Analysis of trials comparing High Frequency Ventilation with Conventional Mechanical Ventilation

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Contents

Chapter 1

Introduction

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Introduction

High frequency ventilation is a relatively new technique to ventilate patients. Based on experimental evidence it was postulated that high frequency ventilation compared with conventional mechanical ventilation would result in a more favorable clinical outcome. In this thesis the clinical evidence for this supposition is examined.

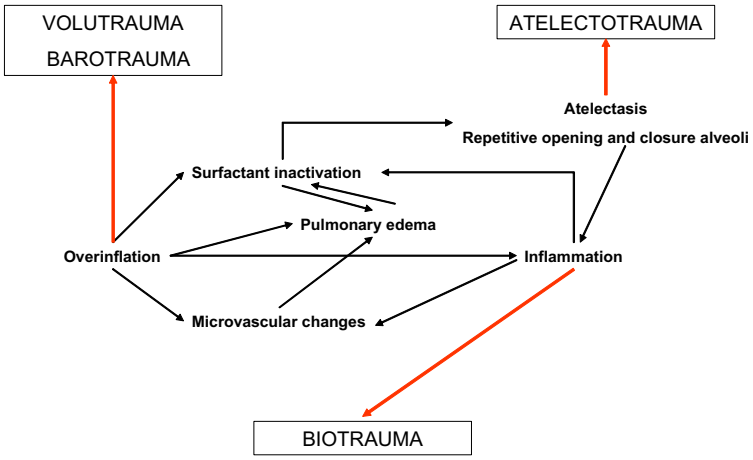
Mechanical ventilation and lung injury

One of the main treatment principles in medicine is 'primum non nocere'. Mechanical ventilation is a basic and commonly applied life supporting modality in neonatal, pediatric and adult intensive care. Mechanical ventilation is not a treatment in the sense that application of mechanical ventilation will cure pulmonary disease, but has to be regarded as a bridge to recovery. A prime requisite to initiate mechanical ventilation should be that the underlying cause of respiratory insufficiency is curable. The purposes of mechanical ventilation, supplying oxygen and removing carbon dioxide, have to be combined with prevention of side effects. The growing recognition that mechanical ventilation in itself can be an independent cause of pulmonary disease puts the principle of primere non nocere at an even more prominent level [1;2].

One of the most important deleterious side effects of mechanical ventilation has been designated as Ventilator Induced Lung Injury (VILI) [3;4]. VILI is a concept that has been extensively investigated in experimental studies [3]. It represents a complex disorder that is caused by a number of factors. The main explanatory mechanisms consist of barotrauma or more importantly volutrauma, atelectotrauma and biotrauma (Figure 1) [3;5-7].

Historically, attention was focused on clinically apparent barotrauma, represented by air leak syndromes [8]. Webb et al. were the first to demonstrate experimental evidence that high airway pressures alone could lead to increased capillary permeability, non-hydrostatic pulmonary edema and tissue damage in rats subjected to positive pressure ventilation [9]. Subsequent studies showed that ventilation with large tidal volumes had more impact on the occurrence of VILI than high airway pressure on itself [10-12]. Therefore, it has been advocated to replace the term 'barotrauma' by 'volutrauma' [6]. The basic premise is that high tidal volumes (volutrauma) cause overdistension of the lungs which is associated with increased capillary permeability, pulmonary edema and histological damage [11;13-16]. Another putative mechanism causing VILI is the concept of 'atelectotrauma' [3]. In the same study by Webb et al., that showed VILI as a result of high airway pressures, a protective effect was found of positive end expiratory pressure (PEEP) as compared with zero end expiratory pressure [9]. Atelectotrauma is thought to be caused by repetitive opening and closing of alveoli resulting in shear stress and mechanical damage, especially in diseased parts of the lungs [17-19]. Overdistension of compliant alveoli in the healthy parts of the lungs can cause additional damage (volutrauma) [20]. Finally, prolonged injurious ventilation results in microscopic abnormalities with inflammatory infiltrates that are indistinguishable from Acute Respiratory Distress Syndrome (ARDS) in humans [21;22]. Experimental studies showed a distinctive effect of ventilatory strategies on cytokine concentrations in lung lavage of isolated unperfused rat lungs [23]. The more harmful ventilatory strategies were associated with major increases in cytokine concentrations. The term biotrauma has been coined to describe potentially injurious local and systemic inflammatory response to physical stress [24;25]. Putting it all together, the sequence of events resulting in VILI can be described as depicted in Figure 1.

Figure 1



Pathogenesis of Ventilator Induced Lung Injury. During mechanical ventilation lung tissue may be damaged by several mechanisms, classified as volutrauma, barotrauma, atelectotrauma and biotrauma. There is a reinforcing interaction between the different mechanisms leading to a number of viscious circles. See text for further explanation.

Volutrauma on the one side and atelectotrauma on the other side result in surfactant inactivation, pulmonary edema and tissue damage. Pulmonary edema fluid inhibits surfactant activity [26]. Moreover, alveolar distension and repetitive opening and closing of alveoli causes inflammation, further aggravating pulmonary edema and tissue damage. Thus, a number of vicious circles ensue.

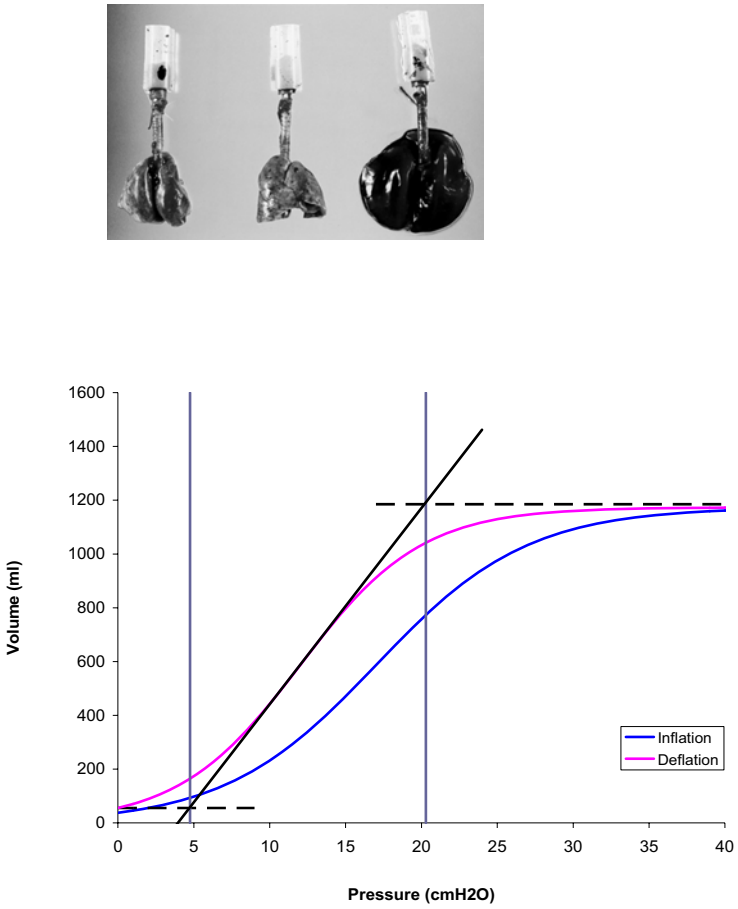
The possibility that mechanical ventilation can actually worsen acute lung disease is now widely accepted [7]. The clinical counterpart of VILI has been described as Ventilator Associated Lung Injury (VALI) [27;28]. VALI has been implicated in the causation of Acute Lung Injury (ALI) and subsequently ARDS [29]. ALI and ARDS are both clinical entities that are diagnosed exclusively by definition [30]. ALI has been defined as acute onset of bilateral infiltrates on chest radiograph and a ratio of partial pressure of arterial oxygen (PaO2) divided by fraction of inspired oxygen (FiO2) of

less than 300 without evidence of left ventricular heart failure. ARDS uses the same definition except that PaO2/FiO2 fraction has to be less than 200. Mortality in ARDS is high and in two recent studies was estimated to be 0.46 in adults and 0.22 in children [31;32]. The exact causative mechanism through which VALI contributes to mortality is not known. It has been postulated that in conjunction to and aggravated by VALI, multiple organ failure can develop with ultimately death [33]. It is thought that this is caused by immunologic active products of lung damage that spill over to the systemic circulation resulting in a systemic inflammatory reactive syndrome with subsequent organ damage [34;35]. However, the importance of an independent role of VALI in multiple organ failure and death by immunological mediators has been debated [36;37].

Lung protective ventilation strategies

As there is abundant experimental and clinical evidence that mechanical ventilation can cause lung damage, avoidance of VALI must be of prime concern while ventilating patients. Obviously, volutrauma can be prevented by use of low tidal volumes. However, this could be in disagreement with the objective to prevent atelectasis [38]. Studies showed that ventilation at very low lung volumes with low level of PEEP caused a significant decrease in lung compliance and progression of lung injury [9;17]. The combined effort of limiting tidal volumes with recruitment of lung alveoli and preventing alveoli to collapse has been designated as the open lung concept [39]. The rationale behind this approach can be described graphically by the pressure volume curve (Figure 2). The pressure volume curve during mechanical ventilation follows a specific pattern [40-42]. During the inflation phase pressure builds up while lung volume only increases slightly. At a specific point the relative volume gain, in response to pressure, increases and follows a more or less linear a more horizontal

Figure 2



Inflation and deflation pressure-volume curve (PV Curve). These curves were calculated by the equation V = a + b / (1 + e-(P-c)/d) (40). V = Lung volume (ml). P = Airway pressure (cmH2O). The lower and upper corner pressures (Pcl, Pcu) are defined by the intersect of the tangent at the steepest part of the curve with the tangent of the more horizontal parts of the curve. The part between the lower and upper corner pressure could be regarded as a safe window between atelectasis and overdistension.

course. The expiration limb of the curve follows a different route. Considerable less pressure is needed to maintain a certain amount of lung volume compared with the inspiration limb of the pressure volume curve. This increase in compliance is caused by recruitment of alveoli and is

called ‘pulmonary hysteresis’ [43]. The upper and lower corner pressures are defined as the points were the slopes of the curves change abruptly [42]. It is generally thought that the lower corner pressure signifies the point of the critical opening pressure of alveoli and that the upper corner pressure is related to start of overdistension [44]. Therefore, protective ventilation strategies should theoretically be dictated by these corner pressures that are specific for individual patients. The zone between these corner pressures has been designated as safe window [45]. However, this model has been differentiated and modified in the fact that the inflation characteristics of the PV curve have been shown not to be simply related to successive alveolar recruitment and overdistension [40]. Between the lower and upper corner point, a substantial number of alveoli may still not be recruited, while, at the same time, already recruited alveoli develop overexpansion. Therefore, the safe window may not be an exactly definable range.

Lung protection with conventional mechanical ventilation

Normal lungs are less susceptible to VALI while gas exchange can be easily achieved within physiological airway pressure and tidal volume limits [46]. In diseased lungs, mechanical ventilation is confronted with a number of problems:

- Gas exchange is disturbed.
- Compliance is decreased.
- Disease activity in the lungs is heterogeneously distributed.

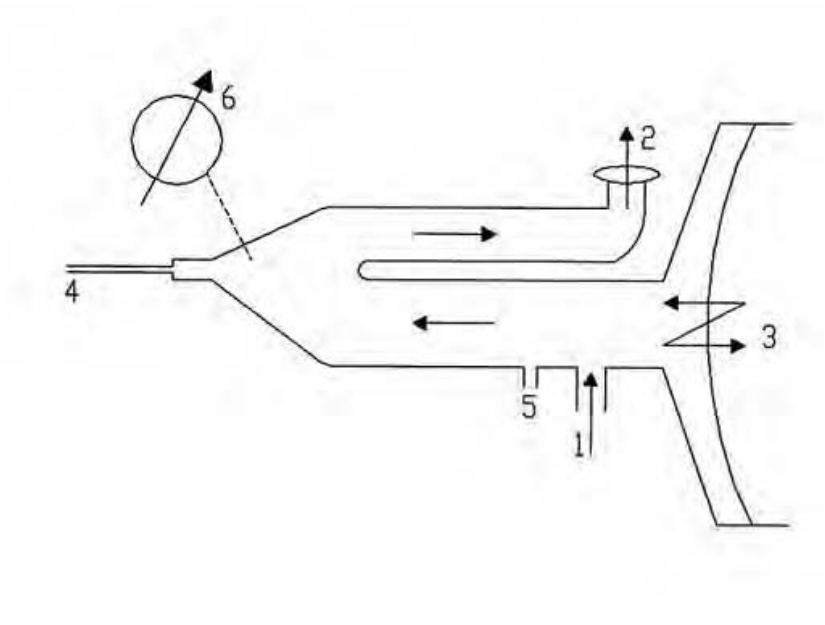
To achieve a lung protective ventilation strategy, limiting tidal volumes on the one hand and applying sufficient PEEP on the other hand have to be combined with maintaining adequate gas exchange. Limiting tidal volumes

will inevitably result in hypercapnia and respiratory acidosis. How much hypercapnia is acceptable is not clear [47]. However, accepting a certain amount of hypercapnia has been associated with better outcome [48]. Another change in pulmonary disease is loss of compliance. This is displayed by the downward displacement of the pressure volume curve. Loss of recruitable lung segments due to lower compliance results in a smaller lung available for ventilation, the so called 'baby lung' [49]. This further limits tidal volumes. Experimental studies showed an exponential increase in VILI when harmful ventilation strategies were combined with prior lung injury compared with prior lung injury alone or injurious ventilation strategies alone [23]. The heterogeneous nature of clinical lung disease further aggravates atelectasis of diseased parts of the lung and overdistension of healthy parts of the lung [50-52]. Yet, a sufficient level of positive end-expiratory pressure has to be maintained to keep the lung open. It can be hypothesized that at a certain point tidal volumes delivered by conventional ventilation superimposed on a level of PEEP sufficient to keep the lung open will fail to stay in the safe window on the pressure volume curve. A specific type of ventilator combining very small tidal volumes with a continuous distending airway pressure is the high frequency ventilator.

