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Merja Kallio

NEURALLY ADJUSTED VENTILATORY ASSIST IN PEDIATRIC INTENSIVE CARE

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UNIVERSITY OF OULU,
FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE,
DEPARTMENT OF PAEDIATRICS;
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Supervised by
Docent Tero Kontiokari
Doctor Outi Peltoniemi

Reviewed by
Professor Matti Korppi
Docent Matti Reinikainen

Opponent
Docent Paula Rautiainen

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University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Guidelines and instructions derived from adult randomized controlled trials are generally followed in pediatric ventilation, as there have been no large trials of this kind in children. Current treatment strategies aim at preventing ventilator-induced lung injury by avoiding too large tidal volumes, supporting patient's spontaneous breathing and preventing lung collapse with positive end-expiratory airway pressure. Neurally adjusted ventilatory assist (NAVA) is a novel ventilation mode that provides respiratory support proportional to the electrical activity of the diaphragm (Edi). The aims of this thesis were to assess daily practices in pediatric ventilation in Finland and to compare NAVA with conventional ventilation in terms of safety and quality of care.

Current treatment practices were studied with a preliminary enquiry and a 3-month prospective survey that was offered to all hospital units providing ventilatory care for children <16 years of age. NAVA was compared with current standard ventilation in a crossover trial involving 18 pediatric patients and in a larger controlled trial in which 170 patients were randomized to receive either NAVA or conventional ventilation.

Respiratory distress was the most common indication for invasive ventilation in neonates, and postoperative care in older children. The principles of lung-protective ventilation were generally accepted and the goals were achieved in the majority of treatment episodes. The low incidence of pediatric invasive ventilation favours centralization.

NAVA proved to be a safe and feasible primary ventilation mode in pediatric intensive care. It improved patient-ventilator synchrony and led to lower peak inspiratory pressures and oxygen requirements. It also reduced the need for sedation during longer treatment periods. Information derived from the Edi-signal could be used to optimize the level of sedation and to identify patients with a potential risk of extubation failure.

Keywords: child, invasive ventilation, lung-protective ventilation, neurally adjusted ventilatory assist, sedation

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Tiivistelmä

Nykyisin käytössä olevat menetelmät lasten hengityskonehoidossa perustuvat suurelta osin aikuisilla tehtyihin tutkimuksiin ja totuttuihin tapoihin, sillä lasten hengityskonehoidosta on olemassa vain vähän tutkittua tietoa. Hengityskonehoidon aiheuttamaa keuhkovauriota pyritään ehkäisemään välttämällä suuria kertahengitystilavuuksia, tukemalla potilaan omia hengityksiä ja säilyttämällä ilmateissä positiivinen paine uloshengityksen aikanakin. Neuraalisesti ohjattu ventilaatio (NAVA) on uusi hengityskonehoitomuoto, joka tukee potilaan omia hengityksiä ohjaamalla koneen antamaa tukea pallealihaksen sähköisen signaalin avulla. Tämän tutkimuksen tavoitteena oli selvittää lasten hengityskonehoidon nykytilaa Suomessa sekä tutkia, voidaanko NAVAa käyttämällä parantaa hoidon laatua ja turvallisuutta.

Nykyisiä hoitokäytäntöjä selvitettiin vuonna 2010 kysely- ja seurantatutkimuksella, johon kutsuttiin mukaan kaikki Suomessa lapsia ja vastasyntyneitä hoitavat tehohoito-osastot. NAVAa verrattiin nykyiseen hengityskonehoitoon 18 potilaan vaihtovuoroisessa tutkimuksessa sekä suuremmassa 170 lapsipotilaan satunnaistetussa kontrolloidussa tutkimuksessa.

Eri syistä johtuvat hengitysvaikeudet ovat yleisin syy hengityskonehoitoon vastasyntyneillä ja suurten leikkausten jälkeinen hoito isommilla lapsilla. Keuhkoja säästävän hoidon periaatteet ovat Suomessa yleisesti hyväksyttyjä ja toteutuvat valtaosassa hoitojaksoja. Hengityskonehoitojaksojen määrän vähäisyys puoltaa hoidon keskittämistä suuriin sairaaloihin.

NAVAa käyttämällä hengityskoneen antama tuki ajoittuu paremmin potilaan omien hengitysten mukaan ja sen avulla saavutetaan matalammat ilmatiepaineet sekä vähäisempi lisähapen tarve. Pitkissä hoitojaksoissa NAVA vähentää rauhoittavan lääkityksen tarvetta, ja pallealihaksen signaalia seuraamalla on mahdollista optimoida sedaatioaste aikaisempaa tarkemmin. Palleasignaalia voidaan myös hyödyntää arvioitaessa potilaan valmiutta hengitystuesta vieroittamiseen.

Asiasanat: hengityskonehoito, lapsi, neuraalisesti ohjattu ventilaatio, sedaatio, säästävä ventilaatio

To all who breathe

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Abbreviations

A/C	assist-control
ALI	acute lung injury
ARDS	acute respiratory distress syndrome
ARF	acute respiratory failure
BPD	bronchopulmonary dysplasia
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CT	computed tomography
DMD	Duchenne muscular dystrophy
ECMO	extracorporeal membrane oxygenation
Edi	electrical activity of the diaphragm
EIT	electrical impedance tomography
EMG	electromyography
FiO_2	fraction of inspired oxygen
HFOV	high frequency oscillatory ventilation
ICP	intracranial pressure
ICU	intensive care unit
IMV	intermittent mandatory ventilation
iNO	inhaled nitric oxide
NAVA	neurally adjusted ventilatory assist
NICU	neonatal intensive care unit
PaO_2	partial pressure of oxygen in arterial blood
PC	pressure controlled
PEEP	positive end-expiratory pressure
PICU	pediatric intensive care unit
PIP	peak inspiratory pressure
PPS	post-polio syndrome
PPHN	persistent pulmonary hypertension of newborn
Ppl	pleural pressure
PPV	positive pressure ventilation
PRVC	pressure-regulated volume-controlled
PRIS	propofol infusion syndrome
PS	pressure support
RCT	randomized controlled trial
RDS	respiratory distress syndrome

RSV	respiratory syncytial virus
SAS	sedation agitation scale
SIMV	synchronized intermittent mandatory ventilation
T_{insp}	inspiratory time
T_{exp}	expiratory time
TV	tidal volume
VC	volume controlled
VILI	ventilator-induced lung injury

List of original articles

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Ålander M, Peltoniemi O, Saarela T, Anttila E, Pokka T & Kontiokari T (2013) Current trends in paediatric and neonatal ventilatory care – a nationwide survey. Acta Paediatr 102(2): 123–128.

II Ålander M, Peltoniemi O, Pokka T & Kontiokari T (2012) Comparison of pressure-, flow- and NAVA-triggering in pediatric and neonatal ventilatory care. Pediatr Pulmonol 47(1): 76–83.

III Kallio M, Peltoniemi O, Anttila E, Pokka T & Kontiokari T (2014) Neurally adjusted ventilatory assist (NAVA) in pediatric intensive care. Pediatr Pulmonol. In press

IV Kallio M, Peltoniemi O, Anttila E, Jounio U, Pokka T & Kontiokari T (2014) Electrical activity of the diaphragm during neurally adjusted ventilatory assist in pediatric patients. Pediatr Pulmonol. In press

In addition, some previously unpublished data will be included in the Results section.

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1 Introduction

Mechanical ventilation is the core of intensive care when treating many life-threatening conditions. Up to one in every two children in pediatric intensive care needs invasive ventilation, as acute respiratory failure is the most common indication for treatment (Farias *et al.* 2004, Farias *et al.* 2012, Wolfler *et al.* 2011). Mechanical ventilation is also often used as a part of postoperative care following major surgery (Wolfler *et al.* 2011).

An adequate oxygen supply to vital organs, sufficient removal of carbon dioxide to maintain homeostasis and the facilitation of breathing without causing lung damage are the main goals for mechanical ventilation (Artigas *et al.* 1998). Since late 1990s, increasing efforts have been directed towards understanding and preventing ventilator-induced lung injury (VILI), the current recommendations for which include avoiding large tidal volumes (TV) and using an adequate level of positive end-expiratory pressure (PEEP) (Artigas *et al.* 1998, The Acute Respiratory Distress Syndrome Network 2000). Guidelines and instructions derived from adult randomized controlled trials are generally followed in pediatric ventilation as well, since no large trials of this kind have been performed on the small and heterogeneous group of pediatric intensive care patients.

There are numerous modes of invasive ventilation, with different types of patient triggering, cycling and limiting the support, but none has risen above the others in its observance of the lung-protective principles. Time-cycled pressure-controlled (PC) ventilation is generally used for neonatal patients, and synchronized intermittent mandatory ventilation with pressure support (SIMV+PS) for older children (Kaam *et al.* 2010, Wolfler *et al.* 2011). Neurally adjusted ventilatory assist (NAVA) is a new ventilation mode which provides ventilatory support proportional to the electrical activity of the diaphragm and enables physiological variations in tidal volume and inspiratory time to occur from breath to breath (Sinderby *et al.* 1999).

The aims of this research were to assess current treatment strategies in pediatric ventilation in Finland and to compare NAVA with the present standard modes of ventilation in terms of the quality and safety of invasive ventilation for general PICU patients. The ventilatory strategies required for special patient groups such as those requiring extracorporeal membrane oxygenation (ECMO), extremely low birth weight infants and children undergoing cardiac surgery or organ transplantation lie beyond the scope of this thesis.

2 Review of the literature

2.1 Historical aspects

Successful resuscitation of a man using positive pressure ventilation (PPV) in mouth-to-mouth resuscitation was first described in the mid-18th century (DeBard 1980). A method of ventilation with bellows and pistons was later established and recommended especially for victims of drowning (Baker 1971, Davis *et al.* 2000, DeBard 1980). The safety of this treatment was questioned in the 19th century and a method involving tank respirators enclosing the patient's thorax in a chamber with a subatmospheric pressure created manually with bellows was developed (Drinker & McKhann 1986a). This negative pressure ventilation later became famous during the polio epidemics of the 1930s, 1940s and 1950s, when the "iron lung" played a major role in respiratory management (Chen *et al.* 1998, Drinker & McKhann 1986a, Drinker & McKhann 1986b). The need for artificial ventilation during therapeutic thoracic surgery for tuberculosis patients nevertheless kept positive pressure ventilation in the limelight and several mechanical devices for producing an intermittent air flow arose at the beginning of the 20th century (Baker 1971).

PPV was widely used in physiological research and surgery, but it was only after the great Copenhagen poliomyelitis epidemic of 1952 that it extended to the medical field as a result of the remarkable reduction in mortality that was reported on that occasion (Lassen 1953, Trubuhovich 2004). The evolution of plastic polyvinyl chloride endotracheal tubes in the 1950s and general acceptance of PPV enabled and encouraged its use with pediatric and neonatal patients as well (Delivoria-Papadopoulos & Swyer 1964, Shann *et al.* 2003). Decades of improvement in the technology followed. Intermittent mandatory ventilation (IMV) was developed in 1973, synchronized intermittent mandatory ventilation (SIMV) a couple of years later, and high-frequency oscillatory ventilation (HFOV) in 1980 (Downs *et al.* 1973, Shapiro *et al.* 1976, Slutsky *et al.* 1980).

By the 1990s the increased understanding of lung mechanics, acute respiratory distress (ARDS) and ventilator-induced lung injury (VILI) generated guidelines for the principle now referred to as lung-protective ventilation (Amato *et al.* 1998, The Acute Respiratory Distress Syndrome Network 2000). During the last decade the use of non-invasive ventilation has become increasingly popular, as this has the potential to reduce VILI and intubation-related complications

(Marohn & Panisello 2013). Since issues related to non-invasive ventilation were not studied here, the term "ventilation" may be taken to refer throughout this thesis to invasive ventilation.

2.2 Respiratory mechanics in children

Enormous anatomical and physiological changes in respiratory tract occur throughout childhood. The highly compliant chest wall with only a weak outward recoil that is to be found in newborn infants offers poor support for the lungs and end-expiratory lung volume needs to be dynamically maintained, which makes infants prone to diaphragmatic fatigue in cases of respiratory illness (Frappell & MacFarlane 2005). The configuration of the rib cage alters during the first years of life, however, the chest wall stiffens, and the number of alveoli increases exponentially (Thurlbeck 1982). These anatomical changes lead to associated changes in respiratory mechanics, in that respiratory system resistance and airway resistance decrease, while the compliance of the respiratory system increases with height (Lanteri & Sly 1993). These differences between pediatric and adult respiratory systems may be of prognostic significance and should not be despised when extrapolating recommendations from adult studies to children (Kneyber *et al.* 2014, Kornecki *et al.* 2005).

2.3 Primary lung injury

A severe form of acute lung injury known as acute respiratory distress syndrome (ARDS) may result either from direct injury to the lung (e.g. pneumonia or aspiration) or a severe extrapulmonary condition (e.g. sepsis or polytrauma) leading to indirect lung injury. Widespread inflammation of the lung tissue, extravasation of fluid from the pulmonary capillaries and diffuse alveolar damage are typical of ARDS. Although ARDS was first described in adults in the 1960s, our view of it changed dramatically in the 1980s when reports based on computer tomography (CT) revealed the heterogeneous nature of this condition which had previously been thought of in a monolithic sense as “stiff lung” (Ashbaugh *et al.* 1967, Gattinoni *et al.* 1987). Normally aerated, poorly aerated, non-aerated and over-inflated areas can be found in the injured lung, and the amount of normally aerated tissue may be as low as 300-500g in adult patients suffering from severe ARDS (Gattinoni & Pesenti 2005).

