

From the Department of Molecular Medicine and Surgery  
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**ADVANCED RADIOLOGICAL  
IMAGING IN PATIENTS  
TREATED WITH  
EXTRACORPOREAL  
MEMBRANE OXYGENATION**

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*If I could set the blood burning as it burns in life,  
after its natural combustion has been suspended,  
I should relight the animal lamp,  
and the redevelopment of force, which is life,  
would be reestablished.*

*Benjamin Richardsson 1865 (1)*

*To Mats,  
Gustaf and Karin*

# ABSTRACT

Extracorporeal membrane oxygenation (ECMO) is the use of a modified heart-lung machine to support life during severe acute cardiac and/or respiratory failure. Patients on ECMO are at high risk for complications due to the severe underlying disease and to the ECMO procedure itself. The clinical evaluation of patients on ECMO may be unreliable and the diagnostic value of portable bedside imaging is limited. Advanced radiographic methods like CT are rarely used during ongoing ECMO and MRI has previously never been tested. There is also lack of knowledge of the long term respiratory function in survivors of severe acute respiratory distress syndrome (ARDS) and ECMO.

The frequency, indications, findings and effect on treatment of CT performed in patients during ECMO therapy, at the ECMO department Karolinska University Hospital, were retrospectively reviewed.

*Paper I:* It was found that CT had been performed in nearly half of the treated patients, most often due to suspected complications. In 57% of 104 CT occasions clinically significant findings were revealed. There were no complications to the CT examinations.

*Paper II:* In 25% of 118 performed thoraco-abdominal CT scans clinically important complications, dominated by hemothorax, massive pleural fluid, pericardial tamponade and abdominal hemorrhages, were revealed. The majority resulted in surgery or percutaneous drainage during ECMO, with high survival rates. Accordingly, the role of chest and abdominal CT during ECMO is to identify patients with complications where urgent invasive therapy is essential, when bedside imaging has been inconclusive.

*Paper III:* In 37% of 123 pediatric and adult patients on ECMO, intracranial hemorrhage or infarction was revealed with CT during the treatment. Large hemorrhages or pronounced general edema were reasons to discontinue the ECMO treatment, neurosurgical intervention was motivated in a few patients and in patients with lesions with expected fair prognosis, ECMO was continued with high survival. Thus, the main value of cranial CT is in differentiating patients who have no CNS complications or complications with good prognosis from those with poor prognosis where the treatment should be withdrawn.

*Paper IV:* Twenty-one adult long term survivors of severe ARDS and ECMO, were studied in a follow-up program including CT of the lungs, pulmonary function tests and a dedicated questionnaire for evaluation of respiratory problems. It was found that lung parenchymal changes suggestive of fibrosis, pulmonary function abnormalities and subjective respiratory symptoms can be found more than one year after ECMO-treated severe ARDS. However, the impairments are most often mild and the majority has good physical and social functioning.

*Paper V:* In an experimental study, the ECMO system was tested for magnetic resonance imaging (MRI) compatibility, using a pig model. The study showed that MRI can safely be performed in living subjects on ECMO with high quality images. In the future this may have an impact, especially on early diagnosis and treatment of cerebral complications in patients on ECMO.

# LIST OF PUBLICATIONS

This thesis is based in the following five papers, which are referred to in the text by their Roman numerals:

- I. **CT in the evaluation of patients on ECMO due to acute respiratory failure.**  
Marika Lidegran, Kenneth Palmér, Håkan Jorulf, Viveka Lindén  
Pediatric Radiology 2002; 32:567-574
- II. **Chest and abdominal CT during Extracorporeal Membrane Oxygenation: Clinical benefits in diagnosis and treatment.**  
Marika Lidegran, Hans Ringertz, Björn Frenckner, Viveka Lindén  
Academic Radiology 2005; 12: 276-285
- III. **Cranial CT for diagnosis of intracranial complications in pediatric and adult patients during ECMO: Clinical benefits in diagnosis and treatment**  
Marika Lidegran, Mikael Mosskin, Hans Ringertz, Björn Frenckner, Viveka Lindén  
Academic Radiology. In press.
- IV. **Acute respiratory distress syndrome treated with ECMO: A long-term follow-up study regarding pulmonary morphology, pulmonary function and health related quality of life.**  
Viveka Lindén, Marika Lidegran, Gunilla Frisé, Petra Dahlgren, Björn Frenckner, Flemming Larsen.  
Submitted
- V. **MRI of the brain and thorax during Extracorporeal Membrane Oxygenation: Preliminary report from a pig model.**  
Marika Lidegran, Björn Frenckner, Mikael Mosskin, Bo Nordell, Kenneth Palmér, Viveka Lindén  
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## LIST OF ABBREVIATIONS

ARDS	acute respiratory distress syndrome
CDH	congenital diaphragmatic hernia
CNS	central nervous system
CPR	cardiopulmonary resuscitation
CT	computed tomography
DLco	diffusion capacity of the lung for carbon monoxide
ECG	electrocardiography
ECMO	extracorporeal membrane oxygenation
ELSO	extracorporeal life support organization
FEV <sub>1</sub>	forced expired volume during one second
FiO <sub>2</sub>	fraction of inspired oxygen
FRC	functional residual capacity
HFOV	high frequency oscillation ventilation
HRCT	high resolution computed tomography
HU	hounsfield units
ICH	intracranial hemorrhage
ICU	intensive care unit
MAS	meconium aspiration syndrome
MRI	magnetic resonance imaging
NO	nitric oxide
OI	oxygenation index
PACS	picture archiving and communication system
PaO <sub>2</sub>	partial pressure of arterial oxygen
QoL	quality of life
RV	residual volume
SGRQ	St George's respiratory questionnaire
TLC	total lung capacity
US	ultrasound
VA	venoarterial
VC	vital capacity
VV	venovenous

# 1 INTRODUCTION

## 1.1 BACKGROUND

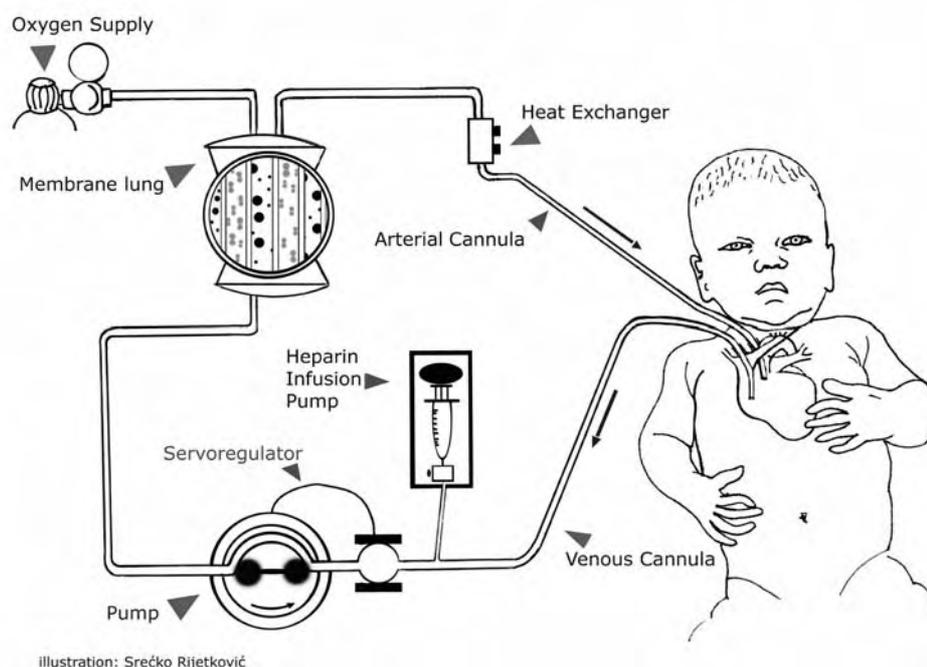
### 1.1.1 Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is the use of a modified heart-lung machine for days or weeks to support life during severe acute cardiac and/or respiratory failure (2). During ECMO therapy the blood is oxygenated and carbon dioxide removed in an artificial membrane lung outside the body, allowing time for injured lungs to recover (3). ECMO is considered for acute, extremely severe cardiac or respiratory failure when the risk of mortality is high despite optimal conventional intensive care (4-6). ECMO has been used for more than 30 years in neonates, children and adults for a number of different disorders. To date, more than 30 000 patients have been treated at approximately 100 centers world-wide (7). Survival rates in patients with acute respiratory failure and ECMO are 50-95% depending on diagnosis and age group, compared to a predicted mortality of at least 80% without ECMO (8).

### 1.1.2 ECMO technique for acute respiratory failure

During ECMO therapy, desaturated blood is drained from a large central vein or usually the right atrium, and pumped through a membrane oxygenator before it is returned to the patient (Fig 1). In the oxygenator, the blood is oxygenated and carbon dioxide is removed over a large surface of membranes or hollow fiber, using the pressure gradient between the blood and gas. Systemic anticoagulation is added to reduce the risk for clot formation in the ECMO system (3).

When the blood is returned to a major artery, the process is referred to as venoarterial (VA) ECMO, whereas if the blood is returned to a major vein the bypass is referred to as venovenous (VV) ECMO.



**Fig 1.** Diagram of venoarterial ECMO circuit.

In VA ECMO, oxygenated blood is generally returned by a cannula inserted through the right common carotid artery into the aortic arch. This technique involves ligation of the common carotid artery (9). VA ECMO supports the heart as well as the lungs and is mainly used for combined cardiac and respiratory failure.

In VV ECMO, the blood is returned via the superior vena cava to the right atrium or via a femoral or iliac vein. VV support is preferred to VA bypass because it includes less risk for cerebrovascular accidents (10) and because normal pulmonary blood flow as well as pulsatile systemic flow is maintained.

As soon as ECMO support has been established, the ventilator settings are reduced, including inspiratory pressure and fractions of inspired oxygen ( $FiO_2$ ), to prevent further ventilator associated lung injury. Adequate patient oxygenation is maintained by increasing or decreasing the blood flow through the membrane oxygenator (3).

### **1.1.3 History of cardiopulmonary support**

The concept of using a pump for “life support” is not new. Benjamin Richardson first experimented with such a system in 1865, but was hampered by the coagulation of blood (1). The discovery of heparin in 1916 was a necessary pre-condition to the successful development of extracorporeal circulation.

The first time extracorporeal circulation was used in a human was in 1953 when Dr John Gibbon successfully repaired an atrial septal defect on cardiopulmonary bypass (11). This first generation of artificial lungs all involved a direct contact between the blood and gas, which caused blood trauma and hemolysis. The possible time on bypass was therefore limited to a few hours and used for open heart surgery. Development of the silicone rubber membrane oxygenator in the 1950’s and early 1960’s, allowed prolonged circulatory support, as the separation of the blood and gas phases reduced the damage to the blood cells.

The first ECMO success came in 1972 when ECMO was used to support a 24-year old man who developed acute respiratory distress syndrome (ARDS) after a motorcycle accident (12). However, early studies of survival in adult ARDS-patients with ECMO treatment were disappointing, with approximately 10% survival with or without ECMO (13), and the interest in ECMO waned.

In 1976, Bartlett reported the successful use of ECMO on an abandoned newborn nicknamed “Esperanza” (Spanish for *Hope*) by the nursing staff (14). Neonates with severe respiratory failure seemed to be ideal candidates for ECMO since the respiratory disease was often reversible with just a few days of ECMO support. In randomized studies, ECMO soon proved to be a life-saving technique in neonates with a number of pulmonary disorders (4, 15, 16). With the success of ECMO in the neonatal population its role for adult respiratory failure was once again revisited. Using the lessons learned from the neonatal age-group, namely: selection of reversible pathology, low level heparinization and lung rest, the use was successfully extended to include pediatric patients (5, 8) and adults (6, 17).

### 1.1.4 The ELSO Registry

The Extracorporeal Life Support Organization (ELSO) was founded in 1989 as a volunteer study group comprised of clinical centers using ECMO (18). To date (Jan 2006), there are 104 member centers from 17 countries reporting to the ELSO Registry, located in Ann Arbor, Michigan (7). One important activity of ELSO is to maintain a large central database for all active centers including their cases, devices, complications and patient outcomes. ELSO also coordinates prospective studies and publishes guidelines for clinical ECMO practice.

### 1.1.5 Indications and contraindications for respiratory ECMO

ECMO can be life-saving in patients with severe respiratory failure (4-6, 8, 15, 17, 19). However, the technique is invasive and has inherent risks for complications. Therefore various criteria have been used to select patients with a predicted mortality of 80% or more, in spite of optimal conventional treatment (4-6). These criteria vary between age groups and different ECMO centers. Criteria recommended by the Extracorporeal Life Support Organization (ELSO) are listed in Table 1.

