the flow of the ductal L-R shunt was compared to the ECMO flow. Looking at the total systemic circulation, the ductal L-R shunt forms 51% part of the total circulating volume. In 5 lambs, the ductal flow approximated to zero after closure using the vesselloop. In two lambs a residual ductal shunt persisted after closure. At autopsy, we discovered in these lambs once a small perforation in the ductal wall and once a not proper totally closed duct demonstrating a residual diameter of 2-3 mm. In all other experiments the duct was found closed at autopsy with the vesselloop thight around the duct. Not one of the lambs demonstrated signs of congenital heart disease at autopsy.

Discussion

From the results of our study, we can conclude that in the lamb a large and significant ductal L-R shunt during ECMO is noticed with a mean percentage of 44 % of left ventricular cardiac output or 51 % compared to the total systemic circulation. In comparison to L-R shunts in neonates or infants because of congenital heart disease such as ventricular septal defect, similar percentages as observed in our study would be haemodynamically important and will usually give way to (surgical) treatment (9). A significant ductal shunt will give support to the onset of pulmonary hypercirculation and decreased renal circulation as described by E.I. Wallgren in infants and by Clyman in lambs (10,11). ECMO will facilitate this pulmonary hypercirculation because of its beneficial effect on pulmonary

resistance and pulmonary hypertension. In this study we measured bloodflow in neonatal lambs immediately after birth when still a certain level of pulmonary hypertension is present. In this way we tried to imitate the pulmonary hypertensive state of neonates on ECMO. In one experiment, we observed a ductal R-L shunt as an expression of pulmonary hypertension. This experiment was complicated by severe systemic hypotension when ECMO was initiated. The administration of large doses of adrenalin and sheep blood was necessary to treat this hypotension, resulting in ventricular fibrillation. Defibrillation and a forced step up in ECMO flow was performed and successful. After this asphyctic period we suggest that acidosis and pulmonary hypertension was involved, resulting in a ductal R-L shunt. Of course, ECMO should be successful in treating this pulmonary hypertension but usually not capable in reversing the ductal shunt within the two hours of our experiment. In neonates, this occurs usually within 12-24 hours after ECMO is started (3).

Anyhow, the demonstrated significant ductal L-R shunt during ECMO will give support to a pulmonary hypercirculation with pulmonary edema at the one side. In neonates on ECMO, severe lung compliance disturbances (12) and the so-called radiographic "white-out" pattern of the lungs (13) could be explained from this ductal shunt. At the other side, a mean ductal L-R shunt of 44% of left ventricular cardiac output is important enough to interfere with the perfusion to the descending aorta and so to the renal perfusion (10,11). In this way some degree of renal hypoperfusion with general edema as consequence, is acceptable and also explicable from the ductal L-R phase during ECMO. Many authors did demonstrate the ductal L-R shunt during bypass in neonates (1, 2, 14). Also other authors quantified a ductal L-R shunt mostly in the animal experiment (15). However, no other studies quantified the ductal L-R shunt during ECMO. Our results concerning the significant ductal L-R shunt agree with the ductal shunt data published by Clyman (11) and by Baylen (15). Perhaps their measurements in preterm lambs treated with surfactant could explain some differences in comparison to our study. We measured the ductal L-R shunt about two hours after birth, usually a period with still a certain degree of pulmonary hypertension and elevated pulmonary resistance. In comparison to neonates, our animal experimental situation is unfavourable for the development of a progressive L-R shunt because of the limited time on ECMO. And yet, we measured already such an important L-R shunt. Hypothetically, inforcement of the ductal shunt could be possible by the flow from the aortic canula which returns from the pump into the aortic arch not far from the origin of the duct, especially when pulmonary resistance drops and bypass is maintained for several days.

At the other side, bloodpressure during veno-arterial bypass is usually less pulsatile, possibly leading to mitigation of the inforcing effects described above. Much more studies are necessary to analyse the different side-effects of the ductal L-R shunt in relation to other organ perfusion and function during ECMO.

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CHAPTER 5

**Ductal dependent changes in left ventricular
dimensions and fractional shortening in neonates
undergoing veno-arterial
extracorporeal membrane oxygenation**

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(resubmitted after revision 2003)

5 Ductal dependent changes in left ventricular dimensions and fractional shortening in neonates undergoing veno-arterial extracorporeal membrane oxygenation

Abstract

The aim of this study was to analyse left ventricular fractional shortening during Extra Corporeal Membrane Oxygenation under the influence of changing volume loading conditions induced by a ductal left to right shunt. In all patients the fractional shortening was observed before, during and after bypass together with the presence or absence of a ductal left to right shunt, using echocardiography. During membrane oxygenation there was a significant decrease in fractional shortening ($p < 0.001$). Fractional shortening before and after membrane oxygenation showed no difference. A greater decrease in fractional shortening was observed in the group with a ductal left to right shunt, compared to patients without this ductal shunt ($p < 0.006$). The diastolic diameter of the left ventricle showed a significant increase in those patients with a ductal left to right shunt during the membrane oxygenation. More-over, patients demonstrating a ductal left to right shunt during the course of membrane oxygenation, showed significant more frequently ($p < 0.05$) a very severe decreased fractional shortening (fractional shortening lower than 10%).

Conclusion During veno-arterial Extracorporeal Membrane Oxygenation, an important decrease in left ventricular fractional shortening is observed. A ductal left to right shunt during bypass will increase the loading conditions to the left ventricle illustrated by a significant increase in diastolic left ventricular dimension in ductus patients. However, despite the volume loading effects of a ductal left to right shunt during bypass, the decrease in fractional shortening is significantly more pronounced for these patients. So during membrane oxygenation the volume loading effects from a ductal left to right shunt cannot prevent a decrease in left ventricular fractional shortening.

Introduction

Cardiac performance is usually determined by preload, afterload, contractility and heart rate. (1) Recently the synchronous contraction of the ventricles is considered as an important factor too. (2) During veno-arterial extracorporeal membrane oxygenation, important changes in preload are observed. (3) Because of the drainage from the right atrium to the pump, the preload for the right ventricle is decreased and because of the bypassed pulmonary circulation also the preload for the left ventricle will be decreased. In contrary to heart surgery, the heart during

extracorporeal membrane oxygenation is not empty. Most ultrasound observations during extracorporeal oxygenation will show a non-collapsed heart even at high pump-flow rates. (4) Usually flow rates of 180-200 ml/kg/min have been used almost equal to the normal neonatal cardiac output. (5) Changes in loading conditions are frequently attributed to alterations in left ventricular dimensions and fractional shortening during bypass. (6,7) Mostly after 24-48 hours of bypass, a significant decrease in fractional shortening is observed. During the same phase of the bypass course, a ductal left to right shunt is observed in a considerable amount of neonates. (7,8,9) This ductal shunt will increase the pulmonary perfusion and thus increase the preload to the left heart. In this study we were interested in intracardiac volume changes induced by a ductal left to right shunt and its consequences for the left ventricular dimensions and fractional shortening. At the one side, because of an increase in loading conditions to the left ventricle, an increase in fractional shortening could be expected. According to the literature this ductal left to right shunt could perhaps protect the left ventricle against a decrease in fractional shortening. (10) At the other side, the stressed myocardium in this phase of the bypass run will possibly be incapable to tolerate the ductus induced increased loading conditions shortly after membrane oxygenation is started.