The 1994 American-European Consensus Conference (AECC) defined ARDS as an acute onset of hypoxaemia ($PaO_2/FiO_2 \leq 200$ mmHg) with bilateral infiltrates visible in a thorax x-ray without any cardiac reason for pulmonary oedema (Bernard *et al.* 1994). A less severe form with milder hypoxaemia ($PaO_2/FiO_2 \leq 300$ mmHg) was referred to as acute lung injury (ALI) (Bernard *et al.* 1994). These criteria were updated and revised in 2012 by the Berlin Definition, which defines three stages of ARDS based on the degree of hypoxaemia: *mild* 200 mmHg < $PaO_2/FiO_2 \leq 300$ mmHg, *moderate* 100 mmHg < $PaO_2/FiO_2 \leq 200$ mmHg and *severe* $PaO_2/FiO_2 \leq 100$ mmHg. This requires the assessment of oxygenation with PEEP or CPAP ≥ 5 cmH_2O and gives more precise criteria for timing (*'within 1 week of a known clinical insult or new or worsening respiratory symptoms'*). Objective assessment of the aetiology of pulmonary oedema (*e.g. echocardiography to exclude hydrostatic oedema if no risk factor is present*) is also needed (ARDS Definition Task Force *et al.* 2012).

The incidence of pediatric ARDS in Europe is 2.2-3.9 cases/100.000/yr, and the AECC criteria for ALI are fulfilled in 9.9% of pediatric intensive care patients, 80% of whom develop ARDS (Bindl *et al.* 2005, Dahlem *et al.* 2003, Kneyber *et al.* 2008, Lopez-Fernandez *et al.* 2012). VILI contributes to the progression of lung injury and multi-organ failure, and high mortality (27.4-31.4%) is associated with severe pediatric ARDS (Dahlem *et al.* 2003, De Luca *et al.* 2013, Lopez-Fernandez *et al.* 2012, Nakos *et al.* 2006). Similar histo-morphological and inflammatory patterns are found in VILI and primary lung injury (Dahlem *et al.* 2007).

2.4 Ventilator-induced lung injury

Mechanical ventilation may both worsen the injury in a previously damaged lung and initiate an injury in healthy lungs. Its potential for causing trauma was soon understood after PPV was adopted in clinical practice, and the term "respirator lung" was later launched to describe lung injury findings in post mortem examinations of these patients (Avignon *et al.* 1956, Slutsky & Ranieri 2013). High airway pressure was for a long time considered to be the main factor causing lung injury, and the term barotrauma was generally used to describe complications such as pneumothorax, pneumomediastinum and subcutaneous emphysema (Cullen & Caldera 1979). Currently, the most important factors considered responsible for VILI are alveolar overdistention due to high TVs and repeated alveolar collapse and reopening due to low end-expiratory volume

(International Consensus Conferences Committee 1999). Primary lung injury, a high inspired oxygen fraction and inflammatory responses also play roles in the progression of VILI (International Consensus Conferences Committee 1999, Paulson *et al.* 1995). VILI is characterized by inflammatory-cell infiltrates, hyaline membranes, alveolar haemorrhage, increased vascular permeability and pulmonary oedema (Nakos *et al.* 2006, Slutsky & Ranieri 2013). The causes and consequences of VILI are summarized in Fig. 1.

2.4.1 Volutrauma

Regional overdistention resulting from heterogeneous lung compliance and high transpulmonary pressure compromise the structure and functioning of the lung during mechanical ventilation (Dreyfuss & Saumon 1993, Pastore *et al.* 2011). In an extreme situation, overdistention can lead to alveolar rupture and the complications previously referred to as barotrauma (e.g. pneumothorax, pneumomediastinum and interstitial or subcutaneous emphysema). Animal studies have shown that high airway pressure alone is tolerated well if there is a factor limiting lung volume progression, such as a stiff chest wall (Dreyfuss *et al.* 1988, Dreyfuss & Saumon 1993, Webb & Tierney 1974). As lung volume is inextricably linked to transpulmonary pressure, a profound understanding of the physical forces related to mechanical ventilation is needed for the prevention of VILI.

2.4.2 Atelectrauma

In the event of failure to maintain adequate end-expiratory lung volume, repetitive collapse and reopening of the airways and lung units can lead to surfactant dysfunction and injury characterized by epithelial sloughing, hyaline membranes and pulmonary oedema (Nakos *et al.* 2006, Sinclair *et al.* 2009). The role of this injury mechanism has been highlighted in animal studies, where the use of PEEP reduced the severity of lung injury (Corbridge *et al.* 1990, Dreyfuss *et al.* 1988, Sinclair *et al.* 2009).

2.4.3 Biotrauma

Mechanical ventilation is associated with increased levels of multiple inflammatory mediators, some contributing to lung injury and others being markers of it (Jaecklin *et al.* 2011, Ranieri *et al.* 1999, Stuber *et al.* 2002). The

association between VILI and increased apoptosis in the kidneys and small intestine ('end organs') shown in animal studies carries a clinically significant message, since multiorgan failure remains the most common cause of death in cases of ARDS (Esteban *et al.* 2013, Imai *et al.* 2003, Nakos *et al.* 2006). It has been shown that only two hours of mechanical ventilation are sufficient to alter the immune response to the proinflammatory cascade in children without any underlying lung pathology (Plotz *et al.* 2002). Circulating mediators seem attractive therapeutic targets for progressive lung and end-organ injury in the critically ill, but further evidence of pathogenicity is still needed before any pharmacological treatment can be developed (Jaecklin *et al.* 2011).

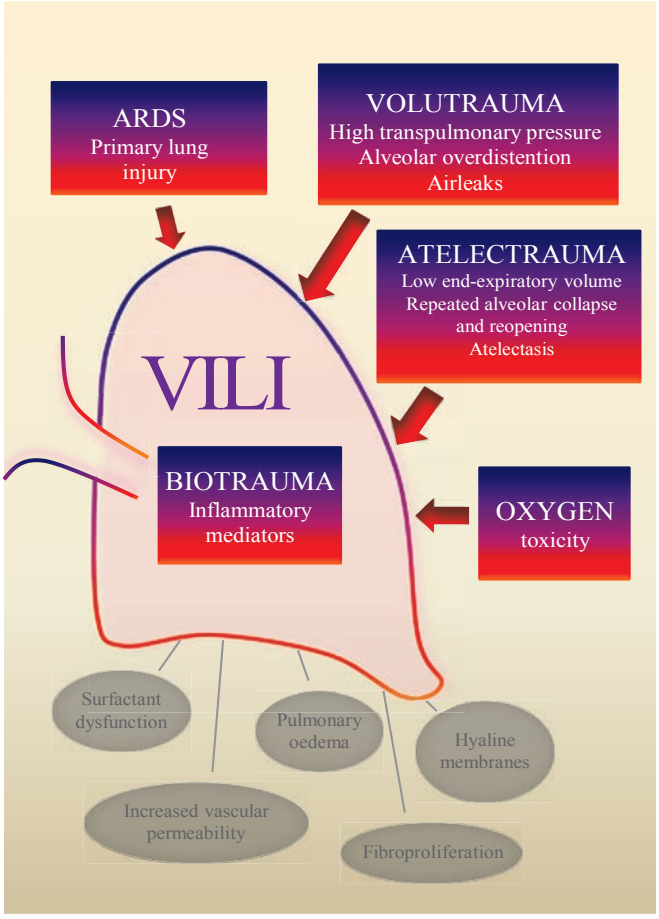

Fig. 1. Ventilator-induced lung injury

2.4.4 Oxygen toxicity

Supplementary oxygen is generally required when respiratory distress patients are treated. High-dose oxygen supplementation produces free radicals and induces potentially lethal lung injury (Aoki *et al.* 2008, Bucher & Roberts 1981, Burger & Mead 1969, Crapo *et al.* 1980). Histopathological findings of acute lung injury after exposure to high oxygen concentrations resemble ARDS, including diffuse alveolar damage with pulmonary oedema followed by fibrosis and pulmonary hypertension (Aoki *et al.* 2008, Burger & Mead 1969, Jackson 1990, Thiel *et al.* 2005). However, the severity of oxygen-induced lung injury has been demonstrated in several animal studies to be dose-dependent, so that only transient deterioration of epithelial function without fibrosis or significant epithelial injury has been reported during long-term supplementation at a low (40%) oxygen concentration (Aoki *et al.* 2008, Bucher & Roberts 1981, Crapo *et al.* 1980). Thus exposure to mild hyperoxia seems to be fairly well tolerated (Aoki *et al.* 2008).

2.5 Lung-protective ventilatory strategies

Our increased understanding of lung injury has modified the mechanical ventilation approach from attempts to maintain perfect gas exchange to providing adequate oxygenation and ventilation without causing further lung injury. This "lung-protective ventilation strategy" has been considered the treatment of choice ever since decreased mortality and an increased number of ventilator-free days was reported in adult ARDS patients in a large multicentre RCT in 2000 (The Acute Respiratory Distress Syndrome Network 2000).

As there are no RCTs on lung-protective ventilation strategies for pediatric patients, current recommendations are based on experimental animal studies, adult RCTs and expert opinions. A ventilation strategy using small tidal volumes, limited inspiratory pressures, adequate PEEP and a minimal amount of supplementary oxygen is currently considered the treatment of choice for neonatal and pediatric patients as well (Dargaville & Tingay 2012, Dellinger *et al.* 2013, Jauncey-Cooke *et al.* 2010, Kaam 2011). The relation between VILI and the lung-protective ventilation strategy is illustrated in Fig. 2.

2.5.1 Tidal volume

Attention has been drawn to TVs since the fundamental role of overdistention in the progression of VILI came to be understood. A small TV (6 ml/kg vs. 12 ml/kg) reduced mortality among adult ARDS patients and increased the number of ventilator-free days (Amato *et al.* 1998, The Acute Respiratory Distress Syndrome Network 2000). In a retrospective cohort study, children with a normal oxygenation ratio on admission suffered a deterioration in oxygenation if TVs above 9 ml/kg were used (Halbertsma *et al.* 2009). General opinions and recommendations concerning TV in pediatric ventilation vary between 6-8 ml/kg and 5-7 ml/kg, with agreement on the avoidance of TVs over 10 ml/kg (Cornfield 2013, Kneyber & Markhorst 2009, Randolph 2009, Santschi *et al.* 2013).

2.5.2 Airway pressure

The guidelines for mechanical ventilation for adult ARDS patients include limiting the plateau pressure to $\leq$ 30 cmH_2O (Dellinger *et al.* 2013). Plateau pressure measured at the end of inspiration in a no-flow phase provides a relatively reliable estimate of the alveolar pressure in a patient who is not breathing spontaneously (Slutsky & Ranieri 2013). The other essential pressure required for calculating transpulmonary pressure, however, is pleural pressure (Ppl), which is not easily measured in clinical practice. Oesophageal pressure may be used as an estimate for Ppl, but at the moment there is no equipment available for measuring it easily and reliably in clinical practice (Slutsky & Ranieri 2013). Ppl is negative for a spontaneously breathing child, but there are several clinical situations, e.g. pleural effusion or ascites, which may lead to high Ppl (Helliesen *et al.* 1958, Talmor *et al.* 1998). Similar airway pressures in these cases would cause very different transpulmonary pressures and lung distending forces. Avoidance of high airway pressures may be used as a surrogate strategy to limit alveolar overdistention, and pediatric intensivists generally report changing the ventilation mode if 35 cmH_2O of PIP is reached (Santschi *et al.* 2013).

2.5.3 Positive end-expiratory pressure

Ventilation with small tidal volumes facilitates the formation of atelectasis if there is a failure to maintain adequate end-expiratory lung volume. PEEP is now considered one of the cornerstones of lung-protective ventilation. Implementation

of PEEP improves oxygenation, reduces the formation of atelectasis and opens collapsed lung areas, thus reducing VILI (Dreyfuss *et al.* 1988, Dreyfuss & Saumon 1993, Gattinoni *et al.* 1987, Serafini *et al.* 1999). The optimal level of PEEP is one that stabilizes lung areas that tend to collapse but causes minimal overdistention in normally aerated areas.

Despite its potential for causing haemodynamic compromise or increasing intracranial pressure (ICP), PEEP from 5 to 8 cmH_2O is generally well tolerated in pediatric intensive care patients, even after neurosurgery (Boriosi *et al.* 2011, Pulitano *et al.* 2013). 5 cmH_2O of PEEP recruits the available alveolar units and opens atelectasis in children without lung disease (Serafini *et al.* 1999). The Berlin Definition of ARDS, which is also considered feasible in pediatric intensive care, requires that evaluation of oxygenation should imply a PEEP equal to or over 5 cmH_2O (ARDS Definition Task Force *et al.* 2012, De Luca *et al.* 2013). Thus PEEP levels below 5 cmH_2O should be used only when the patient's haemodynamic or neurological (high ICP) condition requires it. Pediatric intensivists consider the maximal acceptable PEEP used to obtain adequate oxygenation to be 12-16 cmH_2O for a 5-year-old child and 10-15 cmH_2O for a 2-month-old child (Santschi *et al.* 2013).

Finding the optimal PEEP in clinical practise remains a challenging task. PEEP has traditionally been adjusted together with inspiratory time to aim at an acceptable level of arterial oxygenation with a non-toxic FiO_2 (Artigas *et al.* 1998). Oesophageal pressure-guided adjustment of PEEP gave improved oxygenation and compliance in a pilot study of adult ARDS patients, but the impracticability and inaccuracy of this method has prevented its wider use in clinical practice (Gappa *et al.* 1996, Talmor *et al.* 2008). Electrical impedance tomography (EIT) is a non-invasive method for monitoring regional lung ventilation and seems to be a potential tool for optimizing PEEP in pediatric patients as well (Dargaville *et al.* 2010, Frerichs *et al.* 2001, Krause *et al.* 2014).

2.5.4 Lung recruitment and derecruitment

Although lung-protective ventilation aims at avoiding both volutrauma and atelectrauma, ventilation with small tidal volumes may lead to progressive lung collapse. Several recruitment manoeuvres for maintaining lung volume have been described, and these have improved oxygenation and attenuated VILI in animal studies, but their safety and efficacy in clinical practice remains controversial (Boriosi *et al.* 2011, Koh *et al.* 2005, Meade *et al.* 2008, Rimensberger *et al.*

1999). It has been concluded in a recent review on pediatric lung recruitment that recruitment manoeuvres may be useful in restoring lung volume after circuit disconnection and/or endotracheal suctioning, but insufficient evidence exists to support its universal application (Jauncey-Cooke *et al.* 2014).

