PAEDIATRIC INTENSIVE CARE IN SWEDEN

I. Mechanical ventilation and central haemodynamics.

II. Outcome of paediatric intensive care with special reference to respiratory failure.

Ninna Gullberg

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“You only live once……”

Never give up a dream
Feel - You are free
Don’t wait until tomorrow
Do what You want to do
Take some risks and do it now

You only live once, just take a minute and think about what you can do

To my daughter Jessica
ABSTRACT

The ABC of acute care is to maintain Airway, Breathing and Circulation or oxygen delivery, which depends on the product of cardiac output (CO) and oxygenation. Thus knowledge of how different modes of mechanical ventilation affect central haemodynamics is essential.

**Paper I:** Improved triggering function made pressure support ventilation (PSV) possible for neonates and infants. We evaluated the effect on cardiac output of this mode in comparison with conventional pressure control ventilation in infants (n=9). We found a significant improvement in cardiac output by 16% during PSV. This finding may be of importance for critically ill infants.

**Paper II:** In Paper I we did not find any significant change in heart rate, thus the increase in CO was caused by an increase in stroke volume (SV). The ability of the neonatal heart to change stroke volume has been debated. In a study of anaesthetized infants on mechanical ventilation (n=6), the PEEP-level was changed and CO measured. Data on CO, SV and heart rate were analysed together with data from Paper I. There was an almost linear significant change in CO, from +16% to -13% without changes in heart rate. Thus we found that when mean airway pressure is altered the changes in CO is an effect of changes in SV.

**Paper III:** High frequency oscillatory ventilation (HFOV) is a new method of mechanical ventilation with tidal volumes <dead space. The small tidal volumes make HFOV an attractive method for lung protective ventilation. High mean airway pressures (P_{aw}) are often needed which might affect central hemodynamics unfavourably. To evaluate the effects of changes in P_{aw} on CO we investigated infants already on HFOV; CO was measured at three different levels of P_{aw}. Patients (n=9) were their own controls. A decrease in CO of 11% was found when P_{aw} was increased by 5 cmH_{2}O.

Few studies have been carried out on the incidence and outcome of paediatric intensive care or more specifically on respiratory failure. There are also differences regarding population, mortality and health between different regions. Thus international studies may not apply to Scandinavia. To investigate the circumstances in Sweden the following studies were performed:

**Paper IV:** An ambidirectional multicentre population based collection of data on all admissions to ICU of children aged 6 months (in PICU 1 month) to 16 years of age during 36 months 1998-2001. Only a minority of children needing intensive care in Sweden received that in a designated paediatric ICU (PICU). Mortality was similar in PICU and adult ICUs. There is a continued increased mortality for at least five years after admission to an ICU. Studies are needed to evaluate if centralization of paediatric intensive care in Sweden would be beneficial to the paediatric population.

**Paper V:** The subgroup with respiratory failure in PICU, were further studied; 20% of admissions were ventilated >24 hours. NO, HFOV and ECMO was used in 15% of these cases indicating a severe respiratory disease. This group had an initial increased mortality but one year after discharge from ICU the mortality was not increased. Results from one PICU, show that ARDS is relatively uncommon but accounts for close to 1/3 of the total ICU mortality in this PICU. This suggests that ARDS may be a significant health issue in children in Sweden.
LIST OF PUBLICATIONS

I. Ninna Gullberg, Per Winberg, Hans Selldén
   *Pressure support ventilation increases cardiac output in neonates and infants.*
   Paediatric Anaesthesia, 1996; 6; 311-315

II. Ninna Gullberg, Per Winberg, Hans Selldén
   *Changes in stroke volume cause change in cardiac output in neonates and infants when mean airway pressure is altered.*
   Acta Anaesthesiologica Scandinavica, 1999; 43: 999-1004

III. Ninna Gullberg, Per Winberg, Hans Selldén
     *Changes in mean airway pressure during HFOV influences cardiac output in neonates and infants.*
     Acta Anaesthesiologica Scandinavica, 2004; 48: 218-223

IV. Ninna Gullberg, Håkan Kalzén, Owe Luhr, Sylvia Göthberg, Ola Winsö, Agneta Markström, Ann-Kristin Olsson, Claes Frostell and Scandinavian Critical Care Trials Group
    *Immediate and 5 year cumulative outcome after pediatric intensive care in Sweden.*
    Accepted in Acta Anaesthesiologica Scandinavica 2008.

V. Ninna Gullberg, Sylvia Göthberg, Ann-Kristin Olsson, Marika Lidegran and Claes Frostell
   *Acute respiratory failure in pediatric intensive care in Sweden, a multicenter observational study.*
   Submitted.
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<th>Description</th>
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<tbody>
<tr>
<td>$A_{Ao}$</td>
<td>Aortic cross-sectional area</td>
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<tr>
<td>AECC</td>
<td>American-European consensus committee</td>
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<tr>
<td>ANZPIC</td>
<td>Australian New Zealand paediatric intensive care</td>
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<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
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<tr>
<td>ARF</td>
<td>Acute respiratory failure</td>
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<tr>
<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
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<tr>
<td>CDH</td>
<td>Congenital diaphragmatic hernia</td>
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<td>CMV</td>
<td>Conventional positive-pressure ventilation</td>
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<td>CO</td>
<td>Cardiac output</td>
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<td>CVS</td>
<td>Cardiovascular system</td>
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<td>ECMO</td>
<td>Extra-corporeal membrane oxygenation</td>
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<td>EDRF</td>
<td>Endothelium-derived relaxing factor</td>
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<tr>
<td>ESPNIC</td>
<td>European society of paediatric and neonatal intensive care</td>
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<tr>
<td>ETCO$_2$</td>
<td>End-tidal CO$_2$</td>
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<tr>
<td>FiO$_2$</td>
<td>Fraction inspired O$_2$</td>
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<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
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<td>GI</td>
<td>Gastrointestinal system</td>
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<tr>
<td>HFOV/HFO</td>
<td>High-frequency oscillatory ventilation</td>
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<td>HR</td>
<td>Heart rate</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>iNO</td>
<td>Inhaled nitric oxide</td>
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<tr>
<td>ITP</td>
<td>Intrathoracic pressure</td>
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<tr>
<td>LOS</td>
<td>Length of stay</td>
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<tr>
<td>LVO</td>
<td>Left ventricular output</td>
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<td>MAP</td>
<td>Mean airway pressure</td>
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<tr>
<td>MAS</td>
<td>Meconium aspiration syndrome</td>
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<tr>
<td>MFV$_{Ao}$</td>
<td>Mean aortic flow velocity</td>
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</table>
MOF  Multiorgan failure
MV   Mechanical ventilation
NICU Neonatal intensive care unit
NOS  NO synthase
PaO₂/FiO₂ Ratio between inspired and arterial O₂ content
Paw Continuous distending pressure/mean proximal airway pressure
PCV  Pressure controlled ventilation
PEEP Positive end-expiratory pressure
PICANET Pediatric intensive care audit network
PICU Pediatric intensive care unit
PIP  Peak inspiratory pressure
PP   Pulse pressure
PSV  Pressure support ventilation
PW   Range-gated pulse-waved doppler
RSV  Respiratory syncytial virus
RV   Right ventricle
RVO  Right ventricular output
SaO₂  Peripheral arterial saturation of oxygen
SDAo Stroke distance
SV   Stroke volume
VAP  Ventilator-associated pneumonia
VILI Ventilator-associated injury
Vₘ₉₉ Maximum flow velocity
Vₘ₉ Mean flow velocity
VTI  Velocity time integral
1 INTRODUCTION

1.1 PAEDIATRIC INTENSIVE CARE

To give a seriously ill child the chance of recovering his or her life first has to be saved. Treatment of life-threatening aspects of all diseases must always take precedence over specific therapy aimed at the underlying disease. The main function of intensive care is to support the vital functions, awaiting the effects of therapeutic treatments and or the natural healing process. The ABC of acute care is to maintain Airway, Breathing and Circulation or oxygen delivery. Oxygen delivery depends on the product of cardiac output and oxygen content in the blood delivered. This means that a change in mechanical ventilation that improves oxygenation but decreases cardiac output may not improve oxygen delivery. Thus knowledge of how different modes of mechanical ventilation interact with central haemodynamics is essential.

Primum non nocere; first, do no harm, the aphorism that even though not actually part of the Hippocratic oath, has been a guideline for physicians through the centuries. It may be of greater interest than ever in intensive care today with increased knowledge of the disadvantages of our methods, e.g. mechanical ventilation, with ventilator associated pneumonia (VAP) 1-4, ventilator induced lung injury (VILI) 5-7 and possibly ventilator induced multiorgan failure 8, 9. One of the most current dilemmas of intensive care today is to find the balance between maintaining vital parameters and the injury caused by our methods of maintaining the vital functions. Instead of maintaining “normal” values we are aiming for “acceptable” values, trying to find what they are. Treatment of acute respiratory failure (ARF), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are important factors in improving outcome of intensive care.

1.2 PICU (PAEDIATRIC INTENSIVE CARE UNITS)

1.2.1 History

The history of specialized intensive care units for children is not very long. Sweden was among the pioneering countries; the first PICU in the world was started 1955 in Gothenburg by Göran Haglund. In 1961 this was followed with a PICU in Stockholm
started by Hans Feychting. The third PICU in Sweden is situated in Lund and is more recent.

Throughout the world paediatric intensive care is a growing speciality, with the number of PICUs evolving at different rates in different regions.

In the US there was an increase in the number of hospitals with PICUs in the 1980s; in 1989 there were 276 PICUs, 306 in 1995 and 349 in 2001. At that time about half the PICUs had less than 8 beds. Moreover, the number of PICU beds has grown faster than the number of PICUs (24% vs. 14% between 1995 and 2001). At the same time the occupancy rate, percentage intubated and mortality rate increased.

In Australia, one of the most urbanised countries in the world together with vast remote areas, paediatric intensive care developed in a highly regionalized manner. There are seven PICUs situated in the state capitals. This compares with the UK where the intensive care services for children initially developed in a fragmented and sporadic manner. In 1992 only 51% of the children needing intensive care received that in a PICU, 21% received care in an adult ICU and 28% in a paediatric ward. Despite reports by the British Paediatric Association and Paediatric Intensive Care Society and articles supporting an improvement in intensive care for children, change was slow. In 1997 Pearson et al. provided solid evidence for the need of change in the UK intensive care provision for children. This study compared mortality rates between critically ill children in the state of Victoria in Australia and a UK region (Trent). The authors concluded that if Trent was representative of the UK, there were 453 excess deaths per year in the UK that were probably due to suboptimal results of intensive care. Another study of a region in the UK (Birmingham) where centralisation had already occurred reported an increased number of admissions, shorter length of stay (LOS) and a lower child mortality in the population after centralisation. Since then centralisation has occurred in the UK.

1.3 PHYSIOLOGY “CHILDREN ARE NOT SMALL ADULTS”

It is not only in size that children differ from adults. The physiology in the very young is different in many ways, most of all during the neonatal period.
1.3.1 Respiratory system

Airway resistance

Poiseuille’s law; the resistance to flow $\sim r^4$, means that the airway resistance in a neonate is about 10 times greater than that of an adult. However during normal conditions the minute volume and flow is proportionately lower. It is during increased need for ventilation or if the lumen is further compromised, e.g. by mucosal oedema that conditions can be more serious in a small child.

“Pump”

There are several differences in the respiratory pump between the neonate and the adult. The incomplete ossification of the ribs results in a high compliance of the chest wall. This means that part of the work of breathing is used to move the chest wall before air is moved. That together with the straighter angle of insertion of the ribs and the geometry of the thorax makes intercostal breathing insufficient and the neonate is more dependent on the diaphragmatic breathing. In comparison the infant’s abdomen is larger than the thorax which makes the impact of abdominal distension more severe.

Furthermore, the composition of the diaphragm is immature at birth. Over the first eight months the percentage of type IA fibres which are less sensitive to exhaustion, increase from 25% to 55% 16.

The young infant is thus more vulnerable to exhaustion both from a higher work of breathing and because the ventilatory muscles are more susceptible to fatigue.

Compliance

Compared to an adult the lung of a small child has significantly lower compliance. Even when related to weight the adult lung compliance is more than double that of the neonate. Normal tidal volume/kg is however similar in neonates and adults, 6-8 ml/kg. 17, 18.

Functional residual capacity (FRC)

The normal FRC is also significantly lower in the neonate and infant compared to in the adult 17. This means that already the healthy infant is prone to collapse of alveoli. The low FRC (at relaxation) of only 10-15% of total lung capacity in the neonate puts the newborn at risk for airway closure and atelectasis. It has been shown that
newborns use muscle activity to dynamically maintain an end expiratory lung volume above FRC during active breathing. During apnea, mechanical ventilation and sedation this is lost. FRC can be increased and the risk of lung collapse decreased by the use of positive end expiratory pressure (PEEP).

Metabolic rate, alveolar ventilation

Oxygen consumption/kg is 2-3 times higher in a neonate than in an adult with 6-8 ml/kg/min compared to around 3 ml/kg/min in the adult. Thus the alveolar ventilation also has to be higher. The resistance, proportion of dead space, compliance and other specifics of the respiratory physiology of children are probably the reason why this is accomplished with similar tidal volumes/kg but an increased respiratory rate compared to that in the adult. The normal respiratory rate for neonates is 30-40 versus 12-16 for adults.

The high metabolic rate combined with the smaller oxygen reservoir in the lung with a low FRC is also the reason for children and especially neonates becoming cyanotic quickly during apnea.

1.3.2 Cardiovascular system (CVS)

At birth the cardiovascular system is immature. As invasive methods such as thermodilution carry higher risks or are not clinically available for small children, studies have been performed in animal models. There are significant differences between species which have made the interpretation of the results uncertain. Non-invasive methods (Doppler, echocardiography, impedance measurements, analysis of heart rate variability etc.) are all fairly recent methods. Thus the function and development of the immature human cardiovascular system are not fully investigated.

Autonomic control

The sympathetic nervous system, although rapidly developing, is relatively immature at birth. Circulating catecholamines play a major role in the adrenergic control of the immature cardiovascular system. Cholinergic control seems to be dominating in the neonate and infant. The autonomic control has been shown to develop with age from the premature to the term neonate and then continues during the first years of life with the most rapid changes occurring during infancy.
Myocardial function

The foetal and neonatal myocardium develops less tension per unit compared to the more mature heart. Earlier animal studies have shown several differences between the immature myocardium in the neonate and the older child or adult. The myocytes are not only smaller but also contain a smaller proportion of contractile elements, myofilaments. In the immature heart the myofibrils are also unorganised. Furthermore, the sarcoplasmatic reticulum which plays an important and complex role in the calcium flux and contraction of the myocytes, is underdeveloped. The mitochondriae, the “power plants”, of the cell, are also fewer and less organized. Summarized this gives the immature heart not only a lower contractility but also a lower compliance or diastolic function.

1.3.3 Diagnoses

Apart from the fact that the physiology in children is different from that in adults, they also have other reasons for admission to ICU. During the neonatal period congenital malformations needing urgent care and often surgery within days are common reasons for admissions; severe infections; sepsis and meningitis are also common indications. In older children injury and infections are common in the previously healthy child. Other children with underlying disease such as neurological deficits; epilepsy, developmental delay and cerebral palsy need intermittent admissions, often for respiratory problems. The diagnostic panorama for children admitted to ICU in Sweden has not previously been investigated.