Methods

Consecutively, twenty nine patients were studied prospectively and met the standard criteria (11) for Extracorporeal Membrane Oxygenation. They were all treated with veno-arterial membrane oxygenation also according to the standard of the Extracorporeal Life Support Organization. The group of twenty nine neonates consisted of ten girls and nineteen boys. Mean birth weight was 3306 gram (sd 574). Membrane oxygenation was indicated because of the following diagnoses: Meconium aspiration syndrome in sixteen (55%), congenital diaphragmatic hernia in eight (28%), respiratory distress syndrome in one (3%) and neonatal sepsis in four (14%). Mean age at time of cannulation was 1.8 days (sd 1.3). Cardiac studies were performed with a Toshiba SSH 140 echocardiograph using sector- and M-mode echocardiography with calculation of the fractional shortening in the parasternal long axis view. Fractional shortening was calculated as the diastolic dimension of the left ventricle minus the systolic dimension of the left ventricle divided by the diastolic dimension of the left ventricle, multiplied by 100 and expressed as a percentage. (12) All patients were examined just before cannulation, every 12 hours on bypass during the first 60 hours and all following days including the last investigation made within 24 hours after decannulation. The presence of a patent ductus arteriosus with a left to right shunt was diagnosed

using color-and Doppler echocardiography in the suprasternal and parasternal views. A ductal left to right shunt was defined as a continuous inflow in the pulmonary artery from the aortic arch. Interpretation of all echo Doppler variables took place without any knowledge of the clinical course of the patient to the observer.

Management of patients

All patients were nursed in a special intensive care room on an AirShield IICS 90 table. Body temperature was maintained between 36.8 and 37.5 degrees Celsius. Blood pressure was obtained from an umbilical arterial line placed with the tip in the descending aorta and recorded by a neonatal monitor (HP 78801 B). Central venous pressure was measured by an umbilical line with the tip in the right atrium, and recorded by the same monitor in addition to the heart rate. Pre- and postductal oxygen saturation were monitored with a Nellcor pulsoximeter. Depending on age, weight gain and fluid balance the prescribed fluid intake was at least 50 ml/kg, and maximal 150 ml/kg. Standard diuretic therapy was administered using furosemide 4-8 mg/kg/day depending on fluid balance and urinary production. Antibiotics were routinely prescribed, amoxicillin 100 mg/kg/day and gentamycine 5-7 mg/kg/day. Prior to cardio-pulmonary bypass, heart failure or hypotension not due to hypovolaemia were treated with intravenous administration of dopamine or dobutamine (5-20 mcg/kg/min). Pulmonary hypertension was treated with vasodilating drugs including inhalation of nitric oxide. Before the extracorporeal oxygenation was started, ventilatory support ranged from standard mechanical positive pressure ventilation to high frequency oscillation. During bypass, basic mechanical ventilation was maintained with minimal ventilator settings. Surgical intervention for correction of congenital diaphragmatic hernia was performed only after adequate oxygenation could be obtained with bypass flow weaned to 50 ml/min. All patients were sedated during bypass using midazolam 0.1-0.3 mg/kg/h and fentanyl 2-10 mcg/kg/h. Pancuronium 0.01-0.02 mg/kg/h was used in all patients with diaphragmatic hernia 24 hours after initiation of extracorporeal oxygenation, and also for 24 hours after the surgical correction. Parental consent was obtained for each patient. The study was approved by the local committee on human experimental research. This study was financially supported by the Dutch Heart Foundation (grant no. 94.023).

Statistical analysis

The diastolic and systolic left ventricular dimensions and the fractional shortening in all patients were monitored before, during and after extracorporeal oxygenation.

Figure 1A and 1B: Variations in mean diastolic (1A) and systolic (1B) left ventricular dimensions during extracorporeal membrane oxygenation in all patients. (Ddlv = diastolic dimension of the left ventricle, dsLv = systolic dimension of the left ventricle).

These observations were made as part of a another study published earlier (8) Observations especially made to analyse the influence of a ductal left to right shunt were selected as, before the start of bypass, 24-36 hours on bypass and within 24 hours after decannulation Data are presented as mean and range Because of the still unchanged maximal bypass flow at 24-36 hours after start of the extracorporeal membrane oxygenation together with a high prevalence of a ductal left to right shunt (8 9) , the observation was chosen at 24-36 hours on bypass

Patients were grouped according to the presence of a ductal left to right shunt, 24-36 hours after extracorporeal membrane oxygenation has started, as the “ductus”group and the “non-ductus”group The differences in left ventricular diameter and the fractional shortening before, during and after bypass were computed and assessed with the Wilcoxon test (signed rank test) in all patients and with the Wilcoxon test (rank sum test) for differences between groups P-values of 0.05 or less were considered significant

Results

Results concerning variations in left ventricular dimensions and fractional shortening in all patients

The measured values of left ventricular dimensions and fractional shortening, during bypass are showed in figure 1A/B and figure 2 Bypass flow is unchanged during the first 48 hours on membrane oxygenation because no weaning attempts were undertaken Therefore the first part of the figures 1A/B and 2 represents all patients in the same phase of extracorporeal oxygenation under full bypass flow However, due to the different clinical course of extracorporeal membrane oxygenation, the second part of the figures 1A/B and 2 is difficult to analyze because patients will show a lot of differences among themselves in the weaning process After decannulation all patients are again comparable between themselves in the same way as before bypass and during the first 48 hours on bypass

Looking at the left ventricle(table 1 and 2), the mean diastolic and systolic left ventricular dimensions before bypass were small and approaching the fifth percentile when compared to the normal values for left ventricular dimensions in children (13,14) However, during the first 48 hours of membrane oxygenation, despite the unchanged high bypass flow, an significant increase in diastolic and systolic diameter was observed ($p < 0.02$, $p < 0.001$) in all patients The systolic diameter will show a decrease during the bypass course After membrane oxygenation is stopped, the left ventricular dimensions are still small compared to normal

Figuur 2: Variations in mean left ventricular fractional shortening during extracorporeal membrane oxygenation in all patients. (*sf* = fractional shortening).