As the role of endotracheal suctioning in lung derecruitment and atelectasis formation is well recognized, the current recommendations state that it should only be performed when secretions are present (not routinely). Shallow rather than deep suction should be used and prior normal saline installation should not be performed routinely. The avoidance of disconnection from the ventilator (closed system) is important especially in neonates. (American Association for Respiratory Care 2010).

2.5.5 Gas exchange

Permissive hypercapnia has been closely related to lung-protective ventilation strategies from beginning and is now generally accepted among pediatric intensivists (Santschi *et al.* 2013, The Acute Respiratory Distress Syndrome Network 2000). Hypercapnia-related respiratory acidosis with pH $\geq$ 7.20 seems to be well tolerated and is considered acceptable as long as it does not compromise the haemodynamic status (Jauncey-Cooke *et al.* 2010, Kneyber & Markhorst 2009, Rotta & Steinhorn 2006). It has been suggested in some animal studies that hypercapnia might have a direct lung-protective role in preventing ventilator-induced biotrauma (Peltekova *et al.* 2010, Shibata *et al.* 1998).

Attempts to avoid the toxic effects of supplementary oxygen have led to suggestions that oxygen saturations of 85-90% might be adequate for children with ARDS (Cheifetz & Hamel 2006, Jauncey-Cooke *et al.* 2010). In preterm infants, however, the targeting of oxygen saturation below 90% has increased mortality and the risk for necrotizing enterocolitis (BOOST II United Kingdom Collaborative Group *et al.* 2013, Saugstad & Aune 2014, SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network *et al.* 2010). Pediatric intensivists report accepting *permissive hypoxaemia* from 88% to 95% in mechanically ventilated children with ARDS (Santschi *et al.* 2013).

Monitoring serum lactate levels and central venous oxygen saturation or mixed venous oxygen saturation to verify adequate organ perfusion is recommendable if permissive hypoxaemia is accepted (Abdelsalam & Cheifetz 2010, Fuller & Dellinger 2012). In some cases the facilitation of tissue oxygenation by increasing haemoglobin or cardiac output may be needed

(Abdelsalam & Cheifetz 2010). High-dose oxygen supplementation should be avoided when possible, but as mild hyperoxia seems to be rather well tolerated and an intentional attempt at achieving even mild hypoxaemia may be dangerous, oxygen supplementation should not be restricted at the expense of tissue oxygenation (Aoki *et al.* 2008, Saugstad & Aune 2014).

2.5.6 Spontaneous breathing and patient-ventilator interactions

The maintaining of spontaneous breathing during mechanical ventilation improves ventilation/perfusion distribution, gas exchange, systemic blood flow and tissue oxygenation and prevents repeated alveolar collapse and reopening (Guldner *et al.* 2014, Neumann *et al.* 2005, Tokics *et al.* 1987, Wrigge *et al.* 2003). An attenuation of VILI has been reported in animal studies when pressure support with spontaneous breathing is compared with controlled ventilation, but there are some data pointing to beneficial effects of neuromuscular blocking in the acute phase of severe ARDS in adults, so that when oxygen consumption needs to be minimized in order to handle hypoxaemia or a reduced cardiovascular reserve, neuromuscular blocking agents may be beneficial (Alhazzani *et al.* 2013, Dellinger *et al.* 2013, Forel *et al.* 2006, Papazian *et al.* 2010, Spieth *et al.* 2011).

In addition to the above-mentioned benefits, the goal for maintaining spontaneous breathing is to minimize the risk of ventilator-induced diaphragmatic dysfunction (Futier *et al.* 2008, Jung *et al.* 2010). Patient-ventilator synchrony improves oxygenation, patient comfort and haemodynamic stability (Donn *et al.* 1994, Firme *et al.* 2005, Oliva *et al.* 2012). A high breathing frequency, small tidal volumes and gas leak from the circuit make pediatric patients prone to patient-ventilator asynchrony, and a high proportion of asynchrony has indeed been reported in children (Bernstein *et al.* 1995, Bordessoule *et al.* 2012, Oliva *et al.* 2012, Vignaux *et al.* 2013). In adult patients a high proportion of patient-ventilator asynchrony is associated with a longer duration of mechanical ventilation and the length of stay in the intensive care unit, a higher rate of tracheotomy and lower survival (Chao *et al.* 1997, Thille *et al.* 2006, Wit *et al.* 2009). In cases of severe patient-ventilator asynchrony it is recommended to adjust the inspiratory and expiratory trigger settings and reduce the level of support (Tassaux *et al.* 2005, Thille *et al.* 2006, Thille *et al.* 2008). Detecting patient-ventilator asynchrony from ventilator waveforms is challenging without special expertise and has encouraged attempts to develop tools for better

assessment of asynchrony in clinical practise (Chen *et al.* 2008, Colombo *et al.* 2011, Cuvelier *et al.* 2010, Gutierrez *et al.* 2011).

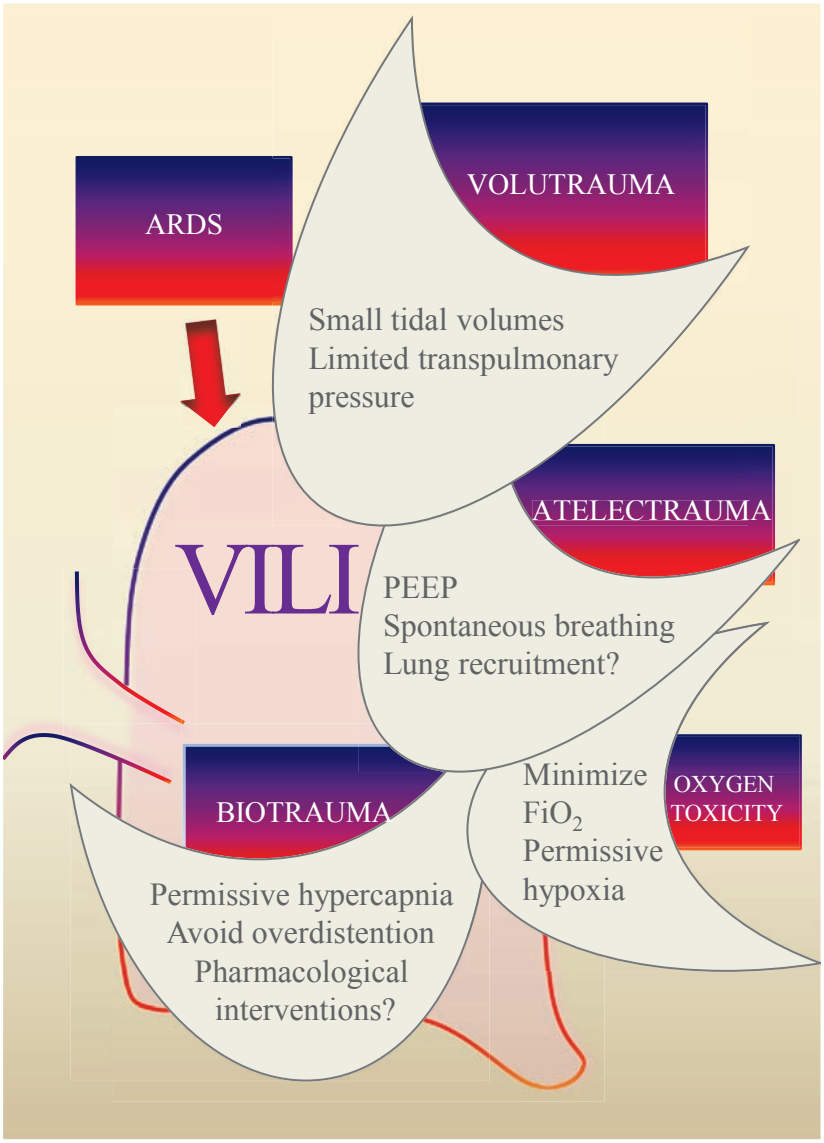

Fig. 2. Lung-protective ventilation

2.6 Conventional ventilation modes

The basic concepts behind conventional ventilation have remained the same, even though ventilators are currently very sophisticated computers. Clinicians should remember that similar elements of the ventilatory cycle exist in every conventional ventilation mode, despite the highly confusing terminology and jungle of abbreviations that beset this section of intensive care. The four phases of the ventilatory cycle are: 1) the transition from expiration to inspiration (the 'inspiratory trigger'), 2) the inspiratory phase, 3) the transition from inspiration to expiration (the 'expiratory trigger') and 4) the expiratory phase (Garnero *et al.* 2013). Since the expiratory phase during mechanical ventilation consists of implementing PEEP, the first three can be defined as describing the ventilation mode. These phases are summarized in Fig. 3 and further discussed below.

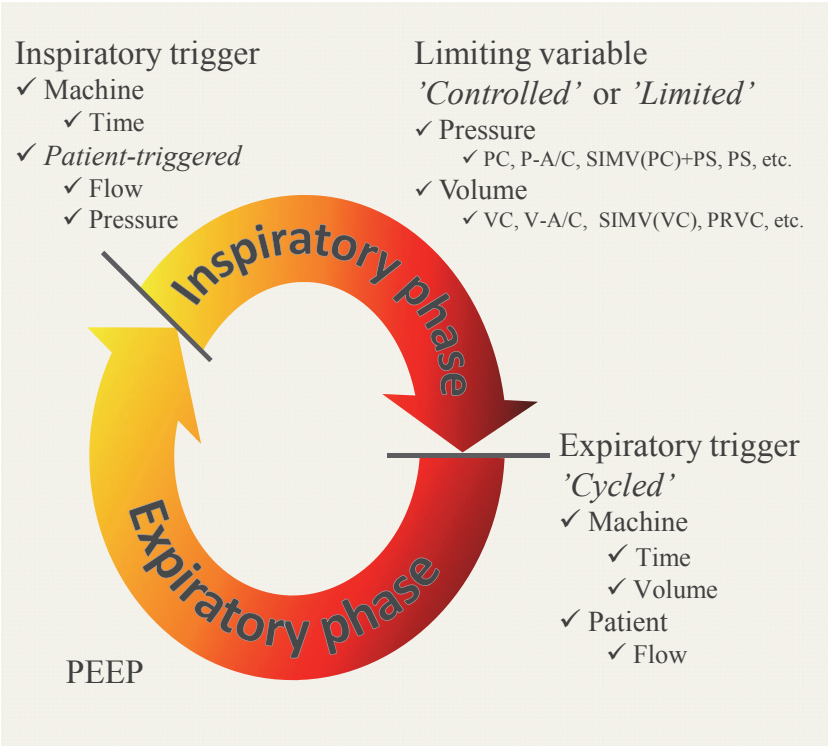

Fig. 3. The ventilatory cycle

2.6.1 Inspiratory trigger

The inspiratory trigger is a predetermined parameter threshold that initiates the taking of a breath (Garnero *et al.* 2013). In conventional ventilation this trigger may be either time (*controlled* ventilation) or patient effort (*'patient-triggered'* ventilation) (MacIntyre 2011). For patient-triggered breaths either a flow trigger or a pressure trigger may be chosen. Practically all current ventilators supply a constant flow around the circuit throughout the respiratory cycle and a deflation in this flow as a result of patient effort initiates a breath when the flow trigger option is used. Analogously, a decrease in the baseline pressure as a result of patient effort initiates a breath during pressure-triggered ventilation. Virtually all the modes of ventilation used in intensive care nowadays have the patient-triggered option, and controlled breathing only exists when the patient's efforts are not sensed or the spontaneous breathing frequency is lower than the ventilator's preset frequency.

The unintended initiation of a breath by the ventilator (e.g. upon movement of the breathing tube or inappropriate trigger settings) is called *autotriggering* (Chatburn *et al.* 2012). Leaks from the circuit in infants ventilated with uncuffed endotracheal tubes can increase the risk of autotriggering and may sometimes necessitate reintubation with a larger endotracheal tube (Bernstein *et al.* 1995). In clinical practice the trigger sensitivity should be as sensitive as possible without causing autotriggering (MacIntyre 2011).

2.6.2 Inspiratory phase

The terms *'pressure controlled'* (PC) and *'volume controlled'* (VC) are generally used to describe the parameters that limit the increase in pressure, flow and volume during inspiration (Chatburn *et al.* 2012). In PC a predetermined pressure level (measured either as PIP or as 'pressure above PEEP') limits the magnitude of support and when VC is used the tidal volume administered in each breath is predetermined (Garnero *et al.* 2013, MacIntyre 2011). Actually, many ventilators measure and limit the inspiratory flow during VC and require settings for both flow rate and pattern, although they calculate volume as reported information (Garnero *et al.* 2013, Singer & Corbridge 2011). The variable that does not increase beyond the pre-fixed value during inspiration is called the 'limiting variable' (Garnero *et al.* 2013). As these limiting variables also exist in assisted

and supportive modes of ventilation, it has been suggested that the terms *'pressure-limited'* and *'volume-limited'* should be used (Chatburn 2007).

When one parameter (pressure or volume) is controlled during the inspiratory phase, the other becomes dependent and changes if there is change in either lung compliance or airway resistance (Garnero *et al.* 2013). Thus, the tidal volume increases with improving lung compliance during pressure-controlled ventilation, while in a similar clinical situation decreasing airway pressures are seen during volume-controlled ventilation. Ventilation modes which both achieve a given TV and limit the pressure are currently available and are often referred as *'dual control'* (Garnero *et al.* 2013). It should be noted that these modes also control either pressure or volume, but not both at the same time, since control over inspiration is started with pressure and then switched to volume (or vice versa) in order to achieve the preset goals (Garnero *et al.* 2013).