1.4 MECHANICAL VENTILATION

1.4.1 History

Positive pressure mechanical ventilation for clinical use was developed during the polio epidemic in the 1950s in Scandinavia and the US. As safe high volume low pressure cuffed endotracheal tubes (ETT) became available, the need for early tracheotomy decreased. For several reasons the risk of trauma to the trachea is higher in small children. Uncuffed tubes with a leak have been used in the paediatric population especially in the youngest age group. The use of pressure controlled ventilation in the paediatric population makes leakage less of a problem.
1.4.2 Conventional positive pressure ventilation (CMV)

CMV uses tidal volume breathing, simulating normal breathing, with respiratory rates and tidal volumes relatively close to the normal range for spontaneous breathing.

The peak pressure (PIP) that drive the mechanical ventilation and the PEEP are propagated during the inspiratory and expiratory phases from the airway to affect the overall intrathoracic pressure (ITP). A mean airway pressure that is directly proportional to the intrathoracic pressure can be calculated. The intrathoracic pressures affect the venous return to the right ventricle (RV); the RV preload.

Modes

The tidal volume ventilation can be controlled in different ways. Some basic modes are:

- **Volume controlled ventilation** (VCV): The ventilator is set to deliver a preset volume over a specific time with a constant flow and the pressure increases during the inspiratory cycle. The variable leak around the ETT, the small tidal volumes and relatively large compressible volumes in the ventilator tubing made older ventilators too insensitive to safely use VCV in small children. With modern ventilators this is less of a problem.

- **Pressure control ventilation** (PCV): The ventilator is set to deliver a set pressure over a set inspiratory time; the flow will be decelerating and the pressure is constant during the inspiratory cycle. The peak pressure is thus naturally limited.

- **Pressure support ventilation** (PSV): The ventilator is set to deliver a set pressure when it is triggered by the patient’s inspiration. The inspiratory time with this pressure is generally dependant on the decrease in flow, with an algorithm depending on the type of ventilator.

Flow triggering

Pressure and volume support modes of ventilation had been available for adults and older children for some time. The trigger mechanism was dependent on the patient’s ability to develop a negative pressure through the ventilator system. For small children this increased the work of breathing and more important the time between the child initiating a breath and delivery of support was too long. During the 1990s new ventilators where developed (Siemens Servo 300, Dräger Babylog 8000) with a continuous flow in the system during the expiratory phase. These ventilators were capable of detecting very small changes in flow, down to 3ml. The response time was
also shorter; < 10ms. \(^{37}\) This made it possible for very small children to trigger the ventilator and pressure support ventilation could be used in clinical practice \(^{38}\).

**Tidal volume, inspiratory time**

When the ventilator has been triggered to give a pressure supported breath, the breath is supported to the set pressure but generally not for a set time. On the Servo 300 the positive pressure is maintained until the flow decreases to 5% of the peak flow velocity in the early phase of inspiration. The thought is that the patient should be able to somewhat regulate both the inspiratory time and tidal volume. The mean airway pressure will then be dependant both on the set pressures (PIP and PEEP) and the inspiratory time which would ideally be depending on the patients needs. This was not always accomplished and in more modern ventilators the % of the peak flow when the ventilator will interrupt the inspiratory phase can often be set at different values.

**1.4.3 HFO**

**History**

The ability of oscillations to eliminate CO\(_2\) was found by chance in 1972 by a group in Toronto including Charles Bryan\(^{39}\). The same year a German group published similar findings when they used oscillations to study impedance \(^{40}\). Three years later K Miyasaka in the Toronto group built the “Oscillator No 1”. In 1980 the first Paper on high frequency oscillation ventilation of humans was published by the same group\(^{41}\).

What amazed the scientists was that CO\(_2\) was eliminated at tidal volumes much lower than the dead space. There are a few theories on how this is achieved; convection, diffusion, asymmetric profile of flow velocity, Taylor dispersion, “pendelluft”, collateral ventilation. No single theory can explain the phenomenon completely, there seems to be a combination of mechanisms.

**Oxygenation and ventilation during HFO:**

In principle CO\(_2\) elimination and oxygenation are decoupled during HFO. The frequency (3- 15 Hz) and amplitude (ΔP) of the oscillations determine the CO\(_2\) elimination whereas oxygenation is accomplished with the fraction of inhaled oxygen (FiO\(_2\)) and mean airway pressure (P\(_{aw}\)). In conventional MV some recruitment of the
lungs can be achieved by tidal volume recruitment during ventilation. This does not occur during HFO so lung recruitment has to be achieved by active recruitment. This can be achieved by increasing $P_{aw}$ until recruitable parts of the lung are opened and then maintaining the mean airway pressure above the lower inflection point.

**Clinical use**

Studies suggested that bronchopulmonary dysplasia (BPD) in the premature neonate was caused by high inflation pressures rather than high FiO$_2$. With the aim to find “gentler ventilation” HFO was first used clinically in the neonatal world. Two different strategies were used, one aiming for low pressures to avoid barotrauma and one aiming for “open lung”.

A large randomised controlled study using the “low-pressure” strategy failed to show benefit and possibly harm by HFO with an increased frequency of intracranial haemorrhage. This study decreased the interest for HFO, but the supporters of the “open-lung” strategy continued their work, using the very small tidal volumes of HFO combined with the “open lung” concept to try protect the lung. Experimental studies were undertaken showing the importance of opening the lung and clinical studies on respiratory failure in the neonatal and paediatric population were carried out showing improved pulmonary and clinical outcome in specific groups of patients.

The “open lung”, small tidal volume strategy is an accepted and used concept today. When looking back at how the strategies and use of mechanical ventilation has evolved over the last decades it seems obvious that HFO has played an important part not only in its use itself but also by improving the thinking on how we ventilate our patients on conventional mechanical ventilation as well.

Recent articles reviewing the use of HFO suggest that with the improvements in how conventional mechanical ventilation is implemented, it is harder to show improved outcome by the use of HFO. It is however likely that patients, (adult and paediatric) may benefit from the use of HFO. Further randomised controlled studies are however needed to clarify the criteria for the use of HFO. In mild disease it is not needed, in end-stage disease with established VILI it will be too late.
1.4.4 Nitric oxide (NO)

History
Endothelium derived relaxing factor (EDRF) was shown to be identical to NO in 1987 \(^{66,67}\). After that intense research and clinical use \(^{68,69}\) soon commenced. It was shown that NO in vivo was synthesized from L-arginine and oxygen and that the process was facilitated by inducible and constitutive isoforms of NO-synthase (NOS) \(^{70,71}\). Inducible NOS is found in several cells and is induced by endotoxins and cytokines as part of the inflammatory response, e.g. in sepsis. Constitutive NOS is found in different types of cells such as the endothelium in the vascular system. The formed NO diffuses freely to the adjacent vascular smooth muscle cells causing vasodilation by increasing intracellular cGMP. NO is rapidly inactivated within seconds at contact with oxygenated haemoglobin.

Physiology of NO in the lung
Endogenous NO is found in exhaled gas from both animals and humans \(^{72,73}\). Inhaled NO (iNO) was shown to cause vasodilation in the vasculature of the ventilated parts of the lung \(^{74,75}\) without systemic vasodilatation. The selective pulmonary vasodilation by NO is thought to depend on the rapid inactivation in blood. NO could also be shown to have effects on hypoxic pulmonary vasoconstriction \(^{76}\) and on pulmonary hypertension in neonates and infants \(^{69,77}\).

Clinical use
The selective pulmonary vasodilation in ventilated parts of the lung was shown to not only lower pulmonary vascular resistance but also improve oxygenation in patients with ARDS \(^{78}\). Inhaled NO has been used as “rescue therapy” in hypoxemic patients and patients with pulmonary hypertension. NO has been shown to reduce the use of ECMO in hypoxic neonates with pulmonary hypertension \(^{79}\) and improve pulmonary outcome in premature babies weighing > 1 kg and reduce the risk of brain injury \(^{80,81}\). Randomised controlled studies on iNO for ARDS and ALI have failed to show improved survival or ventilator-free days \(^{82-84}\). A recent systematic review and meta-analysis have not been unable to show improved outcome \(^{85}\) for ARDS, whereas a Cochrane Database systematic review of respiratory failure in infants born at or near term found the use of NO reasonable\(^{86}\). In 2004 the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) arranged a European Consensus Conference
on inhaled nitric oxide therapy in neonates and children; reaching a European consensus on the use of NO \(^{87}\). The following year a similar European consensus was reached regarding recommendation for the use in adults \(^{88}\).

**1.4.5 Extracorporeal membrane oxygenation (ECMO)**

ECMO has been used for more than 20 years in neonates, children and adults in extremely severe cardiac or respiratory failure. It has been shown to reduce mortality in paediatric patients with ARF \(^{89}\) and in neonates with severe but potentially reversible lung disease \(^{90}\) in addition a randomised controlled study on ECMO in sick neonates demonstrated improved respiratory function after one year \(^{91}\). During ECMO the blood is oxygenated and CO\(_2\) removed through a membrane in an artificial lung outside the body. This allows time for injured lungs to recover with ventilator settings that do not cause further injury.

**1.5 MEASUREMENTS OF HAEMODYNAMICS.**

**1.5.1 Dilution method**

Thermodilution has been the golden standard for clinical measurements of cardiac output. In neonates and small children this technique has not been available as the intravasal catheter sizes were too large to be used safely in the youngest population. The dilution method was initially described using an indicator dye and assumes that the rate at which the indicator is diluted reflects the cardiac output. The method measures the concentration of dye (or temperature) at two different points in the circulation, usually from an intravenous injection and then at a downstream sampling site. Earlier the dye-dilution technique was the one used in children.

**1.5.2 Doppler ultra sound methods**

*History*

Christian Doppler first described the Doppler effect in 1843, but it was only in the 1960’s that the ultrasound Doppler technique could be used to measure the velocity of blood cells in a vessel. Equipment that was easy to use and sensitive and reliable enough to correlate well with thermodilution \(^{92-96}\) became available during the 1980s.
Doppler principle

Doppler equation:

\[ f_d = 2 f_0 \times v \times \cos \alpha \times C^{-1} \]

\( f_d \) = Doppler shift i.e. the frequency difference between emitted and received signal
\( f_0 \) = transmitted frequency,
\( v \) = velocity of moving object (blood cell),
\( \alpha \) = angle of insonation,
\( C \) the velocity of sound in the tissue.

At a given \( f_0 \); \( v \sim f_d / \cos \alpha \) I.e. the frequency shift is directly proportional to the velocity.

With the continuous-wave Doppler the emission and sampling of ultrasound is continuous, thus the reflected signals from moving blood cells along the whole length of the ultrasound beam are recorded.

With range-gated pulsed-waved Doppler short pulses of ultrasound are emitted and the receiving sample gate is opened after a time interval corresponding to the depth of interest. Thus velocity measurements can be performed in a sample volume at a specific distance from the transducer, e.g. right above the aortic valve. The length of the sample volume depends on the duration of the ultrasound pulse and on the length of time the receiving gate is open\(^97\).

In a vessel with a laminar flow the velocity of the blood cells vary across the lumen with the highest velocity in the center\(^98\). Velocity also varies over time due to the pulsatile nature of the flow. Estimated blood flow velocity can be expressed in different ways: Maximum velocity (\( V_{\text{max}} \)) denotes the instantaneous velocity of the blood cells moving with the highest speed. Space average velocity denotes the instantaneous weighted average of all the velocities over the cross-section of the vessel with varying values with the pulse. Mean flow velocity (\( V_{\text{mean}} \)) denotes the temporal mean and is directly proportional to the volumetric flow (provided the vessel is uniformly insonated)\(^97\). In some machines the space average velocity is also integrated in the mean flow velocity. The volumetric flow is obtained by multiplying \( V_{\text{mean}} \) with the cross-sectional area of the vessel.
**Cardiac output (CO) and left ventricular output (LVO)**

During foetal life owing to the foetal shunts the ventricles work in a parallel fashion and both contribute to the systemic circulation. Thus CO is not a meaningful term; instead right ventricular output, left ventricular output (LVO) and their sum, combined ventricular output is used. In the normal neonate the ductus arteriosus and foramen ovale closes functionally soon after birth and once there is no shunt CO equals LVO.

The CO can be obtained by multiplying $V_{\text{mean}}$ in the ascending aorta ($\text{MFV}_{\text{Ao}}$) with the cross-sectional area of the aorta;

$$\text{CO} = \text{MFV}_{\text{Ao}} \times \text{area}_{\text{Ao}}$$

The measurement of the diameter is crucial as the value is squared in the calculation of the area. In newborn and older infants a good correlation has been found between invasive methods and the Doppler technique. In the study by Mellander et al. thermolodilution was compared to different ultrasound methods and the product of $V_{\text{mean}}$ and the area derived from the inner diameter of the aorta gave the best estimate of cardiac output.

**Echocardiography with Doppler**

With echocardiography there are various methods to estimate cardiac output, both two (2D) and three dimensional (3D) methods are available as well as transthoracic and transoesophageal approach. In principle the measurements are the same as described above; a combination of 2D measurement of the area of the aorta, at the annulus, and a measurement of the aortic flow velocity using the ultrasound Doppler technique (see above). In many ultrasound machines, including the one used in our study, the velocity time integral (VTI) is measured, beat to beat. The VTI denotes the area under the velocity curve and represents a distance. The VTI multiplied by the aortic cross sectional area gives the stroke volume (SV). The advantage with using the echocardiographic Doppler is that it is possible to see on the screen where the Doppler sampling volume is placed in relation to the aortic valve and also the angle of the signal versus the flow. The software in the machine can measure the angle and compensate for this when calculating VTI. In our study this was not used as there is a risk of overestimating the flow with this method. Care was taken to achieve the
smallest possible angle between the aortic flow and the ultrasound beam to obtain the highest flow velocity recording. The disadvantage with the VTI is that the signal is integrated over time but not for the surface area, that is the $V_{\text{max}}$ rather than $V_{\text{mean}}$ is measured. The method is nevertheless, clinically well established and of proven accuracy $^{99}$.

### 1.5.3 Other methods to measure cardiac output

#### Pulse pressure (PP) methods

Pulse wave analysis relies on the principle that the pressures in the heart are conducted to the arteries, so the arterial pressure’s waveform reflects the interaction between stroke volume and systemic vascular system. Thus, resistance, compliance and characteristic impedance at the sight of signal detection has to be considered.

Lately invasive and calibrated continuous CO monitors have become available; PiCCO (Pulsion Medical Systems AG, Munich Germany) and PulseCO (LiDCO Ltd, London England). In both cases an independent technique is used to provide calibration of the continuous CO analysis as arterial PP analysis cannot account for unmeasured variables such as compliance of the vascular bed. For both methods dilution principles are used, in the case of PiCCO transpulmonary thermodilution and for LiDCO lithium dilution. Both methods have been investigated and found to be reasonably reliable in the clinical setting considering the specific properties of this technique $^{100-102}$.