Lung protection with high frequency ventilation

High frequency ventilation is a collection of ventilation modes that combines very small tidal volumes at high frequency with a high continuously distending airway pressure. Examples of techniques are high frequency oscillatory ventilation, high frequency jet ventilation, and high frequency flow interruption ventilation. The most commonly used device is the high frequency oscillatory ventilator (HFOV) (Figure 3). Like the other modalities, HFOV employs respiratory frequencies that are significantly

Figure 3



Schematic view of the high frequency oscillatory ventilator. Mean airway pressure is regulated by controlling the inflation of the balloon valve (2) in the expiratory limb of the circuit. As inflation pressure inside the balloon increases, the outflow of gas is restricted, providing mean airway pressure. Superimposed on this mean airway pressure are tidal volumes delivered by electronically driven membrane displacements (3). This Figure was kindly provided by Elmer J. van Vught.

(180-2000 breaths/min) higher and tidal volumes that are markedly lower (1-5 ml/kg) than conventional mechanical ventilation (CMV) [53;54]. The first application of HFOV can be traced back to Lunkenheimer et al. [55].The major difference between HFOV and other forms of high frequency ventilation is the active expiratory phase. A membrane causes oscillating movements of air with a frequency typically ranging from 5 – 10 Hz. These small movements, tidal volumes, are superimposed on a continuously distending pressure. As the movement of air progresses through the respiratory system and airways, the amplitude of airway movement is attenuated to very small tidal volumes at the alveolar level [56-58]. Gas exchange is probably achieved by a complicated diffusion and

convection process rather than by delivery of tidal volumes [59]. Early HFOV devices were only suitable for ventilating infants and small children, because of their limited power. At the present time HFOV devices are marketed that can be used to ventilate adults as well. HFOV has been extensively tested in animals with different models of lung disease. Invariably, these tests showed a reduction in lung damage as compared with CMV. This has been demonstrated both at a physiological level as by histopathological examination of ventilated lungs in animal models (Figure 4) [60-68]. However, evidence in humans is less unequivocal. The majority of trials have been performed in premature neonates with respiratory distress syndrome [69]. Recently two trials have been conducted in adult patients with acute respiratory distress syndrome [70;71].

Analysis of clinical evidence of HFV compared with CMV

This thesis can be divided into two main sections. The first part of the thesis relates to the evidence comparing high frequency ventilation with CMV in premature neonates with IRDS. In the second part of this thesis, evidence comparing HFOV with CMV in adults with ARDS is assessed. In four out of five studies in this thesis meta-analytic techniques were used to provide answers to the research questions that were raised. Meta-analysis can be used to pool results from randomized trials to obtain more precise estimates [72]. Three different forms of meta-analysis were used to summarize the evidence of clinical trials. First, cumulative meta-analysis was performed to determine the progression of evidence over time [73;74]. This enabled us to identify specific sources of heterogeneity between studies. Secondly, meta-regression analysis was used to calculate quantitative effects of important determinants on the relative treatment effect of high frequency ventilation compared with CMV. Furthermore,

Figure 4

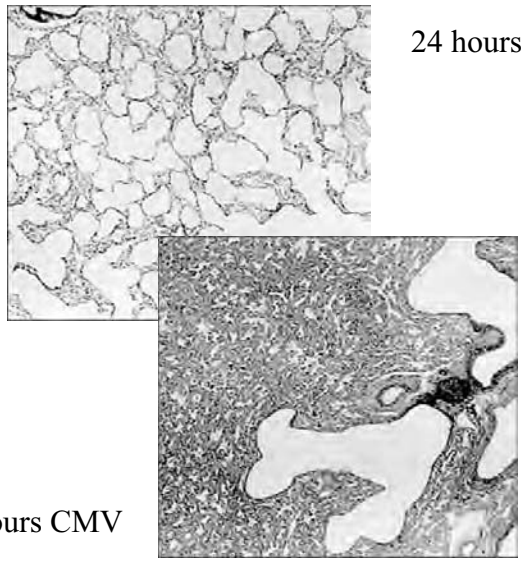


Figure used with permission from Meredith et al. (66). Histological specimens are shown from lungs of premature baboons with hyaline membrane disease ventilated 24 hours with positive pressure ventilation versus HFOV.

meta-regression analysis was used to identify determinants of mortality in HFOV treated adult patients with ARDS. Finally, sequential meta-analysis was applied with trials as unit of analysis to determine the number of trials needed to be conducted to establish the effect of high frequency ventilation on pulmonary outcome [75;76].

Outline of this thesis

Studies in premature neonates

The studies presented in this thesis were initiated to answer the following general question: Is high frequency ventilation better than CMV? The majority of clinical trials have been performed in premature neonates with IRDS due to limitations posed by available high frequency ventilators at that time. Therefore, the following research questions were formulated:

1. Does elective use of high frequency ventilation in premature neonates with IRDS result in better clinical outcome than conventional mechanical ventilation?

In Chapter 2 trials were stratified by different high frequency ventilators and by different ventilatory strategies. In addition, a cumulative meta-analysis was performed within relevant strata, which allowed for examination of development of available evidence over time and assessment of sources of remaining heterogeneity

2. What factors determine the relative treatment effect of high frequency ventilation compared with CMV?

A meta-regression analysis was conducted in Chapter 3 to obtain unbiased estimates of the effects of possible covariates that explained heterogeneity between trials that investigated the elective use of high frequency ventilation compared with CMV in premature neonates with IRDS.

3. Is there enough evidence to establish whether or not high frequency ventilation confers clinical benefit over CMV, or do more clinical trials need to be performed?

Chapter 4 presents a sequential meta-analysis to determine whether or not and at what point in time additional trials comparing high frequency ventilation with CMV, still contributed to available evidence.

Studies in adult patients

Published randomized trials in adults were limited to one study. The remainder of clinical studies comprised observational studies. All research in adult patients presented in this thesis was performed in patients with ARDS. An additional multi-center randomized trial was analyzed and a meta-analysis of observational research was conducted to answer the following questions:

4. Is high frequency oscillatory ventilation as safe and effective as conventional mechanical ventilation in adults with ARDS?
Chapter 5 shows the results of a multi-center randomized trial that compared early treatment with HFOV of ARDS in adult patients with the use of conventional ventilation.

5. What factors determine mortality in adult patients with ARDS treated with HFOV?
In Chapter 6 a meta-analysis of observational research was conducted. Determinants of mortality in HFOV treated ARDS patients were identified using meta-regression analysis.

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Chapter 2

Cumulative Meta-analysis of High Frequency versus Conventional Ventilation in Premature Neonates

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Introduction

Mechanical ventilation can induce lung injury, particularly in premature and diseased lungs. There is increasing evidence that high peak inspiratory pressures and repetitive end-expiratory collapse are major determinants of lung injury [1]. This injury may extend to other organ systems, leading to multi-organ failure [2-4]. Ventilatory strategies that limit high inflation pressures and prevent end-expiratory collapse are designated as lung protective mechanical ventilation [5].

High frequency ventilation is a method of ventilation in which alveolar gas exchange is maintained by pressure swings initiating small displacements of ventilatory gases, considerably smaller than conventional tidal volumes, at frequencies generally from 5-20 Hz superimposed on a continuous positive pressure. High frequency ventilation allows higher end-expiratory pressures with lower peak inspiratory pressures and higher mean airway pressures and is therefore proposed as currently the most optimal form of lung protective ventilation [6;7].

In animal experiments, high frequency ventilation have been shown to prevent ventilator-induced lung injury [8-10]. The majority of clinical trials so far has been performed in neonates but results are equivocal. The two most recent large randomized controlled trials failed to demonstrate a significant advantage of high frequency ventilation over conventional mechanical ventilation or showed only a small benefit [11;12]. The last meta-analysis of the pooled data in neonates showed no reduction in either mortality or oxygen dependency at day 28-30 after birth but a small reduction in the risk of chronic lung disease at 36- to 37 weeks post-gestational age in patients treated with high frequency ventilation with optimized lung volume in comparison with conventional mechanical ventilation [13].

The conventional mechanical ventilation strategies for treating respiratory failure have evolved since the first published clinical trial in 1987 comparing high frequency ventilation with conventional mechanical ventilation due to the introduction of surfactant replacement therapy and the concept of lung protective ventilation [14]. Therefore, early results cannot be easily compared with later studies, a limitation that prior meta-analyses accounted for only partially or not at all [13;15-17].

We reviewed the published comparative data on high frequency ventilation and conventional mechanical ventilation in neonates and performed an updated meta-analysis including the two most recent and largest randomized clinical trials [18;19]. We stratified trials by different high frequency ventilators and by different ventilatory strategies. In addition, we performed a cumulative meta-analysis within relevant strata, which allowed us to examine the development of the available evidence over time and to assess the influence of the introduction of surfactant replacement therapy and of lung protective ventilation.

Methods

Search strategy and data collection

The Embase, Medline and Current Contents databases were searched to identify all systematic reviews and randomized controlled trials of treatment with high frequency ventilation compared with conventional mechanical ventilation. Clinical trials had to meet criteria previously adopted by Bhuta and Henderson-Smart et al. [20]. A more detailed description of the search strategy can be found in the online supplement.

Data on the following outcomes were extracted: mortality at 28 to 30 days of age; bronchopulmonary dysplasia, defined as oxygen dependency at the age of 28 to 30 days with radiologic evidence of bronchopulmonary dysplasia; chronic lung disease, defined as oxygen dependency at the postconceptional age of 36 weeks; intraventricular hemorrhage; and periventricular leukomalacia.

A high lung volume strategy with high frequency ventilation was assumed if two or more of the following items were explicitly stated in the methods: initial use of a higher mean airway pressure than on conventional mechanical ventilation; initial lowering of inspired oxygen before reducing mean airway pressure; and use of alveolar recruitment maneuvers. A lung protective strategy in the conventional mechanical ventilation group was based on specifying the Pco_2 goal, allowing permissive hypercapnia, and a high initial ventilatory rate, targeted at reducing tidal volume as previously suggested by Thome and Carlo [16].

Data analysis and statistical methods

A number of hypotheses were proposed in advance to explain differences between study outcomes. First, differences could be attributed to the type of ventilator being used. We therefore stratified studies by the following subgroups: the SensorMedics ventilator (SensorMedics, Bilthoven, The Netherlands); other high frequency oscillatory ventilators (HFOV); high frequency jet ventilators and high frequency flow interruption ventilators. Another possible explanation of different treatment effects could be the use of surfactant. Subgroups were made of studies with and studies without the concomitant use of surfactant. Finally, recent improvements in ventilation strategies could affect outcome. We therefore defined the following subgroups: no high lung volume strategy in high frequency ventilation and no lung protective strategy in conventional mechanical ventilation; high lung volume strategy in high frequency ventilation and no lung protective

strategy in conventional mechanical ventilation; high lung volume strategy in high frequency ventilation and lung protective strategy in conventional mechanical ventilation.

A cumulative meta-analysis was performed by pooling data again each time a new study was published [21]. To assess changes in relative treatment effects and identify possible sources of heterogeneity, a graph was constructed using pooled estimates and corresponding 95% confidence intervals as a function of the cumulative number of patients included in the analysis in a chronological order. The particular purpose of this graph was to show the ratio of the cumulative treatment effect to the previous cumulative treatment effect. This so-called recursive cumulative meta-analysis was created to identify graphically sources of heterogeneity emerging at specific points in time [22]. Furthermore, heterogeneity was statistically evaluated using visual examination of the extent of overlapping confidence intervals and Cochrane's Q test [23;24]. Different treatment effects were assumed in case of graphical evidence for heterogeneity and a significant test for heterogeneity ($p < 0{\cdot}10$). Differences between subgroups were statistically evaluated by a chi-square test. Meta-analyses were performed in different subgroups to eliminate heterogeneity. Cumulative meta-analyses were visualized again to assess remaining heterogeneity or changes in treatment effects. A random effects model was used to calculate pooled treatment effects. Publication bias was assessed by visual appraisal of funnel plots and performing a rank test.

Results

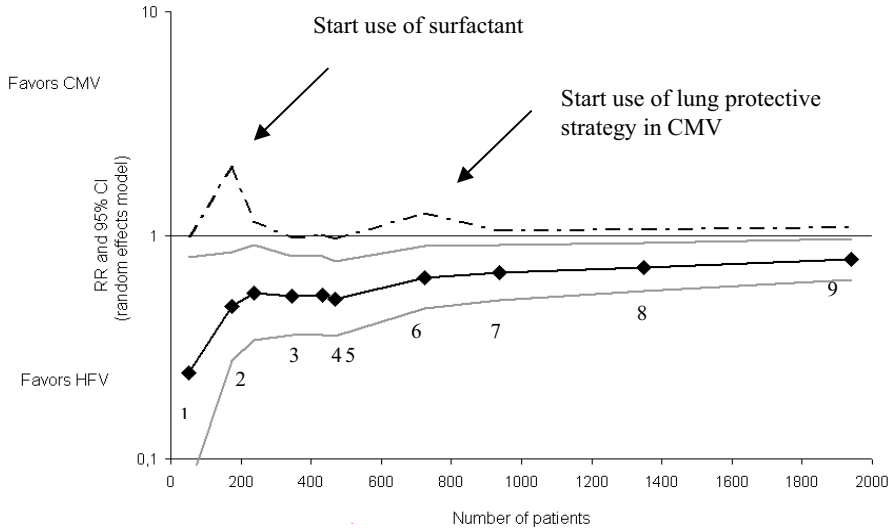
We identified five systematic reviews [13;15;16;20;25]. Using the reference lists of these systematic reviews, 14 original articles were selected. Our

literature search yielded no additional references. Thus, 14 articles were available for our analyses that represented a total of 3260 randomized patients [26-39]. The main features of these articles are summarized in the online supplement in Table E1.