Recent meta-analyses have reported improved outcomes (less BPD and pneumothoraces, a decreased incidence of periventricular leukomalacia and grade 3/4 intraventricular haemorrhage and shorter times on the ventilator) in premature infants ventilated using VC rather than PC (Peng *et al.* 2014, Wheeler *et al.* 2011). No data exist on the superiority of either mode in full-term neonates, children or adults (Duyndam *et al.* 2011, Esteban *et al.* 2000, Garnero *et al.* 2013, Greenough & Bhat 2012).

2.6.3 Expiratory trigger

The transition from inspiration to expiration takes place when a predetermined value for the expiratory trigger (*'cycling variable'*) is reached. In PC this variable is time (*'time-cycled'*) and during pressure support (PS) the preset level of pressure is supplied until the inspiratory flow drops below a predetermined threshold (*'flow-cycled'*) (Singer & Corbridge 2011). Volume-controlled ventilation is either time-cycled or else inspiration ends when the preset volume has been supplied (*'volume-cycled'*) (MacIntyre 2011). Synchronized intermittent mandatory ventilation (PC) with pressure support (SIMV(PC)+PS) is an example of a ventilation mode that includes two types of cycling (time and flow) that vary from breath to breath depending on the timing of the breath.

2.6.4 Mandatory, assisted and spontaneous breaths

The maintaining of spontaneous breathing during invasive ventilation has led to a situation in which, depending on whether a breath is patient or machine-triggered (time) and patient (flow) or machine-cycled (time or volume), the terms mandatory, assisted and spontaneous breath are used. A *mandatory breath* is machine-triggered and/or machine-cycled, a *spontaneous breath* is patient-triggered and patient-cycled (applies to assisted or unassisted breathing) and an *assisted breath* is one for which a ventilator does some or all of the work of breathing (Chatburn *et al.* 2012).

2.6.5 Terminology

The current terminology for ventilation modes is complex and disordered. Very similar or identical names are used for different ventilation modes while, on the other hand, different names are given to the same mode (Chatburn & Volsko 2010). This causes misinterpretation of evidence, barriers to the learning process and may even prevent the clinician from fully understanding how the ventilator should be properly operated, thus putting the patient at risk of lung injury (Chatburn & Volsko 2010). Attempts have been made to create a standard classification and nomenclature for mechanical ventilation (Chatburn 2007, Chatburn & Volsko 2010, MacIntyre 2011, Mireles-Cabodevila *et al.* 2013).

2.7 High frequency oscillatory ventilation

High frequency oscillatory ventilation (HFOV) is a mode that provides ventilation with a constant distending pressure, tidal volumes smaller than the physiological dead space (1-2ml/kg) and high frequencies (3-15 Hz) (Kneyber *et al.* 2012, Slutsky *et al.* 1980). Gas transport mechanisms during HFOV are complex and completely different from those found in conventional ventilation (Pillow 2005, Slutsky & Drazen 2002). HFOV improves oxygenation in pediatric and neonatal patients by comparison with conventional ventilation (Arnold *et al.* 2000, Ben Jaballah *et al.* 2006, Kinsella *et al.* 1997).

Neither the lung-protective ventilation ideology (stable lung volume and small TVs) nor the better gas exchange achieved during HFOV has improved the outcomes for adult, pediatric or neonatal respiratory distress patients as compared with conventional ventilation (Cools *et al.* 2009, Ferguson *et al.* 2013, Gupta *et*

al. 2014, Maitra *et al.* 2014, Young *et al.* 2013). HFOV is currently used to stabilize congenital diaphragmatic hernia patients and, together with inhaled nitric oxide (iNO), as a rescue therapy for newborns with severe persistent pulmonary hypertension (Garriboli *et al.* 2012, Kinsella *et al.* 1997).

2.8 Neurally adjusted ventilatory assist

NAVA is a new ventilation mode that provides support proportional to the electrical activity of the diaphragm (Edi) (Sinderby *et al.* 1999). It uses Edi to trigger, cycle off and adjust the assist profile in each breath, enabling physiological variation in tidal volume and inspiratory time from breath to breath. The requirement for this mode of ventilation is integrity of the phrenic nerve and neuromuscular junction (Sinderby *et al.* 1999).

2.8.1 Neural control over breathing

Breathing is controlled by the respiratory centre in the brainstem, the neurons in which generate electrical impulses that travel through the motoneurons and neuromuscular junction to the respiratory muscles, causing contraction. The phrenic nerve transmits an impulse to the diaphragm, which is considered to be the main inspiratory muscle.

Breathing is then regulated by feedback from peripheral and central chemosensors and the bronchopulmonary vagal afferent nerves, their primary goal being adequate gas exchange. "Air hunger" is an uncomfortable sensation that may be provoked by both hypercapnia and hypoxia (Banzett *et al.* 1996, Moosavi *et al.* 2003). Although mild hypoxaemia is well tolerated during normocapnia, intense air hunger is common in critically ill adults during mechanical ventilation, being closely associated with anxiety, and may often be alleviated by optimizing the ventilator settings (Schmidt *et al.* 2011).

The reflexes that terminate inspiration if lung overdistention occurs and induce inspiration in the case of reduced lung volume are called the Hering-Breuer inflation and deflation reflexes, named after Ewald Hering and Joseph Breuer, who first described them in 1868 (Hannam *et al.* 2001). These reflexes are particularly active in neonates but can be provoked by PPV in older children, too (Giffin *et al.* 1996, Hannam *et al.* 2001, Hassan *et al.* 2001). Integration of the stretch receptor activity and reflex response is disturbed by anaesthesia (Brown *et al.* 1998).

2.8.2 Electrical activity of the diaphragm

The myoelectric signals related to muscle contraction can be measured and described by electromyography (EMG). Both surface electrodes and oesophageal electrodes have been used to observe the electrical activity of the diaphragm. Since an adequate electrode position relative to the muscle is essential for obtaining the optimal signal, it is reasonable to place the electrodes in the oesophagus when measuring the diaphragmatic EMG (American Thoracic Society/European Respiratory Society 2002). Oesophageal recording of the crural diaphragm EMG with an *'Edi catheter'* is used during NAVA.

An Edi catheter is a special nasogastric tube with electrodes mounted on it, the size of the catheter and the distance between the electrodes being optimized for each age group based on patients' length and, in neonates, also on weight. Eight pairs of electrodes are used to minimize electrode filtering and to cover motion of the diaphragm with all sizes of catheter (Beck *et al.* 1995, Beck *et al.* 1996, Sinderby *et al.* 1997). Insertion of the catheter at the optimal point can be ensured by using a modification of the nose-ear lobe-xiphoid process distance, and the optimal position of the catheter in relation to the diaphragm is continuously monitored by the ventilator using software that samples data from all the electrodes and selects the pair closest to the crural diaphragm at each point in the respiratory cycle (American Thoracic Society/European Respiratory Society 2002, Barwing *et al.* 2009).

The Edi signal can be used to define the neural timing of breathing. The neural inspiratory time (T_{insp}) is the difference in time between the onset of the Edi increase and the peak Edi at the end of inspiration. Correspondingly, the neural expiratory time (T_{exp}) is the difference in time between the peak Edi and the onset of the next inspiratory Edi, and the neural breathing frequency may be calculated as 60/(neural T_{insp} +T_{exp}) (Beck *et al.* 2004). Mandatory breaths during mechanical ventilation are highly asynchronous in relation to neural breathing, so that they increase the neural T_{exp} and reduce the neural breathing frequency in infants (Beck *et al.* 2004).

The Edi in healthy, spontaneously breathing term newborns varies from 11 ± 5 μV during inspiration (peak Edi) to 3 ± 2 μV during expiration (Edi min), and levels fluctuate with changes in the state of alertness (Stein *et al.* 2012b). Large variability in the peak Edi and substantial fluctuations in Edi during expiration are typical of infants, and expiratory Edi activity as a part of the normal breathing pattern has been associated with the maintenance of end-expiratory lung volume

(Beck *et al.* 2011, Stein *et al.* 2012b). In clinical practice, Edi monitoring may be used to observe the patient's breathing pattern and identify central apnoeas, to assess the work of breathing, readiness for extubation and the risk of reintubation, and to optimize the ventilatory settings during invasive ventilation (Ducharme-Crevier *et al.* 2013, Wolf *et al.* 2011).

2.8.3 Neuromechanical coupling

Neural control together with the mechanical properties of the respiratory system and the strength of the respiratory muscles will determine the effectiveness of breathing. The relation between the tidal transdiaphragmatic pressure and the Edi is used to describe neuromechanical coupling, i.e. the ability to convert neuromuscular activation to a change in intrathoracic pressure by means of diaphragm contraction (Beck *et al.* 1998).

Relative diaphragm activation in healthy subjects is 8% of maximal voluntary activation during quiet breathing, while a higher activation level of up to 43-45% is found in patients with chronic respiratory insufficiency and hypercapnia [chronic obstructive pulmonary disease (COPD), post-polio syndrome (PPS) and Duchenne muscular dystrophy (DMD)] (Beck *et al.* 2006, Sinderby *et al.* 1998). While COPD and PPS patients develop TVs and pressure differences similar to healthy subjects, poor neuromechanical coupling in DMD patients leads to low TVs (Beck *et al.* 2006).

Increased neural respiratory drive (i.e. a high Edi) with an impaired ability to convert neuromuscular activity to tidal ventilation due to diaphragmatic weakness is associated with failure to wean from invasive ventilation in critically ill adult patients (Dres *et al.* 2012, Liu *et al.* 2012). Studying the interactions between the central respiratory drive, muscle strength and diaphragm activity with Edi can also provide valuable clinical data on pediatric patients with difficult weaning from respiratory support (Fine-Goulden *et al.* 2012).

2.8.4 Tidal volume and airway pressure

During NAVA ventilation a conversion factor called the *'NAVA level'* determines the pressure supplied for a given Edi amplitude. The patient's respiratory centre determines the Edi input and provides protection against excessive TV by downregulating Edi with increasing NAVA levels (Sinderby *et al.* 2007, Vagheggini *et al.* 2013). Large breath-to-breath variability in both TV and PIP is

seen during NAVA (Bordessoule *et al.* 2012, Coisel *et al.* 2010, Liet *et al.* 2011, Moorhead *et al.* 2013, Schmidt *et al.* 2010). Excessive increase in PIP may be constrained by placing alarm limits on the ventilator, and this is particularly important in patients with severe respiratory distress and air hunger combined with poor lung compliance (Ducharme-Crevier *et al.* 2013, Stein *et al.* 2012a).

Back up modes turn on in the NAVA software when the Edi signal fails to lead to ventilatory support, either as a result of central apnoea (silent Edi) or because of errors in detecting the signal (catheter position, technical error). Pressure support is activated when the patient triggers the ventilator with a pneumatic trigger but a silent Edi signal is seen, and back-up ventilation (PC) if the patient becomes apnoeic, i.e. is not triggering the ventilator in any way. The PS and PC settings should be determined individually for each patient following the basic principles of conventional ventilation.

A beneficial effect on ventilation distribution during NAVA has been reported in a small group of adult patients, but so far there are no clinical data on the attenuation of VILI with NAVA ventilation (Blankman *et al.* 2013).

2.8.5 Positive end-expiratory pressure

Edi activation above the noise level during expiration, '*tonic Edi*', is a vagally mediated reflex that aims at keeping the lung open, and is instantaneously increased with intubation and the removal of PEEP in animal models (Allo *et al.* 2006, Beck *et al.* 2007). Implementing PEEP has been found to reduce tonic Edi and facilitate phasic Edi in an animal model of lung injury (Allo *et al.* 2006).

A higher level of tonic Edi is found in infants during low PEEP (0-3 cmH_2O) as compared with a PEEP of 5 cmH_2O, and a reduction in PEEP of about 6 cmH_2O in adult patients causes a small but significant increase in the mean expiratory Edi (Brander *et al.* 2009, Emeriaud *et al.* 2006). The level of PEEP at which tidal breathing occurs at minimal cost to the Edi may be identified by monitoring the TV/Edi ratio during PEEP changes (Passath *et al.* 2010). Thus, minimizing the expiratory Edi activity and finding the highest TV/Edi ratio may be used as tools for optimizing PEEP during invasive ventilation.

2.8.6 Inspiratory and expiratory triggers

The inspiratory trigger during NAVA works on a first-come first-served basis between the Edi and pneumatic trigger (flow or pressure). The Edi trigger

threshold is a preset level of increase in the signal from the previous value that triggers inspiratory support and it should be set above noise level to avoid autotriggering. Neurally triggered breaths have less trigger delay and improved ventilator response times, but not all breaths during NAVA are neurally triggered, since signal processing causes some delay and sometimes, in approximately one third of breaths, the pneumatic trigger is faster (Bengtsson & Edberg 2010, Breatnach *et al.* 2010, Clement *et al.* 2011, Oliva *et al.* 2012).

The thresholds for both neural and pneumatic inspiratory triggers are adjustable but a fixed threshold for cycle off during NAVA has been set to 70% of peak Edi. This neural cycle-off terminates the breath in 85-88% of respiratory cycles during NAVA in children (Bengtsson & Edberg 2010, Breatnach *et al.* 2010).

2.8.7 NAVA in PICU

There have been several small crossover trials aimed at assessing the effect of NAVA on patient-ventilator synchrony in pediatric patients (Bengtsson & Edberg 2010, Bordessoule *et al.* 2012, Breatnach *et al.* 2010, Clement *et al.* 2011, Oliva *et al.* 2012, Vignaux *et al.* 2013). Case reports and small observational patient series describing the use of NAVA in infants with bronchiolitis or diaphragmatic hernia have been published (Durrani *et al.* 2011, Gentili *et al.* 2013, Liet *et al.* 2011).