#### Impedance cardiography (biologic impedance)

Impedance cardiography is a method which uses a constant electrical current stimulation for identification of thoracic variations induced by vascular blood flow. Lower impedance indicates larger intrathoracic fluid volume. The only fluid volume that changes beat to beat within the thorax is blood, thus the impedance can be used to calculate the stroke volume and combined with the heart rate the CO. This allows for non-invasive estimations of CO and total peripheral resistance using only four paired skin electrodes. The clinically available equipment is still new and the reliability and reproducibility may need further investigation $^{103-106}$. 
1.6 THE HAEMODYNAMIC EFFECTS OF MECHANICAL VENTILATION

Both spontaneous ventilation and positive pressure ventilation affects lung volume and ITP \(^{107}\). Although lung volume increases during inspiration in both, the swings in ITP are opposite with a decrease in ITP during inspiration in spontaneous breathing and an increase during conventional positive pressure mechanical ventilation. Thus most differences between spontaneous and mechanical ventilation reflects the differences in ITP. But since changes in lung volume can profoundly affect pulmonary vascular resistance and capacitance and at high lung volumes can compress the heart, it’s haemodynamical effects cannot be dismissed. Other things that may affect pulmonary vascular resistance are pO\(_2\), pCO\(_2\) and pH. Accordingly, changes in lung volume, ITP, oxygenation and CO\(_2\) elimination have to be considered when assessing the haemodynamic effects of ventilation.

The effects of positive pressure ventilation especially with high mean airway pressures and PEEP can affect cardiac function in a complex and often unpredictable way \(^{108}\). Apart from if the ventricle is failing, high mean airway pressures and PEEP usually decreases cardiac output, a well known fact since the classical studies by Cournand and Werkö in 1948 \(^{109}\). They concluded that positive pressure ventilation restricted venous return into the thorax by the increase in ITP and thereby reduces cardiac output. These findings are still the basis of our understanding of the effect of PPV on central haemodynamics. It has however been difficult to define the precise effects of PEEP and the intrathoracic responses appear multiple and complex. Haemodynamic effects of ventilation can be simply grouped into processes affecting left ventricular (LV) preload, contractility and afterload.

1.6.1 Preload

Clinically, LV preload is synonymous with LV end-diastolic filling and is dependent on systemic venous return and LV diastolic filling. LV diastolic function can be affected by right ventricular filling since they share the septum and the pericardial sack \(^{110}\). But the primary effect of positive pressure ventilation is the increase in ITP, impending venous return. This is partially caused by an increase in right atrial pressure \(^{111-115}\) and subsequently the decreased venous return gives a decrease in RV output, thus decreasing LV preload. This effect can be attenuated by volume loading \(^{116}\) and an accentuated reaction can be a sign of hypovolemia \(^{117},^{118}\). Other
mechanisms influencing venous return to the LV via decreased RV output are lung distension compressing the small pulmonary vessels \cite{119} or ITP levels above the pulmonary arterial pressure leading to vascular collapse. Likewise decreases in lung volume may increase pulmonary vascular resistance as a result of hypoxic pulmonary vasoconstriction \cite{120,121}.

The effects of positive pressure ventilation on preload is not yet fully understood, it is more complex than initially thought. The effects on afterload and contractility are equally complex.

### 1.6.2 Myocardial function

The effect of PEEP on LV contractility has generated a lot of controversy; there has been difficulty in defining myocardial function and in measuring it. The Frank-Starling relationship; the relationship between filling pressure and mechanical ventricular output is affected by the raised ITP, which complicates measurements of contractility. Studies have failed to demonstrate if positive pressure ventilation affects contractility.

### 1.6.3 Afterload

In general LV afterload is reduced by increased ITP, partially since the gradient to extrathoracic vessels is increased \cite{122,123}; inversely analogous to the increased resistance to venous return. This decrease in afterload does not normally translate into an increased cardiac output, as the adverse effects on LV filling normally predominate.

### 1.6.4 “New methods”: PSV in neonates and infants and HFOV

When new methods are being introduced in clinical practice it is important to investigate how it affects different organ systems. To utilise a new method fully and safely an understanding of the most important physiological effects are needed.

**PSV**

How the then new ventilator mode PSV affected cardiac output was not known. The active breathing effort with triggering the pressure supported breath and the possibly better adaptation to the patients needs could theoretically increase the venous return
and cardiac output. This would result in an increase in oxygen delivery. To test this hypothesis we decided to study changes in cardiac output in infants comparing PCV and PSV (Paper I).

**HFOV**

\( \text{P}_{\text{aw}} \) is frequently kept higher during HFOV than during CMV see above \(^{124-126} \) to open up and keep the lung open without the recruitment effect of large tidal volumes, at least early during treatment. It is known from animal and human studies \(^{112}, 114, 116, 127, 128 \) that increasing mean airway pressure adversely affects cardiac output. This reduction in CO could adversely affect oxygen delivery and potentially be harmful. Studies on the effect of HFOV on CO have produced conflicting results. HFOV has been reported not to alter LVO in experimental studies \(^{129-132} \), and in children \(^{125, 133} \). Other studies have shown a decreased CO with HFOV compared with CMV in animal experiments \(^{134-136} \) and human studies \(^{126, 137} \). Few experimental studies have been made on the effect of changes in CDP/\( \text{P}_{\text{aw}} \) on CO during HFOV \(^{137-139} \) and even less is done in humans.

Paper III was designed to evaluate the relationship between CO/LVO and \( \text{P}_{\text{aw}} /\text{CDP} \) during HFOV ventilation in neonates and small children.

**1.6.5 Stroke volume, heart rate and cardiac output during MV**

Based on the knowledge of the properties of the immature heart (above 1.3.2) and earlier studies \(^{140} \) it has been thought that cardiac output in neonates and infants is mainly altered by changes in heart rate and not by changes in stroke volume. This opinion was often stated in textbooks modern in the 1990’s \(^{141, 142} \) even though more recent studies on lambs have suggested that neonates can change their stroke volume. During more recent years, data have been presented indicating that human neonates and infants may have a greater capacity to alter the stroke volume than earlier believed \(^{128}, 143-145 \). Paper I of this thesis suggested that the effects on cardiac output were mainly caused by changes in stroke volume. To further investigate this finding the study in Paper II was carried out.
1.7 ACUTE RESPIRATORY FAILURE (ARF)

1.7.1 Definitions

Acute respiratory failure can and has been defined in various ways, ranging from the given treatment to pathophysiological factors and combinations of both. If defined by given treatment the most common definition used in clinical studies is; intubation and mechanical ventilation, usually with a required time of treatment which exceeds 24 hours \(^{146,147}\). This group can include patients without respiratory disease or impaired gas exchange; mechanical ventilation is used for instance after major surgery, for patients with traumatic brain injury or other neurological impairment such as Guillain-Barré. Intubation and mechanical ventilation more than 24 hours is now more commonly used for screening of populations to find patients with ALI and ARDS. Sometimes the term ARF is defined as intubation and mechanical ventilation combined with impairment in gas exchange with a \(\text{PaO}_2/\text{FiO}_2\) ratio < 300, similar to that of ALI/ARDS but without requiring specific findings on chest X-ray \(^{148}\). For this the term acute hypoxic respiratory failure is a more specific term used by some authors \(^{89,149,150}\) and the one used in Paper V.

1.7.2 Acute respiratory distress syndrome (ARDS) and Acute Lung Injury (ALI)

History

In an article in the Lancet in 1967; “Acute respiratory distress in adults”, Ashbaugh et al described 12 patients between 11 and 48 years old receiving respiratory support and not responding to the usual methods of therapy. “They exhibited a clinical, physiological and pathological course of events that was remarkably similar to the infantile respiratory distress syndrome (hyaline membrane disease)” \(^{151}\). In 1971 an article describing the syndrome using the name Adult respiratory distress syndrome was published \(^{152}\) and through the following years this term was commonly used. Several studies were carried out on incidence and/or mortality of ARDS \(^{153-157}\). Results from studies were diverging both in incidence and mortality (10-90%) and were hard to interpret. There was heterogeneity in diseases underlying ARDS but also a lack of uniform definitions of ARDS. The American-European Consensus Committee (AECC) on ARDS was formed to focus on these issues and on the
pathophysiologic mechanisms of the process. It was also felt that international coordination of clinical studies was needed.

Definitions
In 1994 the report of the AECC on ARDS was published with definitions of ARDS and ALI. It was decided to go back to the original term acute (rather than adult) respiratory distress syndrome. It was agreed that ALI could be applied to a wider spectrum of the continuum of pathological process and ARDS be reserved for the more severe cases. ALI was defined as: a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiological and physiological abnormalities that cannot be explained by, but may co-exist with left atrial and pulmonary capillary hypertension. ALI and ARDS are acute in onset and persistent, lasting days to weeks.

Recommended ALI criteria
- Acute onset.
- $\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$.
- Bilateral infiltrates seen on frontal chest radiograph.
- Pulmonary wedge pressure $\leq 18 \text{ mmHg}$ or no clinical evidence of left atrial hypertension.

The criteria for ARDS were the same except
- $\text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$.

Later studies suggest that a definition including the use of PEEP would better define the degree of lung injury $^{62, 158-160}$ but no consensus has yet been reached regarding this.

1.8 INCIDENCE AND OUTCOME OF PAEDIATRIC INTENSIVE CARE
As described above (1.2.1) children are cared for both in adult ICUs and PICUs depending on national and regional availability. Some studies have been carried out on incidence and outcome of paediatric intensive care $^{89, 161-171}$ these studies are based on a single or a group of PICUs or investigate outcome for specific diagnoses. Few population based studies have been performed $^{14, 172-174}$. In 2005 Macrae and Duncan described the “burden of paediatric intensive care” based on information from the PICANET and ANZPIC registries. Still the reports from the Australian New Zealand
Paediatric Intensive Care (ANZPIC) registry \(^{175}\) and the Paediatric Intensive Care Audit Network (PICANET) \(^{176}\) in the England and Scotland are among the few sources of information on a national level. The hope is that the Swedish Intensive Care Registry (SIR) will provide similar data for Swedish children in the near future.

### 1.8.1 Long term outcome

Data on long-term survival is scarce and usually confined to single-centre longitudinal follow-up studies with limited scope for diagnoses and follow up time \(^{172, 177-183}\). In addition, critically ill children are admitted to adult ICUs with little data on long-term outcome. Hence, the true demand of paediatric intensive care beds is unknown.

### 1.8.2 National differences

There are differences between countries and regions not only in how paediatric intensive care is provided, but also in the population and therefore the need for intensive care. The percentage of the population under 16 years of age varies, as well as the overall health and mortality in this group. Sweden has a low neonatal and infant mortality; 2 and 3/1000 live births respectively. This compares with 3 neonatal and 5 infant deaths/1000 live births in the UK and Australia, 4 and 7 in the United States (US) and > 40 neonatal and > 100 infant deaths/1000 live births in several developing countries e.g Afghanistan, Nigeria and Rwanda \(^{184}\). The risk of dying before 5 years of age in Sweden is 4/1000 live births, in the UK and Australia 6 and the US 8/1000 live births In developing countries this number can be > 250 (e.g. Afghanistan)

Therefore international data on the need for intensive care cannot easily be extrapolated from other national reports.

### 1.8.3 The Swedish perspective

**Paediatric intensive care**

Sweden is a country with a publicly funded health care system and care is provided to all patients regardless of socioeconomic status. In addition, vital statistics for all Swedish citizens can be followed in the mandatory File of National Registration creating unique possibilities to trace vital statistics prospectively. Between 1998 and
2001, intensive care was provided to children through three PICUs and 78 adult ICUs. In Sweden there is a perceived lack of available ICU-beds, both in adult and paediatric ICUs, creating ethical and practical problems in the daily care of patients.

As described above (1.2.1) designated paediatric intensive care units (PICUs) are thought to improve ICU survival of critically ill children. According to the survey by Nipshagen et al Sweden placed 18/23 in number of PICU beds/population in Europe. Only Albania, Italy, Macedonia, Poland and Rumania had less beds/population. The Swedish neonatal and infant mortality is however low (1.8.2).

As designated PICU beds are few in Sweden the thought is that consequently many critically ill children might be cared for in adult intensive care units. Since no population-based studies on paediatric intensive care had previously been performed in Sweden, little is known about the national incidence, diagnoses and mortality of intensive care for children. The proportion of children admitted to adult ICUs was also unknown; hence the true demand of paediatric intensive care beds is unknown. Paper IV is designed to address these issues.

**Incidence and outcome of ARF, ARDS and ALI.**

Much effort is put into improving care of patients with respiratory failure, especially for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Studies have been performed on the incidence and outcome of patients with respiratory failure ventilated in the intensive care unit (ICU) in the adult population and some on long term mortality and morbidity. Few studies have been performed on the incidence and short term outcome in the paediatric population. Little is known on long term outcome in this group and outcome of more advanced respiratory therapy, e.g. high frequency oscillatory ventilation (HFO) and nitric oxide (NO), outside the neonatal group, is even less studied. Few studies in this area have been performed in Sweden.

As discussed above (1.2.1) there are large differences regarding population age-profile, mortality and health between different regions and nations. This is likely to influence the incidence and outcome of acute respiratory failure as well. There might also be local differences in used therapies and quality of care.
Apart from the direct benefit of increased knowledge of incidence, therapies and outcome in respiratory failure, this knowledge can be used to better plan future randomised control studies. This makes it interesting to investigate the incidence, used therapies and outcome of respiratory failure in the paediatric population in PICU in Sweden (Paper V).
2 AIMS

This thesis has two parts:

I) Part I (Papers I-III):

Is concerned with how mechanical ventilation affects central haemodynamics.

Papers I and III are investigating the effect of two, at that time, new ventilatory modes; pressure support ventilation (PSV) and high frequency oscillation (HFO) on central hemodynamics. The second study was initiated by a finding in Paper I which suggested that the change in cardiac output was mediated by a change in stroke volume rather than heart rate. As this was not widely known the study in Paper II was carried out to verify the finding.

II) Part II (Papers IV-V):

Is concerned with the incidence and outcome of paediatric intensive care with special reference to respiratory failure, mechanical ventilation and especially ALI /ARDS and adjunctive therapies.

The specific questions addressed for the separate studies in part I were:

1. Is cardiac output improved during pressure support ventilation compared to pressure control ventilation?
2. Is the change in cardiac output during positive pressure ventilation mediated by changes in stroke volume rather than heart rate?
3. Is cardiac output affected by changes in mean airway pressure during HFO?

The aims of the studies in part II were to:

4. On a national level evaluate the incidence and the short and long term outcomes of intensive care for children depending on; diagnosis, age, season and type of ICU.

5. Evaluate: on a national level; the incidence and outcome of different respiratory diseases. For PICUs; the incidence and outcome of mechanical ventilation and used adjunctive therapies (NO, HFO and ECMO). In one PICU evaluate also the incidence, used therapies and outcome of ALI and ARDS.
3 MATERIAL AND METHODS

CLINICAL STUDIES (Papers I-III)

3.1 PATIENTS

All study protocols were approved by the local ethical committee at the Karolinska Hospital in Stockholm Sweden, and infants included after informed parental consent.