There was significant heterogeneity between different studies for chronic lung disease ($p = 0.05$) and periventricular leukomalacia ($p = 0.08$) (Table E2 in the online supplement). This corresponded with significant differences between subgroups of surfactant ($p = 0.02$ for chronic lung disease and $p = 0.07$ for periventricular leukomalacia) and ventilatory strategy ($p < 0.01$ for chronic lung disease and $p = 0.02$ for periventricular leukomalacia) but not between ventilator subgroups. Significant differences between subgroups of ventilatory strategy were also detected for death or chronic lung disease ($p < 0.01$), intraventricular hemorrhage all grades ($p = 0.03$), and intraventricular hemorrhage grades 3 and 4 ($p = 0.05$) (Table E2).

Graphical presentation of the cumulative relative risk of chronic lung disease showed a distinctive shape (Figure 1). There was a convergence of the 95% confidence interval with a regression of the estimate to the line of no effect. The recursive cumulative meta-analysis was depicted by the dotted line in Figure 1. A ratio above one implied overestimation of the treatment (high frequency ventilation) effect. The first peak thus visualized corresponded with the first trial in which surfactant was used to treat respiratory distress syndrome and chronic lung disease was reported as an outcome [29]. The second peak coincided with the start of protective lung ventilation in conventional mechanical ventilation 40. Thus, the use of surfactant and lung protective strategy in conventional mechanical ventilation was graphically indicated to be two major sources of study heterogeneity.

Figure 1. Cumulative and Recursive meta-analysis of Chronic Lung Disease indicating two important sources of heterogeneity.



Cumulative and Recursive meta-analysis of Chronic Lung Disease indicating two important sources of heterogeneity. CMV: conventional mechanical ventilation. HFV: high frequency ventilation. LPVS: lung protective ventilatory strategy. X-axis: cumulative number of patients included in trials. Y-axis: relative risk (RR) and 95% CI. Diamonds: cumulative estimates of RR. Grey lines: 95% confidence intervals. Dotted line: ratio of RR estimate to prior RR estimate. A ratio > 1 indicates an overestimation of the treatment (HFV) effect. A ratio < 1 indicates an underestimation of the treatment (HFV) effect. Each diamond represents an addition of a study in the cumulative meta-analysis, the following studies were included: 1. Clark 1992; 2. Gerstmann 1996; 3. Wiswell 1996; 4. Keszler 1997; 5. Rettwitz 1998; 6. Plavka 1999; 7. Thome 1999; 8. Morriette 2001; 9. Courtney 2002; 10. Johnson 2002.

Table 1 describes the meta-analyses stratified by ventilatory strategy and ventilator subgroups with the remaining heterogeneity. In none of the ventilatory strategy subgroups was there a difference in mortality when high frequency ventilation was compared with conventional mechanical ventilation. Respiratory outcomes were better in the ventilation strategy

subgroup in which high frequency ventilation with high lung volume strategy was compared with conventional mechanical ventilation without lung protective strategy. However, high frequency ventilation without high lung volume strategy lost the ability to prevent lung damage. Furthermore, high frequency ventilation without high lung volume strategy resulted in an elevated risk of intraventricular hemorrhage, intraventricular hemorrhage grades 3 and 4 and periventricular leukomalacia. The beneficial effects on respiratory outcome also disappeared when high frequency ventilation with high lung volume strategy was compared with conventional mechanical ventilation with lung protective strategy. Remaining significant heterogeneity existed only for intraventricular hemorrhage grades 3 and 4 in the subgroup of high frequency ventilation with high lung volume strategy and conventional mechanical ventilation with lung protective strategy.

Stratification by the type of ventilator being used had less impact on treatment results and did not eliminate heterogeneity for chronic lung disease, intraventricular hemorrhage and periventricular leukomalacia (Table 1). Significantly better respiratory outcomes were reported only in the SensorMedics subgroup. In this subgroup, the relative risk of chronic lung disease was 0·57 (95% confidence interval, 0·36-0·93). However, there was significant heterogeneity , and visual examination of the cumulative meta-analysis revealed a progressive trend of the estimate of the relative risk to the line of no effect. The relative risk of death or chronic lung disease was not statistically different when high frequency ventilation with the SensorMedics was compared with conventional mechanical ventilation (relative risk = 0·67, 95% confidence interval 0·43-1·04). There was still unexplained significant heterogeneity for intraventricular hemorrhage all grades and grades 3 and 4 in the high frequency oscillatory Figure 2 is a graphical presentation of our main cumulative analysis of

Table 1. Meta-analyses in subgroups.

Ventilatory strategy subgroups

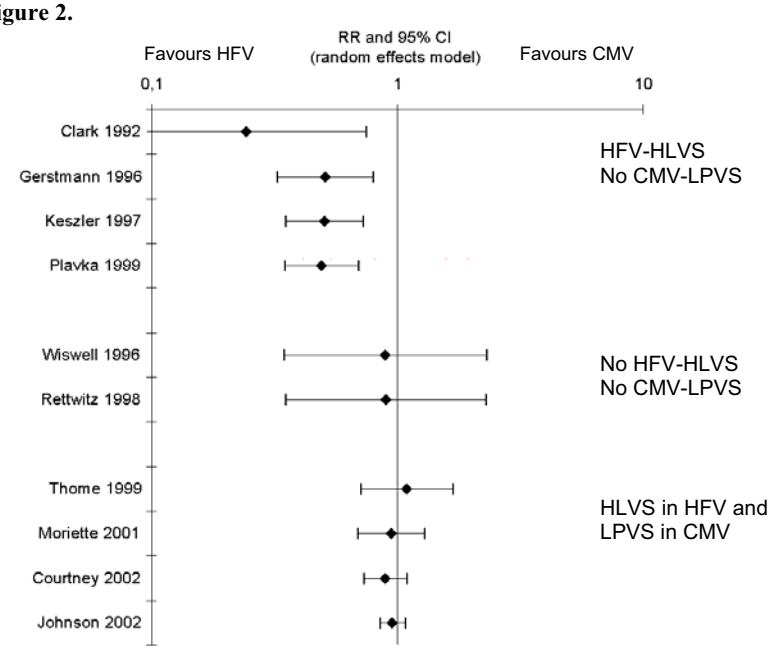
	HFV-HLVS No CMV-LPVS			No HFV-HLVS No CMV-LPVS			HFV-HLVS and CMV-LPVS		
Outcome	RR (95% CI)	P het	P pub	RR (95% CI)	P het	P pub	RR (95% CI)	P het	P pub
Death	0·86 (0·52-1·44)	0·86	0·35	1·07 (0·80-1·44)	0·89	0·50	0·96 (0·80-1·15)	0·87	0·50
BPD	**0·66 (0·44-0·98)**	0·92	0·62	1·02 (0·89-1·16)	0·68	0·50	0·96 (0·81-1·13)	0·80	0·32
CLD	**0·49 (0·35-0·69)**	0·52	**0·04**	0·90 (0·35-2·29)	0·94	0·32	0·95 (0·85-1·07)	0·62	0·50
Death or CLD	**0·54 (0·38-0·77)**	0·92	0·12	~~	~~	~~	0·99 (0·91-1·07)	0·94	0·50
IVH all grades	0·95 (0·78-1·16)	0·84	0·62	**1·16 (1·01-1·34)**	0·75	1·00	0·89 (0·78-1·02)	0·36	0·60
IVH grades 3 and 4	0·85 (0·49-1·47)	0·71	0·62	**1·49 (1·14-1·94)**	0·61	0·12	1·05 (0·73-1·52)	**0·05**	0·50
PVL	0·65 (0·31-1·37)	0·42	0·50	**1·99 (1·07-3·71)**	0·32	0·60	0·86 (0·49-1·52)	0·32	0·12

Ventilator subgroups

	HFJV and HFFI			HFOV			SensorMedics		
Outcome	RR (95% CI)	P het	P pub	RR (95% CI)	P het	P pub	RR (95% CI)	P het	P pub
Death	0·91 (0·58-1·43)	0·84	0·17	1·01 (0·85-1·20)	0·92	0·85	0·89 (0·61-1·30)	0·77	0·50
BPD	0·94 (0·82-1·09)	1·00	**0·05**	1·02 (0·89-1·16)	0·64	0·33	**0·51 (0·35-0·74)**	0·62	0·32
CLD	0·80 (0·48-1·35)	0·13	0·60	0·97 (0·84-1·11)	0·68	0·60	**0·57 (0·36-0·93)**	**0·06**	**0·04**
Death or CLD	~~	~~	~~	0·98 (0·89-1·07)	0·82	0·60	0·67 (0·43-1·04)	**0·02**	0·50
IVH all grades	1·04 (0·86-1·25)	0·43	0·60	0·99 (0·73-1·35)	**0·06**	0·50	0·93 (0·80-1·09)	0·83	0·33
IVH grades 3 and 4	1·25 (0·83-1·87)	0·45	0·60	1·27 (0·80-2·02)	**0·02**	0·33	0·96 (0·69-1·35)	0·54	0·50
PVL	1·99 (0·26-15·32)	**0·02**	0·60	1·30 (0·76-2·22)	0·32	0·50	0·82 (0·49-1·37)	0·61	0·12

HFV-HLVS: high frequency ventilation with high lung volume strategy. CMV-LPVS: conventional mechanical ventilation with lung protective ventilatory strategy. HFJV: high frequency jet ventilator. HFFI: high frequency flow interrupter. HFOV: high frequency oscillatory ventilator. BPD: bronchopulmonary dysplasia. CLD: chronic lung disease. IVH: intraventricular hemorrhage. PVL: periventricular leukomalacia. RR: relative risk fixed model. CI: confidence interval. ~~: insufficient data. Statistically significant results are printed in bold.

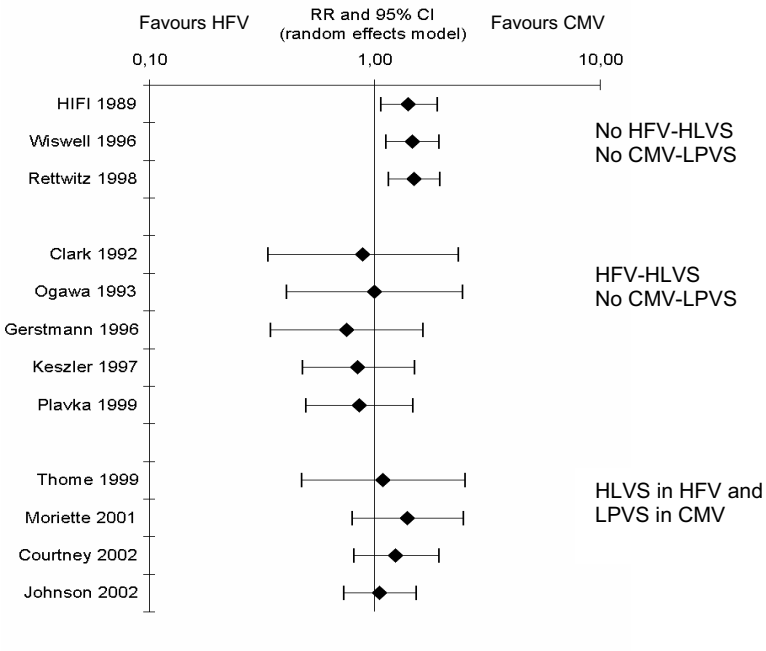
Figure 2.



Cumulative meta-analyses of Chronic Lung Disease in Ventilatory strategy subgroups. HFV: high frequency ventilation. CMV: conventional mechanical ventilation. HLVS: high lung volume strategy. LPVS: lung protective ventilatory strategy. Within each of the three subgroups of studies each later estimate is a pooled estimate of results of all previous studies. ventilation subgroup ($p = 0.06$ and p-value = 0.02, respectively) and there was significant heterogeneity for periventricular leukomalacia in the high frequency jet and high frequency flow interruption ventilator subgroup ($p = 0.02$).

chronic lung disease, which is in subgroups of ventilatory strategy. The cumulative estimate of the relative risk of chronic lung disease in high frequency ventilation with high lung volume strategy compared with conventional mechanical ventilation without a lung protective strategy did not change any further during the last three trials of the total of four studies and remained significant. The cumulative meta-analyses of chronic lung disease in the subgroup with high frequency ventilation without high lung volume strategy and the subgroup of high frequency ventilation with high lung volume strategy but also lung protective strategy in conventional

Figure 3



Cumulative meta-analyses of Intraventricular Hemorrhage in Ventilatory strategy subgroups. IVH: intraventricular hemorrhage. HFV: high frequency ventilation. CMV: conventional mechanical ventilation. HLVS: high lung volume strategy. LPVS: lung protective ventilatory strategy. Within each of the three subgroups of studies each later estimate is a pooled estimate of results of all previous studies.

of no effect. Cumulative meta-analysis of the relative risk for intraventricular hemorrhage grades 3 and 4 in the subgroup of high frequency ventilation without a high lung volume strategy showed a harmful effect compared with conventional mechanical ventilation (Figure 3). When a high lung volume strategy was being used, this effect disappeared. Thus, within comparisons of optimized high frequency ventilation and optimized conventional mechanical ventilation, including the latest large trials, there was no beneficial effect of either treatment, nor was there an indication of significant remaining heterogeneity or change in treatment effect.

Discussion

When optimized high frequency ventilation with high lung volume strategy was compared with optimized conventional mechanical ventilation with lung protective strategy there was no reduction in chronic lung disease. As in previous meta-analyses on high frequency ventilation versus conventional mechanical ventilation in neonates, we also did not find differences in mortality [13;15;16;20;25]. Cumulative meta-analysis of the data allowed us to analyze the development of the evidence and to investigate how consecutive trials contributed to the estimation of the treatment effects [19].