NAVA improves patient-ventilator synchrony even in the presence of an air leak from the circuit (Beck *et al.* 2009, Bengtsson & Edberg 2010, Bordessoule *et al.* 2012, Liet *et al.* 2011, Vignaux *et al.* 2013). A reduction in PIP and lower supplementary oxygen requirements relative to conventional modes are generally seen during NAVA (Bengtsson & Edberg 2010, Breatnach *et al.* 2010, Liet *et al.* 2011, Piastra *et al.* 2014, Stein *et al.* 2013). We do not have any data on NAVA in pediatric intensive care beyond these findings, and the effects of the above-mentioned changes on clinical outcomes remain to be evaluated. Existing trials reporting experiences with NAVA in pediatric intensive care (excluding case reports and patient series) are summarized in Table 1.

Table 1. Summary of reports on NAVA in pediatric intensive care.

Study	Study design	Ventilation modes	n	Age	Main results	Observations
Bengtsson 2010	Prospective crossover	PS vs NAVA Time on NAVA from 1 to 8 hours	21 (15 post cardiac surgery)	Mean 15.7 mo (2 d to 15 yr)	PIP decreased Neural trigger was first in 68% of breaths and neural cycle off in 88% (Pneumatic trigger and cycle off thresholds not reported)	Edi catheter was easy to place 1 pt had total asynchrony between Edi signal and patient respiratory pattern (malposition of the catheter) 1 catheter did not detect Edi and was replaced
Breatnach 2010	Prospective crossover	PS vs NAVA Time on NAVA 4 hours	16 (11 cardiac pathology)	Mean 9.7 mo (2 d to 4 yr)	PIP decreased Neural trigger was first in 65% of breaths and neural cycle off in 85% (Pneumatic trigger -1 cmH_2O and cycle off 25%)	No adverse events Neural trigger remains viable despite concurrent use of sedative medication
Clement 2011	Prospective randomized crossover	VS vs. NAVA Time on NAVA 12 min (10 breaths analyzed)	23 VS / 19 NAVA (bronchiolitis)	Mean 1.6 mo (SD 1.0 mo)	Neurally triggered breaths have less trigger delay and improved ventilator response times	4 pts at which no Edi signal could be obtained Reduced pressure-time product (PTP) during NAVA might predict decreased work in breathing
Bordessoule 2012	Prospective crossover	NAVA vs. PC vs. PS Time on NAVA 5 hours	10 (General pediatric intensive care patients)	Mean 4.3 mo (3 wk to 7 mo)	Asynchrony index during NAVA 11 %, PC 24% and PS 25% (Pneumatic trigger 0.25l/min, T_{insp} 0.53 s and cycle off 25% in PC and PS)	A large variability in the Edi was seen during all three modes of ventilation but was translated to PIP only during NAVA

Study	Study design	Ventilation modes	n	Age	Main results	Observations
Oliva 2012	Prospective crossover	PS vs. NAVA Time on NAVA 30 min	12 (PICU patients with asynchrony)	Mean 12.5 mo (9 d to 7 yr)	Asynchrony index during NAVA 2.0% and PS 7.5-8.5% Neural trigger was first in 66% of breaths during NAVA (Pneumatic trigger settings were individually optimized)	Breath-to-breath mechanical variability increased during NAVA NAVA reduced the neural drive required to trigger the ventilator NAVA improved patient comfort
Vignaux 2013	Prospective randomized crossover	PS vs. NAVA Time on NAVA 20 min	19 (16 post cardiac surgery)	Median 18 mo (IQR 7.5-34 mo)	Asynchrony index during NAVA 3.8% and PS 29% (Pneumatic trigger settings were individually optimized)	1 pt at which no Edi signal could be obtained despite visible inspiratory efforts
Piastra 2014	Retrospective case-control	PS vs NAVA Time on NAVA 41±17 hours	20 vs 10 (ARDS infants in weaning phase after HFOV)	Mean 8 mo (SD 0.6 mo)	Less increase in mean arterial blood pressure and heart rate in NAVA patients Less decrease in PaO_2/FiO_2 in NAVA group Lower PIP and $PaCO_2$ during NAVA	Improved COMFORT score in NAVA patients Shorter duration of ventilatory support in NAVA patients (PS vs. NAVA), but longer duration of preceding HFOV in NAVA patients

PS = pressure support, NAVA = neurally adjusted ventilatory assist, PC = pressure controlled ventilation, SIMV = synchronized intermittent mandatory ventilation, PIP = peak inspiratory pressure, T_{insp} = inspiratory time

2.9 Sedation

Critical illness and intensive care with several invasive procedures cause fear, anxiety and pain in pediatric patients, and a significant amount of sedation is generally needed and used to relieve these feelings, especially among infants and young children who cannot be comforted verbally (Kudchadkar *et al.* 2014). The increasing evidence on sedation-related adverse events and long-term consequences for neurocognitive development has recently drawn attention to this area of pediatric intensive care. There is an urgent need for evidence-based treatment protocols, and all attempts to improve the quality of care so that less sedatives would be needed are desirable.

2.9.1 Sedative agents

An ideal sedative agent for PICU patients is one that has rapid onset, is effective and short-acting without any accumulation, side effects or drug interactions. As no drug fulfils these criteria, a combination of intravenous opioid and benzodiazepine infusion is generally used to achieve sedation in PICUs (Amigoni *et al.* 2012, Kudchadkar *et al.* 2014, Rhoney & Murry 2002). Midazolam is the most popular, recommended and universally used benzodiazepine, despite the fact that changes in pharmacodynamics and pharmacokinetics with age cause great variability in drug responses in pediatric patients (Amigoni *et al.* 2012, Gast-Bakker *et al.* 2007, Playfor *et al.* 2006, Vet *et al.* 2013). The two most commonly used opioids are morphine and fentanyl, with an increasing trend favouring the latter, although morphine seems to have lower prevalence of withdrawal and less need for dose escalation when used as an infusion (Amigoni *et al.* 2012, Anand *et al.* 2013, Kudchadkar *et al.* 2014).

The two sedatives that have attracted most attention lately have been propofol and dexmedetomidine. Both have rapid onset, a short half-life and clinically relevant benefits as compared with older sedatives. Propofol, 2,6-diisopropylphenol, is generally used for inducing general anaesthesia and as a sedative for mechanically ventilated adult patients, but has not been indicated for prolonged sedation in children after reports of a potentially deadly propofol infusion syndrome (PRIS) in the 1990s (Bray 1998). Even so, it has remained in off-label use due to its attractive pharmacological and clinical profile, and it is currently used in many PICUs with advice to restrict the dose to below 4 mg/kg/h

and the duration of infusion to 48 hours (Cornfield *et al.* 2002, Kruessell *et al.* 2012, Kudchadkar *et al.* 2014, Svensson & Lindberg 2012). Dexmedetomidine is an α-2 adrenergic agonist that induces a form of sedation that bears more similarities to natural sleep than with any other sedative agent (Huupponen *et al.* 2008). This improved adult patients' ability to communicate pain and reduced the duration of mechanical ventilation relative to midazolam (Jakob *et al.* 2012). The minimal respiratory depression involved also makes dexmedetomidine attractive for pediatric sedation, but attention should be paid to its relatively common haemodynamic adverse effects (hypotension and bradycardia) which may have a greater impact on cardiac output in critically ill children than in adults (Carney *et al.* 2013, Hosokawa *et al.* 2010, Tobias & Berkenbosch 2004, Tobias *et al.* 2011).

2.9.2 Optimizing the level of sedation

Sedation-related adverse events are typically associated either with oversedation (prolonged duration of invasive ventilation and hospitalization, extubation failure and withdrawal syndrome) or undersedation (accidental extubation, unintentional removal of catheters, agitation and distress). Startling amounts of oversedation, up to 73% of patients, have been reported from pediatric intensive care units (Kudchadkar *et al.* 2014, Triltsch *et al.* 2005, Vet *et al.* 2013). Several scoring systems for the level of sedation are available but often these are not routinely used, and a wide variety is seen in the 'optimal sedation level' aimed at (Ista *et al.* 2005, Kudchadkar *et al.* 2014, Playfor *et al.* 2006, Vet *et al.* 2013).

Sedation protocols and daily interruption of sedatives have appeared to be beneficial in reducing the amount of sedation both in adults and in pediatric patients (Deeter *et al.* 2011, Verlaat *et al.* 2014). A change in attitudes towards mechanical ventilation and an improved awareness of sedation-related problems are needed among personnel in order to revise sedation practices (Guttormson *et al.* 2010). A prudent use of sedatives together with systematic assessment of the sedation level, evaluation of any withdrawal symptoms and recognition of delirium would be necessary for improving the quality of pediatric intensive care (Fisher *et al.* 2013, Kudchadkar *et al.* 2014, Traube *et al.* 2014).

3 Aims of the research

The aims of the research were as shown in Fig. 4.

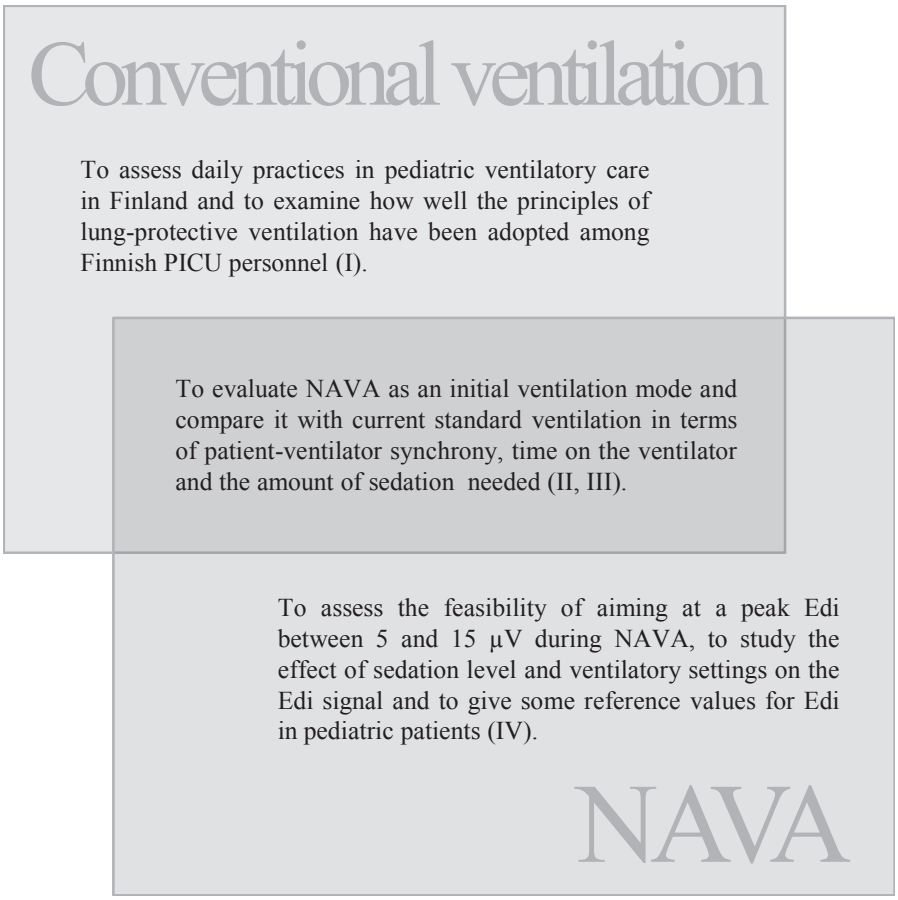

Fig. 4. Aims of the research

4 Materials and methods

4.1 Current trends in pediatric ventilation (I)

A questionnaire including detailed items on ventilation strategies was sent to the leading physician responsible for ventilatory care in every pediatric and neonatal intensive care unit in Finland (11 university hospital units and 14 central hospitals) in March 2010, and 24/25 physicians (96%) returned a completed form.

Based on the results of this enquiry, a 3-month prospective survey lasting from September 13th to December 19th, 2010 was offered to all hospital units providing ventilatory care for children <16 years of age. Seventeen of the eighteen hospitals (94%) joined the survey, and 211 episodes of neonatal and pediatric invasive ventilation were monitored during the follow-up. Demographic data, reasons for respiratory support, previous disease history, ventilatory and clinical parameters, sedation details and the need for re-intubation within 24 hours of extubation were reported for each episode without patient identification.

4.2 NAVA in pediatric ventilation (II-IV)

The previously published proportion of asynchrony, 53.4 ± 26.2% of the total breath duration (Beck *et al.* 2004), was used for estimating the sample size for the patient-ventilator synchrony study (II), and retrospective data on the duration of invasive ventilation at the PICU of Oulu University Hospital (13.0 ± 13.4hr) for the RCT (III). A 50% decrease in the proportion of asynchrony (II) and a 6 hr reduction in time on the ventilator (III) were considered clinically significant. A power of 0.8 and $\alpha = 0.05$ were used in both studies. The calculated sample sizes were 15 patients for the crossover study (II) and 160 (80 patients/group) for the RCT (III). To ensure these numbers in the final analysis, 18 and 170 patients were recruited. These were enrolled at the PICU and NICU of Oulu University Hospital, Finland, from February to May 2009 (II) and from September 2009 to May 2012 (III).

4.2.1 Subjects

Patient-ventilator synchrony (II). Eighteen patients from 30+1 weeks of postconceptional age to 13.8 years of age who needed invasive ventilation were enrolled and studied during the weaning phase of ventilation. Prematurity and neonatal RDS was the reason for ventilation in four cases, postoperative care in nine, neonatal sepsis in one and respiratory infection (RSV bronchiolitis or pneumonia) in four.

NAVA in PICU (III, IV). One hundred and seventy patients ranging from full-term neonates to adolescents aged 16 years who were expected to need invasive ventilation for at least 30 minutes were enrolled in the trial. The majority of these, 131/170 (77%), were ventilated as a part of postoperative intensive care. Respiratory infections, neonatal diseases and trauma or miscellaneous reasons were indications for treatment in 8%, 9% and 5% of cases, respectively. The patients who were randomized to the NAVA group and for whom Edi signal data were available (81/85) were included in the Edi study (IV). A flow chart showing the randomization, treatment and follow-up is provided in Fig. 5.