Looking at the fractional shortening, a normal mean fraction of 36% (sd 11) was measured before bypass. After extracorporeal oxygenation was initiated, mean fractional shortening decreased to 20% (sd 11) and thus demonstrated a significant decrease. This significant decrease in mean fractional shortening, was observed in all patients during bypass. ($p < 0.001$) Mean fractional shortening after membrane oxygenation was 40 % (sd 11) and showed no significant difference in comparison to the values for fractional shortening before bypass.

Results in subgroups

In 18 patients a ductal left to right shunt was demonstrated after 24-36 hour on membrane oxygenation. Table I and II together with figure 3A/B and 4 will present the mean values for diastolic and systolic left ventricular dimensions and fractional shortening in patients with and without a ductal left to right shunt, measured before, at 24-36 hours on bypass and after decanulation. In the "ductus" group, mean diastolic and systolic dimensions showed a significant increase comparable to the total group. ($p < 0.05$, resp. $p < 0.0005$) After bypass is stopped no important changes were observed in the diastolic diameter. The systolic

diameter however, decreased again to its original level before bypass. Looking at the fractional shortening in this “ductus” group before, during and after bypass, we measured respectively a mean value of 37% (sd 12), 16% (sd 10) and 40% (sd 13). Comparison between fractional shortening before and during bypass, showed also a significant decrease in fractional shortening ($p < 0.001$) in the “ductus” group with a mean decline of 21% (sd 13).

Table 1. Patients with ductal left to right shunt ($n=18$)

	mean DdLV	(range)	mean DsLV	(range)	mean FS	(range)
before	13.3	(9.2 - 17.7)	8.5	(3.8 - 12.5)	36.5	(15 - 69)
24-36	15.5	(12.1 - 21.4)	13.0	(8.7 - 18.8)	16.4	(0 - 41)
after	14.8	(9.1 - 20.5)	8.9	(3.8 - 16.2)	40.1	(37 - 61)

Table 2. Patients without ductal left to right shunt ($n=11$)

	mean DdLV	(range)	mean DsLV	(range)	mean FS	(range)
before	14.7	(11.0 - 26.9)	9.7	(4.8 - 18.5)	35.1	(21 - 56)
24-36	16.9	(11.2 - 23.1)	12.3	(8.1 - 17.1)	29.0	(16 - 39)
after	15.8	(12.9 - 19.2)	9.5	(6.7 - 14.7)	40.3	(23 - 50)

In the “non-ductus” group of 11 patients, the mean diastolic dimension did not increase significantly during bypass. Systolic dimension showed the same significant increase as earlier observed ($p < 0.009$). Fractional shortening in this group before, during and after bypass was calculated as respectively 35% (sd 12), 29% (sd 7) and 40% (sd 7). The observed decrease of 6% in fractional shortening in these patients was not significant.

Prior to bypass, no differences in fractional shortening were observed between the “ductus” group and the “non-ductus” group. On the contrary, during membrane oxygenation, the decrease in fractional shortening was significantly more pronounced in those patients who developed a ductal left to right shunt with a significant difference ($p < 0.006$). This difference in fractional shortening during bypass disappeared again after bypass was terminated. Furthermore, 65% of patients in the “ductus” group showed a very severe decreased fractional shortening

Figuur 3A and 3B: Variations in mean diastolic (DdLV) and systolic (DsLV) left ventricular dimensions before, at 36-48 hours on and after extracorporeal membrane oxygenation in patients with (3A) and without (3B) a ductal left to right shunt during bypass.

Figuur 4: Variations in mean left ventricular fractional shortening before, at 24-36 hours on and after extracorporeal membrane oxygenation in patients with and without a ductal left to right shunt (FS = fractional shortening)

smaller than ten percent, against 22% of patients in the “non-ductus” group. This difference in very severe decreased fractional shortening between the “ductus”- and the “non-ductus” group is significant. ($p < 0.05$)

Discussion

Before extracorporeal membrane oxygenation is started the measured mean left ventricular diastolic and systolic dimensions are much lower in comparison to the left ventricular dimensions in the normal population. Other authors described dimensions within the same range as we observed, but did not comment the low percentiles of the left ventricular dimensions in this particular patient group. (4,6,15) It is unclear why the left heart chamber is so small before membrane oxygenation. Possibly the severe pulmonary hypertension resulting in a ductal right to left shunt, will reduce the preload to the left ventricle in this situation. Also the pressure overload of the right ventricle before bypass could be of influence by a shift in the position of the interventricular septum. Once on bypass, we observed a significant increase of diastolic and systolic diameter for all patients. Looking in the “ductus” subgroup we found the same significant increase especially in diastole which was not found in patients of the “non-ductus” group. The observed increase in diastolic dimension in the ductus group, will illustrate the

volume loading to the left ventricle, once a ductal left to right shunt has developed

The left ventricular fractional shortening was not depressed before the start of extracorporeal oxygenation, especially when the clinical picture of the critically ill patients before bypass is taken into account. The temporary administration of dopamine and dobutamine could also influence this pre-bypass phase because of the positive inotropic effects. During bypass a drop in fractional shortening is noticed, possibly related to various factors such as decreased preload, post-hypoxic injured myocardium and reperfusion injury or increased afterload (4,6,15,16). Other authors have described this drop in fractional shortening and have postulated that the decrease in preload was responsible for the bad fractional shortening (3). Ofcourse left ventricular performance is also measured and monitored with parameters that are more insensible to the preload, such as heart-rate-corrected mean circumferential fiber fractional shortening (17). However, our study was performed to analyze the volume loading effects of a ductal left to right shunt. For that reason we selected the fractional shortening, a preload dependent parameter (4), and examined whether a ductal left to right shunt will have an increasing effect on the fractional shortening. So, a ductal left to right shunt will create a better preload state for the left ventricle. A ductal left to right shunt will also influence the coronary oxygen saturation because the ductal shunt will increase the oxygen saturation of the blood in the left atrium and the left ventricle. The oxygen saturation in the left atrium is usually decreased in this phase of membrane oxygenation because of intrapulmonary right to left shunting. It has become clear, that the coronary perfusion is in particular determined by the antegrade flow from outflow tract into the ascending aorta and less influenced by the retrograde flow from the aortic cannula (18). Nevertheless concerning the fractional shortening, we observed no preserving effect from a ductal left to right shunt. Nakamura (10) described a better coronary oxygen saturation and perfusion when a small left to right shunt is present in dogs placed on extracorporeal membrane oxygenation. On the contrary, we observed a significant decrease in the fractional shortening during bypass, in those patients with a ductal left to right shunt. Possibly, this volume loading to the left ventricle is not tolerated very well shortly after extracorporeal oxygenation is started. In this context, an important ductal left to right shunt could, at the other side, decrease the coronary perfusion by stealing the blood in diastole from the aorta into the direction of the pulmonary artery. In all patients the decreased fractional shortening normalized without any specific therapy after decannulation. The duct was also closed in all these patients. Holley et al (4) pointed out that the decrease in cardiac performance is not influenced by