There is a growing understanding that clinical evidence is a dynamic process, not a static estimation of a single treatment effect at a single time point [41]. In this respect, cumulative meta-analysis should be distinguished from an updating of an existing meta-analysis. In a cumulative meta-analysis the accumulating results allow assessment of changes in patient and treatment characteristics over time. Although there was clearly significant heterogeneity, precluding pooling of estimates, a cumulative meta-analysis of chronic lung disease, including all studies, was performed exclusively to identify graphically such effects at specific points in time. As such, this analysis was not intended to calculate a single pooled treatment effect.

A first important source of heterogeneity might be small trial bias (publication bias) which results in systematic differences in effect size estimates derived from small versus large trials [42]. The other possible explanation is the improvement of conventional ventilation over time. One of the major advances in neonatal respiratory care is the introduction of surfactant [43]. Numerous clinical studies have confirmed the beneficial effect of surfactant administration on outcome of premature infants with

respiratory distress [44]. Our results indicate that introduction of surfactant therapy is reflected in a considerable change in relative treatment effects. Another advance in ventilatory care is the application of lower tidal volumes and higher positive end-expiratory pressure levels, designated as lung protective ventilation [45]. A ventilatory strategy to maintain lung volume (higher mean airway pressures) with low tidal volumes has the potential for better alveolar recruitment compared with a low volume strategy with higher tidal volumes and thus would result in better outcome in terms of chronic lung disease. Although in adult respiratory care there is increasing evidence of the beneficial effect on mortality and morbidity of lung protective ventilation [46], a large body of controversy remains [47-50]. In neonates, only few studies have addressed this topic [51;52]. We speculate that the introduction of lung protective ventilation also reflected an important change of relative treatment effects, albeit smaller than with the introduction of surfactant.

It is now generally believed that high frequency ventilation is most beneficial if the lungs are optimally recruited [53-56]. However, the evidence for this comes mainly from animal experiments [57;58]. There are no clinical studies comparing high frequency ventilation with high lung volume strategy and high frequency ventilation without high lung volume strategy. We show that the best effects of high frequency ventilation on chronic lung disease were reported in studies in which high lung volume strategy was part of the high frequency ventilation protocol but in which the conventional mechanical ventilation protocol did not meet the criteria for lung protective ventilation [29;30;33;59]. Studies not mentioning high lung volume strategy and lung protective ventilation as part of their protocol failed to show differences in effect of high frequency ventilation on chronic lung disease [34;36]. Instead these studies demonstrated an increased incidence of intraventricular hemorrhage. When lung protective conventional mechanical ventilation was compared with high frequency

ventilation with high lung volume strategy there were no differences in either chronic lung disease or intraventricular hemorrhage [35;60-62].

In previous reports it has been suggested that particularly in premature neonates with a higher baseline risk of chronic lung disease would benefit more from high frequency ventilation [35;63]. It has also been suggested that using high frequency ventilation as the primary mode of ventilation immediately after birth would increase its effectiveness [30;64]. In consecutive studies patients had lower birth weights and were more premature. In consequence this would imply a higher risk of chronic lung disease. Furthermore, institution of high frequency ventilation after birth was earlier in the more recent trials. However, our cumulative analysis of chronic lung disease showed that this did not result in a larger benefit of high frequency ventilation over conventional mechanical ventilation over time, as would have been expected.

A limitation of our analysis is the varying definitions of high lung volume strategy in the high frequency ventilation group and of lung protective strategy for conventional mechanical ventilation used in the original studies. In the definition of high lung volume strategy, a higher mean airway pressure was limited to initial use, and use of recruitment maneuvers did not necessarily mean that an open lung strategy was used the entire study period. Furthermore, the definition of lung protective ventilatory strategy did not include tidal volumes standardized to body weight or levels of positive end-expiratory pressure being applied. The actual implementation of these strategies could not be accounted for either in our analysis.

In the most recent meta-analysis published by the Cochrane Library, the use of a high lung volume strategy and treatment with surfactant was taken into account as well [13]. However, this did not eliminate existing

heterogeneity between trials. It was concluded that high frequency oscillatory ventilation caused a modest reduction in chronic lung disease. In our analyses, we did not only identify the use of surfactant as a source of heterogeneity but also the application of a lung protective strategy in the conventional mechanical ventilation group. The most significant differences between subgroups were found between trials using different ventilation strategies, not only in the high frequency ventilation group but also in the conventional mechanical ventilation group. By stratifying trials by ventilation strategies, we were able to minimize heterogeneity. We therefore explain heterogeneity between trials mainly by changes in the conventional treatment of respiratory distress in premature neonates over time. Unlike the Cochrane meta-analysis we did not find differences in chronic lung disease between optimized high frequency ventilation and optimized conventional mechanical ventilation. We suggest that future investigations should be directed towards identifying the specific pulmonary conditions in which optimized high frequency ventilation does have benefits compared with optimized conventional mechanical ventilation [65].

Cumulative meta-analysis and subsequent stratification are valuable methods to summarize and interpret the effects of changes in patient characteristics and treatments over time. These methods enabled us to show that use of surfactant and the emergence of lung protective ventilation strategies in conventional mechanical ventilation moderates the relative beneficial effect on chronic lung disease of high frequency ventilation.

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Online data supplement

Description of included studies

Included trials were assessed for methodological validity according to explicit criteria as has been described by Jadad et al E1. Disagreements about the validity score of articles were resolved by discussion. Data abstraction was not performed blinded and independently but was cross referenced to the existing meta-analyses.

All trials used valid randomization procedures. Withdrawals and dropouts were described in all trials. Follow up was sufficient (> 80%) in all included studies as well. Outcome assessment was blinded in 6 of 14 trials E2-7. However, in only 3 trials there was a clear description of how outcome blinding was achieved E4-6.

In 10 trials a high frequency oscillatory ventilator was used, in 4 of these trials this was the SensorMedics ventilator. Three studies used a high frequency jet ventilator. In one study a high frequency flow interrupter ventilator was used E10.

The first studies included patients with a mean weight ranging from 1•1 to 1•4 kg and a gestational age ranging from 28 to 30 weeks. In the last three studies birth weight ranged from 0•85 kg to 0•99 kg with a gestational age of 26 to 28 weeks. In the first trials HFV was instituted 6 to 15 hours after birth, in the last trials this was achieved 0•25 to 2•7 hours after birth. From the trial by Ogawa et al. onwards, surfactant has been used as concomitant therapy for respiratory disease E11. A high lung volume strategy was used in the first study by Froese et al E12. However, in the HIFI study and the trial by Carlo et al. this was not explicitly stated E2;8. In the last 5 reports

high lung volume strategy was specifically mentioned in the study protocol E5-7;10;13. Criteria consistent with a lung protective strategy in CMV were explicitly mentioned in the last 4 trials E5-7;10.

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Figure E1.

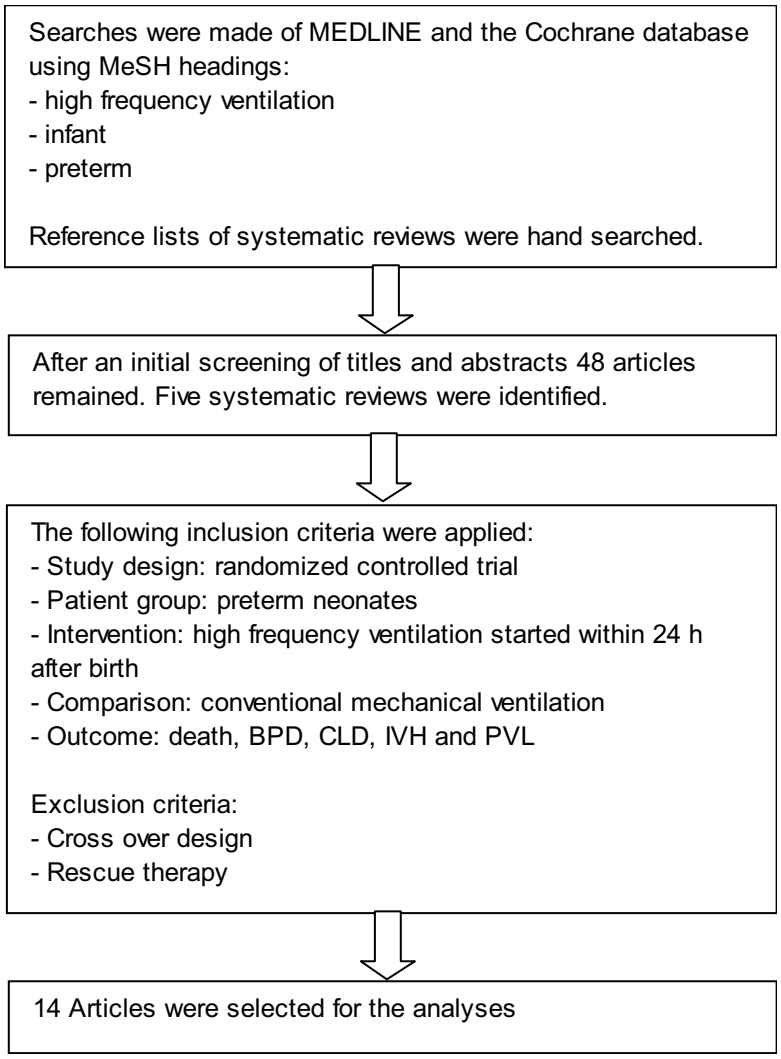
Searches were made of MEDLINE and the Cochrane database using MeSH headings:
- high frequency ventilation
- infant
- preterm
Reference lists of systematic reviews were hand searched.
After an initial screening of titles and abstracts 48 articles remained. Five systematic reviews were identified.
The following inclusion criteria were applied:
- Study design: randomized controlled trial
- Patient group: preterm neonates
- Intervention: high frequency ventilation started within 24 h after birth
- Comparison: conventional mechanical ventilation
- Outcome: death, BPD, CLD, IVH and PVL
Exclusion criteria:
- Cross over design
- Rescue therapy
14 Articles were selected for the analyses

Table E1.

Author	Year	No. of Patients Randomized	Type HFV	HF Ventilator	Mean birthweight (kg)	Mean gestational age (weeks)	Mean age HFV started (hours)	Surfactant	HFV with HLVS	CMV with LPVS	Validity
Froese	1987	15	HFOV	HSMVB, (Metrex Instruments)	1·1 (0·8)	28 (1)	Not reported	No	Yes	No	2
HIFI	1989	673	HFOV	Hummingbird, (Senko Medical Instrument Manufacturing)	1·1 (0·3)	28 (2)	6 (0·5)	No	No	No	4
Carlo	1990	42	HFJV	Research device	1·4 (0·3)	30 (2)	15 (4-30)	No	No	No	3
Clark	1992	98	HFOV	Sensormedics 3100, (Sensormedics)	1·1 (0·3)	28 (3)	9 (5)	No	Yes	No	4
Ogawa	1993	92	HFOV	Hummingbird BMO 20 N, (Senko Medical Instruments Manufacturing)	1·2 (0·3)	29 (2)	2 (2)	Yes	Yes	No	3
Gerstmann	1996	125	HFOV	Sensormedics 3100 (A), (Sensormedics)	1·5 (0·5)	31 (2)	3 (1)	Yes	Yes	No	3
Wiswell	1996	73	HFJV	Life Pulse HFJV, (Bunnell Inc)	0·9 (0·3)	27 (2)	7 (5)	Yes	No	No	5
Keszler	1997	130	HFJV	Life Pulse HFJV (Bunnell Inc)	1·0 (0·2)	27 (2)	8 (4)	Yes	Yes	No	3
Rettwitz-Volk	1998	96	HFOV	Stephan SHF 3000,(F Stephan Medizintechnik)	1·1 (0·1)	28 (1)	1 (0·5)	Yes	No	No	3
Plavka	1999	43	HFOV	Sensormedics 3100A (Sensormedics)	0·85 (0·2)	26 (2)	Not reported	Yes	Yes	No	3
Thome	1999	284	HFFI	Infant Star	0·87	27	0,5	Yes	Yes	Yes	3
Moriette	2001	292	HFOV	Dufour	0·99	28	0,25	Yes	Yes	Yes	5
Courtney	2002	500	HFOV	SensorMedics	0·85	26	2·7(0·9)	Yes	Yes	Yes	5
Johnson	2002	797	HFOV	Babylog 8000, Sensormedics, SLE 2000	0·85	26	Not reported	Yes	Yes	Yes	4

Table E2.

Outcome	*P het*	*P pub*	*P het ventilator*	*P het surfactant*	*P het strategy*
Death	0·99	0·48	0·79	0·62	0·72
BPD	0·17	**0·02**	**<0·01**	0·77	0·10
CLD	**0·05**	0·13	0·10	**0·02**	**<0·01**
Death or CLD	0·10	0·22	0·59	**0·04**	**<0·01**
IVH all grades	0·38	0·78	0·55	**0·05**	**0·03**
IVH grade 3 and 4	0·10	0·68	0·49	0·15	**0·05**
PVL	**0·08**	0·33	0·29	**0·07**	**0·02**

Chapter 3.

Meta-regression analysis of High Frequency Ventilation versus Conventional Ventilation in Infant Respiratory Distress Syndrome

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Submitted

ABSTRACT

Objective

Meta-analyses have been conducted of randomized trials to determine whether high frequency ventilation (HFV) in premature neonates with respiratory distress syndrome resulted in favourable pulmonary outcome compared with conventional mechanical ventilation (CMV). Considerable heterogeneity was detected. Hypotheses have been formulated to explain differences in outcome between these trials.

Design

Meta-regression analysis was used to evaluate these hypotheses.