Critically ill patients with a severe respiratory, haemodynamic or bleeding disorder and patients needing HFOV were excluded from the series. Children with a known defect of the diaphragm and those for whom positioning of the nasogastric or orogastric tube was not possible were also left out.

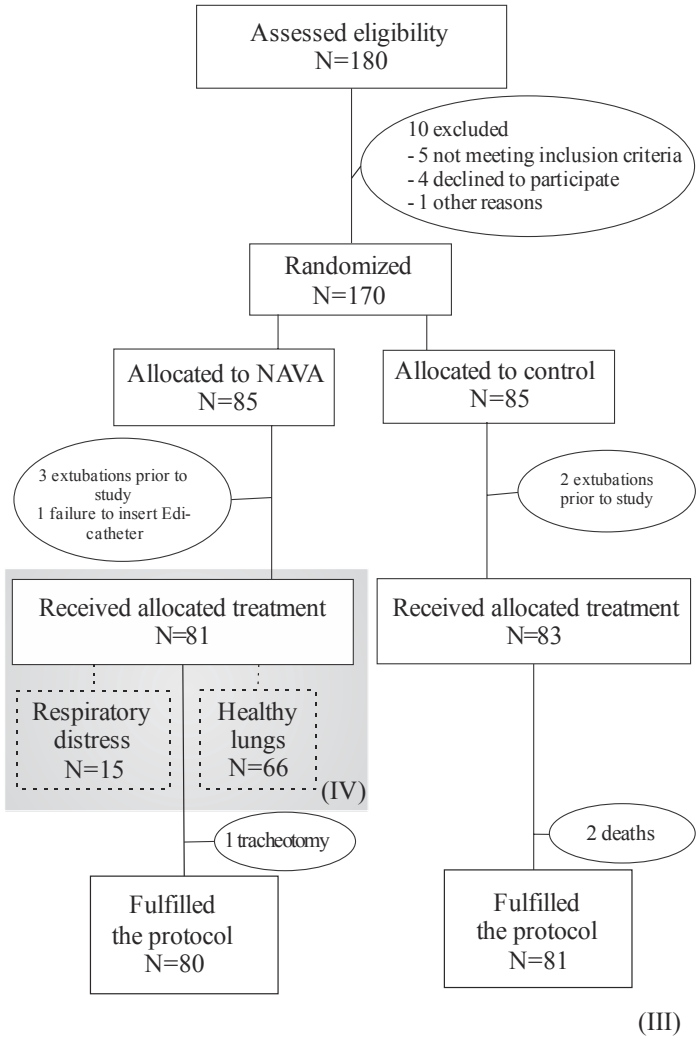

Fig. 5. Flow chart of the patients included in the randomized controlled trial (III) and the Edi study (IV).

4.2.2 Methods

Patient-ventilator synchrony (II)

A crossover setting, in which each patient was ventilated using three trigger modes (flow +5, which is equivalent to 0.25 l/min in infants and 1 l/min in adult

mode, pressure -2 cmH_2O and NAVA, i.e. flow or Edi 0.5μV) for 10 min each in random order without wash-out periods in between, was used. The ventilator settings during the study period were the same as had been determined on a clinical basis prior to the study. Special software designed to collect all the ventilation data from the ventilator (NAVA-tracker, Maquet Nordic, Solna, Sweden) was used for data collection, and data on blood gas values, blood pressure, heart rate and oxygen saturation were obtained before each change in the trigger mode and at the end.

The neural timing of breathing was used to assess patient-ventilator synchrony by means of a specially designed program (graphical user interface [GUI] running in Matlab [MathWorks, Inc], Tuomo Ylinen, Finland), which included pressure, flow and Edi signal curves in one picture frame. Synchrony was defined as 1) simultaneous patient inspiration (increasing Edi-signal) and increasing or steadily high pressure supplied by the ventilator, and 2) patient expiration (decreasing Edi signal) simultaneously with decreasing pressure support from the ventilator. Periods of silent Edi were left out of the analysis, but as the role of the ventilator is to keep the patients alive during long periods of apnoea, the data were also analysed with this time included in the synchrony.

NAVA in PICU (III)

Patients were randomly allocated to the NAVA or control group, and the ventilation mode for the NAVA patients was changed to NAVA as soon as a regular Edi signal was obtained. The level of support was adjusted during NAVA when needed, aiming at peak Edi above 5 μV and below 15 μV. The patients in the control group were ventilated following the lung-protective strategy and current treatment practices in the PICU (i.e. PC for neonates and PRVC for older children) without any strict ventilation protocol related to this study. The extubation criteria in both groups were: normothermia, stable haemodynamics and oxygenation and adequate spontaneous breathing (i.e. frequency >15/min and tidal volume ≥5ml/kg despite reduction in the level of support).

The level of sedation was aimed at four (calm and cooperative) on the Sedation Agitation Scale (SAS) in both groups, with a continuous Edi signal maintained in the NAVA cases. The primary sedative agents were morphine, midazolam and S-ketamine but other sedatives were also used when considered relevant by the responsible clinician. To enable comparison between the sedative agents, a "sedative unit" was determined for each drug as shown in Table 2.

The primary endpoint was time on the ventilator, and secondary endpoints were length of stay in the PICU, sedation level and the amount of sedation needed, ventilatory and vital parameters, arterial blood gas values and complications. Data collection was started on arrival in the PICU in the case of the postoperative patients, and otherwise as soon as written informed consent was obtained from the parents and the Edi catheter could be inserted.

Table 2. Sedative units determined for each drug

Drug	Dose (boluses)	Dose (infusion)	Sedative unit[1]
Midazolam	0.1 mg/kg	0.1-0.4 mg/kg/hr	0.1 mg/kg
Diazepam	0.1-0.2 mg/kg	None	0.133 mg/kg
Propofol	1-3 mg/kg	1-4 mg/kg/hr	1.0 mg/kg
S-Ketamine	1-3 mg/kg	0.5-3.5 mg/kg/hr	0.875 mg/kg
Thiopental	3-7 mg/kg	1-5 mg/kg/hr	1.5 mg/kg
Dexmedetomidine	0.5-1 µg/kg	0.2-0.8 µg/kg/hr	0.5 µg/kg
Phenobarbital	Loading 20 mg/kg maintenance 3-6 mg/kg/d	None	4 mg/kg

[1]A sedative unit was calculated to correspond to one-fourth of the maximal infusion dose per hour. For drugs in which this size of unit differed clearly from the bolus instructions (thiopental and dexmedetomidine), the size of the unit was adjusted upwards. The sedative unit of diazepam was determined to be equivalent to that of midazolam, and that of phenobarbital corresponded to a typical daily dose used during the maintenance treatment.

Edi during NAVA in children (IV)

An observational study of the Edi signal during NAVA was conducted as a part of the RCT. A comparison of ventilatory parameters and Edi values was performed between the respiratory distress patients and those being ventilated as a part of postoperative care, without respiratory distress or lung disease. The effects of age, sedation level, PEEP, NAVA level, extubation and the level of blood gas carbon dioxide on Edi were studied.

4.3 Statistical methods (I-IV)

SPSS Statistics, versions 18-21, were used for data analysis. Longitudinal changes in the ventilator parameters between hospital units (I) and the effect of

trigger mode order and differences in variable means between trigger modes (II) were compared using a repeated measures analysis of variance. When sphericity was violated, the degrees of freedom were subjected to the Greenhouse-Geisser correction, while Bonferroni adjustment was used for post hoc pairwise comparisons (II).

In the RCT (III) the data were analysed on an intention-to-treat basis, Student's t-test being used to compare the group means for the amount of sedation and the chi-square test to compare the numbers of complications. Kaplan-Meier curves were plotted for the time on the ventilator and the length of stay in PICU, and the Log Rank test was used to evaluate the survival distributions between the groups. A split plot design was used to evaluate the effect of ventilation mode on the ventilatory and vital parameters (III) and the effect of underlying lung condition on the Edi signal (IV) in case of repeated measurements. The ventilation mode (III) and respiratory status (IV) were considered to represent the whole plot intervention and the subject within the whole plot was used as a replication term for testing the effects of the intervention.

Linear mixed model analysis with a compound-symmetry covariance structure was used for testing the effects of sedation level, age, PEEP, NAVA level and blood gas carbon dioxide on the Edi signal, and Student's t-test to compare the group means for the ventilatory parameters between the respiratory distress patients and those with healthy lungs during the three treatment phases (start, before extubation and after extubation) in the Edi study (IV).

4.4 Ethical issues

The study protocols were approved by the ethical committee of the Northern Ostrobothnia Health Care District. There was no need for informed consent in the follow-up study (I) due to the quality control nature of the surveys and the anonymity of the patients. For the other studies, written informed consent was obtained from a parent or legal guardian before performing any procedures related to this research.

5 Results

5.1 Current trends in pediatric ventilation (I)

An average of 2.3 invasive ventilation episodes per day were observed during the 3-month follow-up, 179 (85%) at the university hospitals and 32 (15%) at the central hospitals. 115 (55%) periods took place in NICUs, 71 (34%) in PICUs and 25 (12%) in adult ICUs.

5.1.1 Reasons for invasive ventilation

Pulmonary problems (64%) were the most common indications for invasive ventilation in neonates, with RDS alone accounting for over 40% of the neonatal episodes. Older children were ventilated as a part of postoperative care in 68% of cases (Fig. 6). The neonates treated in the PICUs were mainly postoperative patients (27%), but there were also patients suffering from meconium aspiration, persistent pulmonary hypertension, RDS or pulmonary adaptation failure. Neurosurgical postoperative care, major trauma and postresuscitation status were the main reasons for treating pediatric patients in an adult ICU.

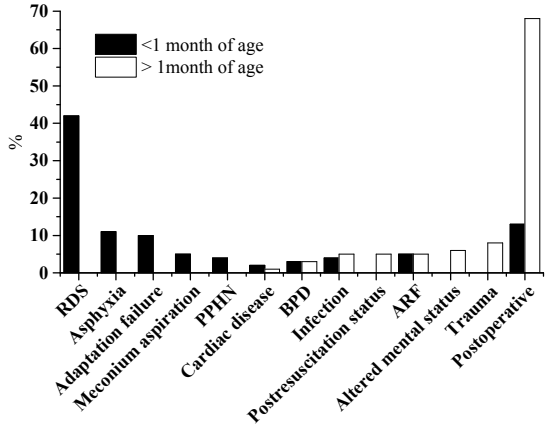

Fig. 6. Reasons for invasive ventilation during the prospective survey (I). RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the newborn; BPD, bronchopulmonary dysplasia; ARF, acute respiratory failure.

5.1.2 Lung-protective ventilation

All the clinicians were agreed on the basic principles of lung-protective ventilation, such as support for spontaneous breathing and routine use of adequate, individually set PEEP (Fig. 7).

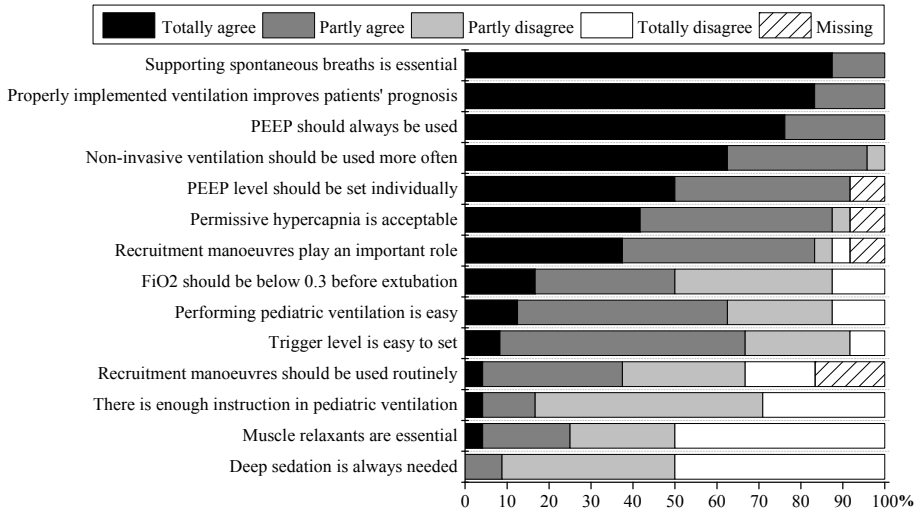

Fig. 7. Results of the questionnaire on pediatric ventilation

Tidal volume and airway pressure

Fifteen physicians (62%) reported that they monitor tidal volumes during invasive ventilation, 14 of them aiming at 5-7 ml/kg. Tidal volumes during the prospective survey were 6.5 ± 3.8 ml/kg (mean ± SD) in neonates and 7.1 ± 1.5 ml/kg in older children.

An acceptable PIP for a newborn infant was considered to be between 15 and 30 cmH_2O (mean 22.5 cmH_2O) and under special circumstances 22-40 cmH_2O (mean 28.8 cmH_2O). For a 5-year-old patient a PIP from 20 to 35 cmH_2O (mean 25.5 cmH_2O) or 25-35 cmH_2O (mean 31.0 cmH_2O) under special circumstances was thought acceptable. The mean PIP during the prospective survey was 18.3 ± 3.6 cmH_2O and 19.2 ± 4.7 cmH_2O in neonates and older children, respectively.

Positive end-expiratory pressure

All the respondents reported using PEEP during invasive ventilation, its initial level varying from 4 to 6 cmH_2O (4.7 ± 0.6 cmH_2O). The reasons reported for adjusting the level of PEEP were a change in lung compliance (71%), hypoxia (71%), hypercapnia (54%), hypocapnia (42%) and thorax x-ray findings (33%). Two respondents (8%) replied that they had never changed the level of PEEP.

PEEP of 4.8 ± 0.9 cmH_2O was used for neonates and 4.9 ± 0.7 cmH_2O for older children during the prospective survey. The level of PEEP was kept relatively constant through the episodes.