Neonates and infants requiring mechanical ventilation in the Paediatric Intensive Care Unit at KS/St.Göran’s Hospital were included in Paper I (n=15), cardiac output was measured in 8 patients. The measurements of CO in patients in Paper I were also used in Paper II (n=8) together with a group of otherwise healthy infants requiring anaesthesia and intubation before undergoing surgery (n=6). (Table 1) Paper III included 14 neonates and infants <1 year of age treated with High Frequency Oscillation Ventilation (HFOV) in the Paediatric Intensive Care Unit (PICU) at Astrid Lindgren Children’s Hospital at the Karolinska Hospital. (Table 2) Patients had to be in stable ventilatory and circulatory condition to be included in all the studies. All PICU patients had previously been examined using echocardiography without findings of a persistent ductus arteriosus, the otherwise healthy surgical patients had no history or clinical signs of such.
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Details for the patients of papers I and II.
RSV – Respiratory Syncytial Virus, MAS - Meconium Aspiration Syndrome, BPD – Bronchopulmonary Dysplasia
### Table 2
Details for the patients of paper III.
RSV – Respiratory Syncytial Virus, MAS - Meconium Aspiration Syndrome.

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3.2 PROCEDURES

3.2.1 Change from PCV to PSV

In Paper I and thus the group also used for studying the effects of a decrease in airway pressure in Paper II the study protocol consisted of 15 minutes of PCV, followed by 15 min. PSV, and finally 15 min. of PCV. (Figure 1) The patients were not sedated during the measurements. FiO₂ was increased by about 0.05 before the study but was not changed during the procedure. This was done to reduce the risk of hypoxemia during the procedure.

To ensure stable ventilation and avoid significant changes in ETCO₂ between modes of ventilation, the following measures were undertaken: Every patient was tested during PSV for 5-10 minutes before implementation of the study protocol while registering spontaneous respiratory rate and ETCO₂. The ventilator was then changed to PCV with a similar respiratory rate and the peak airway pressure was adjusted to obtain the same ETCO₂ level as during the PSV test. After this was achieved the study protocol was initiated. During the study period the peak airway pressures was adjusted to the PIP levels found to give equivalent ventilation for PSV and PCV respectively.

3.2.2 Changes in PEEP during anaesthesia

In the patient group in Paper II undergoing anaesthesia the mean airway pressure was increased by increasing positive end-expiratory pressure to influence CO. Patients were anaesthetized according to local standard procedure and received maintenance fluids 5 ml/kg/hour of isotonic balanced solution with 2.5% glucose and electrolytes, (Rehydrex, Pharmacia, Sweden)) at a set rate via an infusion pump during the procedure. Infants > 3 months old (n=2) received morphine 0.05 μg/kg and atropine 20 μg/kg i.v. before leaving the ward for the operating room. Younger infants received atropine 20 μg/kg at induction. Anaesthesia was induced with Pentothal 5-10 mg/kg followed by inhalation anaesthesia with isoflurane. Atracurium 0.5 mg/kg, and fentanyl 1-2 μg/kg was administered after which patients were intubated and connected to mechanical ventilation. Rapid sequence induction was carried out in one patient with pyloric stenosis using succinylcholine 1.5 μg/kg instead of atracurium. All patients were given fentanyl at induction, except the two patients operated for pyloric
stenosis and hernia where pain was managed with local anaesthesia and ilioinguinal block respectively. We used pressure control ventilation with frequency and pressures to normoventilate the infant at 3 PEEP. The patients were ventilated using Isoflurane 1-1.5% in N₂O/O₂ mixture with 33% oxygen. Study procedure and measurements were started 5-10 minutes after induction with a sequence of 0 PEEP, 3 PEEP, 6 PEEP, 3 PEEP and finally a return to 0 PEEP. The procedure was completed within 30 minutes, and no additional drugs were administered during this period (Figure 1).

### 3.2.3 Changes in P_{aw} during HFOV

The patients in Paper III had all been treated with HFOV for at least 12 hours and the mean airway pressure (P_{aw}) had been decreased compared to the highest pressure during the initial treatment period. Treatment proceeding the study period had been in accordance with standard treatment for the PICU unit, including lung volume recruitment, fluid volume resuscitation and inotropic support when necessary. It did not follow a study protocol. Lung expansion was assessed clinically and also with chest radiography (when HFOV was initiated and then depending on the clinical course), aiming for lung expansion to the ninth costal margin except in patients with pulmonary hypoplasia (e.g. CDH). During the study period the patients received maintenance fluid at a set rate, either 10% glucose with electrolytes or standard total parenteral nutrition. Infusion rates were kept constant in patients receiving morphine infusion or inotropic support; dopamine 2.5-6 μg · kg⁻¹ · minute⁻¹ for seven patients, one patient also received dophexamine 1 μg · kg⁻¹ · minute⁻¹ during the study. No fluid boluses, muscle relaxants or other medication was given just prior to or during the study period.

No changes in ventilation frequency or amplitude were made over the study period. FiO₂ was changed only to maintain a SaO₂ of 95-99%, a slightly higher level than the ordinary treatment goals. This was done to allow for a better safety margin during changes in P_{aw}.

As the patients were determined clinically stable at the start of the study period, their current ventilator settings were used as “baseline”. The first measurement was made
at this baseline level in all patients. After each change in $P_{aw}$, patients were given a stabilization period of about two minutes before further measurements.

A pilot study including five patients was carried out where $P_{aw}$ was first increased and then decreased by $+3\text{cmH}_2\text{O}$. This design did not result in any significant changes in CO related to changes in $P_{aw}$. This could be attributed to lingering effects of recruitment/derecruitment or that a change of $\pm 3 \text{cmH}_2\text{O}$ was not sufficient to cause significant changes. $P_{aw}$ was therefore increased by 5 cmH$_2$O for study purposes, but the level of decrease remained the same to avoid risks of derecruitment. Based on the pilot study the patients were divided in a study group ($n=9$) and a control group ($n=5$). To avoid any bias from lingering effects of derecruitment/recruitment by the changes in $P_{aw}$, two different protocols were created for the study group to which patients were randomly assigned. Initial measurements were made at baseline in both protocols. In the first protocol (A) this was followed by a sequence of $P_{aw}$ changes/measurements at $+5 \text{cmH}_2\text{O}$, baseline, $-3 \text{cmH}_2\text{O}$ and a second return to baseline. In the second protocol (B) the sequence was $-3 \text{cmH}_2\text{O}$, baseline, $+5 \text{cmH}_2\text{O}$ and finally a return to baseline. (Figure 2) This procedure took about 30 minutes in both cases. The control group had no changes in ventilator settings but measurements were made five times over the same time period.
Protocols for Papers I and II.
Protocols for Paper III.

Mean airway pressure ($P_{aw}$) was increased 5 cmH$_2$O and decreased 3 cmH$_2$O relative to baseline settings.
3.3 MEASUREMENT OF CARDIAC OUTPUT

3.3.1 Paper I and II

Changes in cardiac output were assessed by measuring blood flow velocity in the ascending aorta using the ultrasound Doppler technique. The Doppler technique for CO measurement has earlier been described and validated in the new-born and infants in good agreement with the thermodilution technique\(^{93, 96}\). We have earlier described the method in detail\(^{144, 200}\).

A 5 MHz transducer with an 8 mm diameter tip was positioned in the suprasternal notch and MFV\(_{Ao}\) was measured 5-10 mm above the aortic valves. The signals from a range-gated Doppler velocimeter (Alfred, Vingmed. A/S, Oslo, Norway) were recorded on an oscillograph (Mingograph 34 or 81, Siemens Elema, Stockholm, Sweden). This velocimeter measures the velocity integrated both over time and space (area).

CO is equal to the product of aortic mean flow velocity and the cross sectional area of the ascending aorta, $\text{CO} = \text{MFV}_{Ao} \times A_{Ao}$. Changes in MFV\(_{Ao}\) will thus directly reflect changes in CO and can therefore be used as a relative measure of cardiac output.

Similarly stroke volume is equal to the product of $A_{Ao}$ and the stroke distance, thus $SD_{Ao}$ can be used to calculate changes in SV.

At all levels MFV\(_{Ao}\) was measured during a minimum of one minute and the maximum value during that time was used since any error in angulation would underestimate the true CO. Heart rate was calculated from the Doppler registration curve at the concomitant value.

$SD_{Ao}$ was calculated from the MFV\(_{Ao}\) and this heart rate ($SD_{Ao}$ (cm) = MFV\(_{Ao}\) (cm/s) x 60 / HR).

All examinations within each group were performed by the same investigator to minimize interpersonal differences.

3.3.2 Paper III

Cardiac output was assessed with the ultrasound Doppler technique\(^{93, 96, 201}\) by an investigator blinded to the changes in $P_{aw}$. An Acuson 128XP ultrasound machine (Mountain View, Ca, USA) with a 5MHz transducer was used. The cross sectional
aortic valve area was determined from a suprasternal short axis view with the Doppler sampling volume placed at the level of, or just above the aortic valve. To obtain the highest flow velocity recording, care was taken to achieve the smallest possible angle between the aortic flow and the ultrasound beam. Three consecutive beats were selected at a stable Doppler recording and the velocity time integral (VTI) over these beats was calculated by the internal software. Mean VTI for a single heartbeat was thus determined by dividing by three. The obtained value is a distance and a relative measure of SV. The calculated aortic area (cm²) was multiplied by mean VTI (cm) to obtain SV (cm³). HR was determined from the concomitant ECG recording and CO was calculated as the product of HR and stroke volume.

3.4 VENTILATORS
All patients in Paper I and the group of patients in Paper II treated in the PICU were ventilated with a Servo 300 (Siemens-Elema, Stockholm, Sweden) with tubings and humidifier (Fisher & Paykel, MR 600, New Zealand) for neonates and children. For the group undergoing anaesthesia before surgery in Paper II the Servo 900C (Siemens-Elema, Stockholm, Sweden) in PCV mode was used.

3.4.1 HFOV
A Sensormedics 3100 A high frequency ventilator, (Sensor Medics BV, Bilthoven, and the Netherlands) was used in all patients in Paper III. It is the most commonly used high frequency oscillator in PICUs and the one regularly used in our unit.

3.5 DATA COLLECTION PAPER I - III
Levels of PEEP, peak and mean airway pressures, inspiratory fraction of oxygen (FiO₂) and respiratory rate in Papers I-II, and frequency, amplitude, fraction of inspired oxygen (FiO₂) and Pₘₐₓ in Paper III were registered from the respective ventilators. In Paper I the pressure and flow signals of inspiration and expiration were taken from the Servo 300 and registered on a Mingograph T4 (Siemens-Elema, Stockholm Sweden). The registrations were used for calculation of respiratory rate and I:E ratio. In Papers I-II the heart rate, blood pressure (sphygmomanometric method), peripheral oxygen saturation (SaO₂), end-tidal carbon dioxide (ETCO₂) and respiratory rate were registered from a Hewlett & Packard monitor model 66S.
Respiratory rate was recognised when the same value was obtained from the Hewlett & Packard monitor, the ventilator, and the Mingograph.

All patients in Paper III had indwelling arterial catheters and invasive blood pressure measurements were registered using a standard intensive care pressure transducer (Pressure Monitoring Kit, Baxter Healthcare Corp., California, USA) connected to an intensive care monitor (Hewlett & Packard 48S, Boeblingen, Germany) from which SaO₂ was also recorded. The heart rates used in calculations were taken from the ultrasound Doppler registrations.

### 3.6 STATISTICAL ANALYSIS

In Paper I and the PICU-group of Paper II the first period of PCV was used as baseline. The anaesthesia patients in Paper II used the first period of 0 PEEP as baseline. All parameters were registered three times during each 15 minute period and mean values were used. Patients were always used as their own controls; initial settings were used as baseline and study outcomes compared to this level. An analysis of variance (ANOVA for repeated measures) was used to compare data. To evaluate differences between the study and control group in Paper III the Mann–Whitney test was used. All data are presented as mean ± SEM. A p-level <0.05 was regarded as statistically significant.

In Paper I-III STATISTICA statistical software, Statsoft Inc, Tulsa OK, USA was used for all analysis.

### EPIDEMIOLOGICAL STUDIES (PAPERS IV-V)

### 3.7 COHORT DESIGN

#### 3.7.1 Inclusion criteria

All paediatric patients between 6 months and 16 years of age receiving treatment in a Swedish ICU or PICU were registered for study purposes during a 3-year period between March 15th 1998 and March 14th 2001. A second data collection was later made for PICU patients between 1-6 months of age for the same time period. Together, these patients formed a national, closed cohort. Exposure was defined as
admittance to intensive care and outcome defined as survival up to five years after the last registered ICU admission during the study period.

A subgroup of patients included in Paper IV was studied more closely for Paper V. For this cohort exposure was defined as intubation and ventilatory support > 24 hours or death during the first 24 hours after admission (defined LOS = 1).

3.7.2 Eligible wards

ICU was defined as a hospital ward with resources to treat patients with intubation and mechanical ventilation for more than 24 hours, a definition previously used in ICU epidemiological studies. 78 eligible adult ICUs and three PICUs were asked to participate in the study.

3.7.3 Screened hospitals

All three PICUs located in major university hospitals participated in the study.

Of the 78 eligible adult ICUs, all except four responded regarding treatment of children during the study period. An estimate of the number of missing admissions from the four adult ICUs that were unable to respond was made. For every non-participating adult ICU, data was substituted using the average admission number of three comparable adult ICUs (of comparable size and serving a similar population). The derived number of lost admissions was 400, thus the number of registered admissions in the study most likely include ≥ 95% of the true number of admissions to ICU of children 6 months to 16 years old during the study period.

At one of the adult ICUs, no exact record of dates for admission or discharge was available even though these patients were registered as being admitted within the specified time period. Six more units reported incomplete data regarding total admission numbers, diagnosis or admission discharge dates but could be included in reported number of admissions and 5-year mortality.

In summary, 5-year mortality data was available, for 98.7% of all included admissions during the period March 15th 1998 and March 14th 2001. In addition, complete data including diagnosis and ICU periods, were available for 95.2% of cases.
3.8 DATA COLLECTION PAPER IV -V

3.8.1 All ICUs (Paper IV)
Admission data, consisting of admission and discharge dates, LOS and diagnoses were collected from each participating hospital, as well as personal identification number.

3.8.2 All PICUs (Paper V)
Personal identification number, information on ventilatory support and adjunctive therapy in the form of HFO, NO and/or ECMO were collected from local PICU registers when available for all patients with respiratory support > 24 hours.

3.8.3 PICU A (Paper V)
PICU A was specially analysed and had the largest total number of admissions and the highest number of admissions for respiratory diagnoses but no local registry of ventilated patients. The electronic and paper records were manually searched for ICD 10 diagnoses and possible mechanical ventilation > 24 hours. In unclear cases whether the patient was ventilated >24 hours, all records, including monitoring charts and laboratory reports were manually reviewed. This was also done in the 16 cases where the patient died within the first day of admission and in all cases known to be ventilated > 24 hours.

Data on PaO2/FiO2 ratio (day one and worst recorded) as well as ventilator settings at this time were recorded. Data for calculating PIM II 202 and PRISM score 203 according to respective protocol and limitations in therapy before death were also recorded.