Since ECMO is essentially a method of “buying time” it is only applied for disorders that are potentially reversible within a reasonable time. Furthermore, a maximum of 7-10 days of mechanical ventilation prior to ECMO is accepted by most centers, due to the risk of irreversible ventilator induced lung injury after longer times. The need for systemic anticoagulation during ECMO also contraindicates treatment of patients with uncontrollable bleeding, especially intracranial hemorrhage (8). Currently most centers exclude infants <34 weeks of gestational age and <2 kg birth weight due to higher mortality rate and a near 50% risk for intracerebral hemorrhage (ICH) (20). Also adults over 65 years of age are generally excluded. However, these limitations are under constant reconsideration.

The most common diagnoses for neonates treated with ECMO are meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), sepsis/pneumonia and persistent pulmonary hypertension (PPHN) (15). The disease pattern of pediatric respiratory patients resembles that of adult ECMO patients, with ARDS due to pneumonia/sepsis, trauma or aspiration being the most prevalent underlying diagnoses (7, 8).

<b>NEONATES</b>
OI>40 for 3 h or more
HFOV 1-2 h without any improvement
NO ½-1 h without any improvement
<b>CHILDREN AND ADULTS</b>
PaO <sub>2</sub> /FiO <sub>2</sub> ratio <60
Pulmonary shunt >30%
OI >30

**Table 1.** Criteria for ECMO initiation, after considered optimal conventional treatment, according to ELSO. OI (oxygenation index)(21), HFOV (high frequency oscillation ventilation,) NO (nitric oxide), PaO<sub>2</sub> (partial pressure of arterial oxygen), FiO<sub>2</sub> (fraction of inspired oxygen)

### **1.1.6 The acute respiratory distress syndrome**

The first description of ARDS appeared 40 years ago for patients with severe dyspnea, cyanosis refractory to oxygen therapy, decreased lung compliance and diffuse alveolar infiltrates on chest radiographs (22). Initially called the adult respiratory distress syndrome this entity is now termed the acute respiratory distress syndrome, since it does occur in children.

A four-point lung-injury scoring system (the Murray score) has been widely used for the last 20 years to quantify the respiratory impairment in ARDS (23). The scoring system is based on the degree of infiltrates on chest radiographs, the ratio of partial pressure of arterial oxygen (PaO<sub>2</sub>) to the fraction of inspired oxygen (FiO<sub>2</sub>), the level of positive end-expiratory pressure (PEEP) and the static lung compliance. ARDS patients have scores of 2.5 or more on the four-graded scale.

Today ARDS is defined as a syndrome of inflammation and increased permeability that is acute in onset and associated with one or more risk factors, of which the most common are sepsis, aspiration, pneumonia or trauma. It is characterized by arterial hypoxemia resistant to oxygen therapy alone and diffuse radiological lung infiltrates, in the absence of clinical evidence of left atrial hypertension (24). ARDS is distinguished from less severe lung injury by a PaO<sub>2</sub> to FiO<sub>2</sub> ratio of  $\leq 200$  mm Hg. The mortality rate of patients with ARDS is high with published reports ranging from 10-90%. ECMO-therapy is today used for extremely severe ARDS, unresponsive to regular intensive care and conventional ventilatory treatment and has in previous studies proved to increase survival for these patients (6, 17).

### **1.1.7 Short term results of respiratory ECMO**

Since ECMO is used only in patients with a predicted very high mortality, the results focus on survival to discharge. The current reported cumulative survival rate for respiratory failure is for neonates 76%, for pediatric patients 56% and for adults 52%, according to the ELSO Registry (7). Reasons for mortality are most often irreversible cardiopulmonary failure, brain injury or multiple-organ failure.

### **1.1.8 Long term results of respiratory ECMO**

#### *1.1.8.1 Neonates*

There are numerous studies which address the medical and neurodevelopmental morbidity in neonates after ECMO treatment (25-28). Results show that, in spite of the clinical presentation of critical illness prior to ECMO, the risks inherent to ECMO therapy and the high survival rate, the occurrence of major disability among neonatal survivors is remarkably low (29).

Significant developmental delay and/or neurological abnormality is reported in 10-15% of ECMO treated patients by 1-2 years of age (30, 31). By 5 years of age 15% have one or more handicapping condition of which cognitive impairment is most frequent, while <5% have severe or profound impairment. In a report concerning older children, seventy percent of preschool-age and 90% of school-age children had normal development (32).

Significant respiratory symptoms can be seen in neonates after ECMO during the first two years, with a 15% reported frequency of chronic lung disease (CLD) defined as

oxygen requirements at 28 days of life (29). However, long term oxygen requirement (>4 months) is not expected among ECMO survivors. By the age of two, ECMO survivors are reported to have a lower rate of reactive airway disease than similar infants treated with conventional therapy (33). Reactive airway disease is however, more common in ECMO survivors than in normal controls with 16% taking asthma medication at 5 years of age compared to a prevalence of asthma in the normal population of 5%.

#### *1.1.8.2 Pediatric patients*

Pediatric intensive care unit (ICU) survivors are not routinely seen in follow-up and there are few long-term outcome studies of respiratory ECMO patients (34). Two small studies points to an abnormal neurological outcome in slightly less than 1/3 of the patients after respiratory ECMO. Of 13 children in school age, ten performed normal, one above and two below normal (30, 35).

#### *1.1.8.3 Adults*

Adult patients with ECMO-treated ARDS are often transferred to other hospitals after decannulation and lost for follow-up. The overall reported frequency of intracranial complications in adults following ECMO is approximately 10% (7). However, neuroimaging is rarely used in adults during ECMO and reports after ECMO are few in number and thus the reported frequency of neurological sequelae is probably unreliable. Concerning the respiratory condition, it has been shown that conventionally treated adult ARDS patients often are left with chronic pulmonary fibrosis, impaired pulmonary function and reduced quality of life (36-42). Patients who require ECMO probably have a more severe ARDS which theoretically may result in more serious long-term respiratory sequelae. However, the gentle ventilation and lung rest that comes with ECMO is thought to protect from ventilator induced lung injury. Since there are few follow-up studies in ECMO-treated patients after severe ARDS (43, 44) little is known of the long term respiratory function. The CESAR study from England, a randomized controlled study in adult ARDS patients treated with ECMO, will be presented in 2007, and will include a follow-up study (45).

### 1.1.9 The ECMO department, Karolinska University Hospital

The present ECMO program at the Karolinska University Hospital, Karolinska Institute, started in 1987 at St Görans Children's Hospital in Stockholm with neonates and children and since 1995 also includes adults. In 1998 the Children's hospital and ECMO department moved to the Karolinska University Hospital, Stockholm and is now located at the pediatric ICU, at Astrid Lindgren Children's Hospital.

Since 1994 the department has used specially designed mobile ECMO units for transport of patients during ECMO. This enable ECMO to be initiated at the referral hospital ICU, permitting stable elective transfer on ECMO by ground ambulance, helicopter or fixed-wing vehicle (46).

In addition to inter-hospital transfer, the mobile systems are used for intra-hospital transportation, most often to the radiology suite to obtain more specialized diagnostic imaging than is routinely available at the bedside (Fig 2). Of the approximately 100 ECMO centers in USA and Europe, only a handful centers have transport possibilities during ongoing ECMO (47).



**Figure 2.** Transportation of a neonate from the ICU to the CT unit. Here entering the elevator.

### 1.1.10 Emergencies during ECMO

Patients on ECMO are at high risk for complications. In large multicenter studies the reported frequency of serious patient complications ranges from 1.8 to 2.1 per case (48). The complications can be attributed to the severe underlying disease but also to the ECMO procedure itself.

A significant amount of morbidity and mortality among patients on ECMO therapy are related to ICH or cerebral infarction (49). Risk factors for intracranial complications are pre- ECMO asphyxia and hypotension, ligation of the right common carotid artery and internal jugular vein at ECMO initiation and thrombocytopenia, coagulopathy and systemic hypertension during the ECMO treatment. Although central nervous system lesions are the most frequent major complications, life-threatening thoracic complications, requiring emergent intervention while on ECMO, have been reported in 9% of neonates on ECMO therapy, and in 8% of adult patients (48, 50). Previous surgery, needle punctures and chest tubes are obvious sites for increased risk of bleeding, with pleural hemorrhage reported in 30% of neonates on ECMO after CDH repair (51). As a result of systemic anticoagulation and coagulopathy, gastrointestinal, abdominal and retroperitoneal bleedings have all been observed (48).

Patients on ECMO are difficult to evaluate clinically due to sedation, respiratory support, assisted circulation and sometimes muscle relaxation. Therefore radiological imaging is essential in the diagnosis of suspected complications (50).

## 1.2 IMAGING OF PATIENTS DURING ECMO

### 1.2.1 Chest radiography

Radiologists have an important role in the treatment of patients receiving ECMO (50). As part of the intense clinical monitoring of these patients, serial bedside chest radiographs are obtained. Chest radiographs are essential in assessing the placement of ECMO cannulae, tracheal tubes and any other catheters present, monitoring the severity of the lung disease and to evaluate potential problems such as the development of barotrauma or rapidly enlarging pleural effusions (52, 53).

The initial radiograph is useful in confirming that the positions of the ECMO cannulae are appropriate to ensure sufficient flow rates and to help reduce possible complications. The tip of the venous draining cannula is generally in the right atrium, and the tip of the arterial returning cannula (in VA ECMO) projects over the aortic arch at the origin of the innominate artery (50, 54) (Fig 3).

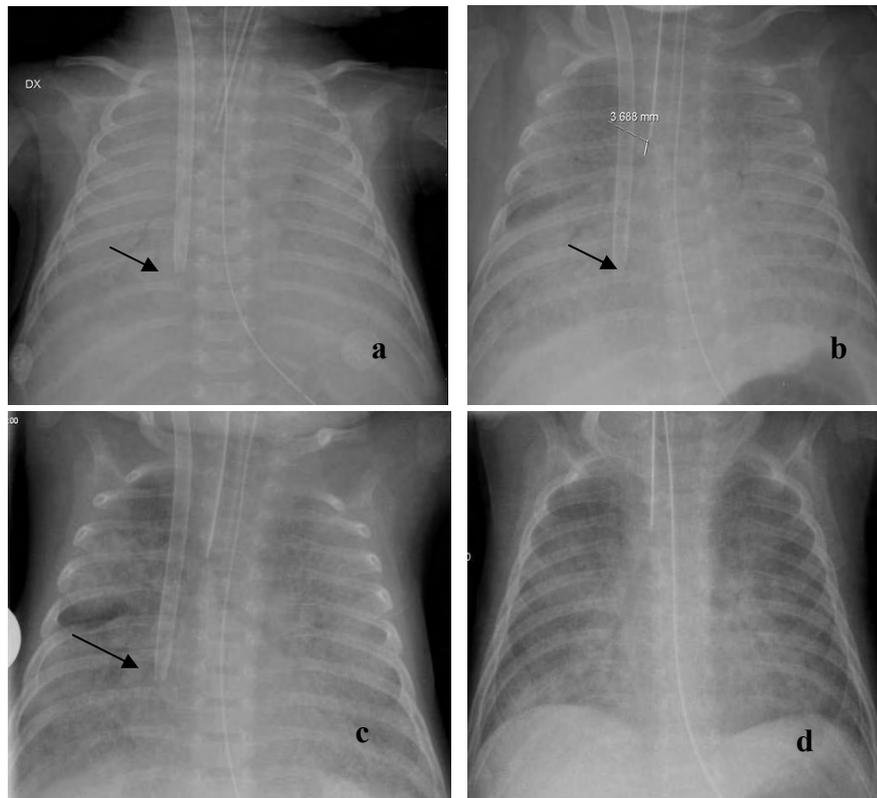
When patients are initially placed on ECMO, lung opacity typically increases, the chest radiograph “goes from bad to terrible” (Fig 4a). Often a complete opacification of the lungs (“whiteout”) is seen. This usually occurs within hours of initiation of ECMO. The most likely explanation for the increased opacification is alveolar edema and atelectasis as a result of changing from maximal ventilatory support with high pressure to ECMO with minimal ventilatory settings (55). In addition a transient activation of inflammatory mediators, resulting from blood contact to the large artificial surfaces, when ECMO is initiated, increases capillary permeability resulting in fluid filled alveoli (50).



**Fig 3.** Chest radiograph in neonate on VA ECMO due to sepsis, showing venous ECMO cannula with tip in the right atrium (white arrow on marker) and arterial cannula projecting just above the aortic arch (black arrow).

After the initial increase in opacity however, there is an association between degree of pulmonary opacification and ECMO flow needs. Radiographs taken during periods of increased ECMO requirements generally show worse lung opacity while clinical improvement, with decreased ECMO requirements, are reflected in improving chest radiographs (52, 53) (Fig 4).