Measurements and results

Variables were extracted to explain heterogeneity: year of publication, use of SensorMedics 3100A ventilator for HFV, time on CMV prior to start of study, gestational age, use of surfactant, high lung volume strategy in HFV, lung protective ventilation strategy in CMV and baseline risk. Chronic lung disease (CLD) and death or CLD were outcome measures. Relative risk rates were calculated to estimate effect sizes of explanatory variables on reported relative risks. Adjusted estimates of relative risk rates of use of high lung volume strategy and lung protective ventilation strategy were 0.42 (95% CI 0.06-2.48) and 2.02 (95% CI 0.18-23.12) for CLD, respectively. The effect of gestational age was less pronounced (RRR = 1.17 (95% CI 0.16-8.32) for CLD, respectively). Use of SensorMedics and prior time on CMV had the smallest effects (RRR = 0.96 (95% CI 0.47-1.94) and RRR = 0.85 (95% CI 0.58-1.24) for CLD, respectively). The same results applied to CLD or death as outcome.

Conclusions

Differences between trials comparing HFV with CMV on pulmonary outcome in premature neonates with respiratory distress syndrome could be largely explained by differences in ventilation strategies adjusted by other explanatory variables.

Introduction

High frequency ventilation (HFV) has been compared with conventional mechanical ventilation (CMV) since the 1980s. In HFV, patients are ventilated with small tidal volumes, even smaller than the dead space of their airways, at high frequencies, normally between five and ten Hz. Because HFV combines high mean airway pressures with small tidal volumes, this technique of ventilation has been regarded by some to be the most optimal form in patients with infant respiratory distress syndrome (IRDS), adult respiratory distress syndrome (ARDS), and other forms of severe lung disease [1].

HFV has been extensively investigated in premature neonates with IRDS, a population very susceptible for chronic lung disease (CLD). Unfortunately, the results of these studies were equivocal. Thus, the question remains whether or not HFV is able to prevent CLD as compared with conventional mechanical ventilation (CMV) in patients with severe lung disease. A significant number of meta-analyses have been performed to answer this question [2-6]. Pooled estimates of pulmonary outcomes failed to show clinically relevant differences between HFV and CMV [5]. However, significant heterogeneity existed between studies included in these meta-analyses. In a recent cumulative meta-analysis, we identified improvements of the conventional treatment of IRDS and ventilation strategies applied in both HFV and CMV as important sources of heterogeneity [2]. These associations could be confounded by other explanatory variables. Although a meta-analysis may pool results from randomized trials, differences between trials will not be randomly or independently distributed. A meta-analysis constitutes an observational study of trials, subjected to bias inherent to observational research. In a meta-regression analysis it is possible to adjust for confounding covariates.

A number of alternative hypotheses have been formulated to explain heterogeneity between trials [7;8]. Therefore, meta-regression analysis was used to obtain less biased estimates of the effects of explanatory variables on relative treatment effect by adjusting by other covariates.

Methods

Trials were included based on a previous meta-analysis that we conducted [2]. An additional literature search yielded two more studies that could be included for this meta-regression analysis. The same inclusion and exclusion criteria were used. Validity of studies was assessed by criteria published by Jadad et al. [9]. The validity was generally deemed as high with adequate allocation concealment in all trials. Blinding of treatment was not possible due to the nature of the interventions.

Data extraction was performed as has been reported in our previous meta-analysis. The following outcome measures were used: mortality, chronic lung disease (CLD) as defined by supplemental oxygen need or ventilator dependency at the age of 30-36 weeks post-menstrual. A number of explanatory variables were extracted as well: year of publication, type of ventilator used for HFV (SensorMedics 3100A ventilator versus other), ventilation strategies applied in the HFV and CMV treatment groups were obtained as previously described [2], time on CMV before study initiation, gestational age and birth weight and outcome rates in the control population were taken as proxy for baseline disease severity in the source population.

In a cumulative meta-analysis we showed that improvements in management of IRDS, i.e. introduction of surfactant and employment of lung protective strategies in CMV was associated with a diminishing

relative benefit of HFV on pulmonary outcome independent of whether or not a high lung volume strategy was used in HFV [2]. A number of competing hypotheses could bias this association: (1) the observed regression of the cumulative relative risks to the level of unity was due to publication bias, (2) use of the SensorMedics ventilator resulted in better results in HFV treated patients, (3) a prolonged ventilation on CMV before initiating HFV treatment could reduce the benefits of HFV, (4) in subgroups of more premature neonates, i.e. with lower birth weight with a higher susceptibility for CLD, HFV could result in better pulmonary outcome, and (5) with increasing outcome rates representing increasing disease severity HFV could have an increasing advantage over CMV.

Statistical analysis

All data were extracted according to the intention-to-treat principle. The number of patients surviving without chronic lung disease was subtracted from the total number of randomized patients in each treatment arm to calculate the composite outcome of death or chronic lung disease. To calculate the risk of chronic lung disease, the number of surviving patients was put in the denominator. Publication bias was assessed by funnel plots. A stratified analysis by ventilation strategies of publication bias was performed to determine whether the observed association between the inverse of the standard error with the risk ratio was confounded by ventilation strategies (Figure 6). Meta-regression analysis was used to evaluate other hypotheses. First, univariate linear regression analyses were applied to explanatory variables using the natural logarithm of relative risks for CLD and death or CLD as dependent variables. Individual studies were weighted by inverse variances of relative risks of outcomes of interest. Secondly, univariate linear regression analyses with continuous covariates were conducted stratified by HLVS, LPVS and use of surfactant. Finally, multivariate linear regression analyses were performed to calculate adjusted contributions of different explanatory variables of

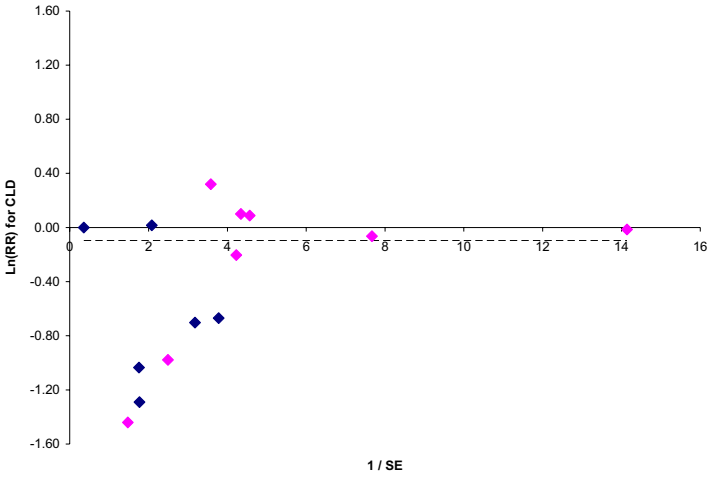
rivalling hypotheses to changes in RR. The relative effects of covariates were evaluated by relative risk ratios (RRR). For continuous variables the RRR was calculated for the extremes of these variables that were reported in trials. All analyses were conducted using SPSS 12.0.1 for Windows software (SPSS Inc., Chicago, Illinois, U.S.).

Results

For the analyses 15 studies were available that specified either CLD in survivors or death or CLD as outcome measures [10-24]. In the HFV group a total of 1141 patients were included for the outcome of CLD with 373 events and a total of 1457 patients with 671 events for the outcome death or CLD. In the CMV group a total of 1159 patients were reported for the outcome of CLD with 428 events and a total of 1473 patients with 730 events for the outcome death or CLD.

Table 1 summarizes the main characteristics of the studies. The outcome of CLD was available in all studies but one [22]. Time on CMV to start of the study was not reported by Plavka et al. and Craft et al. [15;21]. In only one study surfactant was not used as concomitant treatment [10]. A high lung volume strategy (HLVS) was used in all but two studies [12;14]. A ventilation strategy in the CMV treated patients that could qualify as lung protective (LPVS) was reported in the most recent 9 studies [16-24]. Studies were published over a range of 13 years. Other reported ranges of covariates were 8.7 hours, 5 weeks, 0.65 kg for average time on CMV before start of study, average gestational age, and average birth weight, respectively. These ranges were used to calculated relative risk rates. Two studies dominated the analyses by virtue of the weight they received in the analyses, Johnson et al. and Courtney et al. (together 69% for CLD and 73% for death or CLD as outcome) [19;20].

Figure 1. Funnel plot



Selection bias in reporting RR of CLD as suggested by asymmetry of the distribution of studies. X-axis: Inverse of the standard error of the RR. Y-axis: natural logarithm of the RR. Blue diamonds: studies with either no HLVS or no LPVS. Pink diamonds: studies with both HLVS and LPVS. Dotted line;: estimated RR including all studies.

A funnel plot of inverse of the standard error versus the natural logarithm of risk ratio for CLD was indicative of publication bias with a rank test p-value of 0.112 (Figure 1). Stratification by ventilation strategy (HLVS and LPVS versus either no HLVS and/or no LPVS) showed p-values of 0.456 and 0.851, respectively. Publication bias for the composite outcome of death or CLD was less likely with a p-value of 0.329. Stratified analysis showed p-values of 0.677 and 1.000.

Figures 2 to 4 show the results of the univariate linear meta-regression analyses for continuous explanatory variables; number of years form the first study, time on CMV before start of the study, gestational age and birth weight. Two studies dominate these figures, signified by their size relative to the weight they received in the analyses [19;20]. Furthermore, relatively

Table 1.

Study	*Year*	*Time on CMV*	*Gest. Age*	*Birth Weight*	*SensorM*	*HLVS*	*LPVS*	*Surf*	*CLD lnRR*	*Weight*	*Death or CLD lnRR*	*Weight*
Clark	1992	9.0	28	1.100	Y	Y	N	N	-1.29	0.01	-0.58	0.01
Gerstmann	1996	3.0	31	1.500	Y	Y	N	Y	-0.67	0.04	-0.55	0.02
Wiswell	1996	7.2	27	0.950	Y	N	N	Y	0.02	0.01	-0.23	0.10
Keszler	1997	8.0	27	1.020	N	Y	N	Y	-0.70	0.03	0.48	0.03
Rettwitz	1998	1.0	28	1.100	N	N	N	Y	0.00	0.00	0.31	0.00
Plavka	1999		26	0.850	Y	Y	N	Y	-1.03	0.01	-0.74	0.01
Thome	1999	0.5	27	0.870	N	Y	Y	Y	0.09	0.06	0.01	0.04
Durand	2001	2.6	26	0.840	Y	Y	Y	Y	-0.98	0.02	-0.59	0.02
Moriette	2001	0.3	28	0.990	N	Y	Y	Y	-0.20	0.05	-0.06	0.05
Courtney	2002	2.7	26	0.850	Y	Y	Y	Y	-0.06	0.16	-0.22	0.13
Johnson	2002	1.0	26	0.850	N	Y	Y	Y	-0.01	0.54	-0.02	0.60
Reempts	2003	1.0	29	1.200	Y	Y	Y	Y	0.32	0.03	0.27	0.04
Schreiber	2003	14.0	27	0.980	Y	Y	Y	Y			-0.04	0.05
Craft	2003		26	0.726	N	Y	Y	Y	0.10	0.05	0.09	0.03
Vento	2005	0.3	27	0.880	N	Y	Y	Y	-1.44	0.01	-1.20	0.00

Year: Number of years after the first included study. Time CMV: Mean time on CMV before start of the study in hours. Age: Mean gestational age (weeks). Weight: mean birth weight (kg). HLVS: High lung volume strategy in the HFV group. LPVS: Lung protective ventilation strategy in the CMV group. Surf: Use of surfactant in the study. CLD: Chronic Lung Disease, defined as on oxygen at 30-36 weeks postmenstrual age. LnRR: Natural log of the relative risk.

Figure 2. Linear regression analyses of Year of Publication

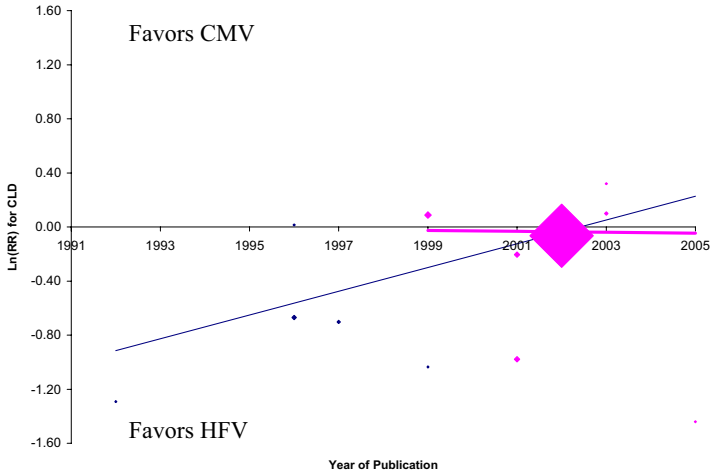
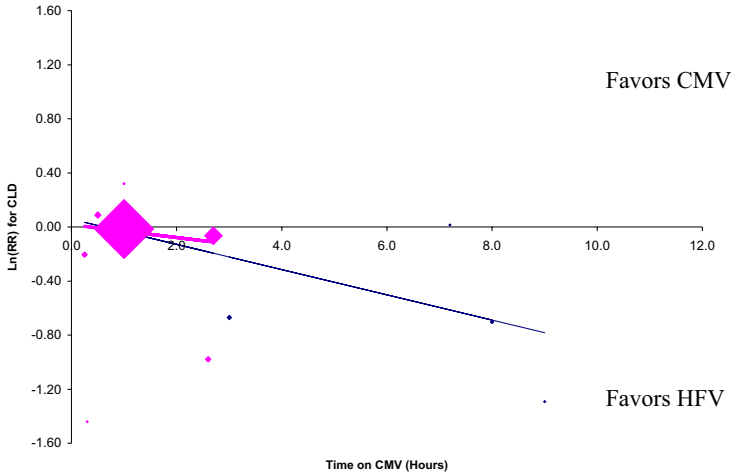
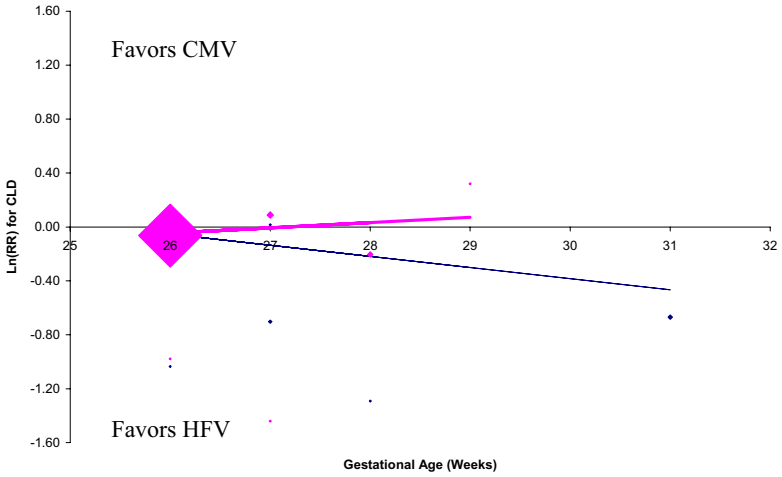