3.8.4 Data from national registries
Survival data for the whole cohort were prospectively collected from the File of National Registration, Centre for Epidemiology, the National Board of Health and Welfare. Data was obtained > 6 months after study endpoint to allow for the files and registers to be accurately updated, and enable calculation of cumulative 5-year survival after last registered ICU admission to determine spread of mortality over the years. To compare the study group with natural background mortality vital data was
collected for all children living in Sweden in the same age group and for the same time period.

3.9 DIAGNOSES AND DIAGNOSTIC GROUPS

Most of the ICUs used ICD 10 codes (the World Health Organization’s International Statistical Classification of Diseases and Related Health Problems version 10). In the absence of a national agreement on ICU diagnosing at the time of the study a minority used local codes for diagnosing or descriptive texts instead of valid diagnoses. All patient information in the study was examined by an experienced paediatric intensivist, who assigned a valid diagnosis for the ICU admission where possible. In cases where a patient had several diagnoses a principal diagnosis was chosen. This was done in accordance with the principles described for the uniform diagnostic coding system used in Australia and New Zealand (ANZPIC registry) 204. To create comparable diagnostic groups all patients were then grouped using the same principles, resulting in seven main diagnostic groups. These consisted of cardiovascular (CVS), gastrointestinal/renal (GI), injury, respiratory, neurological, postoperative (ENT/thoracic, neuro, and other surgery) and a miscellaneous group (Misc.). The miscellaneous group included malignancies, endocrine disorders, allergic reactions, sepsis and post cardiac arrest, as recommended by ANZPIC registry. The three postoperative groups are presented together. Adjustments were made due to the retrospective nature of the coding. For example, the ANZPIC registry group “Postoperative Cardiovascular” had to be included in the CVS group since it was not possible to differentiate postoperative admissions from other patients with cardiovascular diagnoses.

3.10 DATA MANAGEMENT AND VALIDATION

All received data were entered into an Excel spreadsheet (Microsoft Excel 2000) and both manually and electronically checked for errors. ICU admission dates were checked for consistency. Patients found to have a non-valid identity number and those assigned with a number identifying them as non-Swedish residents were also excluded as they cannot be followed up in the National Registry.

The personal identification number of each patient in the study made it possible to follow them through all ICU admissions during the 3-year period and in national
registries for prospective outcome measurements. Data on patients being ventilated in PICUs could also be connected to other data collected for the same ICU admission.

In some cases LOS was recorded in hours, others had only admission and discharge dates. As an admission of < 24 hours uses ICU resources, the first date of admission was rounded up to 1 day. The last day of admission is also generally < 24 hours, thus the last day of admission was rounded down to 0. Consequently, patients with one or two consecutive recorded dates for admission both have a LOS of 1 day. Death during the day of admission was defined as LOS= 1.

3.10.1 Mortality calculations

*Paediatric intensive care (Paper IV)*

Long-term mortality was calculated over a five year period from the last registered admission to an ICU/PICU during the study period. That is mortality per patient rather than per admission. In studies over time when patients can have more than one admission there are several ways of calculating mortality. Since follow up of mortality is done using the personal identification number attributed to each admission, the mortality would be falsely high if mortality was attributed to every admission, and patients with more than one admission before dying would be registered as more than one death. Mortality has to be attributed to only one admission, normally the first or last registered. In the study of paediatric intensive care the expectation was that very sick patients would be transferred to PICU. If mortality was attributed to the first admission it would increase the mortality figure in referring hospitals. We thought this would give an unfair virtually higher mortality in referring hospitals, mainly adult ICUs. So the decision was to calculate mortality from the last registered admission. In the study on all admissions of children to ICU the main interest was to follow outcome for individuals who had been subjected to intensive care. Mortality was therefore calculated/ individual rather than admission.

At one of the adult ICUs, no exact record of dates for admission or discharge were available even though these patients were registered as being admitted to the ICU within the specified time period. Consequently, 87 patients accounting for 92 admissions were excluded from survival analysis since no exact survival time could be determined.
In this study the interest was to evaluate the incidence and outcome of respiratory failure and disease in all PICU and of hypoxic respiratory failure in PICU A. Earlier studies have calculated incidence and mortality related to admissions and/or relating it to the background population covered by the studied ICUs. In this study the aim was to evaluate incidence and outcome for specific diagnoses, treatments and conditions and to be able to compare these numbers to previous studies from other regions. Mortality was therefore attributed to last registered admission but mortality calculations were made relative to admissions with the specified variable. Thus mortality in Paper IV and V may seem to be different as mortality in Paper IV is related to # of patients and in Paper V to # of admissions.

3.10.2 Diagnoses

In 297 cases the diagnosis for ICU admission was missing. These patients were included in mortality calculations but not in diagnostic groups.

3.10.3 Estimation of ICU consumption

To accurately estimate the demand for paediatric intensive care beds in Sweden, missing data from the four wards that didn’t participate in the study was interpolated from wards comparable in size and serving a similar population.

3.10.4 ARDS and ALI estimation

Chest X-rays at the time closest to the worst measured PaO₂/FiO₂ ratio, if < 300, were reassessed by one paediatric radiologist for bilateral infiltrates. In five patients all paper records were missing. In other admissions parts of data such as arterial blood gases were missing.

3.11 STATISTICS

Descriptive statistics and survival functions are calculated using the statistical software STATISTICA (1999; StatSoft Inc., Tulsa, OK) and Excel (Microsoft Office 2003).
4 RESULTS

CLINICAL STUDIES (PAPERS I-III)

4.1 CHANGES IN CARDIAC OUTPUT (CO)

In the PICU patients (n=8) in Papers I/II where cardiac output was measured (group I), aortic mean flow velocity (MFV$_{Ao}$) increased significantly at the lower mean airway pressures caused by a decrease in I:E ratio due to the change in ventilatory modes from PCV to PSV. MFV$_{Ao}$ increased from 15.0 ±1.7 cm/sec to 17.4 ± 2.0 cm/sec, p<0.01 from PCV1 to PSV and decreased to 15.6 ± 1.9 cm/sec, p< 0.05 with PCV again, indicating a 16% increase in cardiac output and a subsequent decrease to 5% above baseline. The surgical patients of Paper II (group II) showed a decrease in MFV$_{Ao}$ with increasing mean airway pressures caused by an increase in PEEP, corresponding to a decrease in CO with the lowest value of -12.6%, at 6 PEEP (Figure 3)

In the patient group ventilated with HFOV in Paper III (group III), CO changed significantly (p=0.001) when the continuous distending pressure was changed (Figure 4). A decrease in CO by 12.0±6.6 % was found when P$_{aw}$ was increased by 5 cmH$_2$O. This corresponds to a decrease in cardiac index from 4.1 to 3.6 l · min$^{-1}$ · m$^{-2}$ (p= 0.0002). Post-hoc analysis shows that the significant change occurs when P$_{aw}$ is increased.
Figure 3.

Changes in cardiac output during CMV (Paper I and II).

PCV = pressure control ventilation.
PSV = pressure support ventilation.
PEEP (cmH$_2$O)

Figure 4.

Changes in cardiac output during HFOV (Paper III).

Mean airway pressure ($P_{aw}$) was changed by +5 and +3 cmH$_2$O from baseline $P_{aw}$. 
4.2 CHANGES IN STROKE VOLUME (SV)

Significant changes in stroke distance were found in both groups I and II. In group I there was a significant increase in stroke distance indicating an increase in stroke volume of 17% during PSV compared with PCV1. There was no significant change between the two measurements during PCV. Group II showed a significant decrease in stroke distance when 3 and 6 cmH₂O PEEP were applied. The lowest value found at 6 cmH₂O PEEP was -13.8 % compared with 0 PEEP. There was no significant change in stroke distance between the two measurements at 0 PEEP. In group III stroke volume decreased by 8.2±6.9% to (p=0.003) when Paw was increased by 5 cmH₂O.

Figure 5.

Mean changes in SV versus CO (n = 15).
4.3 OTHER HAEMODYNAMIC PARAMETERS

4.3.1 Study groups
There were no significant changes in heart rate or blood pressure during the study period in either group I or II. Group II displayed a higher heart rate compared to group I, possibly due to administration of atropine to this group as part of the anaesthetic routine at the time. In group III a small but statistically significant decrease in systolic blood pressure \( (p=0.04) \) was found with a baseline mean systolic pressure of \( 75 \text{ mmHg} \pm 15 \), and a decrease to \( 71 \pm 15 \text{ mmHg} \) was noted when \( P_{aw} \) was increased by 5 cmH\(_2\)O.

4.3.2 HFOV control group
No significant changes in cardiac output, heart rate, mean blood pressure or ventilatory parameters over time were found when analysing all repeated measures in the control group in Paper III where \( P_{aw} \) was not changed. No significant differences between any measured baseline values were found between the study group and the control group. Cardiac index at baseline was \( 4.9 \pm 1.8 \text{ l \cdot min}^{-1} \cdot \text{m}^{-2} \) in the control group and \( 4.1 \pm 1.6 \text{ l \cdot min}^{-1} \cdot \text{m}^{-2} \) in the study group (mean \( \pm \) standard deviation, \( p=0.2 \)).

4.4 RESPIRATORY PARAMETERS
In Paper I the mean airway pressure and I:E ratio decreased significantly during PSV compared with both periods of PCV.

A small but significant increased in \( \text{SaO}_2 \) was found in the whole group when changing from PCV to PSV, but the decrease when changing back to PCV was not significant.

End tidal CO\(_2\) and respiratory rate did not change significantly, and there were no significant differences in respiratory rate and ETCO\(_2\) during the PCV - PSV - PCV procedure. In three patients where I:E relationships were measured the peak inspiratory pressure had to be altered during the PSV compared with PCV for stable ventilation; in two patients the peak inspiratory pressure was increased by 10 and 2 cmH\(_2\)O respectively, and in one patient lowered by 5 cmH\(_2\)O.
In two of the eight patients in group I where CO was measured the peak inspiratory pressure was altered between modes; in one patient the peak inspiratory pressure was increased by 6 cmH\textsubscript{2}O during PSV compared with PCV, in the other lowered by 3 cmH\textsubscript{2}O, to maintain the same ETCO\textsubscript{2}.

In group II there was a significant increase in ETCO\textsubscript{2} with increasing PEEP.

In the patient group ventilated with HFOV there were no significant changes in ventilatory parameters aside from the change in P\textsubscript{aw}.

EPIDEMIOLOGICAL STUDIES (PAPERS IV-V)

4.5 ICU ADMISSIONS

4.5.1 Paediatric intensive care (Paper IV)

A total of 6661 identifiable patients and 8063 ICU admissions were registered during the study period. Of these 925 were admissions (676 patients) of infants 1-6 months old to PICU. In the age group 6 months to 16 years there were 7137 admission of 6011 patients. In this age group 63\% of admissions were to an adult ICU.

872 patients (13\%) had two or more admissions during the period. 213 of the multiple admissions were readmissions to the same ICU within 2 days of the previous admission and 165 were transfers between ICUs in different hospitals. 65 of the interhospital transfers were from an adult ICU to a PICU. The total rate of readmission within 2 days was 2.7\%; 3.5\% in PICU and 2.0\% in adult ICU.

4.5.2 PICU; Respiratory failure and support (Paper V)

During the three year study period there were 3588 admissions of 2824 patients to PICUs. 1652 admissions had a LOS \(>1\) day, with 736 receiving mechanical ventilation for more than 1 day (45\%). 25 patients died during the first day of admission.

4.5.3 PICU A; Respiratory failure, ALI and ARDS

A total of 1659 admissions to PICU A were recorded during the three-year study period. From records of LOS and patient records 1257 admissions could be excluded
from being intubated and mechanically ventilated > 24 hours. 153 patients between 1 month and 16 years of age were intubated and ventilated > 24 hours or died with LOS ≤ 1. Four admissions were excluded from the study as the patients had been ventilated since birth due to congenital disease.

Of the remaining 149 patients, 16 died within the first day of admission (LOS=1), thus 133 patients were ventilated > 24 hours. In these patients PaO₂/FiO₂ ratio was calculated to determine the number of patients with acute hypoxic respiratory failure. In 48 cases there was not enough data to obtain PaO₂/FiO₂ ratio due to incomplete records, 10 of which had FiO₂ > 0.4 recorded at some point. The calculated PaO₂/FiO₂ ratio was > 300 in 19 cases.

Around half of the patients (n=66) in this group had a recorded PaO₂/FiO₂ ratio < 300. Two had a congenital cardiac malformation and one was in cardiac failure. Out of the remaining group, 50 patients had bilateral infiltrates on chest X-ray fulfilling criteria of ALI. 46 also met the criteria for ARDS, with 31 suffering from severe ARDS with a PaO₂/FiO₂ ratio <100.

3% (50/1659) of admitted patients in PICU A had ARDS on admission or later developed ARDS (four died during first day of admission). Of the children ventilated > 24 hours 35% (46/133) had or developed ARDS

### 4.6 DEMOGRAPHICS

The median age of admission for all ICUs was 6.1 years. For PICUs the median age was 2.1 years for all included patients and 4.8 if only patients older than 6 months were included, with a corresponding age of 9.5 years for adult ICUs. Of patients admitted to PICU 46% were females and 54% males, in adult ICUs 44% of admitted patients were females and 56% males.

### 4.7 LENGTH OF STAY (LOS)

The median LOS for patients in both PICUs and adult ICUs was one day. 46% of PICU admissions had a LOS more than 1 day, and 19% > 3 days. For adult ICU patients the corresponding figures were approximately half, 23% and 8% respectively. Of the patients ventilated > 24 h in PICU 26% had a LOS > 7 days compared to 7.5% of all PICU admissions.
4.8 CONSUMPTION OF PAEDIATRIC ICU DAYS
A total number of 20400 ICU days (6800/year) were registered for the entire study population. Of these, 11472 (3824/year) were days in PICU with infants 1-6 months of age contributing with 4789 days (1596/year).

4.9 DIAGNOSES AND DIAGNOSTIC GROUPS

4.9.1 Paediatric intensive care (Paper IV)
The distribution of patient diagnoses for admissions were: Injury 32%, neurological 12%, respiratory 13%, cardiovascular 16%, gastrointestinal/renal 6%, postoperative care 7% (cardiac surgery was included in the cardiovascular group) and miscellaneous 10%. 4 % of admissions lacked ICU diagnosis (Figure 6).

While a seasonal variation in the number of admitted patients due to respiratory, injury and CVS diagnoses was observed, no overall seasonal variation in admittance to the ICUs could be seen.
Diagnostic groups: (% of admissions) in adult vs. paediatric ICU (PICU); CVS = cardiovascular (includes postoperative cardiac surgery), GI = gastrointestinal/nephrology, Injury, Misc. = Miscellaneous, Neuro, Resp. = respiratory, Postop. = postoperative (including postop. neuro, ear-nose- and throat and “other” surgery), Unknown = admissions where no diagnose was recorded.
The most common primary diagnoses (Figure 7) were congenital cardiac malformation 214 admissions/year in PICU and concussion 172 adm./year in adult ICU. It was noted that 75 admissions/year are children treated in ICU for ingestion of alcohol, and 133 adm./year are for other kinds of ingestion.

Figure 7.