the underlying diagnosis but mainly is determined by loading conditions. The ductal left to right shunt during bypass is, in general, haemodynamically important and will lead to pulmonary hyperperfusion that is demonstrated in the lamb (19). This volume loading effect is regarded to be beneficial. In contradiction to Holley (4), we could not observe any protecting effect from a ductal left to right shunt in relation to the fractional shortening. Perhaps other factors than preload are more important during extracorporeal membrane oxygenation, for example, the afterload, left ventricular wall stress or coronary artery resistance. The results of studies concerning these factors are somewhat conflicting. Kimball (6) pointed out that during bypass no significant changes in contractility or afterload were observed when volume load independent determinants of cardiac output were used (heart rate-corrected velocity of circumferential fiber fractional shortening in relation to wall stress and left ventricular end systolic wall stress). Berdjis et al (17) measured also volume load independent variables and found no disturbances in contractility when corrected for afterload and suggested that there was no depression on myocardial function. On the contrary, Kato and co-workers demonstrated in dogs a decrease of coronary perfusion because of an increased coronary arterial resistance (20). Comparison of studies after the cardiac performance in veno-venous extracorporeal oxygenation make clear that disturbances in cardiac performance are mostly observed in veno-arterial extracorporeal oxygenation (4). Much more studies are necessary to analyze and understand the working mechanism of the left ventricle under altered volume- and pressure loading conditions during extracorporeal membrane oxygenation.

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CHAPTER 6

**Summary, conclusions and
future perspectives**

6 Summary, conclusions and future perspectives

Summary and Conclusions

Critically ill neonates subjected to veno-arterial ECMO will show important circulatory alterations in relation to the typical signs of the fetal circulation. The clinical picture of “persistent pulmonary hypertension of the neonate” is present in almost all patients prior to ECMO and forms the “final common pathway” for all connected diagnosis to ECMO. The anatomic structure of the pulmonary vasculature in the neonate is the substrate for producing this severe pulmonary hypertension and for the severe elevated pulmonary vascular resistance. Once on ECMO, the process that decreases pulmonary blood pressure begins and the involved circulatory changes are interpreted as a circulatory “renaissance” because of the great similarity in comparison to the circulatory adaptation immediately after birth when fetal circulation is transformed into the neonatal circulation. In chapter 1, an overview is presented as introduction into the perinatal circulation, the disturbances and the first pioneering efforts concerning treatment. To monitor the disturbances in the neonatal circulation, this study was designed using echo-Doppler cardiography and described in chapter 2. A very early and important decrease in pulmonary hypertension was observed already after 12 hours on ECMO. This decrease in pulmonary hypertension was independently of ECMO flow because ECMO flow was not changed during the first 48 hours. Several pressure related-variables were investigated such as the peak flow velocity of tricuspid- and pulmonary valve regurgitation, the peak flow velocity of the ductal R-L and L-R shunt and the systolic time intervals of the right- and left ventricle. To monitor systolic pulmonary blood pressure in relation to ECMO, pressure predictions derived from tricuspid valve regurgitation are preferential because of the high incidence of tricuspid valve regurgitation in these neonates and fare results in pressure prediction. Together with the drop in pulmonary vascular resistance, we observed an increasing number of patients up to almost 50% after 12 hours and 30% after 24 hours on ECMO, in whom the ductal R-L shunt reversed into the L-R shunttype. Also this change in direction of the ductal shunt is independently from ECMO flow. Besides the decreasing systolic pulmonary artery pressures derived from peak flow velocity of the tricuspid regurgitation, the demonstrated reverse of the ductal shunt into the left to right form, is another proof of decreasing pulmonary vascular resistance. **In conclusion:**

- **Severe pulmonary hypertension is present in all patients and will decrease very early, within 12 hours during the ECMO course monitored by echo-Doppler variables.**

- **The duct is patent in 82% of cases, the shunt initially R-L and will reverse into L-R mostly after 24-36 hours on ECMO.**
- **During ECMO, the duct will close spontaneously in almost all patients.**

In chapter 3, the clinical impact of the ductal L-R shunt on the ECMO course is studied. Before ECMO no patients with signs of a ductal L-R shunt were found. Almost all patients (82%) showed the R-L or bidirectional ductal shunt before ECMO. In 18% of the patients no shunt was demonstrated. During ECMO, in total, the ductal L-R shunt was noticed in 62% of patients. No L-R shunt was demonstrated in 38% of the patients during ECMO. When compared to patients without this ductal shunt, there was a significant longer ECMO duration of 46 hours in the patients who showed a ductal L-R shunt during ECMO. Spontaneous closure was observed in almost all patients after 120 hours, except one patient who showed rebound pulmonary hypertension. In the patients with the ductal L-R shunt, also a decrease was observed in LA/Ao ratio when the LA/Ao ratio is compared during and after the ductal L-R shunt period, illustrating the decrease in volume loading to the left heart after the duct is closed. The demonstrated differences in ECMO duration were not due to one of the underlying diagnoses, especially congenital diaphragmatic hernia.

Originally the intention was to analyse the signs of volume overloading during the ductal L-R shunt by means of the radiological patterns of the chest X-ray, also known as the “typical white-out pattern”. During ECMO the typical white-out pattern will resolve after some time possibly parallel to the disappearing ductal L-R shunt. However, it was not possible to organize a randomized observation and evaluation of all chest X-ray’s by two independent experts in this field. The scientific work of Taylor et al (chapter 3, reference 12) has illustrated the improvement of the radiological pattern together with the improvement in lung compliance in relation to the ductal shunt or its closure. In conclusion

Patients with a period of ductal L-R shunting during ECMO will show a longer ECMO duration with a mean value of 46 hours. The observed ductal L-R shunt will interact with the pulmonary- and renal function and interfere with weaning from bypass.

Because of the impossibility to perform such a study in the neonate, the animal study was chosen to perform an invasive circulatory study.