Routine daily chest radiographs in periods of clinical stability has not been found helpful in providing additional information during the ECMO run (52, 53). However during periods of worsening of the clinical status, chest examinations can often assist in diagnosing the cause, such as malposition and migration of various tubes and catheters, air collections or rapidly enlarging pleural effusion (53, 54). A rapidly increasing pleural effusion in a patient receiving ECMO is indicative of hemothorax, due to anticoagulant therapy and ECMO induced coagulopathy (50).



**Fig 4.** Serial chest radiographs in neonate on VV ECMO due to MAS, showing initial dense consolidation after ECMO initiation (a) thereafter gradually clearing in parallel with clinical improvement (b,c). First control after decannulation (d). Tip of double lumen VV cannula in right atrium (black arrows).

## 1.2.2 Ultrasound

Ultrasound (US) is often used in the evaluation of patients on ECMO due to its portability and lack of ionizing radiation, the latter is especially important for children and neonates.

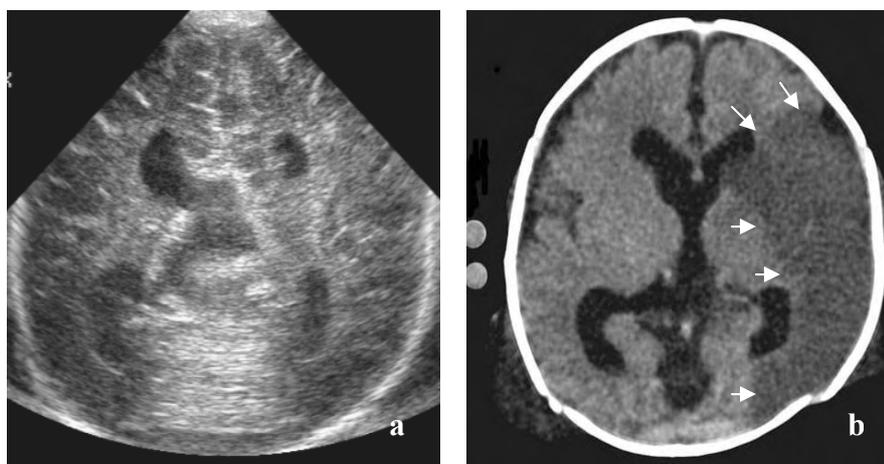
### 1.2.2.1 Cranial ultrasound

Cranial US is routinely used as a screening technique for evaluating the neonatal brain before and during ECMO therapy. Before cannulation, US is obtained mainly to exclude preexistent hemorrhage that may extend after anticoagulation. Evidence of ICH greater than grade I-II on a IV grade scale is, in most centers, a contraindication for ECMO (56).

After ECMO initiation, it has been shown that the risk of ICH in neonates is greatest during the first days on ECMO, with 85% of the hemorrhages occurring within 72 hours of initiation of bypass and nearly all within 5 days (57, 58). The late occurring bleedings have all been associated with significant clinical neurological changes or multiorgan failure. Consequently, daily cranial US are recommended for the first 3-5 days, thereafter as clinically indicated.

The use of heparin and ECMO induced coagulopathy is probably responsible for an unusual appearance and distribution and a rapid expansion of ICH seen during ECMO (28). Most striking is the hypoechoic or anechoic appearance of acute hemorrhage in some neonates (56). The location of ICH is predominantly in the parenchyma, with predilection for the occipital lobes and cerebellum (25, 59). Especially the cerebellum might be difficult to evaluate with US (60).

In other series hypoxic ischemic brain injury (ischemic infarction or severe cerebral edema) has been a more common finding than ICH (26, 27). Hypoxic-ischemic injuries probably most often occur before ECMO with a delay in visualization. A problem with US screening is that cranial US is less sensitive to non-hemorrhagic lesions (Fig 5) and often unable to distinguish between infarction and hemorrhage (27). Furthermore cranial US is of no use in adults and children, after the closing of the fontanel.



**Fig 5.** US (a) and CT (b) in neonate on ECMO due to CDH. Large infarction in the cerebra media territory was not diagnosed on US but was obvious on CT (white arrows) performed the same day.

### 1.2.2.2 Chest and abdominal ultrasound

Thoracic complications of ECMO include malposition of various tubes and catheters, abnormal air collections, pleural and pericardial effusions and hemorrhages as well as pulmonary hemorrhage (54). Portable chest radiographs can correctly identify many of these complications. However, with the complete opacification of the lungs, which is often seen during ECMO treatment, identification of fluid collections and hemorrhages, on radiographs, can be difficult if not impossible. Chest radiographs may show evidence of mass effect with mediastinal shift but US is superior for documenting and follow-up acute pleural effusions and hemorrhages and is also helpful in distinguishing hemothorax from pleural effusion (51).

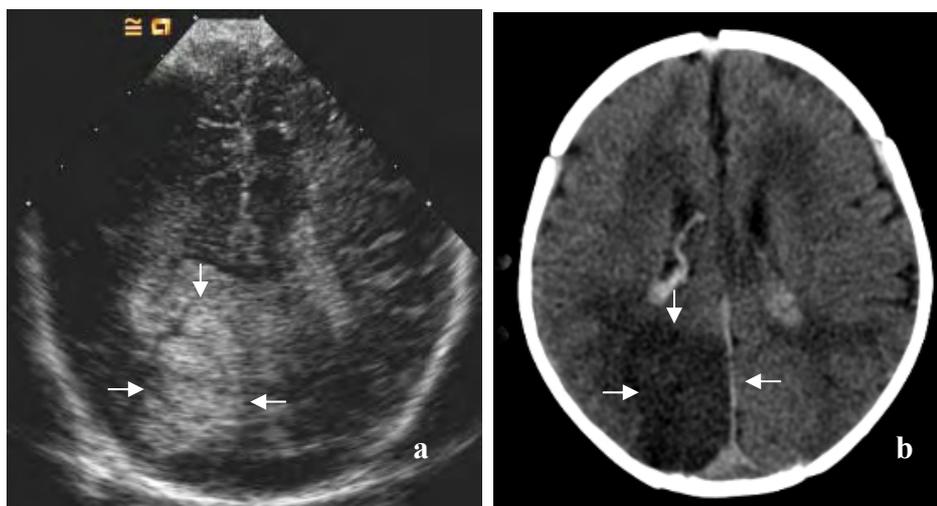
Echocardiography is routinely used to evaluate the cardiac function and hemodynamic state of patients during ECMO. It is also a sensitive method for showing pericardial effusions. However, echocardiography and US are dependent on an adequate acoustic window, and can be inconclusive in some patients.

For evaluating suspected abdominal or retroperitoneal hemorrhages during ECMO, US should be the method to start with, especially in infants.

### 1.2.3 Computed tomography

#### 1.2.3.1 Cranial CT

Due to its portability and sensitivity for large ICH cranial US is an acceptable screening method for evaluation of the neonatal brain during ECMO. However, computed tomography (CT) has been shown to be more accurate than US, especially in detecting general edema, non-hemorrhagic infarctions and small, peripheral or extra-axial hemorrhages (25, 28). Besides, US is often unable to distinguish between infarction and hemorrhage (27, 59) (Fig 6). In a large study comprising 386 infants on ECMO therapy, examined with daily US during the treatment, CT performed after decannulation added information in 73% of the neonates with CT-proven intracranial abnormalities (25). Furthermore, CT is the method of choice for diagnosis of intracranial lesions in adults and children after the closing of the fontanel.



**Fig 6.** Neonate on ECMO due to CDH, with ICH suspected on US (arrows) (a). CT revealed a non-hemorrhagic infarction (arrows) (b).

### 1.2.3.2 Chest and abdominal CT

Thoracic CT is known to improve evaluation of mediastinal, pericardial, pleural and chest wall processes compared with chest radiographs, because of its greater contrast resolution and absence of superimposition of findings (61). It is also more sensitive than chest radiography in detecting abnormalities in the lung parenchyma. CT has proved extremely helpful as an adjunct to portable plain film radiography in the evaluation of ICU patients (61-63) adding clinically useful information in 24% to 75% compared to bedside radiographs in different studies (64). Among these important findings are large pleural effusions and empyema, pneumothoraces requiring thoracostomy tubes, malpositioned pre-existing thoracostomy tubes, parenchymal infections and abscesses as well as pericardial effusions. Pleural effusions, parenchymal infection and pneumothoraces are stated to be the most common unsuspected findings on CT of ICU patients (64).

In spite of the proven benefit in other critically ill patients in the ICU, the evaluation of patients on ECMO therapy at most centers still relies almost exclusively on bedside radiographs and US. This is unfortunate since the evaluation of thoracic complications, using chest radiographs, is particularly difficult in ECMO patients because of the pronounced opacification of the lungs often seen during ECMO therapy (Fig 7). Furthermore, the quality of US and echocardiograms are often limited by overlying bandages, obscuring air in the lungs and gas-filled bowel loops in the abdomen (51, 54). CT is independent of an “acoustic window” and in addition gives a more complete survey of the examined region than bedside methods. This is of obvious advantage in ECMO patients who are often difficult to evaluate clinically and, as a result of sedation, muscle relaxation, mechanical ventilation and assisted circulation, often lack focal signs even when there are severe complications.



**Fig 7.** Chest radiograph in neonate with MAS. Total opacification of lungs after ECMO initiation, makes further diagnosis with radiography almost impossible. VA ECMO cannulae (arrows) (a). Chest CT scan in the same patient could exclude intrathoracic complications (b).

### *1.2.3.3 CT at the ECMO department, Karolinska University Hospital*

At the Karolinska ECMO center, the possibility to transport patients with a mobile ECMO system has contributed to a liberal use of CT, as an adjunct to bedside methods, for diagnosis of suspected complications during ongoing ECMO since 1994.

The obvious clinical benefit of CT diagnoses in managements of ECMO patients has led to an increasing frequency of CT examinations. To date more than 680 CT examinations (cranial, chest- and abdominal scans) have been performed at approximately 300 occasions. There are to our knowledge no previously published studies with CT during ECMO.

### **1.2.4 Magnetic resonance imaging**

Magnetic resonance imaging (MRI) is a sensitive and non-invasive method for assessment of changes in the brain parenchyma, patency of vessels and measurement of brain perfusion. MRI can reveal cerebral hypoxic events earlier and more precisely than CT. In addition, it has lately been shown that functional MRI can predict the final volume of an infarct and reveal the presence or absence of salvageable brain tissue in acute cerebral infarction (65, 66), information that can be extremely important for the clinical care in ECMO patients. MRI can also be used to study heart function and flow dynamics in thoracic and cranio-cervical vessels that may be of special interest in research concerning the ECMO procedure.

However, the strong magnetic field near and within the MRI magnet is known to influence electronic equipment, thereby making examinations of patients depending on such equipment difficult or even potentially dangerous. Furthermore, the medical equipment can disturb the imaging process. Some of the frequently used life-supporting equipment have been adjusted and tested for a normal function in these magnetic fields. The ECMO system however, has as far as we know, never previously been tested for use with MRI (Fig 8).



**Fig 8** Mobile ECMO system pumping water through phantom during test in MRI environments at the MRI department, Astrid Lindgren Children's Hospital, Karolinska University Hospital.

## 2 AIMS OF THE THESIS

The main aims of the present investigations were

- I. To retrospectively review the frequency, indications and findings on CT of patients with acute respiratory failure on ECMO and to evaluate the risk of complications during transports and CT examinations.
- II. To retrospectively evaluate the clinical utility of thoracic and abdominal CT examinations as a routine complement to bedside imaging and to assess the impact of thoracic and abdominal CT findings on treatment of patients during respiratory ECMO.
- III. To retrospectively evaluate the frequency of ICH and infarction in children and adults during ECMO therapy due to acute respiratory failure, to evaluate the clinical utility of cranial CT during ongoing ECMO and to assess the impact of the CT findings on the treatment in these patients.
- IV. To evaluate the long-term results from ECMO treatment of severe ARDS with special respect to pulmonary morphology assessed with HRCT, pulmonary function and pulmonary disease specific quality of life.
- V. To evaluate if MRI can safely be used as a diagnostic tool during ECMO for evaluation of cranial complications including hypoxic/ischemic events, for assessment of brain perfusion and diffusion and for flow measurements in central vessels.

### 3 MATERIALS AND METHODS

For further details see paper I-V.

#### 3.1 RETROSPECTIVE CT STUDIES (I-III)

In May 1994 a CT scanner was installed at the department of pediatric radiology. The possibility to transport patients with a mobile ECMO system to the radiology department has, since that date, contributed to a liberal use of CT during ECMO, as a complement to bedside studies when needed.

##### 3.1.1 Patients and study designs

**Paper I:** One-hundred-twelve consecutive patients with acute respiratory failure were treated with ECMO from May 1994 until Jan 2001. Fifty-three of these patients were neonates (0-1 month), 34 children (1 month-17 years) and 25 adults (18-60 years) (Table 2).