Gas exchange

Permissive hypercapnia was generally considered acceptable (Fig. 7), but normocapnia was maintained during the survey, the arterial blood gas CO_2 tension being 5.8 ± 1.3 kPa in neonates and 5.6 ± 1.2 kPa in older children. Several occasions of hyperventilation were observed and the cumulative number of arterial blood gas CO_2 tensions below 3.5 kPa in the 211 ventilation episodes was 54.

The use of inspired oxygen for neonatal ventilation was more liberal in the central hospitals than in the university hospitals, but this did not lead to any significant differences in arterial pO_2 levels. The high fraction of inspired oxygen used for pediatric cases in the adult ICUs frequently caused hyperoxia, while normoxia was maintained better in the PICUs.

5.1.3 Ventilation modes

Virtually all the ventilation modes chosen included some kind of patient triggering and support for spontaneous breathing. The primary ventilation mode in nearly a half of the cases among both neonates and older children was synchronized intermittent mandatory ventilation with pressure support (SIMV+PS). Time-cycled pressure-limited ventilation was extensively used in the neonates and time-cycled volume-limited ventilation among older children.

Only one ventilation mode was used in 73% of the episodes, two in 24% and three or more in 3%. If the ventilation mode was changed during treatment, the secondary modes used were typically either NAVA (27%) or HFOV (20%). ECMO was used once.

5.1.4 Patient-ventilator synchrony

All the respondents agreed that support for spontaneous breathing is essential during invasive ventilation, but 33% considered it hard to optimize the inspiratory trigger level. Autotriggering in particular was frequently mentioned as a problem.

The inspiratory trigger threshold was reported for 52% of the ventilation episodes during the prospective survey. A flow trigger was used in 83% of cases, pressure trigger in 13% and Edi in 4%.

The preset breathing frequency was 37.4 ± 10.0 per minute for neonates and 26.7 ± 11.9 for older children, but the observed frequencies were higher, 52.6 ± 14.0 in neonates and 31.3 ± 12.6 among older children.

5.1.5 Time on the ventilator

The duration of invasive ventilation in the majority of the cases in both pediatric and neonatal intensive care was short, but a small proportion of patients required a very long period of respiratory support. The median time on the ventilator during the 3-month prospective survey was 20.1 hours and 13.8 hours in the neonates and older children, respectively, and the longest reported treatment period was 1418 hours (59 days).

Twelve patients (5.7%) were transferred to another hospital after starting the invasive ventilation. Mechanical ventilation discontinued upon death six times (2.8%) and on account of accidental extubation in four cases (1.9%). On 13 occasions (6.2%) reintubation was needed within 24 hr of extubation.

5.1.6 Sedation

Sixty-five per cent of the neonates were reported to be fully awake during mechanical ventilation, 30% lightly sedated and 6% heavily sedated. Opiates were the primary choice for analgesia and sedation, being used in 81% of episodes. The most commonly used sedative, in 10% of episodes, was midazolam. Ketamine, phenobarbital, thiopental and dexmedetomidine were only occasionally used.

Of the older children, 69% were lightly and 21% deeply sedated, and the remaining 10% were reported to have been fully awake during ventilation. First-line medications differed depending on the unit. One PICU preferred midazolam and morphine, and another dexmedetomidine and oxycodone. Although propofol

was only occasionally used in the PICUs, it was often the first line of medication in the adult ICUs.

5.2 NAVA in pediatric ventilation (II-IV)

5.2.1 Lung-protective ventilation (II-IV)

Tidal volume and airway pressure

Lower PIPs were seen during NAVA than in conventional ventilation in both the patient-ventilator synchrony study (II) and the RCT (III), the latter as shown in Fig. 8, but tidal volumes did not differ between NAVA and conventional ventilation (II, III). Smaller tidal volumes (4.6 ± 1.8 ml/kg vs. 6.2 ± 2.3 ml/kg) prior to extubation were found during NAVA ventilation in the respiratory distress patients than in those with healthy lungs (IV).

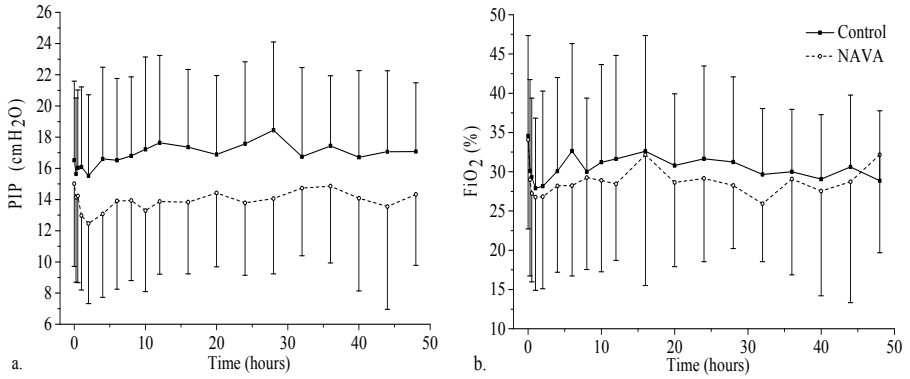

Fig. 8. Comparison of the peak inspiratory pressure (a) and inspired oxygen fraction (b) between the control and NAVA groups (III). P = 0.001 for both. Mean ± SD is presented at each point in time.

Positive end-expiratory pressure

The level of PEEP was kept constant during the patient-ventilator synchrony study (II) and was similar between the NAVA and control groups in the RCT (III). Within the NAVA group, higher preset levels of PEEP were used for the respiratory distress patients than for the patients with healthy lungs (Fig. 9) (IV).

Gas exchange

Stable blood gas values were seen in all phases of the patient-ventilator synchrony study (II), but a lower fraction of inspired oxygen (Fig. 8) and an improved oxygenation index were found in the NAVA patients in the RCT (III). Within the NAVA group, arterial blood oxygen tension was significantly higher in the patients with healthy lungs than in the respiratory distress cases in all phases of the treatment (IV).

A statistically significant difference in arterial blood gas CO_2 tension was seen between the NAVA and control groups, with higher levels in the NAVA group at the beginning of the treatment and lower after 32 hours of treatment (III). Slightly higher CO_2 tension was found in the respiratory distress patients within the NAVA group at the beginning of the treatment, but normocapnia was equally well maintained before and after extubation as compared with the patients with healthy lungs (IV).

5.2.2 Patient-ventilator synchrony (II)

The proportion of time in asynchrony during NAVA was 8.8%, while higher proportions, 33.4% and 30.8%, were found during pressure and flow triggering, respectively ($P < 0.001$ for both). Visual evaluation of the pressure, flow and Edi curves showed NAVA to be more accurate in both the initiation and termination of ventilatory support for each breath cycle.

A higher proportion of time without spontaneous respiratory efforts was seen in conventional ventilation with both pressure and flow triggering (8.1% and 12.2%, respectively) than in NAVA (1.3%). Four patients altogether (21%) had long periods of absent Edi (over 100 sec/600 sec), one in pressure triggering, one in flow triggering and two in both pressure and flow triggering, but none in NAVA. The low Edi was associated with deep sedation in the postoperative period in two patients and with probable over-assistance during conventional ventilation in the other two.

5.2.3 Electrical activity of the diaphragm (IV)

Higher peak Edi values were found in the respiratory distress patients in all three treatment phases, the difference being two to three-fold relative to the patients

with healthy lungs. The peak post-extubation Edi levels of the respiratory distress patients and patients with healthy lungs were 20 ± 14 and 9 ± 7μV, respectively.

Roughly two-fold higher NAVA levels, up to 4.0 $cmH_2O/\mu V$, were used for the patients with respiratory distress than for those with healthy lungs at the beginning of ventilation, and the difference remained significant throughout the treatment (Fig. 9). The mean NAVA level had decreased to 0.7 $cmH_2O/\mu V$ in both groups just prior to extubation. Higher preset levels of PEEP were used for the respiratory distress patients than for the patients with healthy lungs, and a higher Edi min was found in the respiratory distress cases (Fig. 9).

A lighter level of sedation (higher SAS) and younger age were associated with higher Edi in the linear mixed model analysis, but neither the effect of NAVA level nor that of the preset level of PEEP was statistically significant. Two out of three patients for whom extubation failed had an atypical Edi pattern prior to extubation.

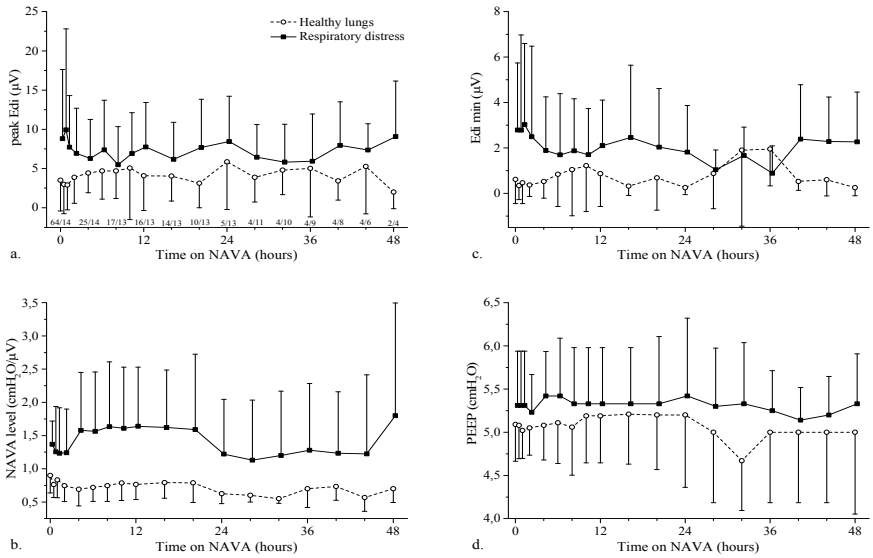

Fig. 9. Electrical activity of the diaphragm, NAVA levels and preset PEEP during invasive ventilation in patients with either healthy lungs or respiratory distress (mean ± SD). The peak Edi (a) in the patients with or without respiratory distress did not differ significantly (P = 0.07), provided that higher NAVA levels (b) were used for the respiratory distress patients (P < 0.001). The Edi min values (c) were higher in the respiratory distress patients (P = 0.01), and their preset levels of PEEP (d) were also higher (P = 0.02). The numbers of patients in each group at each point in time are presented in panel a (Healthy lungs/Respiratory distress).

5.2.4 Time on the ventilator (III)

Cumulative extubation rates calculated by the Kaplan-Meier method showed no difference in the duration of ventilation (Fig. 10). The duration of invasive ventilation prior to the trial was similar in both groups (4.7 hr and 5.2 hr in NAVA and control patients, respectively).

Accidental extubation occurred once in the NAVA group and twice in the control group, and three patients in the former and four in the latter required reintubation within 24 hr of extubation. Similarly, the total number of treatment complications did not differ between the groups.

The median length of stay in the PICU was 49.5 hours in the NAVA group and 72.8 hours in the control group (Fig. 10). Per protocol analysis showed the length of stay in the PICU to have been significantly shorter in the NAVA group.

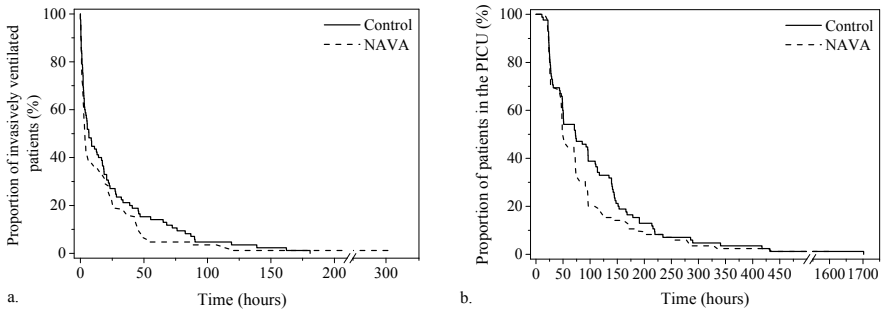

Fig. 10. (a) Effect of ventilation mode on the proportion of invasively ventilated patients over time. Time on the ventilator after inclusion in the trial is presented. Log Rank P=0.17 (per protocol P=0.07). (b) Length of stay in the PICU. Log Rank P=0.10 (per protocol 0.03).

5.2.5 Sedation (III)

The level of sedation as assessed with SAS was similar for the NAVA and control groups. The amount of sedation used in the NAVA group was 1.42 units/hr, compared with 1.81 units/hr in the control group (Table 3). The three most commonly used sedatives apart from opiates were midazolam, S-ketamine and dexmedetomidine. When the groups were compared regarding the use of these drugs, no statistically significant differences were found (P = 0.18, 0.21 and 0.55, respectively).

When the postoperative patients were excluded, the amount of sedation needed was significantly lower in the NAVA group, but there were no significant differences between the groups in the use of opiates (Table 3).

Two patients in the control group accidentally received more sedative medication than planned, whereas there were no dosage errors in the NAVA group. Exclusion of these two patients from the data analysis had no effect on the group means.

Table 3. Amounts of sedatives used during the trial

Group of the patients		NAVA Mean (SD)	Control Mean (SD)	Difference of the means	95% CI	P-value[1]
All patients	N	85	85			
Sedation units per hour		1.42 (1.76)	1.81 (2.16)	-0.39	-1.00 to 0.21	0.20
Amount of opiates per hour[2]		0.048 (0.061)	0.057 (0.079)	-0.009	-0.031 to 0.012	0.39
Postoperative patients	n	66	65			
Sedation units per hour		1.58 (1.85)	1.68 (2.03)	-0.10	-0.78 to 0.58	0.77
Amount of opiates per hour[2]		0.052 (0.067)	0.065 (0.088)	-0.013	-0.040 to 0.015	0.36
Postoperative patients excluded	n	19	20			
Sedation units per hour		0.80 (1.16)	2.23 (2.54)	-1.43	-2.79 to -0.07	0.03
Amount of opiates per hour[2]		0.030 (0.022)	0.032 (0.030)	-0.002	-0.020 to 0.015	0.78

[1]Independent samples t-test
[2]Morphine equianalgesic dose (mg) per weight (kg)

6 Discussion

6.1 Centralization of pediatric ventilation

The pediatric intensive care patient population is small and heterogeneous. Only approximately 2.3 new ventilation episodes were started per day during the prospective survey period, and even in the university hospitals a new ventilation episode was commenced only once a day or every second day. In the central hospitals new cases of pediatric invasive ventilation occurred at rates of zero to five per 3 months of follow up. Such a very low incidence favours centralization of invasive ventilation for children to larger units.