The most common diagnoses: Number of admissions during the 36 month study period. Cong. = congenital, “Other“ = not any of the specified diagnoses, ARF = Acute respiratory failure, TBI = traumatic brain injury.
4.9.2 PICU; Respiratory failure and support (Paper V)

Cardiovascular was the most common diagnostic group in patients ventilated > 1d (53%), followed by respiratory (14%), miscellaneous (10%) and neuro (7%), most likely due to the fact that two of the PICUs are centres for cardiac surgery. In the third PICU the most common diagnostic group was respiratory (33%) followed by Neuro (19%).

**Figure 8.**

- **Mechanical ventilation > 24h**, ■ Death day 1, □ Total admissions.

**Diagnostic groups at admission**, number of admissions, mechanical ventilation and mortality in all PICUs and in PICU A.
4.10 ICU MORTALITY

4.10.1 Paediatric intensive care (Paper IV)

The ICU mortality was 2.1% when looking at the last registered ICU admission for all patients and ICUs. For the different diagnostic groups the ICU-mortality was: Injury 1.0%, Miscellaneous 6.0%, Respiratory 2.4%, Neurological 2.9%, CVS 2.1%, GI/renal 2.4% and postoperative 0.2%.

The youngest patients had a generally higher mortality. Mortality in infants less than 6 months of age was 3.1% while infants between 6 months - 1 year of age had a mortality of 3.6 %, compared to 2.0% in the other age groups.

Mortality during last registered ICU admission was 2.5% for PICU patients and 1.9% for adult ICU patients. However, these two patient groups differed significantly in diagnoses, LOS and age difference. Within the adult ICU group the university hospital ICUs were more similar to PICUs than other adult ICUs both in distribution of median age, LOS, and mortality (Table 3). A higher mortality was seen in patients with a LOS > 1 day. For all registered patients in this group the ICU mortality was 4 % (82/2034), for PICU 3.8% (46/1210) and for adult ICU patients 4.4% (36/824) with 5.9% (28/471) in university ICUs.

The overall ICU mortality was 2.1%. The mortality for readmissions and patients transferred to the last registered admission was approximately twice as high, 4.2% (6/142) and 4.4% (6/135) respectively. 65 patients were transferred from adult ICUs to PICUs, with 52 of these (80%) occurring within 2 days of admission. Patients transferred to PICU had an ICU-mortality of 6.1%, considerably higher than the whole PICU group. A predominance of males 44/65 (68%) and respiratory diagnoses 24/65 (37%) was found in this subpopulation.

4.10.2 PICU; Respiratory failure and support (Paper V)

The total PICU mortality was 2.0% of all admission. The mortality of admissions with a LOS > 1 day was 2.7%, and was found to be twice as high if the patient was ventilated > 1 day (5.4%) (These mortality numbers seem lower than the ones above
Table 3. Number of admissions, demographic, length of stay (LOS) and mortality for different groups of paediatric patients.

<table>
<thead>
<tr>
<th></th>
<th>Number of admissions</th>
<th>Number of patients*</th>
<th>Age median (years)</th>
<th>LOS median (days)</th>
<th>LOS &gt; 3 days</th>
<th>ICU mortality</th>
<th>5-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>All admissions</td>
<td>8064</td>
<td>6661</td>
<td>6.9</td>
<td>1</td>
<td>1038 (13%)</td>
<td>137 (2.1%)</td>
<td>389 (5.8%)</td>
</tr>
<tr>
<td>PICU (n=3)</td>
<td>3562</td>
<td>2753</td>
<td>2.1</td>
<td>1</td>
<td>661 (19%)</td>
<td>67 (2.4%)</td>
<td>213 (7.7%)</td>
</tr>
<tr>
<td>PICU age 1-6 months</td>
<td>925</td>
<td>676</td>
<td>0.2</td>
<td>2</td>
<td>179 (26%)</td>
<td>20 (3.0%)</td>
<td>67 (11%)</td>
</tr>
<tr>
<td>PICU age 6 m – 16 yr</td>
<td>2636</td>
<td>2079</td>
<td>4.8</td>
<td>1</td>
<td>394 (15%)</td>
<td>47 (2.3%)</td>
<td>137 (6.6%)</td>
</tr>
<tr>
<td>Adult ICU (n=52)</td>
<td>4502</td>
<td>3908</td>
<td>9.5</td>
<td>1</td>
<td>377 (8.5%)</td>
<td>70 (1.8%)</td>
<td>176 (4.5%)</td>
</tr>
<tr>
<td>University ICU (n=10)</td>
<td>1629</td>
<td>1348</td>
<td>8.4</td>
<td>1</td>
<td>240 (15%)</td>
<td>41 (3.0%)</td>
<td>108 (8.0%)</td>
</tr>
<tr>
<td>General ICU (n=42)</td>
<td>2873</td>
<td>2560</td>
<td>9.9</td>
<td>1</td>
<td>137 (5%)</td>
<td>29 (1.1%)</td>
<td>68 (2.7%)</td>
</tr>
</tbody>
</table>

* in mortality and LOS calculations 87 patients (in a General ICU) are excluded as they lack dates for ICU admission.
as they are related to all admissions whereas the numbers above are related to last registered admission, see methods 3.10.1).

For the respiratory diagnostic group the ICU mortality was 2.2%. The patients in this group receiving mechanical ventilation > 1d had a mortality of 3.9%.

The highest mortality among respiratory diagnoses was attributed to chronic respiratory failure (P27.1, J96.1) 10.3% (3/29) and acute respiratory failure (J80, J96.0, J96.9) 6.9% (3/43). Among the registered ICU admissions during the three year study period, no mortality was attributed to asthma and upper airway diseases (including croup, epiglottitis and tracheobronchitis) neither in PICUs or adult ICUs.

Table 4. ICU mortality for; all admissions, children mechanically ventilated > 1day and for adjunct therapies and combinations of adjunct therapies.

<table>
<thead>
<tr>
<th>Admissions</th>
<th>ICU mortality</th>
<th>Respiratory*</th>
<th>CVS*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Total admissions</td>
<td>3588</td>
<td>70 (2.0)</td>
<td>509 (14)</td>
</tr>
<tr>
<td>Died day 1</td>
<td>25</td>
<td>25 (0.7)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>MV &gt; 1d</td>
<td>736</td>
<td>39 (5.3)</td>
<td>102 (14)</td>
</tr>
<tr>
<td>NO</td>
<td>84</td>
<td>11 (13)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>HFO</td>
<td>40</td>
<td>8 (20)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>ECMO</td>
<td>16</td>
<td>4 (25)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>NO+HFO</td>
<td>22</td>
<td>5 (22)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>NO+ECMO</td>
<td>4</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td>HFO+ECMO</td>
<td>6</td>
<td>2 (33)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>HFO+NO+ECMO</td>
<td>3</td>
<td>1 (33)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Respiratory and CVS (cardiovascular system) are the diagnostic groups at admission rather than the reason for mechanical ventilation.
Table 5. ICU mortality for all admissions, children mechanically ventilated > 1 day, for adjunct therapies, combinations of adjunct therapies and for ARDS.

<table>
<thead>
<tr>
<th>PICU A</th>
<th>ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admissions (n)</td>
</tr>
<tr>
<td></td>
<td>Total 1659</td>
</tr>
<tr>
<td></td>
<td>Died day 1</td>
</tr>
<tr>
<td></td>
<td>MV &gt; 1d</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>HFO</td>
</tr>
<tr>
<td></td>
<td>ECMO</td>
</tr>
<tr>
<td></td>
<td>NO+HFO</td>
</tr>
<tr>
<td></td>
<td>NO+ECMO</td>
</tr>
<tr>
<td></td>
<td>HFO+ECMO</td>
</tr>
<tr>
<td></td>
<td>HFO+NO+ECMO</td>
</tr>
</tbody>
</table>

* Respiratory is the diagnostic group at admission rather than the reason for mechanical ventilation.
4.10.3 PICU A; Respiratory failure, ALI, ARDS in (Paper V)

In all admissions ventilated > 24 hours with ARDS the ICU mortality was 13%. Patients with ARDS initially admitted for a respiratory disease (direct lung injury) had an ICU mortality of 8.3%, and in patients with non-respiratory diagnoses who later developed ARDS (indirect lung injury) 18% (Table 6). When patients who died within the first day of admission are included, mortality for ALI was 22% (12/55) and ARDS 20% (10/50). Of the 16 patients who died during the first day of admission, five met ALI criteria and four ARDS (Figure 9). There was no significant correlation between PaO₂/FiO₂ ratio and/or ALI and ARDS and mortality.

The total mortality in PICU A was 2.0%. ARDS accounted for 32% of these deaths (10/31) when patients who died within 24 hours of admission are included and 40% (6/15) in patients with a LOS > 24 hours. The corresponding numbers for ALI are 38% (12/31) and 47% (7/15).

Measured mortality for patients with ARDS (20%; (10/50)) was higher than predicted mortality (PIM-2 16.4 ±27 (mean ± SD) and PRISM 13.1 ±9.5)). Total ICU mortality for patients ventilated > 24 hours in PICU A (11.3%) differed less from predicted mortality based on retrospectively collected data (PIM-2 9.6% ± 19 and PRISM 8.8 ± 18).

Of the seven ventilated patients who died without recorded PaO₂/FiO₂ ratio < 300, four had an underlying chronic disease and were either on chronic ventilatory support or had limitations in care at baseline. Over all, limitations in treatment were common. Of the 31 patients who died in PICU, four reached brain death criteria, and 17 of the remaining 28 had limitations in intensive care therapy before death.
Figure 9.

**PICU A**
Ventilated >24h
n=133

- **P/F ratio < 300**
  - n=66  
  - † 8 (12%)

- **Unknown or >300**
  - n=67  
  - † 7 (10%)

- **P/F ratio ≤ 200**
  - n=54  
  - † 6 (11%)

- **P/F ratio 200-300**
  - n=12  
  - † 2 (17%)

Bilateral infiltrates
On chest – X-ray
n=49

- **ARDS**
  - n=46  
  - † 6 (15%)

- **ALI (w/o ARDS)**
  - n=3  
  - † 1 (33%)

- **P/F ratio < 100**
  - n=29  
  - † 4 (14%)

**PICU A. Children mechanically ventilated > 1day**: Number of admissions and mortality for different PaO₂/FiO₂ ratios, ALI and ARDS. † = ICU mortality.
4.11 FIVE-YEAR MORTALITY

4.11.1 Paediatric intensive care (Paper IV)

For the 5-year follow-up period of the study a total of 366 patients were deceased, resulting in a 5-year mortality of 5.6% /patient. Compared to the expected yearly mortality of 0.013% in a non-ICU exposed comparable cohort of children the mortality in the fifth year after admission was still 0.28%.

Table 6.

<table>
<thead>
<tr>
<th>Year</th>
<th>All ICU</th>
<th>PICU</th>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>3.7%</td>
<td>3.9%</td>
<td>0.018%</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.8%</td>
<td>1.0%</td>
<td>0.015%</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.4%</td>
<td>0.4%</td>
<td>0.013%</td>
</tr>
<tr>
<td>Year 4</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.014%</td>
</tr>
<tr>
<td>Year 5</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.013%</td>
</tr>
</tbody>
</table>

Continued increase in mortality after ICU admission.

For the different diagnostic groups the 5-year mortality was: Injury 2.2%, Miscellaneous 15.8%, Respiratory 9.4%, Neurological 8.3%, CVS 6.5%, GI/renal 5.6% and postoperative 4.1% (Figure 10). As with mortality during ICU admission, the 5-year mortality was also higher among the youngest patients (9.4% in children < 6 months and 7.7 in children between 6 months-1 year of age).

The overall 5-year mortality in PICU was 7.3% and the corresponding number for the adult ICU was 4.3%. Patients transferred from an adult ICU to a PICU had a 5-year mortality of 10.8%.
Figure 10.

5-year survival for the different diagnostic groups: ♦ Injury, ◊ Postop. = postoperative (including postop. neuro-, ear-nose- and throat and other surgery), ● GI = gastrointestinal/nephrology, ▲ CVS = cardiovascular (includes postoperative cardiac surgery), □ Neuro, Δ Resp. = respiratory, ◊ Misc. = Miscellaneous.

4.11.2 PICU; Respiratory failure and support (Paper V)

The 5-year mortality for all PICU admissions was 6.0% (214/3588) and 9.8% (72/736) for admissions with mechanical ventilation >1d (see methods 3.10.1). The continued mortality > 1 year after the last recorded ICU admission contributed to the total 5-year mortality for all patients admitted to PICU as well as for patients ventilated > 1d; 2.1% (74/3588) and 1.5% (11/736) respectively.

4.11.3 PICU A; Respiratory failure, ALI and ARDS (Paper V)

The total 5-year mortality for the patients ventilated > 24 hours in PICU A was 28%, (37/133) for patients with a PaO₂/FiO₂ ratio < 300 it was 24% (16/66), for PaO₂/FiO₂ ratio < 200 26%, for ALI 26% (13/50), and ARDS 26% (12/46).
4.12 ADJUNCTIVE THERAPY: NO, HFO AND ECMO

4.12.1 All PICU

Of all patients ventilated > 24 hours in PICU 15% (n=111) received nitric oxide (NO), high frequency oscillation (HFO) and/or extracorporeal membrane oxygenation (ECMO) as adjunctive therapy.

NO was used in a total of 90 admissions. Out of these, four had NO via nasal CPAP and two were intubated and ventilated < 24 hours. These six patients were not included in the analysis, all survived to ICU discharge. The remaining 84 with NO were ventilated > 24 hours, with an ICU mortality of 13.1%. Four patients in this group later went on to ECMO. The mortality in these patients was 50%.

HFO was used in 41 admissions. One patient died during the first day. The remaining 40 were ventilated on HFO > 24 hours, six patients went on to ECMO. The total ICU mortality for HFO was 20%. In 22 admissions both HFO and NO were used. Three of these patients went on to ECMO and one died.

Out of 19 patients treated on ECMO, three died within the first day of admission. 16 were on ECMO > 24 hours. Of these patients, seven had cardiovascular disease and were on ECMO at one of the cardiac centres with an ICU mortality of 29% (2/7). In the patient group receiving ECMO treatment for non-cardiac reasons the ICU mortality was 22% (2/9).

No patients treated with one or a combination of these adjunctive therapies died between 1 and 5 years after the last recorded ICU admission.

4.12.2 PICU A; Acute respiratory failure, NO, HFO and ECMO

HFO was used for 11 admissions, with a mortality of 9% (1/11). All these patients met ARDS criteria. In three of these cases NO was used concomitantly, and two others went on to ECMO. The mortality for HFO was 9% (1/11). The deceased patient had neither been on NO nor ECMO.

Nine patients were treated with NO, with an ICU mortality of 22% (2/9). Six of these had a PaO₂/FiO₂ ratio < 300 and five met ARDS criteria. None of the patients with NO went on to ECMO.
ECMO was used in 11 patients. In two cases ECMO treatment was initiated as acute rescue due to septic shock with non-responding hypotension and in one patient for rewarming after immersion in cold water. These patients died within a day of admission. Of the 133 patients on mechanical ventilation for > 24 hours, 8 were treated on ECMO. Five of these fulfilled ARDS criteria before ECMO treatment and three were started on ECMO at another admitting hospital and brought to PICU on ECMO. Mortality after the first day was 25% (2/8). In ARDS patients, 22% were treated with HFO, 10% with NO and 14% with ECMO.
5 DISCUSSION

5.1 MAIN FINDINGS

5.1.1 Mechanical ventilation and central haemodynamics
The main findings of the first studies were that cardiac output (CO) increased during pressure supported ventilation (PSV) compared to pressure controlled ventilation (PCV). We also found that the increase in CO was mediated through an increase in stroke volume (SV) without changes in heart rate. Since mean airway pressure was affected by changes in I:E ratio, the effect of triggering itself could not be evaluated. The finding that changes in mean airway pressure mainly affect CO through changes in SV and not heart rate was verified in Paper II. During HFOV changes in $P_{aw}$ also affects CO. As during CMV there is a decrease in SV when $P_{aw}$ is increased causing a decrease in CO. The effect of changes in $P_{aw}$ during HFOV might however be less pronounced than during CMV.