The clinical and imaging records for the 112 patients were reviewed for number and type of CT examinations, stated indication for the examination, reported CT findings and any noted complications to the transport or CT examination.

Paper I	Patients on ECMO	With CT
Neonates	53	18 (34%)
Children	34	18 (53%)
Adults	25	16 (64%)
<b>Total</b>	<b>112</b>	<b>52 (46%)</b>

**Table 2** Patients on ECMO May 1994-Jan 2001, included in Paper I. *Patients with CT; see "Results"*.

**Paper II:** Of 131 consecutive ECMO patients treated for acute respiratory failure from May 1994 until Feb 2002, 63 (48%) were examined with chest CT or combined chest and abdominal CT at one or more occasions while on ECMO. Among them were 22 neonates, 15 children and 26 adults (Table 3). A total of 118 thoracic examinations had been performed of which 78 also included the abdomen.

The records concerning the 63 patients and 118 CT examinations were reviewed for: stated indication for CT, reported CT findings, findings on most recent chest radiograph, US or echocardiography, alteration in clinical management as direct results of the CT findings and patient outcome.

Paper II	Patients on ECMO	With CT chest/abdomen	No of CT occasions
Neonates	67	22 (33%)	32
Children	25*	15 (60%)	24
Adults	39	26 (67%)	62
<b>Total</b>	<b>131</b>	<b>63 (48%)</b>	<b>118</b>

**Table 3** Patients on respiratory ECMO May 1994-Feb 2002 included in Paper II. (\* 11 children on cardiopulmonary resuscitation ECMO were excluded.)

**Paper III:** Of 123 pediatric and adult respiratory ECMO patients, treated consecutively from May 1994 until December 2004, 78 (63%) were examined with cranial CT on one or more occasions while on ECMO therapy (Table 4).

The medical records for the 78 patients (31 children and 47 adults) were reviewed for stated indication for cranial CT, reported CT findings, clinical management following CT and outcome.

In addition all 163 cranial CT scans, performed in these 78 patients, were reviewed for the existence of ICH, focal cerebral infarction or general brain edema.

<b>Paper III</b>	<b>Pts on ECMO</b>	<b>With cranial CT</b>	<b>No of exams</b>
<b>Neonates</b>	Not included		
<b>Children</b>	54	31 (57%)	109
<b>Adults</b>	69	47 (68%)	54
<b>Total</b>	123	78 (63%)	163

**Table 4** Patients on ECMO May 1994-Dec 2004, included in Paper III.

### **3.1.2 ECMO technique and transport**

A standard ECMO technique was used in all patients (2). For all transports, a battery operated, mobile ECMO system was used with one meter extra tubing added on each line, to facilitate transports (46). For CT examinations, the patients were transported from the ICU to the CT unit in their ordinary bed, on the ventilator and with the mobile ECMO system. The transport included elevator transport three floors and was managed by four staff members specially trained for transport and surveillance of the patient and equipment. The total time outside the ICU was generally less than 60 min and included transport, transfer from the ordinary bed to the CT table, CT examination and return to the ICU.

### **3.1.3 CT technique during ECMO**

All CT scans were performed on a General Electric High Speed Advantage single slice CT scanner until Nov 2003, thereafter on a sixteen-row General Electric Light Speed 4.X (GE Medical, Milwaukee, Wisc. USA), using the radiology department's standard protocols for the examined body region and patient's age.

Before scanning, it was always checked that the movements of the CT table were in the range of the length of the ECMO tubing (Fig 9).

Intravascular contrast (Visipaque, Nycomed, Amersham, Sweden) was used for most chest and abdominal scans, but avoided in patients with renal failure. In VV ECMO, the contrast was administered into the "arterial" ECMO line after the membrane lung for optimal enhancement. In patients on VA support, a central venous line in the iliac veins or inferior vena cava was preferred, if present, or a peripheral line in the foot. Otherwise the arterial line was used, which however often resulted in suboptimal enhancement of the lungs and pulmonary circulation. During contrast injection, the pump flow was, if possible, reduced to minimize the amount of contrast "steal" to the

membrane lung. The delay from contrast medium injection to the start of scanning of the thorax and abdomen varied from approximately 20 to 60 sec depending on the injection site in relation to the region of interest, the pump speed and the patient's age and circulatory state.



**Fig 9.** Neonate on ECMO therapy prepared for CT examination. Note arterial (black arrow) and venous (white arrow) ECMO tubings.

## 3.2 PROSPECTIVE FOLLOW-UP STUDY (IV)

### 3.2.1 Patients

Thirty-seven adult patients were treated with ECMO, due to extreme severe ARDS, from May 1997 until March 2001. Twenty-six patients (70%) survived to discharge and were included in a follow-up study of pulmonary function 12 months or more post ARDS and ECMO. Of the 26 survivors, 21 agreed to participate in the study. Patient descriptive data are presented in Table 5.

Variable	
No. (%)	21 (100%)
Female	9 (43%)
Male	12 (57%)
Smokers	6 (29%)
Mean value (range)	
Age (yr)	40 (21-65)
PaO <sub>2</sub> /FiO <sub>2</sub> ratio*	56 (33-96)
Murray score*	3,5 (3-4)
ELSO-diagnosis, no (%)	
Bacterial pneumonia	15 (71%)
ARDS (other reason)	6 (29%)
Mean time (range)	
Pre ECMO vent. (h)	89 (7-380)
Time on ECMO (h)	345 (65-1238)
Months to follow-up	26 (12-50)

**Table 5** Descriptive data for 21 follow-up patients late after ECMO-treated ARDS. PaO<sub>2</sub>= partial pressure of arterial oxygen, FiO<sub>2</sub>=fraction of inspired oxygen, \*at the time for ECMO initiation.

### 3.2.2 Study design

The prospective follow-up evaluation consisted of a physical examination, routine blood tests, blood gas analysis, radiography and CT of the chest as well as extensive pulmonary function tests. The 21 study patients were also sent a St. George's Respiratory Questionnaire (SGRQ), to be filled out before the visit to the hospital. For each patient, all tests were performed within two days at the Karolinska University Hospital. Mean time from discharge from the ECMO department to follow-up was 26 months (range 12-50 months).

Follow-up results were compared with patient demographic data, diagnosis according to ELSO classification, time on mechanical ventilation pre-ECMO, PaO<sub>2</sub>/FiO<sub>2</sub> ratio and Murray score (23) before ECMO initiation and time on ECMO therapy.

### 3.2.3 HRCT of the chest

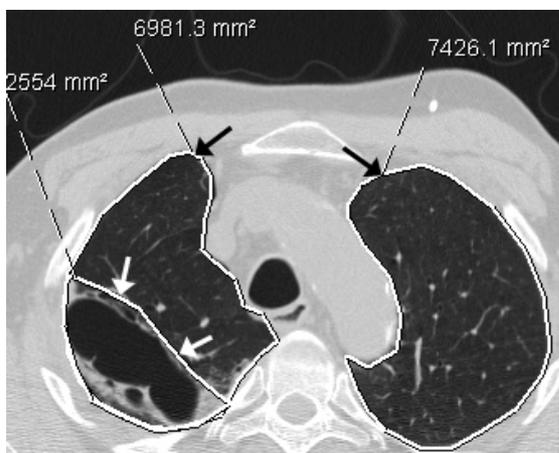
The follow-up CT examinations were performed using a GE High Speed Advantage single slice scanner for the first sixteen patients and a sixteen-row GE Light Speed 4.X scanner for the last five patients and included both spiral and HRCT scans. All examinations were performed in maximal inspiration, without intravenous contrast enhancement.

The HRCT series was used for grading of pulmonary parenchymal changes and was performed with one mm slice thickness at 15-mm intervals from the lung apices to the bases. Images were reconstructed using a high spatial resolution reconstruction algorithm and viewed at window settings appropriate for lung parenchyma [window level -500 HU, window width 1500 HU] and evaluated independently by two radiologists for a number of CT changes, previously described in survivors of conventionally treated ARDS (36).

The following CT patterns (67) were mapped:

1. *A reticular pattern*, defined as interlacing line shadows, with associated distortion of the lung architecture.
2. *Ground-glass opacification*, defined as hazy increased lung attenuation with preservation of bronchial walls and vascular margins.
3. *Consolidation*, defined as homogenous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls.
4. *Decreased attenuation*, including emphysema, small airway disease or parenchymal cysts.

The extent and distribution of these four patterns of disease were evaluated at three representative levels: the apex, the hilum and the base of the lung. The abnormalities were quantified to the nearest 5% by manually tracing regions with the described abnormal CT patterns and total lung area at each level (Fig 10), using standard software in the radiology department's PACS (Sectra Imtec AB, Linköping, Sweden) dividing the achieved sum of pathologic areas with the sum of lung area. A mean figure from the two radiologists was calculated. The distribution of parenchymal abnormalities was visually estimated as predominantly anterior, posterior or with even distribution.



**Fig 10.** HRCT image at the level of aortic arch showing manually traced area of pathology (white arrows) and total lung area (black arrows) at this level. Here in a patient with residual cystic parenchymal destruction after pulmonary necrosis.

### 3.2.4 Pulmonary function tests

#### 3.2.4.1 Lung function and exercise test

Static lung volumes, i.e. total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and vital capacity (VC) were determined in a body box (Autobox 2800, Sensor Medics, Bilthoven, the Netherlands). The forced expired volume during 1 sec (FEV<sub>1</sub>) was obtained with a spirometer (Sensor Medics, Bilthoven, the Netherlands) connected to an IBM computer 486 DX2/SP. Diffusion capacity for carbon monoxide (DL<sub>CO</sub>) was measured by the single-breath carbon monoxide technique. A symptom-limited exercise test was performed on a cycle ergometer, with continuous ECG and blood pressure and pulse oxymetry recorded.

Normal values were calculated following the European Coal and Steel Union guidelines (68). Data from the pulmonary function and exercise tests were expressed as percentages of predicted values and a deviation of more than 20% of predicted was considered abnormal.

#### 3.2.4.2 Pulmonary scintigraphy and radiospirometry

Perfusion and ventilation scintigraphy was performed using <sup>99m</sup>Tc-labelled macro-aggregates of albumin intravenously for perfusion and <sup>133</sup>Xe gas inhalation for ventilation. Images were acquired with a dual-headed gamma camera and a dedicated computer (SMV DST-XL, Sopa Médical Vision, France; Vision work station RS/600, IBM USA). During ventilation, the patient breathed into a close-circuit spirometer and <sup>133</sup>Xe gas was introduced on the inhalation side of the spirometer. When the inhaled Xenon had equilibrated in the lungs, the spirometer was opened to the air and Xenon was gradually “washed out” from the system depending on tidal volume and degree of gas retention in the lungs (radiospirometry). The time (T<sub>1/2</sub>) taken for half of the Xenon gas presented at the start of “wash-out” to disappear was calculated for each lung separately. A wash-out time below 30 sec was considered normal by the lab.

### 3.2.5 St. George’s Respiratory Questionnaire

SGRQ is a self administered questionnaire that measures QoL and impairment of health due to respiratory diseases. SGRQ has 76 items, divided into three sections:

1.) *symptoms* caused by respiratory problems, 2.) restriction of *activity* caused by dyspnoea and 3.) *impact* of daily life caused by the disease. The scores range from 0 – 100 units of possible distress and a summary of total scores is calculated according to the SGRQ manual (69). The questionnaire has been validated and reliability tested in a Swedish population (70).

### 3.3 EXPERIMENTAL MRI STUDY (V)

#### 3.3.1 ECMO technique for MRI

##### 3.3.1.1 Equipment test

The wire reinforced cannulae, normally used in adults and older children, were tested with a magnet and proved to be ferromagnetic. Therefore only non-wired cannulae were used for the MRI experiments. Tests with the mobile ECMO system (46) (without patient) in the MRI environment showed a possibility to acquire high quality phantom images without disturbing the function of the running ECMO circuit (Fig 8).

##### 3.3.1.2 Animal experiment

A 26 kg healthy Yorkshire pig was, during general anesthesia, intubated and put on VA ECMO with cannulation and ligation of the right carotid artery and jugular vein, using non-wired Medtronic DLP<sup>®</sup> cannulae (Medtronic, Grand Rapids, MI) and 2 m extra tubing on each line for transport during ECMO (46). The sedated and ventilated animal was transported with the earlier tested mobile ECMO system to the MRI department and positioned for examination of the brain and thorax in the MR camera.

The ordinary equipment for anesthesia in the MRI suite was used and the ECMO-system was all the time kept outside the 20 mT line (the recommended position for ventilators used for MRI), a distance where the tubing were sufficient for patient examination. The ECMO circuit was tested by the department of Medical Physics before and after the examination for any change in function caused by the magnetic field.