In chapter 4, the ductal L-R shunt during ECMO was mimicked in an animal study to objectivate the shunt size and to study the relation to other haemodynamic parameters such as cardiac output and ECMO flow. In this study the duct was

infiltrated with formalin to prevent closure after birth. The experiment became possible after extensive instrumentation of pregnant ewes and also extensive preparation of the fetal lambs. Once on ECMO, an important L-R shunt was noticed in 6 of 7 studied lambs with a mean shunt volume of 354 ml/min or 82 ml/min/kg. The ductal L-R shunt will represent resp. 44%, 76% and 51% of resp. left ventricular output, ECMO flow and total systemic circulating volume. The demonstrated shunt size is characterized as haemodynamic important and gives support to the hypothesis of pulmonary hypercirculation and also supports the hypothesis of stealing the systemic circulation. Together with the results described in chapter 3, the clinical impact of the ductal L-R shunt during ECMO is more emphasized. On the one hand, the increase in pulmonary blood flow will lead to pulmonary hyperperfusion and pulmonary edema. Weaning of ECMO could be prohibited because of these phenomena. On the other hand, the duct with the L-R shunt will steal an important amount of blood from the systemic circulation in the descending aorta and will induce renal hypoperfusion that is related to the general predisposition to edema during the first days on ECMO. Thus it is acceptable that a ductal L-R shunt during ECMO contributes in the origin of pulmonary- and general edema and so interferes with weaning possibilities. These circulatory aspects are present during ECMO among other immune-mediated factors that also will have their impact on the clinical picture of patients on ECMO. These “non-cardiac” factors, however, were not examined in our study. In the animal model it was the intention to achieve a better insight between the ductal L-R shunt and the renal function. We tried to measure the urine production during the animal experiments before and after closure of the duct. Unfortunately the lamb’s urethra has the shape of a corkscrew. It was impossible to catheterize the lamb’s bladder. So, we performed a suprapubic puncture of the bladder to measure the volume of urine that was produced in the several phases of the experiment. However it appears to be very difficult to achieve a watertight connection to the bladder. Finally in the evaluation the differences in urine production during and after the ductal L-R shunt were not significant although there was an increase in urine production after the duct was closed. Nevertheless, we had to refer to ultrasound studies in which the flow in the renal artery was decreased during the ductal L-R shunt. In conclusion

The ductal L-R shunt during ECMO in lambs is of haemodynamic importance and contributes considerable in left ventricular output, ECMO flow and total systemic circulation.

In chapter 5 the left ventricular performance during ECMO is monitored using the fractional shortening. Before ECMO, despite the poor clinical condition of most patients, the fractional shortening was normal with a mean value of 36%. All patients showed an important decrease in fractional shortening to a mean value of 20% after 24-36 hours on ECMO. A gradual improvement is observed during the following days up to a normal fractional shortening after decannulation. Before ECMO, left ventricular systolic and diastolic dimensions are small. Especially in patients with a ductal L-R shunt during ECMO a significant increase in diastolic dimension is observed illustrating the volume loading to the left ventricle. Fractional shortening is a volume loading dependent variable. Because of the onset of a ductal L-R shunt early in the ECMO course with important volume loading to the left heart, the effects of this volume loading on the fractional shortening were investigated. Despite the increased left ventricular diastolic dimension, the fractional shortening was significantly more decreased in patients with a ductal L-R shunt during ECMO. Also a very severe decreased fractional shortening, smaller than 10 %, was observed more often in the 'ductus' group. Moreover, there are several indications that the coronary circulation during ECMO is provided from the blood stream from the left ventricle into the ascending aorta. The left ventricle outflow will increase when a ductal L-R shunt is present but the influence of a ductal shunt on the coronary circulation during ECMO, needs more investigation. Posthypoxic myocardial injury, reperfusion injury, together with an elevated afterload, are most likely the causes for myocardial dysfunction during ECMO. In conclusion:

Left ventricular fractional shortening before ECMO is accurate and will show a significant deterioration during ECMO after 24-36 hours, followed by a gradual improvement in fractional shortening up to normal after decannulation. Volume loading circumstances such as a ductal L-R shunt will not improve the left ventricular fractional shortening. Before ECMO, left ventricular diastolic and systolic dimensions are small. Especially the left ventricular diastolic diameter will increase after 24-36 hours on bypass in the 'ductus' group illustrating the volume loading to the left ventricle.

Final conclusion

In all patients a severe pulmonary hypertension prior to ECMO is demonstrated. A reasonable pressure prediction from echo-Doppler derived variables is possible and will give the possibility to monitor the therapeutic effect from ECMO on pulmonary hypertension. The ductal shunt will behave as R-L or L-R depending on the pressure relation between aorta and pulmonary artery. A very early

decrease in pulmonary hypertension is demonstrated with an early onset of ductal L-R shunt in patients in which the duct is patent.

Patients who develop this ductal L-R shunt during ECMO will show a longer mean ECMO duration of 46 hours. We did not demonstrate the onset of a ductal L-R shunt together with the onset of the radiological white-out pattern. The ductal shunt was quantified in an animal experiment and demonstrated as an important L-R shunt with considerable impact on several cardiac output parameters. In the animal experiment we could not prove the effects of a ductal L-R shunt on pulmonary and renal function.

Left ventricular fractional shortening was measured and showed an important decrease during ECMO.

From the volume loading ductal L-R shunt no improving effects on fractional shortening during ECMO could be observed.

Future perspectives

This study has demonstrated that veno-arterial ECMO is an excellent treatment for the pulmonary hypertension in critically ill neonates. Pulmonary hypertension is reacting already within 12 hours of ECMO. When the reaction is so quickly it allows perhaps earlier weaning attempts to minimize the number of complications related to ECMO and to shorten the ECMO course.

In this context it should be desirable to draw up weaning criterions.

Also this study showed that, an important ductal L-R shunt becomes possible after the pulmonary hypertension is well treated with ECMO and this shunt is possibly related to ECMO flow. So when pulmonary vascular resistance is low and a significant ductal shunt has developped, perhaps forced weaning from bypass is capable in reducing the ductal shunt and so reducing the pulmonary hypercirculation.

Another study focused on weaning attemts in relation to low pulmonary vascular resistance, ductal L-R shunting and improving left ventricular function, is capable in analyzing the most significant conditions on which an ECMO patient has good prospects concerning weaning from bypass.