Figure 3. Linear regression analyses of Time on CMV



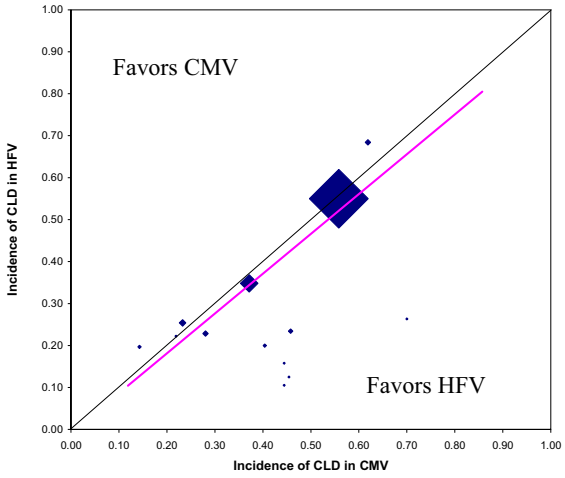
Crude and subgroup linear regression analyses of the effect of year of publication, prior time on CMV and gestational age with natural logarithm of RR of CLD as dependent variable. Y-axis: natural logarithm of the RR. X-axis: explanatory variables. Blue diamonds: studies with either no HLVS or no LPVS. Pink diamonds: studies with both HLVS and LPVS. Thin blue line: regression line including all studies. Thick pink line regression line including only studies with both HLVS and LPVS.

Figure 4. Linear regression analyses of Gestational Age



Crude and subgroup linear regression analyses of the effect of year of publication, prior time on CMV and gestational age with natural logarithm of RR of CLD as dependent variable. Y-axis: natural logarithm of the RR. X-axis: explanatory variables. Blue diamonds: studies with either no HLVS or no LPVS. Pink diamonds: studies with both HLVS and LPVS. Thin blue line: regression line including all studies. Thick pink line regression line including only studies with both HLVS and LPVS.

Figure 5 Incidence of CLD in HFV as a function of incidence of CLD in CMV



Y-axis: incidence of CLD in HFV. X-axis: incidence of CLD in CMV. Thin pink line: regression line including all studies.

Table 3

All Studies

CLD	*Crude B*	*Sig.*	*95% Confidence Interval Lower Bound*	*Upper Bound*	*RRR*	*95% Confidence Interval Lower Bound*	*Upper Bound*
Year	0.09	**0.025**	0.01	0.16	3.13	1.18	8.27
SensorM	-0.17	0.351	-0.55	0.21	0.84	0.58	1.24
TimeCMV	-0.09	0.055	-0.19	0.00	0.44	0.19	1.02
Age	-0.08	0.237	-0.23	0.06	0.66	0.32	1.36
Weight	-0.76	0.163	-1.87	0.35	0.54	0.22	1.33
HLVS	-0.11	0.883	-1.74	1.52	0.89	0.17	4.57
LPVS	0.64	**0.009**	0.19	1.10	1.91	1.21	3.00
Surf	1.21	0.168	-0.59	3.00	3.34	0.56	20.03
CMV	-0.18	0.774	-1.53	1.17	0.90	0.42	1.92

Death or CLD	*Crude B*	*Sig.*	*95% Confidence Interval Lower Bound*	*Upper Bound*	*RRR*	*95% Confidence Interval Lower Bound*	*Upper Bound*
Year	0.05	0.096	-0.01	0.12	2.01	0.86	4.65
SensorM	-0.17	0.132	-0.39	0.06	0.85	0.67	1.06
TimeCMV	-0.01	0.590	-0.05	0.03	0.92	0.65	1.29
Age	-0.02	0.733	-0.13	0.10	0.91	0.52	1.61
Weight	-0.22	0.611	-1.16	0.71	0.84	0.40	1.77
HLVS	-0.37	0.698	-2.44	1.69	0.69	0.09	5.45
LPVS	0.19	0.275	-0.18	0.56	1.21	0.84	1.76
Surf	0.52	0.289	-0.51	1.56	1.69	0.60	4.75
CMV	-0.02	0.963	-0.91	0.87	0.99	0.60	1.63

Univariate linear regression analyses were calculated for CLD: Chronic Lung Disease, defined as on oxygen at 30-36 weeks postgestational age, and death or CLD. The following co-variates were evaluated: Year: Number of years after the first included study. SensorM: Whether or not a SensorMedics was used. TimeCMV: Mean time on CMV before start of the study in hours. Age: Mean gestational age (weeks). Weight: mean birth weight (kg). HLVS: High lung volume strategy in the HFV group. LPVS: Lung protective ventilation strategy in the CMV group. Surf: Use of surfactant in the study. B was the estimated crude coefficient. RRR: relative risk rate= RRcovariate=1/RRcovariate=0, for binary variables (SensorM, HLVS and LPVS), for continues variables the extreme values reported in the studies were used, 13 for years, 8.7 for Time on CMV, 5 for Age, 0.8 for Weight and 0.65 for CMV (RRRyears= RRyear=2005/RRyear=1992, RRRtime on CMV= RRtime=9 hours/RRtime=0.3 hours, RRRage= RRage=31 weeks/RRyear=26 weeks, RRRweight= RRweight=1.5 kg/RRyear=0.7 kg, RRRincidence of CLD in CMV= RRincidence=0.75/RRincidence=0.08).

Studies with Surfactant, HLVS and LPVS

CLD	*B*	*Sig.*	*95% Confidence Interval Lower Bound*	*Upper Bound*	*RR R*	*95% Confidence Interval Lower Bound*	*Upper Bound*
Year	0.00	0.971	-0.23	0.22	0.96	0.05	17.34
TimeCMV	-0.05	0.698	-0.34	0.25	0.66	0.05	8.75
Age	0.04	0.727	-0.22	0.30	1.22	0.33	4.49
Weight	0.41	0.693	-1.99	2.81	1.38	0.20	9.44

Death or CLD	*B*	*Sig.*	*95% Confidence Interval Lower Bound*	*Upper Bound*	*RR R*	*95% Confidence Interval Lower Bound*	*Upper Bound*
Year	0.01	0.846	-0.15	0.17	1.20	0.15	9.72
TimeCMV	0.00	0.819	-0.05	0.04	0.96	0.65	1.43
Age	0.06	0.406	-0.10	0.21	1.34	0.61	2.92
Weight	0.55	0.396	-0.89	1.99	1.55	0.49	4.90

small outlying studies determined the direction of the coefficients of the regression lines [10;11;13;15;17;24]. Crude estimations of these coefficients showed an increase of the RR over the years to the line of no effect. A decreasing time on CMV prior to study initiation seemed to be related to increasing RRs. Higher gestational age and increase of birth weight seemed to be positively associated with increase of RR.

Figure 5 shows how incidence of CLD in the CMV treated patients related to incidence in HFV treated patients. The diagonal line represents the line of no effect in this figure. A trend line was fitted by weighted linear regression, showing a small effect of change in incidence in CMV on incidence in HFV treated patients.

Univariate meta-regression analyses with relative risk of CLD as dependent variable showed significant associations with year of publication and whether or not a protective ventilation strategy was applied

with CLD (Table 2). In the univariate regression analyses with death or CLD as composite outcome no significant associations were detected. Whether or not a SensorMedics high frequency oscillatory ventilator was used and baseline incidence in CMV treated patients displayed the smallest effects on outcomes (RRR = 0.84 and 0.90 for CLD and RRR = 0.85 and 0.99 for death or CLD, respectively).

No change in relative risk for CLD remained over years of publication in the subgroup of studies with HLVS, LPVS and concomitant use of surfactant and a smaller increase in relative risk for death or CLD (RRR = 0.96 and RRR = 1.20, Table 2 and Figure 2). Opposite effects of gestational age (RRR = 1.22 for CLD and 1.38 for death or CLD versus RRR = 0.66 for CLD and 0.91 for death or CLD respectively) and birth weight were detected in the subgroup analysis (Table 2 and Figure 4). Prior time on CMV exerted less effect on outcome compared with the crude

Table 4

Model A

CLD	*Adjusted*		*95% Confidence Interval*			*95% Confidence Interval*	
	B	*Sig.*	*Lower Bound*	*Upper Bound*	*RRR*	*Lower Bound*	*Upper Bound*
(Constant)	-0.66	0.900	-13.03	11.70			
SensorM	-0.04	0.884	-0.75	0.66	0.96	0.47	1.94
TimeCMV	-0.02	0.903	-0.38	0.34	0.85	0.04	19.22
Age	0.03	0.850	-0.36	0.42	1.17	0.16	8.32
HLVS	-0.88	0.306	-2.80	1.04	0.42	0.06	2.84
LPVS	0.70	0.506	-1.73	3.14	2.02	0.18	23.12

Death or CLD	*Adjusted*	*Sig.*	*95% Confidence Interval*			*95% Confidence Interval*	
	B		*Lower Bound*	*Upper Bound*	*RRR*	*Lower Bound*	*Upper Bound*
(Constant)	-1.86	0.412	-7.22	3.49			
SensorM	-0.17	0.309	-0.55	0.21	0.85	0.58	1.24
TimeCMV	0.01	0.722	-0.05	0.06	1.07	0.68	1.69
Age	0.08	0.299	-0.09	0.25	1.47	0.62	3.47
HLVS	-0.88	0.407	-3.38	1.62	0.42	0.03	5.06
LPVS	0.68	0.127	-0.28	1.65	1.98	0.76	5.19

Model B

CLD	*Adjusted*		*95% Confidence Interval*			*95% Confidence Interval*	
	B	*Sig.*	*Lower Bound*	*Upper Bound*	*RRR*	*Lower Bound*	*Upper Bound*
(Constant)	0.07	0.904	-1.21	1.35			
SensorM	-0.06	0.698	-0.38	0.26	0.94	0.69	1.30
HLVS	-0.81	0.203	-2.14	0.52	0.44	0.12	1.68
LPVS	0.72	**0.011**	0.21	1.23	2.06	1.23	3.43

Death or CLD	*Adjusted*	*Sig.*	*95% Confidence Interval*			*95% Confidence Interval*	
	B		*Lower Bound*	*Upper Bound*	*RRR*	*Lower Bound*	*Upper Bound*
(Constant)	0.31	0.706	-1.47	2.09			
SensorM	-0.11	0.318	-0.33	0.12	0.90	0.72	1.13
HLVS	-0.79	0.363	-2.66	1.08	0.45	0.07	2.93
LPVS	0.46	0.089	-0.09	1.01	1.59	0.92	2.74

Multivariate linear regression analyses were calculated for CLD: Chronic Lung Disease, defined as on oxygen at 30-36 weeks postgestational age, and death or CLD. The following co-variates were evaluated: SensorM: Whether or not a SensorMedics type of HFV was used. TimeCMV: Mean time on CMV before start of the study in hours. HLVS: High lung volume strategy in the HFV group. LPVS: Lung protective ventilation strategy in the CMV group. B was the adjusted estimated coefficient. RRR: relative risk rate= RRcovariate=1/RRcovariate=0, for binary variables (SensorM, HLVS and LPVS), for continues variables the extreme values reported in the studies were used, 8.7 for Time on CMV (RRRage= RRage=31 weeks/RRyear=26 weeks).

analysis, RRR = 0.66 for CLD and 0.96 for death or CLD and RRR = 0.44 for CLD and 0.92 for death or CLD in the adjusted and crude analyses respectively (Table 2 and Figure 3).

Multivariate regression analyses were conducted to assess the independent contributions to change in RR by explanatory variables (Table 3). Year of publication was not considered as an independent explanatory variable but rather as proxy for changes in treatment and patient population. Gestational age and birth weight were collinearly related by nature; only gestational age was fitted in the model. One study contributed to the fact that surfactant was not used; therefore, surfactant was not used in the multivariate regression analyses. Two models were fitted. Generally, the resulting estimates showed large confidence intervals. Model A used

SensorMedics, time on CMV, gestational age, HLVS and LPVS as covariates. The largest estimated effects were caused by ventilation strategies, HLVS and LPVS, adjusted for use of SensorMedics ventilator, prior time on CMV and gestational age. These estimations were consistent for the outcomes CLD (RRR = 0.42 and RRR = 2.02 for HLVS and LPVS respectively) and death or CLD (RRR = 0.42 and RRR = 1.98 fro HLVS and LPVS respectively). Use of a SensorMedics ventilator seemed to have a much smaller effect on RR for outcome. The RRR of gestational age, comparing 26 weeks with 31 weeks, for CLD and death or CLD were larger (RRR = 1.17 and RRR = 1.47). The effect of a difference in prior time on CMV of 8.7 hours on CLD versus death or CLD was not consistent (RRR = 0.85 and RRR = 1.07).