#### 3.3.2 MRI technique for ECMO

Imaging of the experimental animal was performed with a 1.5-T MR scanner (Philips Intera, Philips Medical Systems, Best, the Netherlands).

The brain was examined using a standard "bird cage" head coil with pulse sequences for parenchymal and angiographic anatomy, and for evaluation of brain diffusion and contrast enhanced brain perfusion (Fig.11)

The heart and central thoracic vessels were examined, using a flexible phased array coil. Angiography of thoracic vessels was performed with a two-dimensional MR angiography sequence and dynamic cine-sequences were acquired of heart movements. For flow measurements in central thoracic vessels a standard flow sensitive sequence was used. (For detailed imaging protocols see Paper V.)



**Fig 11.** A standard "bird cage" head coil was used for cranial examinations of the pig. Note tubings for venoarterial ECMO (arrow).

### **3.4 STATISTICAL ANALYSIS (I-IV)**

*Paper I-II:* Results are presented using descriptive statistics only.

*Paper III:* To assess any correlation of CNS pathology in our material to some patient variables that have previously proven to be risk factors for intracranial pathology, statistical analysis was performed. For categorical data the chi-square test was used or, when the expected frequencies were less than five, using Fisher's exact tests. For continuous numerical variables comparison was made by use of the Student's t-test for uncorrelated means, after validating for normal distribution by use of the Shapiro Wilk's test. Statistical significance for each test was considered for  $p < 0.05$ .

*Paper IV:* For statistical evaluation Pearson's correlation coefficient was calculated as a measure of linear association between variables (e.g. baseline data, treatment variables, extent of CT pathology, pulmonary function tests and SGRQ scores). All tests were two-sided and considered significant at  $p \leq 0.05$ .

All analyses were carried out by use of the SAS system for Windows (SAS Institute Inc., Cary, NC, USA).

## **4 MAIN RESULTS**

The main results are summarized below. For further details see paper I-V.

### **4.1 RETROSPECTIVE CT STUDIES (I-III)**

#### **4.1.1 Frequency of CT (I)**

CT had been performed in 52 of the 112 patients (46%) in the Paper I (Table 2). Several patients had CT at more than one occasion giving a total number of 238 scans at 104 occasions. Of the 238 scans, 92 were cranial, 92 thoracic and 54 abdominal. There was an increasing frequency of CT examinations over time, also continuing in Paper II and III. CT was more commonly used in older patients, 64% and 52% for adults and children respectively, compared to 34% for neonates. Irrespective of age, CT was more often performed in patients with long ECMO runs, mean time 359 h for patients having CT during ECMO compared to 146 h for patients with no CT requirements.

#### **4.1.2 Indications for CT (I-III)**

The major indications for the CT occasions were suspected complications of the underlying disease and/or ECMO treatment (64%) or an unexplained delay in clinical improvement (14%). Follow-up to previous CT findings was the stated indication in another 18%.

#### **4.1.3 Complications to transports and examinations (I-III)**

There were no patient complications or equipment failure reported in association with the CT examinations or transports. All clinical parameters were stable, the ECMO perfusion was maintained in all patients with no power or pump failure, no dislocation of ECMO cannulae and no kinking of the tubing that could potentially occur during transport, transfer to and from the CT table or during CT table movements.

#### **4.1.4 CT findings (I-III)**

##### *4.1.4.1 Findings in relation to CT occasions (I)*

In a total of 104 CT occasions in Paper I, 59 (57%) revealed significant findings that affected the treatment or the prognosis of the patient. These included intracranial hemorrhages or infarcts, thoracic hemorrhages, effusions or air leakage as well as abdominal or retroperitoneal hemorrhages.

##### *4.1.4.2 Findings in chest and abdominal CT scans (II)*

In Paper II, 118 thoracic- or combined thoracic and abdominal CT examinations had been performed in 63 patients. In 30 (25%) of the 118 CT examinations clinically important new thoracic or abdominal complications were revealed. Twenty-three were thoracic complications dominated by hemothorax, massive pleural fluid and pericardial tamponade. Seven were abdominal hemorrhagic complications (Fig 12). These new findings had not been suspected on bedside imaging or the bedside

examinations were inconclusive in specifying the type, the location or the significance of the pathology.

#### 4.1.4.3 Findings in patients examined with cranial CT (III)

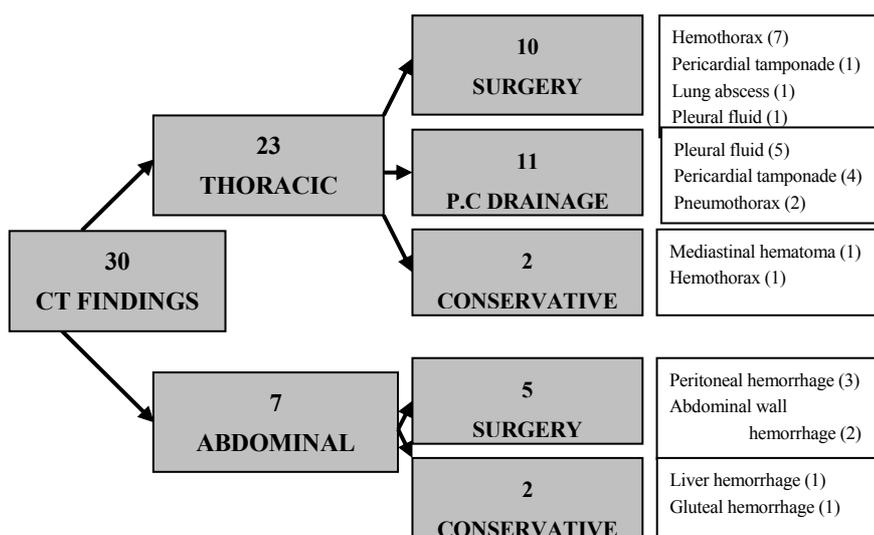
In Paper III, 78 (63%) of 123 ECMO patients were examined with cranial CT on one or more occasions during the ECMO treatment. Intracranial pathology was detected in 45 (37%) of the 123 patients on ECMO. Eighteen patients (15%) had CT evidence of ICH, 11 (9%) had focal non-hemorrhagic infarctions and 16 (13%) had general brain edema. Patients with sepsis had an increased risk of suffering general brain edema (p=0.004). Most intracranial lesions were diagnosed early with 47% (21 of 45) of all lesions found within the first two days on ECMO and 67% (30 of 45) within four days after ECMO initiation.

### 4.1.5 Effect on treatment (II-III)

#### 4.1.5.1 Effect of chest and abdominal CT findings (II)

According to the medical records 30 thoracic or abdominal CT findings affected the immediate treatment or the prognosis of the patient (Fig 12).

Ten of the 23 thoracic complications required thoracotomy. Among them were seven tension hemothoraces, a pericardial tamponade, a lung abscess and a chylothorax. Eleven thoracic complications were successfully treated with placement of percutaneous drainage tubes or catheters. Five were in patients with massive pleural fluid, four were pericardial tamponades and two were complicated pneumothoraces. Two thoracic hemorrhagic complications (mediastinal and pleural hemorrhages, respectively) were conservatively treated, with modification of anticoagulation. Five of the seven abdominal CT findings caused surgical interventions. Three were intra-peritoneal and two abdominal wall hemorrhages. The remaining two, large liver and gluteal hemorrhages, respectively, could be controlled with blood replacement and optimization of anticoagulation.



**Fig 12.** Effect of treatment after 30 thoracic and abdominal CT findings during ECMO.

p.c=percutaneous

These 30 clinically important findings occurred in 20 different patients. In spite of the serious complications 13 of the 20 patients (65%) survived.

4.1.5.2 Effect of cranial CT findings (III)

The result of cranial CT often had a direct impact on the treatment (Fig 13). In 16 of 45 patients with intracranial pathology, CT evidence of large hemorrhages or general edema was decisive to withdraw the ECMO treatment. Another five patients were forcedly weaned from ECMO to avoid further intracranial injury. In four patients the CT findings motivated cranial surgery during ECMO. A hematoma was evacuated in three of these patients. However, postoperative progressive hemorrhage ultimately led to withdrawal of the treatment. In the fourth patient, with cerebellar hemorrhage, a hydrocephalus was successfully decompressed with a ventricular shunt during ECMO. In the remaining 20 patients with intracranial pathology the CT findings, focal hemorrhages or infarctions, suggested a fair prognosis of survival without severe neurological sequelae. In these cases ECMO was continued, with high survival (75%).

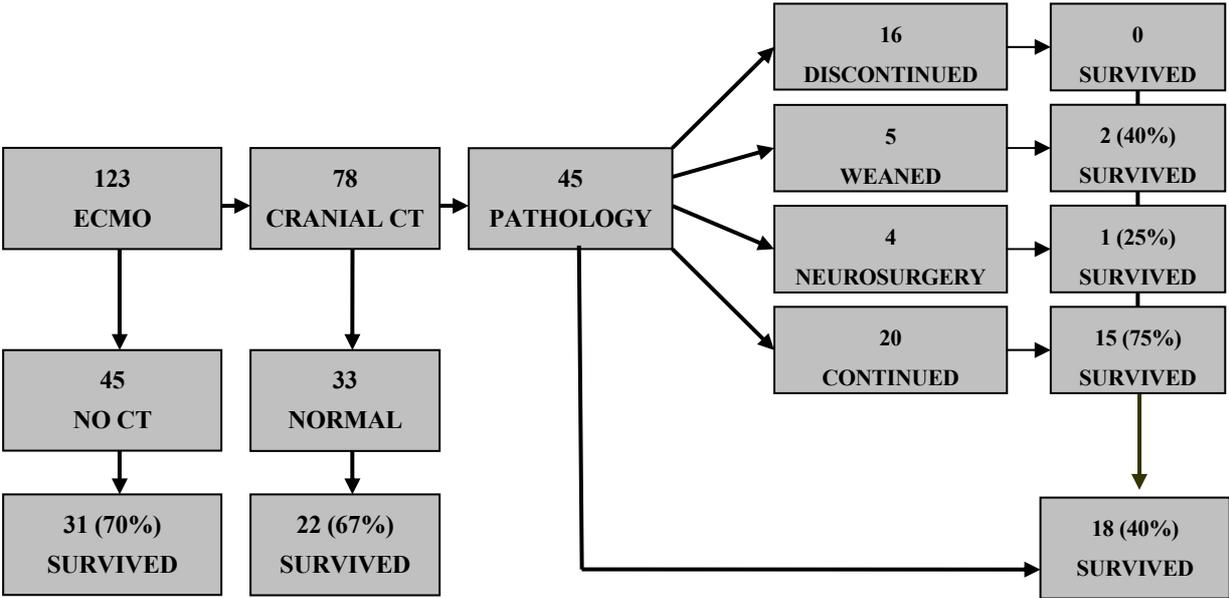


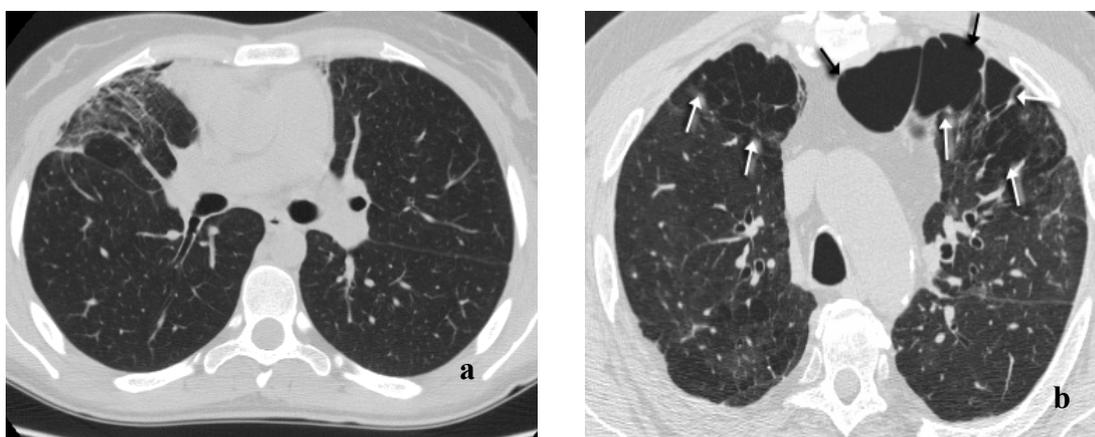
Fig 13. Cranial CT findings, effect of treatment and survival.

## 4.2 PROSPECTIVE FOLLOW-UP STUDY (IV)

### 4.2.1 Lung parenchymal findings on HRCT

The most common residual pathology found on HRCT, late after ECMO-treated ARDS, was a reticular pattern seen in 16 of the 21 patients (76%) (Table 6). Ground-glass opacities were revealed in five patients (24%). Both the reticular and ground-glass patterns were found in combination with parenchymal distortion and were taken to represent interstitial fibrosis (36, 71, 72). Other patterns were less frequent, with areas of decreased attenuation in three patients (14%). None of the patients had dense consolidations (Fig 14).