Samenvatting, conclusies en aanbevelingen voor de toekomst

Samenvatting en conclusies

Ernstig zieke pasgeborenen welke behandeld worden met behulp van veno-arteriele ECMO vertonen circulatoire veranderingen met het accent op de typische verschijnselen van de foetale bloedsomloop. Het klinisch beeld van “de persisterende pulmonale hypertensie van de neonaat” is bij bijna alle ECMO patienten aanwezig voor dat ECMO gestart wordt en vormt een gemeenschappelijke pathofysiologische weg waarlangs zich het klinische beeld van alle aan ECMO verbonden diagnosen afspeelt. De anatomische structuur van de longbloedvaten en de pathofysiologische reactie van de neonaat vormen het substraat voor deze ernstige pulmonale hypertensie en ernstig verhoogde pulmonale vaatweerstand. Indien de neonaat aan ECMO wordt aangesloten, kan het proces beginnen dat de pulmonale bloeddruk doet dalen gepaard gaande met een aantal circulatoire veranderingen die beschouwd kunnen worden als een circulatoire wedergeboorte vanwege de grote gelijkenis van deze veranderingen met circulatoire veranderingen tijdens en kort na de geboorte, wanneer de overgang plaatsvindt van foetale naar neonatale bloedsomloop.

In hoofdstuk 1 wordt een overzicht gegeven van de perinatale circulatie, hiermee samenhangende stoornissen en de eerste pogingen om deze te behandelen.

In hoofdstuk 2 worden observaties beschreven van stoornissen in de neonatale circulatie in deze studie onderzocht met behulp van echo-Doppler echocardiographie. Een snelle en belangrijke daling van de pulmonale bloeddruk werd aangetoond reeds na 12 uur ECMO behandeling. Deze daling in pulmonale bloeddruk was onafhankelijk van de ECMO flow aangezien deze gedurende de eerste 48 uur constant gehouden werd. Verschillende druk-afgeleide variabelen werden onderzocht zoals, maximale stroomsnelheden van tricuspidalis- en pulmonalisklepinsufficiëntie, maximale stroomsnelheden van ductale R-L en L-R shunt en de systolische tijdsintervallen van de rechter en linker hartkamer. Om de systolische bloeddruk in de longslagader te bepalen en deze tijdens ECMO te kunnen vervolgen lijken bloeddrukvoorspellingen gebaseerd op de maximale leksnelheid van de tricupidalisklep het meest aan te bevelen vanwege de acceptabele resultaten en de hoge incidentie van tricuspidalisklepinsufficiëntie in deze populatie. De bovenvermelde daling van de pulmonale bloeddruk reeds na 12 uur ECMO behandeling gaat samen met een tegelijkertijd optredende omslag van een ductale R-L shunt in een L-R shunt. Na 12 uur ECMO behandeling, wordt bij bijna 50% van de neonaten een ductale L-R shunt waargenomen en na 24 uur ECMO behandeling 30% L-R shunt. Ook deze omslag in shuntrichting is onafhankelijk van

de ECMO flow aangezien deze gedurende de eerste 48 uur constant gehouden werd. Naast de reeds aangetoonde daling van de pulmonale bloeddruk tijdens ECMO is de omkering van een ductale R-L shunt in een L-R shunt ook een bewijs van de dalende pulmonale vaatweerstand tijdens ECMO behandeling.

In conclusie betreffende hoofdstuk 2:

- Ernstige pulmonale hypertensie is aanwezig in alle patienten en deze zal , gemeten en vervolgd met behulp van echo-Doppler variabelen snel dalen (< 12 uur) na de start van ECMO behandeling.
- De ductus Botalli is open bij 82 % en de shunt richting, aanvankelijk R-L zal in de meeste gevallen binnen 24-36 uur na ECMO behandeling omkeren in een L-R shunt.
- Spontane sluiting van de ductus Botalli tijdens ECMO wordt in bijna alle patienten waargenomen.

In hoofdstuk 3 wordt de invloed bestudeerd van een ductale L-R shunt op het klinische beloop van de ECMO behandeling. Vóór de start van ECMO wordt in 82 % een ductale R-L shunt of bidirectionele shunt aangetoond. Bij 18 % kon geen ductale shunt worden gevonden. Uiteindelijk doet zich een ductal L-R shunt voor in 62 % tijdens ECMO behandeling. In 38 % kan tijdens ECMO deze shunt niet worden aangetoond. Een significant langere ECMO duur van gemiddeld 46 uur kon worden bewezen in patienten met een ductale L-R shunt tijdens de ECMO behandeling. Spontane sluiting na 120 uur ECMO behandeling was regel met uitzondering van 1 patient waarbij een rebound pulmonale hypertensie optrad. De volumebelasting van het linker hart bij patienten met een ductale L-R shunt kon worden geïllustreerd aan de hand van een afname in LA/Ao ratio na spontane sluiting van de ductus Botalli. De in dit hoofdstuk aangetoonde verschillen in totale ECMO duur kon niet worden geweten aan de onderliggende diagnose, in het bijzonder de hernia diaphragmatica. Oorspronkelijk was het binnen de onderzoeksopzet de bedoeling de volumebelasting ten gevolge van de ductale L-R shunt te analyseren door het typische rontgenologische “white-out”effect op de thoraxfoto te graderen en te vervolgen tijdens ECMO behandeling. Echter, het bleek niet mogelijk een gerandomiseerde onafhankelijke expertise te organiseren. Het wetenschappelijk werk van Taylor (hoofdstuk 3 referentie 12) vermeldt simultane verbetering van de thoraxfoto met het sluiten van de ductus Botalli en het verbeteren van de longcompliance.

In conclusie betreffende hoofdstuk 3:

- Een ductale L-R shunt tijdens ECMO behandeling gaat gepaard met een significant langere ECMO duur met een gemiddelde verlenging van 46 uur.

- De ductale L-R shunt zal de longcompliance kunnen beïnvloeden en als zodanig interfereren met ontwenning van ECMO.