5.1.2 Outcome of paediatric intensive care and respiratory failure
In the national population based study of paediatric intensive care in Sweden (Paper IV), we found that in less than 40% of the admissions, children between 6 months and 16 years of age were treated in a specialized PICU. It is noted that adult ICU and PICU patients displayed similar ICU mortality rates of 1.8 and 2.4 % respectively which is somewhat surprising as the expectation was that the most severe cases were cared for in PICU.

We also found a 20–fold increased mortality up to five years after ICU admission compared to the same age group in the average population.

In the study on respiratory failure in PICU in Sweden (Paper V), the main findings are that 45% of children between 1 month and 16 years of age, admitted to PICU were mechanically ventilated more than one day. Adjunctive therapy, NO; HFO and/or ECMO was used in 15% of cases. This suggests that even though the proportion of patients ventilated > 1 day is relatively small it is likely that a relatively large proportion of the mechanically ventilated patients had or developed severe respiratory disease.
Even though admissions where adjunct therapy (NO, HFO and ECMO) was used had an initially higher mortality than other admissions, these therapies do not have a continued increased mortality following the first year after ICU compared to other children exposed to intensive care.

Results from one PICU, show an incidence of ALI of 3.3% and ARDS of 3% of all admissions, whereas ALI and ARDS accounted for 38 and 31% respectively of the total ICU mortality. This suggests that ARDS may be a significant health issue in children in Sweden.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Measurements of central haemodynamics (Paper I –III)

Changes in CO and SV were assessed by measuring blood flow velocity in the ascending aorta with the ultrasound Doppler technique. The Doppler technique has earlier been described and validated in new-born infants with good agreement when compared with the thermodilution technique 94-96. At the time of the study the more recent methods, based on changes in pulse pressure and bioimpedance were not available and dilution techniques were considered too invasive for this kind of study.

Cardiac output is equal to the product of the aortic mean flow velocity and cross-sectional area of the ascending aorta (CO = MFV\textsubscript{Ao} x A\textsubscript{Ao}). Thus there is a direct relationship between the MFV\textsubscript{Ao} and cardiac output. Changes in MFV\textsubscript{Ao} will directly reflect changes in cardiac output and may consequently be used as a relative measurement of cardiac output. Since we were mainly interested in the changes in cardiac output rather than absolute values in Papers I and II we determined only the MFV\textsubscript{Ao}, measurements of the aortic cross-sectional area would not add to that information 207.

In Paper III cardiac output was also assessed with the ultrasound Doppler technique, but this time using an echocardiography machine. The cross-sectional aortic valve area was determined and the ascending aorta and aortic valve was insonated and the velocity time integral was calculated using the internal software. The calculated aortic area (cm\textsuperscript{2}) was multiplied by mean VTI to obtain stroke volume (cm\textsuperscript{3}). Heart rate was determined from the concomitant ECG recording and cardiac output was calculated.
The main interest was still the changes in SV and CO rather than the calculated absolute values, and the changes were actually calculated without using the aortic area. As there seemed to be an interest in the values for CO and cardiac index and since the aortic area was readily available with echocardiography, the calculated values were also reported, bearing in mind the possible error.

With a blind Doppler there is no visualization of the point of measurement which is a disadvantage. An advantage with the all frequency Doppler (Alfred, Vingmed. A/S, Oslo, Norway) used in Papers I and II is that the measurement is integrated in both time and area, rather than the medium flow velocity integrated only over time (VTI) given by the used echocardiographic Doppler. With the later it is however possible to visualize the placement of the Doppler sampling volume.

**5.2.2 Ventilator settings and modes**

*PSV vs PCV*

One of our aims with this study was to analyse the importance of an active breathing effort on CO. For triggering the ventilator volume-trigger mode was chosen for two reasons. First, at the time of the study, we already had good clinical experience in our PICU of its function in both neonates and children. Secondly, the volume-trigger mode was a new method for triggering and we regarded it of interest to test it’s function in a study.

The found increase in cardiac output during PSV was most likely caused by the decrease in $P_{aw}$. The synchronous breath termination during PSV limits the inspiratory time so that the inspiration is ended by the ventilator when the flow reaches 5% of the peak flow of that breath. Theoretically this gives the patient more control of the frequency and duration of inspiration thus better adapting the mechanical ventilation to patient needs. It is outside the scope of this study if this is actually the case. However the I:E ratio was found to be significantly lower during PSV compared to both periods of PCV in this study, causing a decrease in $P_{aw}$. As the I:E ratio decreased during PSV, we cannot separate the effect of triggering and the effect of the I:E ratio on mean airway pressure and CO.

As the patients in this study did not have indwelling arterial catheters, the ventilation was monitored by means of ETCO$_2$ and pulse oxymetry. In neonates with small tidal
volumes and high respiratory rates ETCO2 may be a less adequate method for monitoring ventilation compared to adults. In this patient material the measured plateau levels of ETCO2 were probably not equal to the arterial values. But as the levels of ETCO2 and respiratory rate were almost unchanged in the individual patients, it is likely that ETCO2 did not change significantly during the procedure.

**PEEP**

End tidal CO2 was measured and we found a significant increase of 0.6% between PEEP 0 and 6 cmH2O. In this study we did not record tidal volumes. As we used the ventilator readings for ventilatory parameters the error from the compressible volumes in the ventilator tubing would have added a significant error with increasing pressures. As tidal volumes was not recorded we do not know if the increasing PEEP affected these. The compliant lungs of the otherwise healthy infants in the PEEP study may have been overexpanded at the higher PEEP levels, reaching the upper plateau of the pressure/volume curve. This may have resulted in smaller tidal volumes and decreased perfusion of parts of the alveoli with increased dead space ventilation.

In non anaesthetized subjects an increase in pCO2 may increase pulmonary and systemic vascular resistance thus influencing CO. During anaesthesia these changes are attenuated. Therefore the increase of 0.6% (from 4.6% at 0 PEEP to 5.2% at 6 PEEP) in end tidal CO2, probably only had a minor influence on the CO. The overall change would still be through change in stroke volume rather than heart rate.

**HFOV**

The patients in the study on central haemodynamics when Paw was changed during HFOV were considered to be in a stable condition with optimal lung volume by the treating physician. Optimal lung volume was evaluated by clinical assessment and X-ray findings; however patients may be ventilated at different points on the pressure/volume curve which may affect the response to changes in Paw. Overexpansion with ventilation on the upper asymptotic part of the pressure/volume curve may cause an increased effect of changes in Paw. A decrease in Paw may cause collapse of parts of the lung, which may increase pulmonary vascular resistance and cause a decrease in CO. There are clinical methods in obtaining optimal lung volume but no golden standard of measuring adequate lung expansion in these severely challenged patients.
5.2.3 Retrospective data collection, Papers IV and V

Included ICUs (Paper IV)

All three PICUs located in major university hospitals participated in the study.

Four adult ICUs did not report any data. Two were university hospital ICUs and two units were situated in small local hospitals. All four units treated children during the study period. We do not know the actual number of lost admissions from these units, but the used method in estimating lost data makes it likely that the registered admission represents at least 95% of all admissions of the intended age group during the study period.

Severity of illness score, $\text{PaO}_2/\text{FiO}_2$ ratio

Unfortunately, there was a lack of consensus in Sweden, at the time of the study, concerning the value of generally applied scoring systems. Thus we lack data for Paediatric Index of Mortality (PIM) or Paediatric Risk of Mortality (PRISM) scores. For this reason we cannot speculate on the risk adjusted mortality in either adult ICUs or PICUs. Number of ventilated patients could be used as a surrogate for severity of illness score. Apart from in two of the PICUs this information was not easily available at this time. It would be necessary to go through patient charts and records manually. This was done in PICU A. Rather than to carry this out for all admissions in all ICUs it was decided that available resources would be better utilised for prospective studies. The Swedish intensive care registry (SIR) was being developed and would include most ICUs in Sweden. It will contain more available data, including severity of illness score and could at least be used for screening.

The retrospective collection of data is a potential limitation also in Paper V. To estimate $\text{PaO}_2/\text{FiO}_2$ ratio and severity of illness score (PIM 2 and PRISM) in PICU A, data was retrospectively collected from patient records.

For example measurements of $\text{PaO}_2$ were missing in ten patients with $\text{FiO}_2 > 0.4$, thus more likely underestimating the true number of patients with $\text{PaO}_2/\text{FiO}_2$ ratio <200. Loss of information may also have affected the PIM 2 and PRISM scores; missing data gives a lower score than pathological values.
5.3 DISCUSSION OF RESULTS

5.3.1 PSV – cardiac output and oxygen delivery (Paper I)

During PSV, cardiac output increased by 16% compared to during PCV. This is an interesting finding; providing oxygenation and haemoglobin content are unchanged, as in our study, an increased cardiac output will result in an increased oxygen delivery. If a PSV mode results in an increased CO, it is of interest when weaning mechanically ventilated patients off the ventilator. An increased CO will result in an increased peripheral oxygen delivery, thus giving better metabolic resources during situations with increased work of breathing.

It could be argued that the found increase in CO is at least partially a response to an increased work of breathing rather than the effect of changed ventilator settings. In a clinical study on infants without possibilities of measuring mixed venous saturation this cannot be ruled out. But studies on patient triggered modes have showed a decrease in work of breathing \(^{208}\) and stress hormone levels \(^ {209}\) rather than increased work of breathing, compared to the controlled modes, which makes this less likely, especially as we did not decrease the PIP.

A 16% increase in cardiac output, in an otherwise stable infant may not have any clinical significance but it may be of importance for critically ill neonates and infants who have high demand for peripheral oxygen delivery and borderline or failing oxygen delivery. There are no outcome studies favouring specific modes of ventilation in sepsis for instance \(^ {210}\), but we think that a ventilator mode improving oxygen delivery should be considered as a possible part of the therapy depending on the specific situation in each case.

5.3.2 Stroke volume, heart rate and cardiac output (Paper II)

We found that a decrease in mean airway pressure of 2 cmH\(_2\)O and an increase in mean airway pressure of 6 cm H\(_2\)O gave a change in CO of +16% and -13% respectively, without significant changes in heart rate. Since there were significant changes in CO but not HR, assuming no changes in the dimensions of the aorta these changes in CO must be caused by changes in stroke volume \(^ {201}\). We found an almost linear relationship between change in CO and stroke volume without change in heart rate (Figure SV vs CO and Fig change HR vs CO).

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A study by McAuliffe et al.\textsuperscript{211} on heart rate and cardiac output after atropine in anaesthetized infants and children, showed that atropine gave an increase in CO caused by an increase in HR without change in stroke volume. The opposite effect was found in the present study. This is not surprising since the pharmacological effect of atropine increases heart rate which in turn gives an increase in CO unless it is compensated by a decrease in stroke volume. Whereas changes in mean airway pressures mainly affects venous return and stroke volume at least at the levels used in these studies.

Anaesthesia influences CO in more than one way; preload, afterload and contractility are all affected as well as heart rate, whereas changes in mean airway pressure are considered to have a more selective effect on preload. Murray et al.\textsuperscript{212} showed an increase in heart rate and cardiac output but not stroke volume of atropine. Their study also showed that the anaesthesia with halothane and isoflurane, before atropine was given, gave a decrease in both CO and stroke volume compared to preanaesthesia values. This is probably true for the anaesthesia group in our study too, but measurements before anaesthesia were not carried out.

In Figure 11 it is noted that there is no correlation between heart rate and CO whereas there is a linear relationship between SV and CO. There is however a different slope for the PSV/PCV protocol compared to the PEEP protocol. This can be explained by a difference in heart rate between groups. The patients in the PEEP protocol are under anaesthesia and have received atropine and have higher heart rate (CO=SV x HR). Thus a change in SV will have a greater impact on CO at a higher heart rate, and the slope of the curve will be affected.

Even if there has been a significant change in CO due to change in depth of anaesthesia, the total effect on CO has been caused by changes in stroke volume.
Figure 11.

**CO correlated to SV and heart rate:** There is no correlation between heart rate and CO whereas there is a linear relationship between SV and CO. There is however a different slope for the PSV/PCV protocol compared to the PEEP protocol. This can be explained by a difference in heart rate between groups (CO = SV x HR).

PCV/PSV protocol = ■,  PEEP protocol = □.

Minute distance = CO/AAo; Stroke distance = SV/AAo.
5.3.3 HFOV; $P_{aw}$ affects central hemodynamics (Paper III)

Changes in $P_{aw}$ during HFOV affect cardiac output; an increase in $P_{aw}$ causes a decrease in CO. This is in accordance with what is previously known about changes in $P_{aw}$ and CO during CMV and CPAP in individuals who are not in cardiac failure \(^{109, 113, 114}\). The changes in CO found in this study are not large, CO decreased by 12% when $P_{aw}$ was increased by 5 cmH\(_2\)O. In many clinical cases this would be of minor importance. However a decrease in CO of $>10\%$ may be of importance to the critically ill patient especially if oxygenation remains unchanged.

Earlier studies have shown that decreases in cardiac output when $P_{aw}$ is increased is caused by impairment of venous return due to the increased intrathoracic pressure \(^{117, 127, 213, 214}\). Studies have also shown that this effect can be attenuated by volume loading \(^{116, 117, 215, 216}\). The study in Paper III was not designed to evaluate venous return or pre-existent filling state in the patients. However the most likely cause of change in CO is change in venous return.

5.3.4 Changes in $P_{aw}$ affects CO; HFOV vs CMV (Paper I and III)

In Paper I we found an increase in CO by 16% when $P_{aw}$ decreased by 2 cmH\(_2\)O. When $P_{aw}$ was decreased by 3 cmH\(_2\)O during HFOV the CO did not increase significantly from baseline (0.4%) (Figure 12).
Changes in mean CO: When $P_{aw}$ is decreased by 2 cmH$_2$O during conventional mechanical ventilation the CO increased significantly by 16% whereas a decrease of 3 cmH$_2$O in $P_{aw}$ during HFOV did not cause any significant changes.

There may be several explanations for the relatively small changes in CO found with alterations in $P_{aw}$ during HFOV compared to CMV:

Apart from the direct effects on venous return by changes in ITP, changes in lung volume may also affect CO. Hyperinflation may passively compress alveolar vessels causing increased PVR and collapse of parts of the lung may increase PVR through hypoxic vasoconstriction. The baseline $P_{aw}$ was significantly higher during HFOV; 17 cmH$_2$O versus 9 cmH$_2$O during PCV when CMV was used. This can be an indication of the more severe lung disease in the patients with HFOV but ventilation may have also occurred at different levels of the P/V curve in between groups, thus changes in $P_{aw}$ will cause different effects on lung volume and indirectly CO.