As the effects of gestational age and time on CMV were susceptible to small studies with outlying results, a sensitivity analysis was conducted by fitting a second model (Model B) with the most important variables, HLVS and LPVS combined with whether or not a SensorMedics ventilator were used. The reported RRRs were comparable with those in the first model. Type of ventilator did not have a large effect compared with ventilation strategies (RRR = 0.94 and RRR = 0.90). HLVS was associated with a decrease of the RRs comparing HFV with CMV (RRR = 0.44 and RRR = 0.45), while LPVS increased the RRs to the line of no effect (RRR = 2.06 and RRR = 1.59).

Discussion

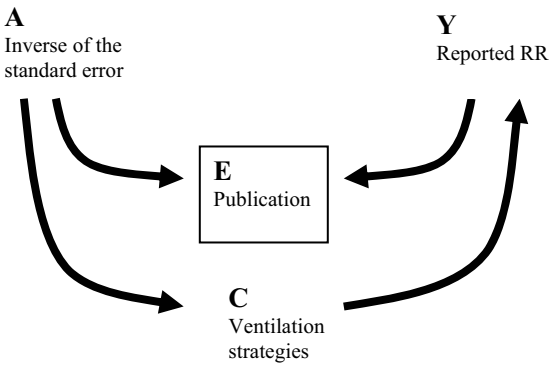
Meta-regression analysis showed a clear trend of decreasing differences in pulmonary outcome between HFV and CMV in randomized trials conducted in premature neonates with IRDS. The most likely hypothesis for this trend was the application of a LPVS in the most recent studies. Use

of surfactant could also have a significant contribution, but only one study did not use surfactant [10]. This made it more difficult to ascertain the effect of surfactant on the change of RR.

In this meta-analysis we evaluated in a quantitative way a number of hypotheses that were raised in randomized trials to account for different results. A relatively large proportion of well conducted trials were available for the analyses. For most explanatory variables there were important differences between trials. The effects of the two most important covariates, HLVS and LPVS, were consistent in the different models and were even increased in effect size by adjusting for other covariates. None of the competing hypothesis were more likely to influence results as shown by calculating the RRRs. However, inferences should be made with caution due to a large amount of uncertainty.

Publication bias was considered unlikely as an explanation of the apparent diminishing relative effect of HFV. Publication bias is selection bias as explained in Figure 6. If only large studies or studies with significant results would be published, then conditioning on only published studies (i.e. selection bias) would result in a relation between study size and reported RR indicating publication bias. However, if larger studies were also associated with changes in ventilation strategies and these strategies resulted in changes in reported RRs, the assumed publication bias would be in fact a real association. Therefore, we conditioned the association between precision and effect size, presumably caused by publication bias, on ventilation strategies. This resulted in a much lower p-value for publication bias. Thus, what appeared to be publication bias was probably due to differences in ventilation strategies related to both study size and observed relative risks.

Figuur 6. Directed Acyclic Graph (DAG) of Publication Bias



A: exposure, Y: outcome, E: common effect, C: confounder. Selection bias is caused by conditioning on the common effect (study being published) of study size/precision and the reported RR. When there is no conditioning on whether or not studies are preferentially published, there is no association. However, if study size and ventilation strategies would be associated and ventilation strategy would be related to RR as well, selection bias could be inferred but in reality not exist.

Other alternative hypotheses that have been formulated to explain differences between studies were also less compatible with the evidence [7]. The type of ventilator, SensorMedics versus other types of high frequency ventilators, displayed low RRR close to one. In the crude analyses, prior time on CMV before study initiation showed contradictory effects to what was hypothesized [8]. The adjusted analyses showed conflicting results depending on the outcome. Therefore, confounding effects of prior time on CMV on HLVS or LPVS could not be established. Gestational age and birth weight could also influence the magnitude of the effect of HFV compared with CMV. Again, a counterintuitive effect was seen in the crude analysis. In the adjusted analysis gestational age did not change the RR for CLD but showed an increase of the RR for less premature neonates. Finally an increased risk of CLD could increase the relative benefit of

HFV. Susceptibility for CLD was estimated using the incidence of CLD in CMV treated patients. Increase in incidence of CLD in CMV was not accompanied by larger RRs comparing HFV with CMV.

The observed effects of continuous variables like time on CMV or gestational age could be exaggerated by small studies with outlying results. However, the meta-regression analysis we conducted was weighted by the inverse variance of the studies. Still, the magnitude of effect could be overstated. For the covariate, time on CMV, the two largest studies showed results that were compatible with the hypothesis that this had no important impact on the results of these trials [19;20]. The same applied to the effect of baseline incidence of CLD or death or CLD. Gestational age and weight were comparable between the two largest trials which made it more difficult to ascertain the relevance of the hypothesis that in smaller and more premature infants HFV performed better than CMV treatment. The observed direction of the effect of gestational age and birth weight, however, was opposite to what the hypothesis predicted. If gestational age was to be interpreted as a higher risk of acquiring CLD, one would expect that an increase in the incidence of CLD was associated with a relatively lower incidence of CLD in HFV treated patients. However, linear regression analysis showed perfectly equal increase in both treatment groups.

Similar findings of the effects of ventilation strategies have been reported by us and other authors as well [2;3]. However, meta-analyses are subject to bias when differences between trials are used to explain differences in reported RRs. In this meta-regression analysis we were able to estimate adjusted association measures, thereby, diminishing the effects of possible confounders. By calculating less biased estimates of the effects of ventilation strategies and the effect of using a SensorMedics ventilator instead of other ventilators on the outcome in the different HFV trials we

were able to reinforce the hypothesis that ventilation strategies are more important than type of ventilator to prevent CLD.

The major advantage of HFV to CMV is delivery of smaller tidal volumes to an optimally recruited lung. Assuming that there is a safe window in the pressure volume curve of a lung between a lower zone with atelectasis and a upper zone with over-distension, surpassing this zone would result in either cyclic recruitment and de-recruitment, over-distension, or both. As this meta-regression analysis did not confirm that subgroups of more premature neonates, avoidance of CMV prior to initiating HFV, or neonates with higher risk of CLD were more likely to benefit form elective HFV in IRDS, future research should be directed at identifying patients in which the safe window becomes too small to harbour tidal volumes delivered by CMV.

In conclusion, confining randomized trials to smaller or more premature children with IRDS did not seem to result in better pulmonary outcomes of HFV compared with CMV. A generally held opinion that a prolonged ventilation time on CMV prior to initiating HFV diminished the benefits of HFV was not in agreement with the current evidence. The most important effects resulting in differences between trials were probably caused by ventilation strategies applied in HFV and CMV treated patients.

Appendix

Oxygenation Index = (FiO2*MAP*100) / paO2, where: FiO2 = Fraction of inspired oxygen, paCO2 = Pressure of arterial carbon dioxide, paO2 = Pressure of arterial oxygen, SaO2 = Arterial oxygen saturation.

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Chapter 4.

Sequential meta-analysis to determine whether or not to start another trial: the high frequency versus conventional mechanical ventilation example

Sequential analysis shows value of new trials

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ABSTRACT

Background

Clinical trials can be stopped early based on interim analyses or sequential analyses. Sequential analyses could also be applied to decide if already enough evidence is gathered in previous trials. In a number of clinical trials, high frequency ventilation has been compared with conventional mechanical ventilation in premature neonates with idiopathic respiratory distress syndrome. Sequential meta-analysis was used to determine whether more trials have to be performed.

Methods

Five trials were selected that compared high frequency ventilation applying a high lung volume strategy with conventional mechanical ventilation using a lung protective ventilation strategy. Death or chronic lung disease and chronic lung disease in survivors were primary clinical outcomes of interest. Sequential meta-analyses were applied to these five studies.

Results

After including the first study of the last five trials in a sequential meta-analysis, the boundary of no clinically relevant effect was crossed for the outcome, death or chronic lung disease. A sensitivity analysis using a reduction in the size of assumed clinically relevant effect showed the same findings after two trials. The same result was found for reduction of chronic lung disease in survivors as outcome.

Conclusions

Sequential meta-analyses showed that already in the first out of five studies a lack of clinically relevant effect was established of high frequency oscillatory ventilation compared with conventional mechanical ventilation in premature neonates. This could have been an important argument in decisions to change the study design or even refrain from performing the last four trials.

Introduction

Whether or not to start a randomized clinical trial (RCT) should depend on the expected ability of the yielded evidence in such a trial to change current clinical opinion, taking into account previously obtained evidence. It is a matter of good statistical practice to make a prior estimate of the required size of a randomized clinical trial, based on the expected clinically relevant difference between treatments, the power 1-β and the significance level α. Stopping randomized clinical trials early, before the estimated fixed size is reached, is readily accepted for ethical or economical reasons. One or more interim analyses can be planned to determine whether enough evidence has been obtained to discontinue a trial prematurely. Interim analyses are performed on cumulative data of patients successively included in a RCT. Sequential testing is a collective noun for these interim analyses. We speak of continuous sequential testing, when cumulative data are analyzed after every new patient response.

Group sequential testing is a series of interim analyses after every new group of patient responses. A meta-analysis pools the results of a number of comparable RCTs in a systematic and quantitative way [1]. A cumulative meta-analysis can be viewed as a number of interim analyses on the aggregated data of successive, chronologically ordered RCTs. A cumulative meta-analysis is thus a group sequential test, but each group now represents patients from another trial [2]. In the following we will introduce the sequential meta-analysis as a particular form of a cumulative meta-analysis with adjustment for multiple testing and a guaranteed power (see Discussion for further comments). We applied a sequential meta-analysis to determine whether or not enough evidence was gathered already in a number of published RCTs.

Avoidance of ventilator induced lung damage is a major issue in research of mechanical ventilation. It is generally thought that prevention of repeated collapse of alveoli and limiting overdistension of alveoli protects the lung from the adverse effects of mechanical ventilation [3]. Therefore, lung protective ventilation strategies aim at reducing tidal volumes and maintaining higher mean airway pressures. A considerable number of randomized clinical trials have been performed to determine whether high frequency oscillatory ventilation improves pulmonary outcome in premature neonates with idiopathic respiratory distress syndrome compared with conventional mechanical ventilation [4-16]. High frequency oscillatory ventilation is a method of ventilation in which alveolar gas exchange is maintained by pressure swings initiating small displacements of ventilatory gases, considerably smaller than conventional tidal volumes, at frequencies generally from 5-20 Hz superimposed on a continuous positive pressure. High frequency oscillatory ventilation allows higher end-expiratory pressures with lower tidal volumes and higher mean airway pressures and is therefore proposed as currently the most optimal form of lung protective ventilation [17;18].

Two recent large randomized controlled trials failed to demonstrate a significant advantage of high frequency oscillatory ventilation over conventional mechanical ventilation, or showed only a small benefit [14;15]. A meta-analysis showed no reduction in mortality. However, a small reduction was shown in the risk of chronic lung disease at 36-37 weeks post-gestational age [19]. Our study used sequential meta-analysis to determine at what point in time additional trials did not contribute anymore to available evidence.

Methods

In a previous report we identified 13 studies in which high frequency ventilation was compared with conventional mechanical ventilation in the treatment of idiopathic respiratory distress syndrome in premature neonates [20]. The last five studies were comparable with respect to patient population, type of high frequency ventilation (oscillator) and ventilation strategies that were applied in both high frequency oscillatory ventilation and conventional mechanical ventilation [11;13-16]. These five studies were included chronologically in our sequential meta-analysis. The following data were extracted: gestational age or birth weight; time of inclusion; type of high frequency ventilator; ventilation strategies applied in both treatment arms; primary outcome measurements; power and estimated effect size upon which power analysis was based. The following outcome measures were identified: chronic lung disease, defined as oxygen dependency at the postconceptional age of 36 weeks; mortality to 36 weeks of age; intraventricular hemorrhage grade III and IV; and periventricular leukomalacia.

A high lung volume strategy with high frequency ventilation was assumed if two or more of the following items were explicitly stated in the methods: initial use of a higher mean airway pressure than on conventional mechanical ventilation; initial lowering of inspired oxygen before reducing mean airway pressure; and/or use of alveolar recruitment maneuvers. A lung protective strategy in the conventional mechanical ventilation group was based on specifying the PaCO2 goal, allowing permissive hypercapnia, and a high initial ventilatory rate and/or explicit avoidance of high peak inspiratory pressures, targeted at reducing tidal volumes.

Statistical analysis

An a priori estimate of the expected effect size of the primary outcome was deduced from reported expected clinically relevant differences in power analyses of included studies. A probability of 0.05 for a type I error and a power of 0.80 were specified in our sequential meta-analyses Sensitivity analyses were performed diminishing the expected differences in effect estimates and excluding studies by Thome et al [11] and Moriette et al [13] from the analyses. Those last studies were excluded in sensitivity analysis because of methodological reasons. Thome et al [11] used a different type of HFV ventilator and the HFV used by Moriette et al [13] was withdrawn from market. Reducing the size of clinically interesting effect would ordinarily require a larger sample size for that difference to be detected. Sensitivity analysis thus was conducted to rule out the need for more trials to establish smaller clinically relevant differences. All data were extracted according to the intention-to-treat principle. For the outcome chronic lung disease or death, the total number of randomized patients was put in the denominator with patients that died or with chronic lung disease in the numerator. To calculate the risk of chronic lung disease, the denominator was equal to the number of patients that survived and the numerator was equal to the number of patients with CLD.. Intraventricular hemorrhage grade III and IV and periventricular leukomalacia were determined with the number of randomized patients in the denominator. Statistical heterogeneity between trials was investigated by calculating the test statistic I^2 ($I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom) [21].