Higher mortality in mechanical ventilation and intensive care has been reported at units with small numbers of patients, in both the pediatric and the adult field (Kahn *et al.* 2006, Kahn *et al.* 2009, Pearson *et al.* 1997, Pearson *et al.* 2001, Tilford *et al.* 2000). However, equally low ICU mortality in children was found in adult ICUs and PICUs in Sweden (Gullberg *et al.* 2008). Simply a large number of patients does not guarantee the quality of care, and a lack of any volume-outcome relation has also been repeatedly reported in adult intensive care (Gopal *et al.* 2011, Moran *et al.* 2012, Needham *et al.* 2006, Shahin *et al.* 2012). Finland is sparsely populated and distances between secondary and tertiary care units are long, so that ventilation quite often has to be started outside the university hospitals. Thus every pediatrician and anaesthesiologist must have the basic skills and knowledge required for neonatal and pediatric ventilation and a proper patient transport system is needed (Ramnarayan *et al.* 2010).

6.2 Lung-protective ventilation

Although wide ranges of machinery and ventilatory strategies were used in Finnish intensive care units, most of the 211 episodes recorded during the prospective survey followed the principles of lung-protective ventilation. As recommended, the tidal volumes were kept small and a sufficient PEEP, from 4.3 to 5.2 cmH_2O, was used. Equal levels of PEEP have been reported in European NICUs (Kaam *et al.* 2010). In most cases hyperoxia and hypocapnia were successfully avoided, and spontaneous breathing was maintained and supported.

Despite recommendations to avoid hyperoxia (Randolph 2009), fairly high concentrations of FiO_2 were frequently supplied to children, especially in the

central hospitals and adult ICUs. This liberal use of oxygen often led to hyperoxia in the adult ICUs, but no corresponding situation was seen in connection with neonatal ventilation in the central hospitals, possibly because of the incomplete data on arterial blood gas readings obtained from the latter. It can be speculated that neonates having an arterial line had a stricter oxygen supply. Although permissive hypercapnia was considered acceptable by all respondents, the patients were generally normocapnic during the prospective survey and hypocapnia was seen repeatedly. Hypocapnia reduces cerebral blood flow significantly and may lead to ischaemic injury, infarctation or intracerebral haemorrhage (Caulfield *et al.* 2009, Curley *et al.* 2011, Fortune *et al.* 1995, Laffey & Kavanagh 2002). It also increases the risk of ventilator-induced lung injury and reduces perfusion to several other organs, including the heart (Barker *et al.* 1991, Fujita *et al.* 1989, Kazmaier *et al.* 1998, Laffey & Kavanagh 2002). Thus care should also be taken to avoid accidental hypocapnia.

We found that NAVA ventilation resulted in improved patient-ventilator synchrony, lower PIP and inspired oxygen fraction with an improved oxygenation index and no significant differences in oxygen saturation. Thus the children ventilated with NAVA were equally able to transfer oxygen to their tissues, while their lungs may have been less stressed. These findings are in line with earlier publications based on selected small groups of patients of various ages (Bengtsson & Edberg 2010, Bordessoule *et al.* 2012, Breatnach *et al.* 2010, Coisel *et al.* 2010, Stein *et al.* 2013). The slightly higher levels of CO_2 tension among the NAVA patients up to 32 hours of treatment indicate a lower risk of hypocapnia, which was surprisingly common during the prospective survey. Higher breathing frequencies and smaller tidal volumes during NAVA were found in the patients suffering from respiratory distress, which emphasizes the capacity of NAVA to follow rapid physiological changes in breathing pattern following changes in lung compliance. In the light of our results, we succeeded in achieving the goals of lung-protective ventilation better with NAVA than with conventional modes. Whether this is of clinical importance needs further research.

6.3 NAVA in clinical practice

NAVA proved to be a safe and feasible primary ventilation mode for most general PICU patients. The strategy of adjusting the level of support with the goal for peak Edi set at 5-15 μV during invasive ventilation was successful in our patients. This relatively wide range allowed patients in different clinical situations to be

ventilated with relatively stable NAVA levels. It has been suggested that the goal during NAVA should be set at the level observed in healthy patients, especially in newborn infants (Stein & Firestone 2014, Stein *et al.* 2012b). Our results are in line with this ideology, as the postextubation Edi values found in the patients with healthy lungs (9 ± 7μV) were very close to the goal we used during invasive ventilation (5-15μV).

Higher Edi values were found in the respiratory distress patients throughout the treatment, with postextubation values of 20 ± 14 μV. Thus there might be a risk of over-assistance and prolongation of treatment if the goal for peak Edi in this group of patients is set too low. Higher levels of Edi during NAVA in patients recovering from respiratory distress may be acceptable if there is no continuous increase in the Edi, the respiratory rate is reasonable and the patient's comfort is monitored closely. Daily spontaneous breathing trials during invasive ventilation might serve as a means of estimating the acceptable Edi level in pediatric patients, too (Brander *et al.* 2009, Roze *et al.* 2011). A knowledge of the Edi values and breathing patterns in different patient groups is essential for using NAVA safely and effectively in clinical practice.

Several factors apart from the respiratory drive, such as pain, agitation and crying, can increase the Edi signal, and two out of three extubation failures in our patient series could perhaps have been prevented if the Edi information had been better understood. According to our findings and experience, a very high Edi that is unresponsive to marked changes in the NAVA level should be regarded as a warning of possible failure in adapting to NAVA, and other ventilatory strategies such as controlled ventilation with adequate sedation should be considered for these patients at the acute phase of their illness.

The time on the ventilator did not differ between the patients ventilated with NAVA and those receiving conventional ventilation. Patients recovering from surgery and needing ventilatory support only for a short time formed the main part of the series, and the time of extubation in these children was evidently determined by the clearance of the sedatives given during the operation, so that the type of ventilation probably played no more than a minor role in this timing.

6.4 Sedation

Most neonates were reported to have been fully awake during mechanical ventilation, and 79% of the older children needed only light sedation. A large proportion of all neonates received no sedative agents at all, and analgesia was

achieved using paracetamol alone. These findings are in line with current recommendations, since the routine use of opioids during neonatal ventilation is not recommended because of their possible detrimental effects, but opiates used selectively as primary rescue medication have advantages over sedatives such as midazolam (Anand *et al.* 2013, Bellu *et al.* 2010).

There are marked differences in the use of sedative agents between the units treating older children, indicating the effect of local routines on treatment and the lack of high-quality evidence to guide clinical practice (Hartman *et al.* 2009, Kudchadkar *et al.* 2014). The use of new sedative agents such as dexmedetomidine may enable invasive ventilation to be carried out on ostensibly alert patients, which may partly explain why 10% of the invasively ventilated older children during our prospective survey were reported to have been fully awake (Huupponen *et al.* 2008, Jakob *et al.* 2012).

The level of sedation was similar between the NAVA and control groups in the RCT when assessed on the sedation-agitation-scale, and the amount of sedatives required to reach SAS 3-4 did not differ significantly between them. Among the children without any preceding surgical anaesthesia, however, the amount of sedatives used was lower in the NAVA group, which is a clinically relevant finding. The key to the lower and more accurate dosage of sedatives among patients in the NAVA group lay in the Edi signal, which is a direct measure of the patient's breathing drive and a valuable tool for assessing the level of sedation. When the Edi signal was maintained with a relatively low dose of sedatives, the children were still no more agitated than otherwise. NAVA has been reported to improve patient comfort in pediatric intensive care (Oliva *et al.* 2012), and according to our results, it also has the potential to reduce the need for sedatives without increasing sedation-related complications. Monitoring the Edi signal may diminish the risk of an overdose of sedatives.

6.5 Methodological aspects

Pediatric intensive care patients show wide variation in age, size and clinical diagnosis. Pulmonary problems were the most common causes of invasive ventilation in neonates and postoperative care in older children during the prospective survey. We wanted to study the feasibility of NAVA in a general PICU and succeeded well, ending up with a highly heterogeneous series of patients, which might have partly obscured possible differences between the ventilation modes. Nevertheless, this represents the group of patients that pediatric

intensivists usually face, and we thus believe that our results are well applicable to most general PICU situations.

There were some limitations inherent in our protocols. The prospective survey was based on voluntary reporting from each centre, it was carried out on a quality control basis and the follow-up time was relatively short. We believe, however, that most of the personnel were motivated to participate in this study as a means of working towards better ventilation practices and, despite the relatively low number of treatment episodes per unit, our results represent current treatment practises in Finland. However, as all pediatric cardiac surgery in Finland is centralized in the fifth university hospital that did not join the follow-up, this special group of patients was excluded from the survey and the special nuances of their ventilatory care could not be taken into account.

We wanted to compare NAVA with current standard modes of ventilation, and ended up comparing two assist-control ventilation modes with a fixed inspiratory time (PC in neonates and PRVC in older children) with NAVA, which allows physiological variation in inspiratory time from breath to breath. This methodological difference may explain some of the findings, especially in connection with improved patient-ventilator synchrony. We studied synchrony as a perfect neuromechanical coupling between the patient and the machine, and aimed at evaluating it as accurately as possible by reference to the Edi signal. The number of clinically significant asynchrony events was not assessed in any other way. This aspect may have highlighted the superiority of NAVA, and it remains to be seen what will be the long-term clinical benefits of achieving this kind of "perfect" synchrony. Even so, 33% of the respondents in the survey considered it hard to optimize the inspiratory trigger level, and the inspiratory trigger threshold was reported in only 52% of the ventilation episodes, which clearly emphasizes the clinical challenge entailed in optimizing synchronized ventilation. Technology that is able to support the patient's spontaneous breathing in detail is needed, especially in the case of neonatal and pediatric patients, since their high respiratory rate, small tidal volumes and gas leak from the circuit impair the accuracy of pneumatic triggers (Bernstein *et al.* 1995, Bordessoule *et al.* 2012).

The non-blinded nature of the RCT could have led to decisions favouring the initial hypothesis of a shortening of the time on the ventilator and a lowering of the dose of sedatives in the NAVA group. However, blinding was not an option in the current case, since concealing the patient's breathing patterns and ventilatory settings from the responsible physicians would pose a serious danger for the patient. We believe that the lack of blinding has not affected the main results to

any marked degree, as there were equally low numbers of reintubations in both groups, indicating the correct timing of extubation, and we also observed equal SAS scores in both groups, indicating similar levels of sedation.

The desire to assess the total amount of sedation led us to define a "sedative unit". One may argue that the doses chosen are not unequivocal, as dosing recommendations vary between units and each drug has its own distinctive pharmacodynamics. Anyhow, since sedation is often administered using more than one drug and no drug is superior in all aspects, we had to accept the use of different sedatives during the trial, so that the only means of measuring and comparing the cumulative amount of sedatives used during each treatment episode was by creating a sedative unit.

7 Conclusions

- ✓ The principle of lung-protective ventilation with small tidal volumes, sufficient PEEP and support for the patient's spontaneous breathing is commonly accepted, and these goals are generally achieved, despite quite a wide variation in machinery and daily practices. More attention should be paid to avoiding hypocapnia.
- ✓ NAVA is a safe and feasible primary ventilation mode for use in pediatric intensive care. It improves patient-ventilator synchrony and reduces the need for sedation in patients requiring longer periods of invasive ventilation. It also improves oxygenation, even with lower airway pressures, but has no effect on the duration of invasive ventilation in mainly postoperative PICU patients.
- ✓ Optimizing the level of support during NAVA by aiming at a peak Edi between 5 and 15 μV is an applicable strategy in pediatric ventilation. Post-extubation levels of peak Edi in patients recovering from respiratory distress are higher than in patients with healthy lungs (20 ± 14μV and 9 ± 7μV, respectively).
- ✓ Continuous information on spontaneous breathing provided by the Edi signal enables more accurate adjustment of sedation and may thus improve patient safety. The information revealed by the Edi signal may also be used to identify patients with a potential risk of extubation failure.
- ✓ The low incidence of pediatric invasive ventilation favours centralization of these facilities.

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List of original publications

I. Ålander M, Peltoniemi O, Saarela T, Anttila E, Pokka T & Kontiokari T (2013) Current trends in paediatric and neonatal ventilatory care - a nationwide survey. Acta Paediatr 102(2): 123–128.

II. Ålander M, Peltoniemi O, Pokka T & Kontiokari T (2012) Comparison of pressure-, flow- and NAVA-triggering in pediatric and neonatal ventilatory care. Pediatr Pulmonol 47(1): 76–83.

III. Kallio M, Peltoniemi O, Anttila E, Pokka T & Kontiokari T (2014) Neurally adjusted ventilatory assist (NAVA) in pediatric intensive care. Pediatr Pulmonol. In press

IV. Kallio M, Peltoniemi O, Anttila E, Jounio U, Pokka T & Kontiokari T (2014) Electrical activity of the diaphragm during neurally adjusted ventilatory assist in pediatric patients. Pediatr Pulmonol. In press

Original publications are not included in the electronic version of the dissertation.

1253. Kaikkonen, Leena (2014) p38 mitogen-activated protein kinase and transcription factor GATA-4 in the regulation of cardiomyocyte function

1254. Finnilä, Mikko A. J. (2014) Bone toxicity of persistent organic pollutants

1255. Starck, Tuomo (2014) Dimensionality, noise separation and full frequency band perspectives of ICA in resting state fMRI : investigations into ICA in resting state fMRI

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