Om een invasieve circulatoire studie te verrichten moest uitgeweken worden naar een diermodel vanwege de onmogelijkheden zo'n studie uit te voeren in de patient. In hoofdstuk 4 wordt de opzet van een diermodel beschreven teneinde een ductale L-R shunt na te bootsen, deze te kwantificeren en de relatie met andere haemodynamische parameters te bestuderen, zoals cardiac output en ECMO flow. Het dierexperiment werd pas mogelijk na uitgebreide instrumentatie van zwangere ooiën en foetale lammeren. De ductus Botalli werd geïnfiltreerd met formaline om sluiting te voorkomen. In 6 van de 7 lammeren kon een belangrijke ductale L-R shunt worden aangetoond tijdens ECMO met een gemiddeld L-R shunt van 354 ml/min. of 82 ml/min/kg. De L-R flow percentages voor wat betreft vergelijking met de linker ventrikel output, ECMO flow en totaal circulerend volume werden berekend op resp. 44%, 76% en 51%. De aangetoonde L-R shunt kon als haemodynamisch belangrijk worden aangemerkt en ondersteunen de oorspronkelijke hypothese waarin de ductale L-R shunt enerzijds bijdraagt aan het ontstaan van een pulmonale hypercirculatie en anderzijds ten koste zal gaan van de circulatie in de aortaboog distaal van de ductus Botalli. De resultaten van hoofdstuk 4 in samenhang met die van hoofdstuk 3 maken de klinische importantie van een ductale L-R shunt meer inzichtelijk. Zoals gezegd ontstaat een situatie van toegenomen longflow en longoedeem, waardoor ontwenning van ECMO bemoeilijkt kan worden. Anderzijds zal de hoeveelheid bloed welke door de L-R shunt naar de longcirculatie stroomt, ten koste gaan van de bloeddorstrooming distaal van de ductus botalli en leiden tot renale hypoperfusie welke aanleiding kan geven tot oedeem gedurende de eerste dagen aan ECMO. Deze circulatoire aspecten van een ductale L-R shunt tijdens ECMO spelen een rol temidden van een aantal andere meer door immuun-activatie bepaalde factoren welke ook oedeem en longoedeem kunnen verklaren. Deze niet-cardiale oorzaken zijn in dit onderzoek door ons niet onderzocht. In het diermodel zijn pogingen ondernomen een beter inzicht te verkrijgen in de relatie tussen ductale L-R shunt en de urineproductie. Echter onmogelijkheden om nauwkeurig de urineproductie te meten in lammeren (lammeren hebben een urethra in de vorm van een kurketrekker) hebben wel geleid tot een stijging van de urineproductie nadat de ductus Botalli was gesloten, maar de verschillen waren niet significant. Referenties naar ultrageluidsstudies welke een daling van de renale bloedflow weergeven tijdens een ductale L-R shunt zijn toegevoegd aan hoofdstuk 4.

In conclusie hoofdstuk 4:

- De ductale L-R shunt tijdens ECMO is van haemodynamisch belang.
- Ten opzichte van cardiac output, ECMO flow en totaal circulerend volume zal de ductale L-R shunt aanzienlijk interfereren.

In hoofdstuk 5 werd een observatie verricht van de linker ventrikel functie gemeten aan de verkortingsfractie. Vóór ECMO, vertonen de meeste patienten een normale verkortingsfractie ondanks de zeer ernstig zieke situatie waarin zij zich bevinden. Gemiddeld bedroeg de verkortingsfractie 36%. Alle patienten laten een daling zien van de verkortingsfractie tijdens ECMO naar gemiddeld 20% na 24-36 uur ECMO behandeling. Nadien doet zich een geleidelijke verbetering voor gedurende de daarop volgende dagen tot aan een normale verkortingsfractie na decannulatie. Vóór ECMO bestaan er opvallend kleine systolische en diastolische diameters van de linker hartkamer. Met name bij patienten met een ductale L-R shunt wordt een toename gezien van de diastolische diameter als uiting van een volumebelasting. Verkortingsfractie is een variabele welke gevoelig is voor volumeveranderingen. De ductale L-R shunt zal door de volumebelasting van de linker kamer, de preload van de linker kamer verbeteren met name tijdens ECMO behandeling. Dit zou kunnen leiden tot een betere verkortingsfractie bij patienten met een ductale L-R shunt. Echter in ons onderzoek kon geen verbetering in verkortingsfractie worden aangetoond in patienten met een ductale L-R shunt tijdens ECMO. Integendeel de verkortingsfractie in patienten met een ductale L-R shunt was significant slechter. Ook werden extreem lage verkortingsfracties (< 10%) veel vaker waargenomen in deze groep. Doordat de coronaire circulatie tijdens ECMO met name wordt verzorgd door antegrade bloedstromen vanuit de linker hartkamer en niet door de retrograde stromen van de aorta canule, kan een ductale L-R shunt hier invloed op hebben. Posthypoxische myocardschade en reperfusie schade in combinatie met verhoogde afterload lijken de belangrijkste oorzaak voor linker hartkamer dysfunctie tijdens ECMO.

In conclusie hoofdstuk 5:

- Linker hartkamer verkortingsfractie vóór ECMO is ongestoord en toont een significante achteruitgang na 24-36 uur ECMO behandeling gevolgd door een geleidelijk herstel tot volledige normalisatie na decannulatie.
- Volume belasting door een ductale L-R shunt geeft niet de te verwachten verbetering in verkortingsfractie.
- Vóór ECMO zijn de diameters van de linker hartkamer klein, zowel systolisch als diastolisch. Vooral bij patienten met een ductale L-R shunt tijdens ECMO

wordt een toename gezien van de diastolische diameter passend bij een volumebelasting voor de linker hart kamer.

Samenvattende eindconclusies

In alle patienten die in aanmerking komen voor ECMO behandeling is een ernstige pulmonale hypertensie aantoonbaar vóór aanvang van deze behandeling. Predictie van de bloeddruk in de longslagader is op acceptabele wijze mogelijk met behulp van echo-Doppler variabelen en geeft de mogelijkheid de bestaande pulmonale hypertensie te vervolgen tijdens de ECMO behandeling en als zodanig het therapeutisch effect van ECMO te evalueren. Afhankelijk van de bloeddrukverhoudingen tussen enerzijds de aorta en anderzijds de longslagader, zal bij open ductus Botalli de shuntrichting R-L, bidirectioneel of L-R zijn. Een zeer vroege en snelle daling van de pulmonale hypertensie werd aangetoond met een vroege omdraaiing van de ductale shunt in die patienten waarbij de ductus open is. Deze patienten met een ductale L-R shunt tijdens de ECMO behandeling, vertonen een langere totale ECMO duur van gemiddeld 46 uur. Het samengaan van deze ductale L-R shunt met het typische radiologische “white-out”aspect op de thoraxfoto werd door ons niet onderzocht.

Kwantificering van de ductale L-R shunt tijdens ECMO behandeling werd verricht in een ECMOmodel bij lammeren. De shunt werd haemodynamisch als belangrijk gekarakteriseerd in samenhang met andere haemodynamische parameters. Binnen dit diemodel konden de effecten van de ductale shunt op long- en nierfunctie om technische redenen niet geheel worden bepaald. De functie van de linker hartkamer gemeten met behulp van de verkortingsfractie laat tijdens ECMO behandeling een belangrijke afname zien. Aangezien de verkortingsfractie van de linker hartkamer voor een belangrijk deel volume bepaald is, werd de invloed van een door de ductale L-R shunt geïnduceerde volumebelasting geanalyseerd. Een verbeterende invloed op de verkortingsfractie kon niet worden aangetoond, integendeel bij patienten met een ductale L-R shunt tijdens ECMO werd een significant lagere verkortingsfractie gevonden.