There was no significant difference in ventral or dorsal distribution of HRCT changes with seven patients having predominantly ventral abnormalities, four having more dorsal changes and seven with equal localization of pathology. Three patients had normal HRCT findings.



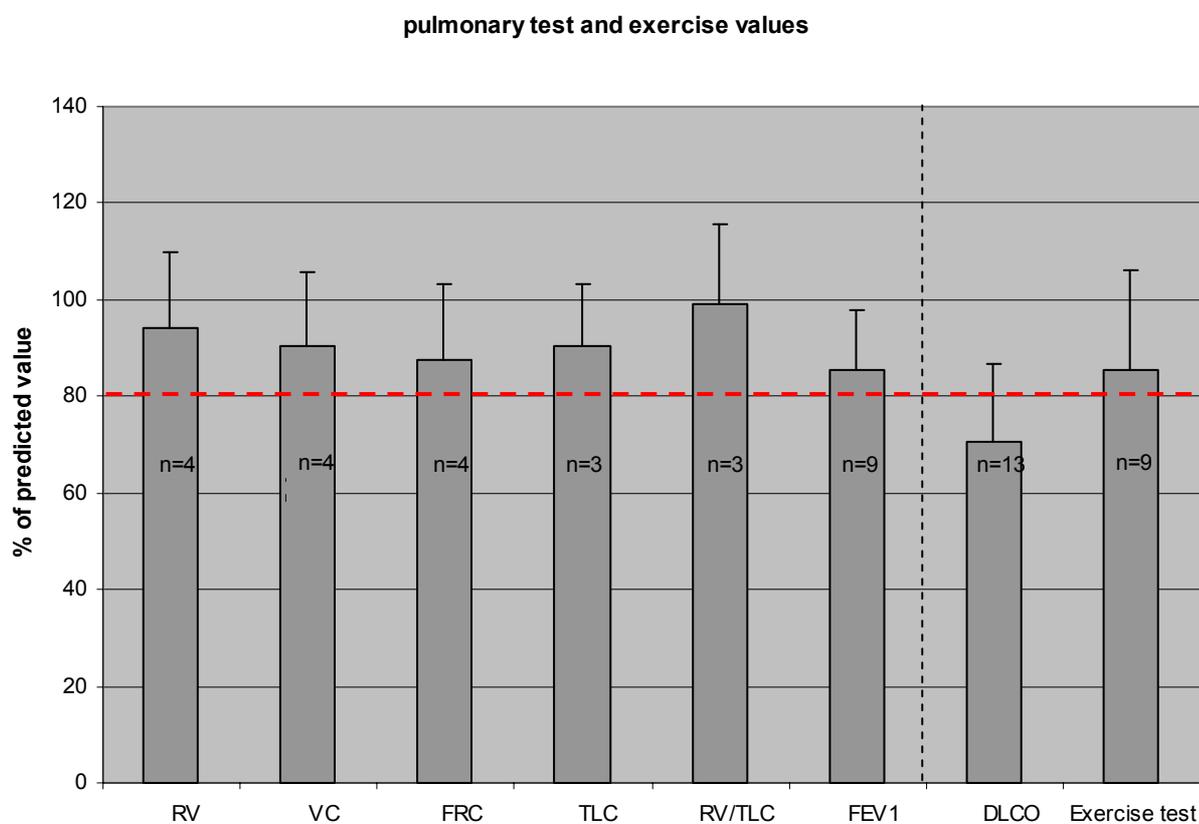
**Fig 14.** HRCT scans in two different patients revealing residual reticular and groundglass pattern with parenchymal distortion (a) and areas with decreased attenuation mainly in anterior parts of the lungs (arrows) (b).

Finding	No. of patients	Mean extent (%)	Range of extents (%)
Reticular pattern	16	7	0-22,5%
Ground-glass opacification	5	1	0-7,5%
Decreased attenuation	3	2	0-20%
Consolidation	0	0	0
Pathology, all patterns	18	10	0-32,5%

**Table 6.** Frequency and extent of HRCT patterns in the 21 ECMO and ARDS survivors. Three patients had normal findings.

## 4.2.2 Pulmonary function tests

Mean values of lung spirometry tests were all in the lower normal interval (Fig 15). However, individual measurements demonstrated considerable variation. Signs of a mild obstructive disorder ( $FEV_1 < 80\%$ ) was observed in nine of 21 patients (43%), in combination with a mild restrictive pattern ( $TLC < 80\%$ ) in three patients (14%). The exercise tests showed mean exercise capacity in the lower normal interval (Fig 15) with nine patients (43%) performing less than 80% of predicted. Diffusion capacity  $DL_{CO}$ , was reduced in 13 of 20 patients (65%). However, the most consistent abnormality, was a delayed outwash of inhaled isotope after ventilation scintigraphy seen in all patients, with mean  $T_{1/2}$  from the right lung 44 sec and left lung 48 sec (normal  $< 30$  sec), consistent with a subclinical obstructivity.



**Figur 15.** Results on pulmonary function and exercise tests expressed as percentage of predicted value (mean $\pm$ SD). N=number of patients with abnormal values eg. deviating more than 20% from predicted.

### 4.2.3 Pulmonary specific quality of life

Of the 21 patients who participated in the follow-up study 15 patients completed the questionnaire. The mean scores were generally higher than values for healthy persons in all domains, indicating moderate subjective respiratory problems with impact on daily life (Fig 25). However, there was a great variability in the scores. One patient, a young male student, scored normal for all domains and an additional four patients scored normal for the symptoms domain.

### 4.2.4 Correlation of CT changes to other patient parameters

The time on mechanical ventilation before ECMO was correlated to the total extent of CT changes on HRCT ( $p=0.05$ ) and to the extent of reticular and ground-glass changes ( $p<0.01$ ). Also the time on ECMO was strongly correlated to the extent of total CT changes ( $p<0.001$ ) as well as to the combined extent of reticular and ground-glass changes, indicating fibrosis ( $p<0.001$ ).

The extent of CT changes was associated to a restrictive pattern on pulmonary function tests (TLC and VC lower than expected) and higher scores on SGRQ, indicating more subjective pulmonary symptoms (Table 7).

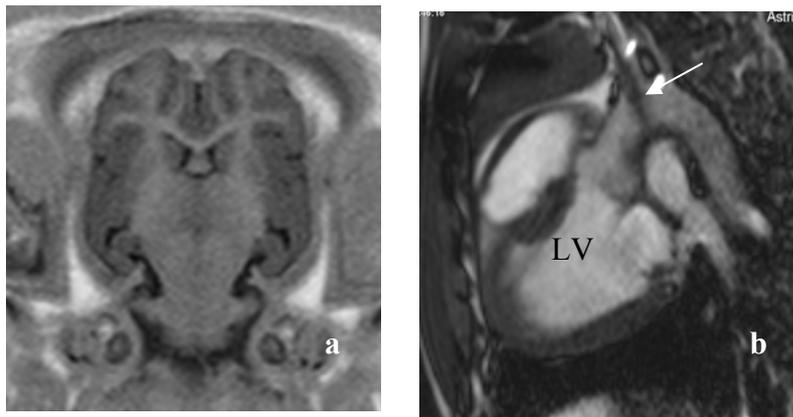
CT changes	Treatment parameters	Pulmonary function	SGRQ scores				
	Mec. vent time	ECMO time	TLC	VC	Total	Sympt	Impact
<b>Total extent</b>	0.43*	0.71***		0.54**	0.53*	0.51*	0.68**
<b>Ret + GG</b>	0.66**	0.72***	0.46*	0.69***			
<b>Reticular</b>	0.57**	0.61**		0.63**			

**Table 7.** Statistical significant correlations between extent of CT changes and patient treatment parameters, pathology in pulmonary function tests and SGRQ scores in Paper IV. Reported values are Pearson's correlation coefficient. Significant at  $p\leq 0.05^*$ ,  $p\leq 0.01^{**}$  and  $p\leq 0.001^{***}$ .  
Ret=reticular pattern, GG=groundglass opacity, Mec.vent=Pre-ECMO mechanical ventilation.

### 4.3 EXPERIMENTAL MRI STUDY (V)

The results in Paper V demonstrate that the ECMO-system is not affected by the magnetic field at a distance from the camera where the tubings are sufficient for patient positioning and examination. The pump function was maintained at all time and no change in function of the system was observed during or after the examination. Furthermore the ECMO system did not negatively affect the quality of images. Cranial images with excellent quality were obtained of the experimental animal's brain parenchyma (Fig 16a) and cranial vessels. Both brain diffusion and perfusion could be visually assessed and the perfusion quantified. The perfusion to the right side of the brain was delayed compared to the left side, probably because of the right carotid artery ligation (Fig 26).

Two-dimensional MR angiography of thoracic vessels was acquired with good quality. Flow measurements and registration of flow patterns in the central thoracic vessels were obtained and seemed accurate according to in vivo validation. Cine-registration of heart movements for visual assessment (Fig 16b) and for calculation of heart function were acquired with good diagnostic quality.



**Figure 16** MRI images of pig brain (a) and heart (b) acquired during ECMO. Note jet from arterial ECMO cannula inflow in aortic arch (arrow). LV=left ventricle.

## 5 DISCUSSION

### 5.1 CT IN PATIENTS DURING ECMO THERAPY (I-III)

The main message of the retrospective studies (Paper I-III) is that CT is feasible, safe and adds important information that affects the management and survival of patients on ECMO therapy.

#### 5.1.1 Complications during ECMO

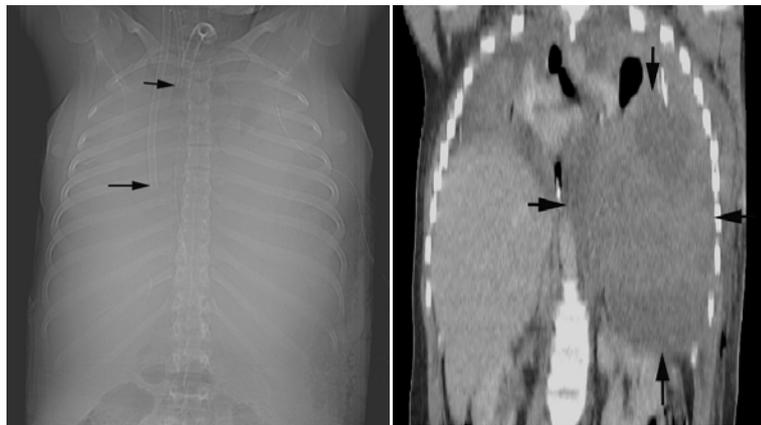
Complications during ECMO are the rule, not the exception, and most often arise unexpectedly and emergently (48, 73). The complications can be attributed to the severe underlying disease but also to the ECMO procedure itself including systemic heparinization and coagulopathy. The most common major complications are intracranial lesions, which often involve a poor prognosis for survival (49). Even though CNS complications are most frequent, life-threatening thoracic and abdominal complications are not uncommon (74). In cases with serious complications quick and reliable diagnoses are mandatory to guide further treatment. However, as a result of sedation, muscle relaxation, mechanical ventilation and assisted circulation, the clinical evaluation of patients on ECMO may be unreliable.

#### 5.1.2 Bedside imaging during ECMO

Radiology has an important role in monitoring the severity of lung disease, evaluating the position of ECMO cannulae and in detecting all kinds of patient complications (52, 53). Traditional evaluation of patients during ongoing ECMO therapy has almost exclusively relied on bedside chest radiography and US. However, portable bedside imaging may be inadequate or suboptimal in the evaluation of complications in a large percentage of patients.

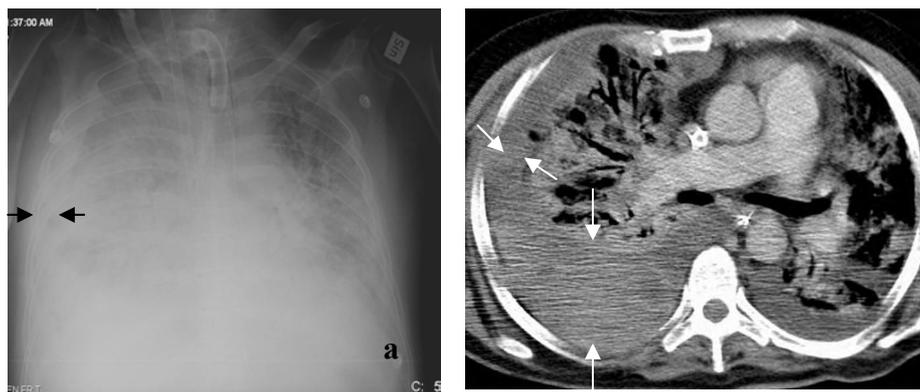
Portable chest radiographs can correctly identify many of the thoracic complications commonly seen

during ECMO (53, 54). However, the complete opacification of the lungs, which is often seen in patients on ECMO, made identification of hemothorax or pleural effusions on chest radiographs difficult or even impossible in many of our patients (Fig 17).