It is also possible that the effect on ITP by changes in $P_{aw}$ was attenuated by the more severe lung disease in the infants on HFOV with “stiff”, low compliance, lungs.

As mentioned above the decrease in CO caused by increased PEEP or $P_{aw}$ can be attenuated by volume loading. The patients in the HFOV study were not treated according to a specific study protocol before inclusion, but therapy had followed standard treatment for the PICU unit, which includes recruitment of lung
volume and fluid volume resuscitation if needed. It is likely that the patients on HFOV had been volume loaded earlier during initiation of HFOV.

Paper III shows that changes in $P_{aw}$ during HFOV do affect CO. It was not designed to investigate if there is an actual difference in the effect on CO between HFOV and CMV, but it raises that question. Further studies are needed to better understand these relationships.

5.3.5 Where do all the children go? (Paper IV)

We found that only 37% of Swedish paediatric admissions between 6 months and 16 years of age were given ICU care in a specialized PICU. This corresponds to a PICU admission rate of 0.52/1000 children in this age group. Including PICU admissions of infants 1–6 months of age, that number is 0.70/1000. Rough data from the PICUs estimate that around 20% of admissions are neonates < 1 month old. This would still make the total number of PICU admissions < 0.9/1000 children. Compared to reports from other developed countries, this figure is low, e.g. Australia/New Zealand report around 1.5 and the UK 1.35 admissions/1000 children\textsuperscript{11,12}.

Earlier studies on mortality in the paediatric population in Australia and the UK\textsuperscript{14,15,169} show an improvement in population mortality when paediatric intensive care is centralized, possibly because the volume for the receiving PICUs increase\textsuperscript{167,217}.

Sweden already has a low paediatric mortality rate, with a risk of dying before the age 5 years of 4/1000 live births compared to 6/1000 live births in the UK and Australia\textsuperscript{218}. The low mortality may be an indicator of the overall health being better and therefore a decreased need for intensive care. It does not however explain the proportion of the intensive care provided in adult ICUs compared to PICUs.

We found that adult ICU and PICU patients displayed similar overall ICU mortality rates, furthermore the mortality for LOS > 1 d was 4.4% for adult ICU and 3.8% for PICU. In the adult university ICUs the mortality was 5.9%, which is surprising; the expectations would be that children with more severe disease were treated in a specialized PICU especially if there was time for transfer. An article evaluating the effects of the centralization of paediatric intensive care in the UK Goh et al,\textsuperscript{219} suggests that a risk of mortality > 1% (PRISM II) is appropriate for transfer to PICU. The found mortality in adult ICUs in this study is significantly higher.
However, in major parts of Sweden neurosurgical paediatric patients are cared for in adult neuro-intensive care units. Liver and kidney transplants and the postoperative care takes place at another location than the PICU in one of the major university hospitals. Both neurosurgical and transplanted patients may have a higher mortality rate than the average ICU patient. As the number of patients would be too small for statistical analysis of separate units this has not been done and it is not known if the higher mortality in university ICUs can be explained by this factor.

The lack of severity of illness score makes it impossible to evaluate the risk adjusted mortality in either adult ICUs or PICUs. It can however be argued that regardless of if there is a difference in risk adjusted mortality between PICU and adult ICU it may be beneficial to the paediatric population to centralize paediatric intensive care. As shown in earlier studies, increasing the volume of paediatric patients in PICU would most likely further improve the outcome in PICU 167, 217, 220.

It is clear that many patients treated in adult ICUs have a short LOS and low short and long term mortality. Patients with an expected short length of stay and low risk of mortality are not likely to benefit from a transfer to PICU. This may be especially true for diagnoses with a very low mortality such as concussion (0/623) and ingestion of alcohol (0/224) or medication (1/400). Some of these patients may have been candidates for high dependency units if such units had existed in the admitting hospital.

There appears to be two different groups of children cared for in adult ICUs,

- One group of patients with short LOS and low mortality (e.g. seizures, ingestion, concussion) who are unlikely to benefit from transfer.
- Another group of patients with significant mortality and longer LOS who may benefit from transfer to a PICU.

This suggests that further studies are needed to evaluate if a centralization of paediatric intensive care in Sweden would be beneficial to the paediatric population.
5.3.6 Incidence respiratory disease, ARF, ALI and ARDS

In this study we found that 45% of children aged between 1 month and 16 years, admitted to PICU for more than one day, were mechanically ventilated. Adjunctive therapy, NO, HFO and/or ECMO was used in 15% of the cases mechanically ventilated > 1d. This suggests that a relatively large proportion of the mechanically ventilated patients had or developed severe respiratory disease.

Our finding of 35% ARDS in patients ventilated > 24 h is high compared to 6% of patients ventilated > 12 hrs in Erickson’s study. A potential limitation of our study is the retrospective collection of data, where measurements of PaO₂ were missing in ten patients with FiO₂ > 0.4. This would underestimate the true number of patients with PaO₂/FiO₂ ratio < 200, and possibly the percentage of ARDS. Another potential source of error is that blood gases may have been taken at times when patients were particularly unstable and the recorded values may then only reflect a short period of time giving an overestimate of actual ARDS.

The large proportion of ARDS found in our study may also be explained by the fact that the national centre for ECMO is situated at this PICU which probably attracts a selection of severe respiratory disease. Another reason may be that no cardiac surgery is performed at this centre which otherwise might “dilute” the caseload of severe respiratory failure. Yet another explanation for the difference in proportion of ARDS may be that lower PEEP was still used during this period, thus affecting the PaO₂/FiO₂ ratio, as an increase in PEEP may improve oxygenation and PaO₂/FiO₂ \( \geq 7 \) cmH₂O. In our study only 15% of patients with PaO₂/FiO₂ ratio < 300 had PEEP > 5 cmH₂O, compared to the more recent study by Erickson et al \(^{196}\) where 75% had a PEEP \( \geq 7 \) cmH₂O.

5.3.7 ICU mortality

*Paediatric intensive care (Paper IV)*

The total ICU mortality found in the paediatric group is low, especially compared to reports from the adult population \(^{222, 223}\) but also compared to reports from paediatric intensive care \(^{34, 176}\). This can at least partially be explained by the relatively large proportion of admissions with short LOS and low mortality diagnoses as discussed above (5.3.5).
Respiratory failure in PICU (Paper V)

As can be expected, patients ventilated > 1d in PICU have a higher mortality 5.4% versus non-ventilated 2.9% after the first day. When ventilated for respiratory disease the mortality of 3.9% is somewhat lower. Earlier studies by Erickson and Dahlem 195, 196 found a lower mortality for ARDS with “direct” lung injury compared to “indirect lung injury” (e.g. sepsis). Our findings from PICU A support this in that we found the mortality for ARDS without primary respiratory diagnoses to be 13% versus 8% for primary respiratory diagnoses.

PICU A, acute hypoxic respiratory failure. (Paper V)

We found an incidence of ALI in 3.3% and ARDS in 3% of all admissions to PICU A, whereas ALI and ARDS accounted for 38 and 31% respectively of the total ICU mortality. These findings are important as it makes acute lung injury an important public health factor for children. Earlier studies 194-197 have reported comparable proportions of admissions of ARDS. The high proportion of the total mortality accounted for by ARDS is not different from that found by Erickson et al in Australia and New Zealand 196.

The mortality of 20% found in the group with ALI/ARDS in PICU A was lower than reported in earlier studies 194-197, 206. PIM-2 data in our study predicted a similar mortality as predicted in Erickson’s study; 16.4% and 16.3% respectively, whereas they found the mortality to be 35%. Interestingly enough PIM-2 underestimated mortality in both studies. The reported differences between predicted and measured mortality in the current study may have several explanations. It may, as suggested by Erickson et al, be explained by the progressive nature of ALI/ARDS, as PIM-2 data is collected at admission and ARDS is frequently developed over time. In our study, another factor may be the retrospective collection of data with an increased risk of loss of information; missing data gives a lower PIM-2 score than pathological values. It could also be an actual increased mortality, although this is contradicted by the fact that a higher than predicted mortality was also found in Australia and New Zealand, the ICUs contributing a major part of the reference material for PIM-2.
5.3.8 Cumulative five year mortality (Paper IV and V)

Continued increase in mortality in adult ICU and PICU up to five years after ICU

Paper IV demonstrates an elevated mortality up to five years after admission to an ICU, as compared to the reference Swedish paediatric population. The mortality in the fifth year after admission to any ICU in Sweden was still 0.3% compared to the expected yearly mortality of 0.013% in a non-ICU exposed comparable cohort of children; a 20-fold higher remaining risk of death compared to the healthier reference population. In the group consisting of all admissions to PICU the mortality in the fifth year after admission was 0.30% and for patients ventilated > 24h it was 0.27%; similar to that found for the whole cohort of children admitted to ICU.

Reasons for continued mortality

The data accumulated in this study does not permit us to fully explain why there is still continued increased mortality four years after ICU discharge. It may be caused by underlying diseases either existing before the first admission to ICU or by incomplete recovery. The major contribution to a continued mortality in the last three of the five studied years after ICU admission was from the neurological and respiratory diagnostic groups. This may be explained by that admission to ICU is often made necessary due to a combination of underlying diseases for example severe neurological impairment and an acute complication such as pneumonia\textsuperscript{224, 225}. In the Injury group it is expected that an underlying chronic disease is less common which is in agreement with what we found; the Injury diagnostic group carries a low ICU- and 5 year mortality. It also accounts for a considerable part of adult ICU admissions. This may explain the increased difference, in 5-year mortality compared to ICU mortality, between PICU and adult ICU admissions.

\textit{NO, HFOV and ECMO}

An important finding was that none of the adjunctive therapies, NO, HFO or ECMO, carried a continued increased risk of mortality following the first year after ICU discharge (no mortality during year one to five). Concerns have been raised that more aggressive treatments e.g. the use of HFO, NO and ECMO initially might save patients who may then have an increased future mortality. The number of patients treated with NO, HFO or ECMO, a total of 111, is not an adequate number to draw conclusions from, but the finding of zero mortality during the first year after...
treatment up to a point four years later was reassuring. However we cannot draw any conclusions on long term benefits of these adjunctive therapies based on these observations and limited number of children.

\textit{ALI and ARDS in PICU A}

The total 5-year mortality for the patients ventilated > 24 hours in PICU A was 28%, the mortality for patients with hypoxic respiratory failure, the patients with PaO\textsubscript{2}/FiO\textsubscript{2} ratio < 200 and < 300 as well as with ALI and ARDS had comparable mortality. This relatively high 5-year mortality was mostly due to an initial high mortality. One hundred of these patients survived > 1 year after ICU admission, the average mortality/year up to five years after ICU admission was 0.7%. Similar mortality was found for patients with hypoxic respiratory failure. This is about double the continued yearly mortality for other ICU patients in the same age group. The number of observed patients is however small.

\textbf{5.3.9 Length of stay (LOS)}

Compared to some earlier reports\textsuperscript{11, 12, 34, 167, 217} we found a somewhat shorter LOS and higher median age. This could partially be explained by the fact that infants less than 1 month old in PICU and less than 6 months old in adult ICU were not included in our study. Both LOS and mortality numbers are skewed with higher numbers for younger patients in other reports\textsuperscript{34, 217}. This correlates well with our findings for the study group. Even though we did not collect data on patients < 1 month old, two of the PICUs in our study reported that \(\approx 20\%\) of their total admissions during the study period were patients < 1 month old, of these 68\% had a LOS > 1 day. Another reason for the short LOS is the nature of some common causes of admission in the paediatric population where rapid stabilisation can be achieved, e.g. seizures and ingestion. Other patients, for example those with concussions, may have been likely candidates for high dependency unit if such units had existed in the admitting hospital at the time. At the time of the study high dependency units were uncommon in Sweden, the number is now increasing. Seizures, ingestion or concussion together accounted for 29\% (1301/4502) of admissions in adult ICU and 11\% (397/3561) in PICU.
5.3.10 Consumption of paediatric intensive care

During the time of study (1998-2001) Sweden experienced peace, no major epidemic outbreaks or social unrest. Thus our figures can be taken as evidence of the absolute minimum national need of ICU care for children between 6 months and 16 years of age. There was no overall seasonal variation in ICU care.

We found an overall ICU admission rate of 1.59/1000 children in our study which was a slightly higher number than reported from the UK and Australia in 1994-95 by Pearson and Shann\textsuperscript{14} but less than that in more recent reports \textsuperscript{10-12, 15, 167, 217}. These latter reports include all children younger than 6 months, which may make up for at least part of the difference since we do not include any children less than 1 month old in PICU and less than 6 months in adult ICU.

Our findings show that the actual consumption of ICU care per year is 6800 days (study period 1998-2001). Assuming an optimal bed occupancy rate of mean 80\% \textsuperscript{226}, this translates to a need for 23 paediatric ICU beds for the country as a whole, or 13.6 beds per million inhabitants for the study age group, not including non-residents.

A number of beds for younger children would have to be added to the calculations. Reports from two of the PICUs show that 20 - 25\% of their admissions are neonates less than 1 month of age. If patients up to the age of 18 need treatment in PICU even further beds are needed.

The European survey by Nipshagen et al in 2002\textsuperscript{186} put Sweden in the 17th place of European countries participating in the study, with 1.04 PICU beds/100,000 inhabitants between the ages 1-18. Only five European countries reported fewer PICU beds (Albania, Italy, Macedonia, Poland and Rumania) compared with the US having 5.4 PICU beds/100,000 in 2001\textsuperscript{10}.

Sweden does have a low paediatric mortality but are children in Sweden really that much healthier than in the rest of Europe?
6 CONCLUSIONS

Pressure supported ventilation in neonates and children increases cardiac output, compared to pressure control ventilation which may be of importance for critically ill neonates and infants who have high demand for peripheral oxygen delivery. We suggest that in cases where the neonate or infant has the ability to trigger the ventilator, a patient triggered mode should be preferred.

Changes in cardiac output can be mediated by changes in stroke volume without changes in heart rate in neonates and infants, at least when cardiac output is influenced mainly by changes in mean airway pressure.

Changes in mean airway pressure during HFO affects cardiac output, possibly to a lesser degree than conventional mechanical ventilation.

Sweden has a low immediate ICU-mortality in children less than 16 years old. This low figure is similar to that reported for other Western countries and was also of the same order for adult ICU and PICU.

Only a minority of children who needed intensive care in Sweden received that in a designated PICU. Studies are needed to evaluate if a centralization of paediatric intensive care in Sweden would be beneficial to the paediatric population.

In addition we have found that the group as a whole is characterized by a continuous increased mortality risk up to at least five years after being admitted to an ICU, for reasons left to be clarified.

Adjunctive therapy to mechanical ventilation, NO, HFO and ECMO, is used in 15 % of cases ventilated > 24 hours. Even though the initial mortality is higher than for other admissions, these therapies do not have a continued increased mortality following the first year after ICU discharge, compared to other children exposed to intensive care.

Results from one PICU show that ARDS is relatively uncommon in the paediatric population, but accounts for close to 1/3 of the total ICU mortality in this PICU. This suggests that ARDS may be a significant health issue in children in Sweden.
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