Aanbevelingen voor de toekomst

Deze studie heeft aangetoond dat ECMO een uitstekende behandeling is voor patienten met ernstige pulmonale hypertensie. Deze pulmonale hypertensie daalt al snel tijdens de behandeling. Gezien deze vlotte respons is het misschien mogelijk de patient eerder en vlotter te onttrekken van de ECMO machine om met deze behandeling samenhangende complicaties te kunnen reduceren en de ECMO duur te verkorten. Binnen dit kader zou het belangrijk kunnen zijn criteria op te stellen

voor ontwenning van de ECMO machine en deze te toetsen. Daarnaast is het de vraag of, indien zich tijdens ECMO een ductale L-R shunt voordoet, geforceerde ontwenning therapeutische voordelen heeft aangezien de ductale shunt versterkt kan worden door de ECMO flow in de aorta ascendens, om zo een bepaalde mate van pulmonale hypercirculatie te reduceren.

Een toekomstige studie die zich bezig houdt met ontwenning van de ECMO machine binnen de voorwaarden van lage pulmonale weerstand, ductale L-R shunting en een betere linker hartkamerfunctie zou die condities kunnen aantonen waaronder een ECMO patient optimaal behandeld wordt.

Dankwoord

Dankwoord

Dit proefschrift zou niet tot stand gekomen zijn zonder de belangrijke hulp van vele anderen. Daarom wil ik grote dank uitspreken aan:

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Curriculum Vitae

Curriculum Vitae

Ronald Tanke werd op 2 April 1955 geboren te Hengelo (O) alwaar het HBS-B diploma in 1972 aan het R.K. Carmellyceum “de Grundel” werd behaald. De in 1972 voor het eerst geldende Numeris Fixus noopte hem tot 1973 de grondbeginselen van de klassieke talen aan het gymnasium van bovengenoemd lyceum, zich eigen te maken. In 1973 werd de studie Geneeskunde begonnen aan de Katholieke Universiteit Nijmegen. Vóór zijn artsexamen in 1980 was hij werkzaam als organist aan de H. Hart Parochie te Hengelo (O), als student-assistent Fysiologie aan de Katholieke Universiteit Nijmegen en als arts-assistent Psychiatrie aan het Geestelijk Gezondheidscentrum “de Welterhof” te Heerlen. Het begrip werkstudent is dus niet nieuw. Na het artsexamen werd de militaire dienstplicht vervuld als luitenant-arts in de regio ‘s-Hertogenbosch. Alvorens in 1982 met zijn opleiding tot kinderarts (Opleider: Prof. dr. E.D.A.M. Schretlen) te beginnen was hij werkzaam op de afdeling Intensieve Zorg van het Academisch Ziekenhuis St. Radboud te Nijmegen. Het was hier waar de definitieve basis werd gelegd voor zijn belangstelling in stoornissen van hart en circulatie. De opleiding tot kinderarts werd voltooid in 1986, waarna de vrijgekomen opleidingsplaats werd doorgegeven aan zijn vrouw Esmeralda Spanjaards. Tot 1987 was hij werkzaam als kinderarts op de afdeling kindercardiologie van het Sophia Kinderziekenhuis te Rotterdam. Nadien was hij werkzaam als algemeen paediater in Ziekenhuis Ziekenzorg te Enschede tot het nieuwe hoofd Kindercardiologie van het Academisch Ziekenhuis St. Radboud hem vroeg om de vrijgekomen stafplaats op te vullen na het afscheid van Dr. H.J. Busch. Tot 1990 werd de opleiding tot kindercardioloog doorlopen (Opleider Prof dr. O Daniëls) en de aanvullende examens in ultrageluid en stralingshygiëne behaald. Vanaf deze periode is hij werkzaam als kindercardioloog aan het sinds 1993 opgerichte Kinderhartcentrum Nijmegen van het UMCN. Binnen zijn werk als kindercardioloog heeft hij zich gespecialiseerd in de interventionele hartcatheterisatie en de pathologie van de neonatale circulatie. Als consulent kindercardioloog is hij sinds 1991 verbonden aan de neonatale intensive care unit van het Maxima Medisch Centrum te Veldhoven.

Stellingen

behorend bij het proefschrift

*Cardiac and circulatory effects of patent ductus arteriosus
during extracorporeal membrane oxygenation.*

- Daling van de pulmonale hypertensie bij de pasgeborenen treedt tijdens ECMO veel sneller op dan tot nu toe bekend was. *(dit proefschrift)*
- De ductale L-R shunt tijdens ECMO treedt vaker op en is belangrijker dan oorspronkelijk verondersteld werd. *(dit proefschrift)*
- Een ductale L-R shunt tijdens ECMO behandeling leidt tot een belangrijke verlenging van de totale ECMO duur. *(dit proefschrift)*
- De afname in verkortingsfractie van de linker hartkamer tijdens ECMO kan niet alleen maar verklaard worden door een afname van de preload. *(dit proefschrift)*
- Naast peak velocity metingen van tricuspidale lekkage zijn peak velocity metingen in de ductale shunt ook geschikt voor het vervolgen van pulmonale hypertensie tijdens ECMO. *(dit proefschrift)*
- Bij de organisatie en het uitvoeren van proefdieronderzoek moet rekening gehouden worden met de invloed van besmettelijke ziekten in de intensieve nederlandse bio-industrie. *(eigen ervaring)*
- Proefdieronderzoek is eerder acceptabel indien binnen hetzelfde diermodel meerdere onderzoekers of experimenten participeren. *(eigen ervaring)*
- Gelet op de salariëring van medisch specialisten met vergelijkbare werkbelasting geldt voor een groot aantal dat er eerder sprake is van een maandelijkse belediging dan een maandelijkse bevrediging.
- De vier wielen onder een echocardiograaf zijn in de ogen van de ARBO-dienst veel eerder een rem.
- De kerstroos is geen roos en bloeit ook niet met Kerstmis. *(R. v.d. Kaa)*
- Het aantal volwassenen met een aangeboren hartafwijking in onze maatschappij zal het aantal kinderen met deze afwijking vele malen gaan overtreffen.

**Cardiac and circulatory effects of patent
ductus arteriosus during extracorporeal membrane oxygenation**

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