**Fig 17.** Young adult woman with pneumonia and ARDS. Slight dislocation of the ECMO cannulae (arrows) on chest radiograph (a) was the only sign of a huge pleural hemorrhage (arrows) diagnosed with CT (b). (Paper II.)

Thoracic US has proven useful as a complement to chest radiographs for documentation of presence and nature of pleural effusions or hemorrhage in patients on ECMO (51, 54) and echocardiography is often used for diagnosis of suspected pericardial effusions. US can be performed bedside and do not involve any radiation exposure and should therefore be the first choice to confirm any radiographically suspected fluid collection in thorax and abdomen, especially in neonates and children. However, overlying bandages and difficulties in patient positioning sometimes precluded an effective evaluation with US in Paper II. Furthermore, we found that the amount of pleural fluid or hemorrhage was often underestimated with US (Fig 18).



**Fig 18.** Adult with pneumonia and ARDS. Right sided hemothorax (arrows) that was diagnosed with chest radiograph (a) and US, but the amount of hemorrhage was underestimated. CT shows abundant hemorrhage predominantly located dorsally (arrows), with compression of the lung (b).

### 5.1.3 CT examination during ECMO

For the last 12 years the ECMO department at Karolinska University Hospital has used CT as a routine complement to bedside imaging, in adults, children and neonates on ECMO primarily for a suspicion of complications or delay in improvement. The obvious benefit of CT in diagnosis and treatment can probably explain an increasing frequency of CT examinations during the years. In approximately 50% of all our ECMO patients CT has been required during ongoing ECMO.

From May 1994 until Nov 2006 we have performed more than 680 CT examinations (cranial, chest or abdominal scans) at over 300 different occasions, in patients during ongoing ECMO. To our knowledge there are no previously published studies with CT during ECMO.

To avoid complications and failure of CT we have adjusted the technique for the special demands that ECMO patients exhibit. The staff is especially trained for transport and surveillance of the patient and equipment outside the ICU and the time outside the ICU is kept as short as possible with return to the ICU immediately after completed scan.

Using these precautions, we had no patient complications or equipment failure in association with the CT examinations or transports.

## 5.1.4 CT findings during ECMO

### 5.1.4.1 Chest and abdominal CT findings (II)

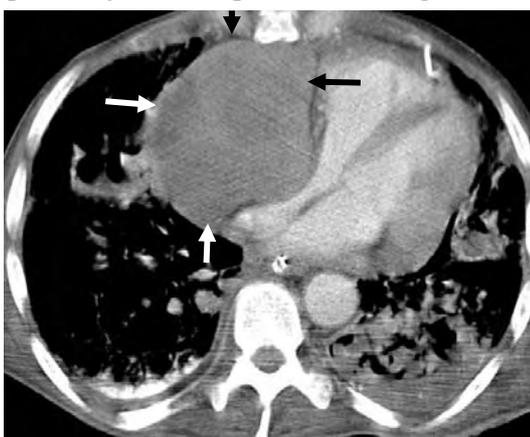
Clinically important new thoracic or abdominal complications were revealed in 25% of the thoraco-abdominal CT examinations performed in study II. These complications were potentially life-threatening or would by experience seriously delay the recovery if left untreated. Similar figures for the benefit of CT have been found in studies on other critically ill patients in the ICU with 22% and 26% clinically important new findings revealed (62, 63).

The most frequent serious chest complications among our patients were hemothorax and massive pleural effusion. Due to opaque lungs the diagnosis had been difficult or impossible on chest radiographs. US had in many cases been hampered by overlying bandages or had underestimated the amount of fluid or hemorrhage. CT was the only modality to show the mass effect on the lungs (Fig 19) and also gave important anatomic information prior to surgery or drainage. The more complete examination of the thorax and abdomen that CT can afford is therefore often preferred by the referring clinician in patients with suspected thoracic complications.

CT also added important information compared to echocardiography in patients with pericardial tamponade, since CT is not dependent on an adequate acoustic window (Fig 20). Transesophageal echocardiography as an adjunct to transthoracic echo could probably have improved the diagnostic accuracy (75).



**Fig 19.** Adult with ARDS. CT scan showing abundant pleural effusion on right and hemothorax on left (black arrows) with obvious compression of the lungs that had not been appreciated on chest radiographs or US. ECMO cannula in superior vena cava (white arrow).



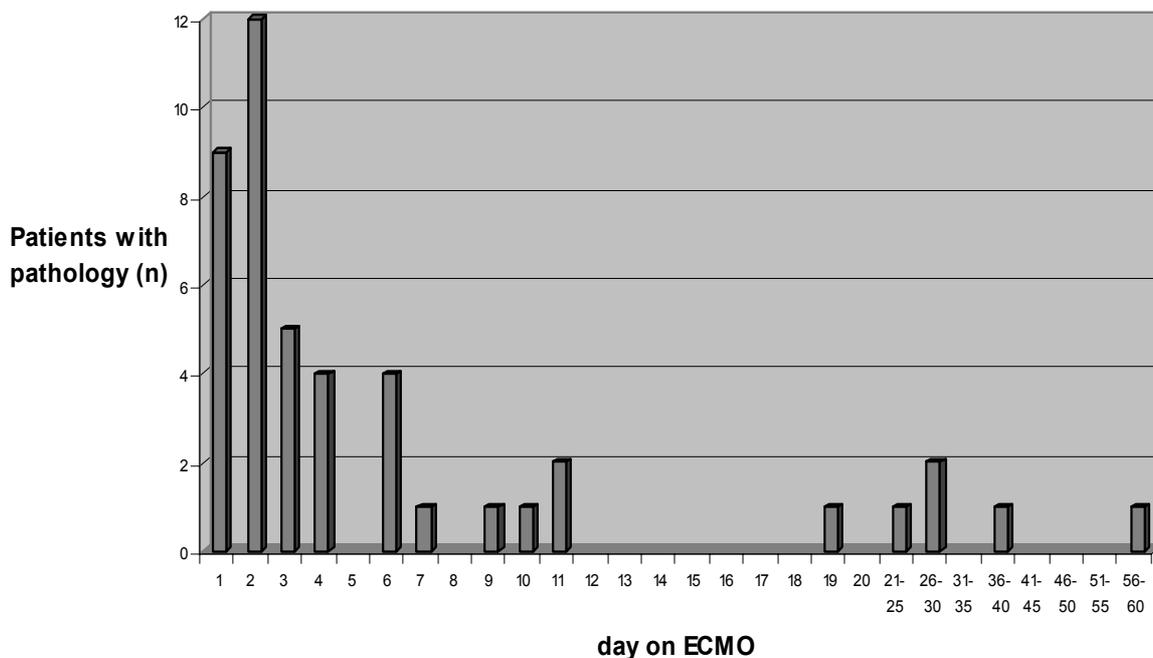
**Fig 20.** Adult with pneumonia and ARDS. CT revealed huge pericardial hematoma (arrows) missed by echocardiography, probably due to limited acoustic window. (Paper II)

An obvious advantage of CT is the wide field of view, especially in patients with suspected complications without focal symptoms or with an unexplained delay in clinical improvement. On several occasions unexpected pathology of urgent importance was obtained with CT in these patients. US could in a few cases retrospectively provide equal information as CT but had not been requested or were focused on the wrong region since focal signs had been lacking or misleading.

### 5.1.4.2 Cranial CT findings (III)

In 37% of the pediatric and adult patients treated with ECMO in Paper III, ICH or infarction was detected with CT during ECMO-therapy. Fifteen percent of the patients had CT evidence of ICH, 9% had focal infarction and 13% had general brain edema. This is a higher rate of intracranial complications than reported to the ELSO Registry by other centers (7). However, the reported frequencies of cranial complications in adults and children during ECMO are often partly based on clinical evaluation or diagnosis after disconnecting ECMO, and are therefore probably unreliable. Since survival in our adult and pediatric patients compares favorably to the reported survival in the ELSO Registry, the difference is probably explained by a more active use of CT for diagnosis at our center (76, 77). The ease of obtaining US in neonates during ECMO may explain why ICH and infarction are reported more frequently in neonates than in children and adults (25-28, 34). The low utilization of neuroimaging in adults and children during ECMO can explain an under-reporting of intracranial complications.

We found a striking predominance of early intracranial complications with 67% of the lesions revealed within the first four days on ECMO (Fig 21). Our findings are in agreement with findings in neonates on ECMO, in whom controls with daily US has shown as much as 85% of ICH to appear within the first three days of ECMO bypass (58). These early intracranial complications probably reflects lesions due to pre-ECMO hypoxia, acidosis, hypotension or cardiopulmonary resuscitation. A delay in visualization on CT of up to 48 hours can be expected for hypoxic ischemic injury. Accordingly, liberal examination with cranial CT during the first days on ECMO should be considered in adults and children when there are clinical reasons to suspect neurological complications.



**Fig 21.** Time for CT-diagnosis of cerebral pathology, presented as day after ECMO initiation.

## 5.1.5 Effect on treatment during ECMO

### 5.1.5.1 Effect of chest and abdominal findings (II)

In the majority of the thoracic and abdominal complications found with CT, surgery or percutaneous drainage during ECMO was essential for the patient recovery (Fig 12). In a total of 30 thoracic and abdominal complications, occurring in 20 different patients, 15 were surgically treated and 11 required percutaneous invasive procedures. All interventions were performed while the patients were still on ECMO. The interventions were all successful and caused no further complication. In spite of the serious complications 13 of the 20 patients (65%) survived.

The role of chest and abdominal CT during ECMO is thus to identify patients with complications where urgent invasive therapy is essential, when bedside imaging has been inconclusive (Fig 22).

We think that the use of CT in our institution has led to an early active treatment of complications during ECMO and that this could have contributed to a high survival rate especially in the adult ECMO patients.



**Fig 22.** Young adult on ECMO, due to bacterial pneumonia, with sudden profuse lung hemorrhage. Chest radiograph shows complete opacification "whiteout" **(a)**. CT scan revealed multiple mycotic pulmonary artery pseudo-aneurysms (arrow) **(b)**. The aneurysms were treated with transcatheter embolization with coils and glue, during ECMO, and the patient survived. Post-ECMO chest radiograph with coil on left side (black arrow) and glue and a residual hematoma on the right (white arrow) **(c)**.

### 5.1.5.2 Effect of cranial CT findings (III)

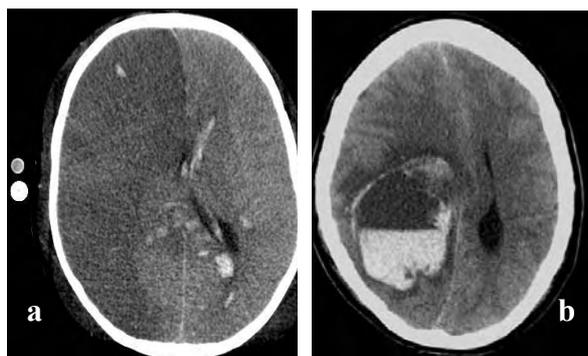
Four different clinical decisions were found to follow CT diagnosis of intracranial injury (Fig 13):

1. Large hemorrhages or pronounced general edema were reasons to immediately discontinue the treatment (Fig 23). The support from CT diagnoses facilitated earlier and more confident decisions compared to clinical diagnosis.
2. With serious but less fatal injuries, efforts were made to wean from ECMO as soon as possible.
3. Neurosurgical intervention was performed in a few patients but showed a low success rate due to postoperative continued bleeding.

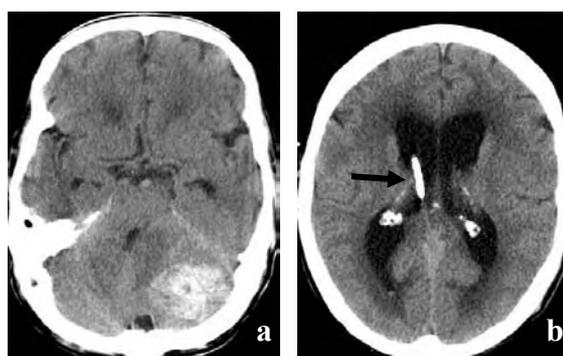
One patient survived after decompression of hydrocephalus and had no clinical neurological sequelae at follow-up one year after ECMO (Fig 24).

4. In patients where CT revealed lesions with expected fair prognosis, as focal hemorrhages and infarction, the ECMO treatment was continued with adjustments in anticoagulation or, in a few cases, treatment with mild hypothermia to reduce edema. The survival in this group was not significantly different from patients without proven intracranial complications.

In addition to the benefit of proven abnormality on CT, negative findings can often be equally important, to exclude intracranial pathology in confused patients, thereby encourage continued ECMO. In three of our patients with alarming neurological symptoms during the ECMO therapy a normal cranial CT supported continued treatment. These patients later proved to have critical illness poly-neuropathy (78). Accordingly, cranial CT has a great impact on the treatment during ECMO. The main value is in differentiating patients who have no CNS complications or complications with good prognosis from those with poor prognosis where treatment should be withdrawn to avoid unnecessary patient suffering and cost.



**Fig 23.** General edema in child with sepsis (a) and large ICH in young woman with ARDS (b). Both findings motivated withdrawal of ECMO support.



**Fig 24.** Adult patient with cerebellar hemorrhage (a) and hydrocephalus (b) which was successfully decompressed with a ventricular shunt (arrow) during ECMO.

## **5.2 FOLLOW-UP LATE AFTER ARDS AND ECMO (IV)**

ARDS is a life-threatening pulmonary syndrome caused by various conditions (24). Treatment of ARDS requires aggressive supportive care, including positive pressure ventilation and increased oxygen concentrations with risks of barotrauma and oxygen toxicity which can further aggravate the lung injury. It has been shown that post-ARDS patients often are left with chronic pulmonary fibrosis, reduced pulmonary function and diminished health related QoL (36-42).

ECMO can be an alternative technique in severe ARDS resistant to conventional therapy where the overall expected mortality is very high (2). Patients who require ECMO treatment probably have a more severe ARDS which might be expected to result in more serious long-term respiratory sequelae. However, the gentle ventilation strategy that comes with ECMO may contribute to minimize the ventilator induced lung injury and shorten the recovery phase (79).

ECMO patients require maximal use of the intensive care resources over prolonged periods of time with high costs. It is therefore important to evaluate not only survival but also the extent of residual pulmonary injury and the pulmonary function as well as the health related QoL in survivors. Follow-up studies in ECMO-treated patients after severe ARDS are few in number and little is known of the long term pulmonary function in these patients (39, 43, 44). In Paper IV we present an extensive follow-up program in ECMO treated ARDS patients, including HRCT of the lungs, pulmonary function tests as well as a dedicated questionnaire for evaluation of respiratory problems. To our knowledge, no previous study of ARDS patients has included all of the above mentioned tests.

### **5.2.1 Parenchymal changes on HRCT**

In recent studies HRCT has been used to evaluate the nature and frequency of persistent lung parenchymal abnormalities in survivors after conventionally treated ARDS. The described residual morphological changes resemble those found in pulmonary fibrosis but are in ARDS patients strikingly more pronounced in the anterior parts of the lungs (36, 37). It has been suggested that these abnormalities represent effects of the ventilator induced lung injury rather than effects of ARDS itself (36). Also in our study a HRCT pattern presumed to represent fibrosis was a common finding. However, this was less frequent in our material and the anterior predominance of parenchymal pathology, described in conventionally treated ARDS patients, was not seen in our patients. This may reflect that ECMO treatment allows a more gentle ventilation which spares the lungs from further ventilator induced lung injury.

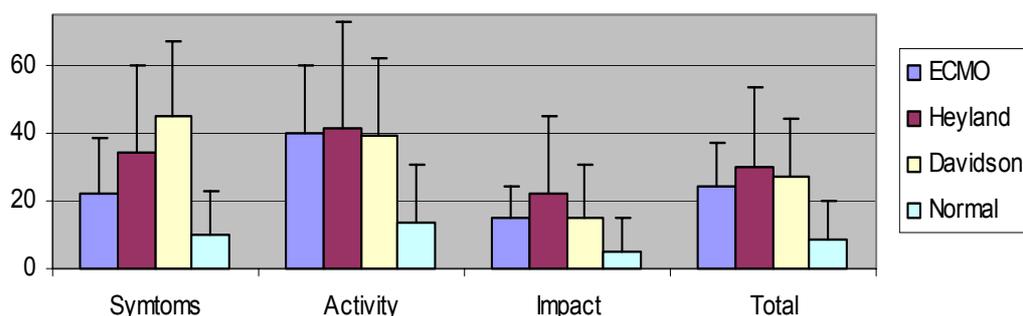
### 5.2.2 Pulmonary function tests

In our study group, most lung function values had normalized with mean values for all lung spirometry tests in the lower normal interval. However, a number of patients had a persistent mild restrictive or obstructive disorder. Exercise tests revealed values for exercise capacity in the lower normal interval, as for normal but untrained individuals. These findings are consistent with previous studies of conventionally treated ARDS patients (39-41, 43, 44).

Reduced diffusion capacity is the most common residual impairment described in conventionally treated ARDS patients with frequencies most often between 40-80% of the patients (36, 40) and was also seen in 65% of our patients. However, the most sensitive test for residual impaired pulmonary function in our study was the T<sub>1/2</sub> for wash-out of inhaled isotope reflecting air-trapping in the peripheral airways, which is thought to be one of the most important reasons for pulmonary symptoms after ARDS (22). Wash-out of isotope has to our knowledge not previously been used to evaluate patients after ARDS.

### 5.2.3 Pulmonary specific quality of life

Our patients had mean scores in the SGRQ that in all domains were higher than normal values according to the SGRQ manual, indicating subjective respiratory problems. Prior studies in conventionally treated ARDS patients show similar results with a tendency for even higher scores (41, 42, 80). The scores in the symptom domain were, in our study, significantly lower ( $p < 0.05$ ) compared to a previous study after conventional treatment of ARDS by Davidson et al (42) (Fig 25) suggesting less subjective pulmonary symptoms after ECMO treated ARDS than after conventional treatment.



**Fig 25.** Results on SGRQ. Scores for adult post ARDS ECMO patients and comparison with normal values and two previous studies on conventionally treated ARDS patients, by Heyland and Davidson respectively.

#### **5.2.4 Correlations with follow-up results**

In previous studies in conventionally treated post ARDS-patients, the duration of aggressive mechanical ventilation has been found to be significantly correlated to the extent of HRCT changes suggestive of pulmonary fibrosis (36, 37) and to a restrictive disorder in pulmonary function tests (39). This has been presumed to represent ventilator induced lung injury. The same correlation was found in our material even though most patients were less than seven days on mechanical ventilation prior to ECMO. Our study indicates that irreversible lung injury can occur even after short times with aggressive mechanical ventilation preceding ECMO.

The total extent of CT changes was associated with higher scores on SGRQ, indicating more subjective pulmonary symptoms. HRCT in routine follow-up may therefore be a valuable test to predict residual respiratory symptoms (Table 7).

Long time on ECMO was associated with extensive CT changes, with obstructive and restrictive pulmonary function tests and with impaired gas diffusion. This may however be explained by the severity of the underlying lung disease rather than an effect of ECMO, considering that ECMO therapy itself has previously not been correlated to any specific effect on pulmonary morphology (81).

However, to evaluate if ECMO has a significant positive primary influence on pulmonary outcome and sequelae after severe ARDS further studies have to be done.

#### **5.3 MRI DURING ECMO (V)**

Hypoxic-ischemic cerebral complications are not uncommon during ECMO treatment. Among possible risk factors are pre-ECMO asphyxia and changes in intracranial hemodynamics with an altered brain perfusion during ECMO (82). To prevent or mitigate cerebral damage and to guide further treatment, early diagnosis of cerebral complications is mandatory. Unfortunately, methods available for early diagnosis of cerebral hypoxic events during ECMO are limited, especially in adults and older children.

At our institution the use of mobile ECMO-systems has contributed to the use of CT as a routine complement to bedside cranial US for diagnosis of cerebral complications since 1994 (76). However, CT is not very sensitive in detecting early ischemic changes and has limitations in imaging of the posterior fossa and brain stem due to artifacts.

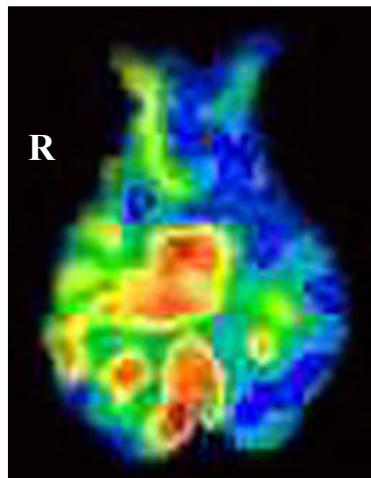
MRI is a sensitive and relatively non-invasive method for assessment of vessel patency, brain parenchymal changes and for measurement of functional parameters such as brain diffusion and perfusion. With diffusion weighted imaging, ischemic changes can be shown within ½ hour after a hypoxic ischemic event and with perfusion weighted imaging, altered perfusion can be seen as soon as minutes after the insult (Fig 26).

These methods are used in clinical practice for early diagnosis of cerebrovascular insults and to evaluate if some of the hypoperfused areas are still possible to salvage with thrombolytic treatment (65, 66). MRI also provides a tool for characterization and quantification of flow in thoracic and craniocervical vessels that may be of special interest in ECMO patients.

Our experiments have demonstrated that the devices used for transport on ECMO can work exceedingly well in an MR environment including a test with an experimental animal.

However, the results only apply to the specific ECMO- and MRI systems tested and other systems must be independently tested prior to use. Another limitation is the inability to image patients with wire reinforced cannulae, used for VA ECMO and for VV ECMO in adults and older children. The most commonly used double lumen venovenous cannula is not wire reinforced and could be used to support children up to 12-13 kg. Hopefully there will be a greater supply of MRI compatible cannulae in the future.

To move from this stage of animal experiments to clinical trials, extremely strict instructions are needed, and it should not be performed without dedicated MRI- and ECMO teams with deep knowledge in MR-safety and transports on ECMO.



**Fig 26.** Color coded map of brain perfusion in pig model showing delayed contrast passage through right hemisphere (green-yellow-red for increasing delay.) R = right

## **5.4 FUTURE RECOMMENDATIONS**

### **5.4.1 CT during ECMO (I-III)**

Bedside imaging should remain the mainstay for routine monitoring in patients during ECMO treatment due to its portability, low cost and low radiation dose.

CT has in our studies proved to have an important role during ECMO to show or exclude complications and to guide further treatment when bedside imaging is insufficient. We recommend liberal use of CT as an adjunct to bedside radiographs and US for diagnosis of suspected complications or a delay in improvement.

However, transportation during ECMO carries a potential risk for patient complications and requires special equipment and an experienced team.

### **5.4.2 Follow-up in adults after ARDS and ECMO (IV)**

Our study demonstrates that a follow-up program can provide important information about respiratory function in adult patients late after ARDS and ECMO. The follow-up program may include HRCT of the lungs, pulmonary function and exercise tests, DL<sub>CO</sub>, T<sub>1/2</sub> for wash-out of inhaled isotope and the SGRQ.

A similar follow-up program could also be applied for children post-ECMO treatment.

### **5.4.3 MRI during ECMO (V)**

Our study suggests that MRI in a near future may be used for early diagnosis of cranial complications in patients on ECMO. In ECMO patients, hypothermia might be a feasible method to reduce the cerebral damage after ischemic infarction or neonatal asphyxia (83). MRI may also provide a useful tool for further research on flow dynamics and brain perfusion during ECMO.

We plan further studies on the ability of MRI to detect hypoxic-ischemic brain injury during ECMO using our pig model, before proceeding to patient examinations.

## 6 CONCLUSIONS

The main conclusions from the present investigations were:

- I. A large number of CT was performed during ECMO with high frequency of clinically important findings. CT is feasible, safe and most useful in patients with severe acute respiratory failure on ECMO. The main value is for evaluation of suspected complications or a delay in improvement.
- II. Chest and abdominal CT have an important role in patients on ECMO therapy, as a complement to bedside imaging. CT can provide quick and reliable diagnoses when bedside radiographs and US are inconclusive or non-diagnostic, and expedite early surgical or percutaneous treatment, which may contribute to a better outcome.
- III. Our study suggests an under-reporting of intracranial complications in children and adults during ECMO, due to low utilization of neuroimaging. Cranial CT has an important role, to reveal or exclude severe intracranial complications where ECMO treatment should be discontinued. Less severe complications have a favorable prognosis with continued treatment.
- IV. Lung parenchymal changes on HRCT suggestive of fibrosis, pulmonary function abnormalities and subjective respiratory symptoms remain common and can be detected more than one year after ECMO treated severe ARDS. However, the impairments are most often mild and the majority has good physical and social functioning and a high rate of employment. The extent of HRCT changes are associated with residual subjective pulmonary symptoms and could therefore be valuable in routine follow-up.
- V. MRI can safely be performed in living subjects on ECMO with high quality images. In the future this may have an impact, especially on early diagnosis and treatment of cerebral complications in patients on ECMO.

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