Sequential meta-analysis

The ith of the chronologically appeared RCTs contributes two quantities V_i and Z_i to the cumulative amount of information. V_i is a measure for the amount of information in that RCT, i.e. V_i is approximately proportional to the number of patients included in that RCT. Z_i is a measure for the effect

size in that RCT. After every new RCT the total amount of information is cumulated in $V = \Sigma V_i$ and $Z = \Sigma Z_i$. Z and V are thus the pooled results from different trials and the sequential meta-analysis can be viewed as a stratified analysis (see Appendix). Every new RCT thus results in a new (Z,V)-point, depicted in a graph with V on the horizontal and Z on the vertical axis. Four boundaries are plotted in the graph. These boundaries depend on the two-sided type I error α, the power $1-\beta$ and the expected effect size (in terms of the logarithm of the odds ratio (OR)) as stated under the alternative hypothesis. If the successive (Z,V)-points cross the upper or lower boundary, the sequential meta-analysis can be stopped: the null hypothesis of treatment equivalence is rejected in favour of the alternative hypothesis, i.e. significant evidence is gathered for the expected effect size. If the successive (Z,V)-points cross one of the inner, wedge-shaped boundaries, the sequential meta-analysis can be stopped for 'futility': the null hypothesis is accepted, i.e. it is very unlikely that the treatments will be concluded different in the amount as stated under the alternative hypothesis. If the successive (Z,V)-points remain within the triangular boundaries, results of a new RCT are added to the analysis. The outer straight-line boundaries represent the theoretical limits for decision-making. The inner, curved boundaries represent a continuity correction, because the unit of analysis is the trial (a group of patients) and not the individual patient. (For illustration see Figures 1 and 2). Specifically, when one of the inner boundaries is crossed one can stop the analysis.
For further details on the construction of the boundaries and on sequential analysis see ref. 1, 22 and 23 [1;22;23].

Results

Five high frequency ventilation studies were evaluated with a total number of 2152 patients randomized. Those five trials used both a high frequency

oscillatory ventilator with a high lung volume strategy in the high frequency oscillatory ventilation group, and a lung protective ventilation strategy in the conventional mechanical ventilation group. In Table 1 the exact numbers of the outcomes of interest are tabulated. The cumulative evidence of those five studies comparing high frequency oscillatory ventilation with conventional mechanical ventilation showed an OR of 0.92 (95% CI 0.77-1.09) for death or chronic lung disease, an OR of 0.98 (95% CI 0.80-1.21) for chronic lung disease in survivors, an OR of 1.01 (95% CI 0.79-1.29) for intraventricular hemorrhage grade III and IV and an OR of 0.90 (95% CI 0.62-1.33) for periventricular leukomalacia.

Table 1. Randomized Clinical Trials comparing high frequency ventilation with conventional mechanical ventilation.

	Author	Year	HLVS	LPVS	Death or CLD at 36 weeks or discharge		CLD 36 weeks in survivors	
					HFOV	*CMV*	*HFOV*	*CMV*
1	Thome	1999	Y	Y	43/140 (31%)	44/144 (31%)	32/126 (25%)	30/129 (23%)
2	Moriette	2001	Y	Y	55/148 (37%)	57/144 (40%)	24/105 (23%)	30/107 (28%)
3	Courtney	2002	Y	Y	103/244 (42%)	133/254 (52%)	70/201 (35%)	93/210 (44%)
4	Johnson	2002	Y	Y	265/400 (66%)	268/397 (68%)	165/300 (55%)	163/292 (56%)
5	Reempts	2003	Y	Y	49/147 (33%)	39/153 (25%)	24/122 (20%)	19/133 (14%)

	Author	Year	HLVS	LPVS	IVH		PVL	
					HFOV	*CMV*	*HFOV*	*CMV*
1	Thome	1999	Y	Y	19/140 (14%)	18/144 (13%)	3/140 (2%)	0/144 (0%)
2	Moriette	2001	Y	Y	34/148 (23%)	19/144 (13%)	14/148 (9%)	18/144 (13%)
3	Courtney	2002	Y	Y	45/244 (18%)	45/254 (18%)	18/244 (7%)	26/254 (10%)
4	Johnson	2002	Y	Y	38/400 (10%)	55/397 (14%)	8/400 (2%)	8/397 (2%)
5	Reempts	2003	Y	Y	14/147 (10%)	13/153 (8%)	11/147 (7%)	8/153 (5%)

Table 1. HLVS: high lung volume strategy in high frequency ventilation. LPVS: lung protective ventilations strategy in conventional mechanical ventilation. CLD: chronic lung disease at 36 weeks postconceptional age. HFOV: high frequency oscillatory ventilation. CMV: conventional mechanical ventilation.

Table 2. Study design of the last five trials.

Author	Year	Patients		Outcome	Power analysis		
		Age or Weight	*Time (hours)*	*Primary*	*Effect*	*alpha*	*power*
Thome	1999	≥24 and <30 wks	6	treatment failures	difference of 12%	0.05	0.80
Moriette	2001	≥24 and ≤29 wks	6	death or chronic lung disease at 28 days	improvement from 45% to 65%	0.05	0.80
Courtney	2002	601 to 1200 g	4	death or chronic lung disease at 36 weeks	improvement from 50% to 65%	0.05	0.90
Johnson	2002	23 to 28 wks + 6 d	1	death or chronic lung disease at 36 weeks	difference of 9-11%	0.05	0.90
Reempts	2003	<32 wks	6	death or chronic lung disease at 36 weeks	reduction of 60%	0.05	0.80

Table 2. Study design of the last five trials. Time: Age at randomization in hours.

In Table 2 the patient groups, primary outcomes and sample size specifications are mentioned. All studies included very low birth weight patients. Time prior to randomization was no more than 6 hours. Thome et al and Moriette et al used variants of the definition for the primary outcome upon which a power analysis was based [11;13]. However, in both studies death and chronic lung disease were part of the primary outcome. Overall, a reduction in death or chronic lung disease of 15% was expected (corresponding to an OR of 0.54). All trials specified a value of 0.05 for the type I error α. Power for detecting a difference was 0.80 or 0.90.

Treatment with high frequency oscillatory ventilation was comparable between trials (Table 3). Two trials used the SensorMedics ventilator, in two studies the Infant Star was used and Moriette et al used an OHF 1 Dufour ventilator [13]. Mean airway pressure was 2 cmH2O above MAP measured on conventional mechanical ventilation in 2 trials and varied from 6 to 16 cmH2O depending on gestational age of the patient or on FiO2 that was needed. In all but one trial, MAP was decreased only if FiO2

was less than 0.3-0.4. The ventilation strategy in the conventional mechanical ventilation groups did not differ much either between trials. Frequency was set at 60-80 breaths/min and a PEEP of at least 3 cmH2O was applied. Peak inspiratory pressures were explicitly limited in three studies and in all trials a certain amount of hypercapnia was accepted up to 50-70 mmHg. Inconsistency in primary outcome assessed by I^2 was 7.5%, indicating a low percentage of total variation across studies due to heterogeneity.

Sequential meta-analysis showed that one trial already provided enough evidence for no reduction in death or chronic lung disease of 15% (Figure 1). In a sensitivity analysis decreasing the effect to be a reduction of 10% it took only two trials before the boundary for no such reduction was crossed (OR=0.97 with 95% CI(0.68-1.41)). Sensitivity analysis excluding the studies by Thome et al and Moriette et al resulted in an OR of 0.98 (95% CI (0.68 ; 1.39) (data not shown). The same result was found with chronic lung disease as outcome with an estimated effect of 15% reduction (Figure 2). After one trial, by Thome et al, the boundary for no such reduction was crossed (OR=0.89 with 95% CI(0.50-1.58)) [11]. Sequential analyses were also applied with intraventricular hemorrhage grade III and IV and periventricular leukomalacia as outcome measures. For both outcomes there was not enough evidence to draw a definitive conclusion yet (data not shown).

Discussion

To be of value, a new RCT must add to current knowledge. Assessing whether clinical equipoise was present at the start of a new RCT should be general research practice [24]. *"Science is meant to be cumulative, but many scientists are not cumulating scientifically."* (Chalmers in his Comment

Figure 1. CLD or death: 50% (CMV) versus 35% (HFOV)

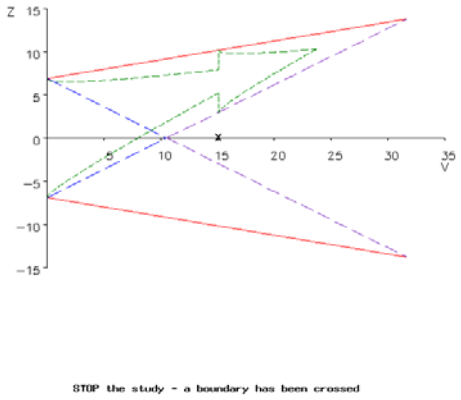
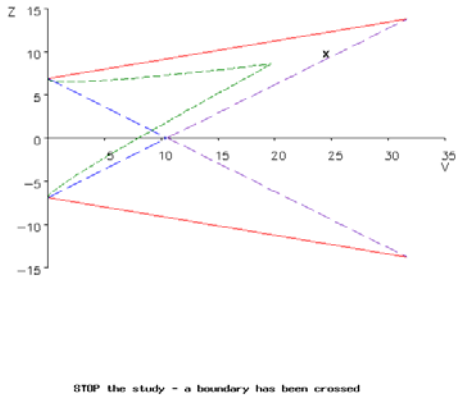


Figure 2. CLD: 50% (CMV) versus 35% (HFOV)



Legend of Figures 1 and 2.

CLD: Chronic Lung Disease. CMV: Conventional Mechanical Ventilation. HFOV: High Frequency Oscillatory Ventilation. The horizontal axis denotes the cumulative amount of information (V) (i.e. a function of the number of patients included). The vertical axis denotes a measure for the cumulative effect size (Z). When one of the upper or lower lines is crossed, the null hypothesis of treatment equivalence is rejected. When one of the inner, wedge-shaped boundariesis crossed, the null hypothesis is accepted. The x-symbol reflects the contribution of the one decisive study. The dashed lines within the straight-line boundaries represent a continuity correction. (see text and Appendix for further explanation.)

on Fergusson et al. (2005)) [25]. Cumulative meta-analysis is recognized as a systematic review technique. Various authors performed cumulative meta-analyses of RCTs on different research questions (amongst others, Lau et al. (1992); Fergusson et al. (2005)) [24;26]. The general approach used is to perform an analysis of the currently available studies and to test the null hypothesis that the two treatments are equally effective. If the test result is not significant, a new trial is added (when its results become available) and the analysis and testing procedure is repeated. This approach continues until a statistically significant result is found, i.e. the null hypothesis is rejected. Berkey et al. (1996) noticed that this general approach does not adjust for the multiple testing and lacks a formal stopping rule and a quantification of the power of the conclusion [27]. We performed a sequential meta-analysis according to the approach as described by A. Whitehead (1997) [28]. Using this approach the overall significance level α (the type I error) is preserved, thus preventing the increase of the cumulative α by multiple testing. Moreover, a prespecified power to detect a clinically relevant treatment difference is guaranteed. Furthermore, this approach permits stopping when enough evidence is gathered either to reject the null hypothesis of treatment equivalence or to accept it.

This is a second report that discusses the relevance of new trials using sequential meta-analysis. In trials with high frequency oscillatory ventilation versus conventional mechanical ventilation as an elective treatment of idiopathic respiratory distress syndrome in premature neonates, a reduction in the composite outcome of death or chronic lung disease at 36 weeks of 10% to 15% was expected. However, after one trial sequential meta-analysis showed no evidence for such reduction. Yet, four more studies were performed, powered to show the same amount of effect [14-16].

To compare trials, equality of treatment between trials is an important requirement. In a recent article we showed that ventilation strategies in high frequency oscillatory ventilation and conventional mechanical ventilation have changed in recent years [20]. In a cumulative meta-analysis ventilation strategies were an important source of heterogeneity between trials. In the last five trials, however, ventilation strategies were comparable and results were homogeneous between trials. A more formal approach showed that only a small amount of variation between trials was due to heterogeneity.

The most important differences between trials consisted of two major advancements in the therapy of idiopathic respiratory distress syndrome: the use of surfactant therapy and the application of a lung protective strategy in patients on conventional mechanical ventilation [20;29]. Both modalities have been applied in the last five trials. In the only trial that showed a reduction in chronic lung disease, the conventional mechanical ventilation therapy was most rigidly controlled [14]. Therefore, it seems unlikely that in daily practice the same difference between high frequency oscillatory ventilation and conventional mechanical ventilation will occur [30]. Various high frequency oscillatory ventilation devices have been applied in different trials. However, we showed that these differences did not explain heterogeneity between trials [20]. Sensitivity analyses excluding studies by Thome et al [11] for use of a flow interrupter type of HFOV and Moriette et al [13] for use of a ventilator that was subsequently withdrawn from the market showed the robustness of our analyses. Furthermore, it has been demonstrated that when applying the same ventilatory objectives, differences between devices are irrelevant because settings are adjusted to achieve the desired effect resulting in comparable high frequency oscillatory ventilation treatment [31;32].

Table 3. Ventilation strategies of the last five trials.

Author	Year	HFOV strategy				
		Ventilator	*Frequency*	*Mean Airway Pressure*	*FiO2*	*Chest X-ray*
Thome	1999	Infant Star	10 Hz	1-2 cmH2O above MAP on CMV; 10-12 cmH2O when primary HFOV	MAP increased until FiO2<0.3	ninth pair of ribs
Moriette	2001	OHF1	Not stated	14 cmH2O if FiO2 < 0.4; 16 cmH2O if FiO2>0.4	MAP increased until FiO2<0.4	Not stated
Courtney	2002	SensorMedics 3100A	10 to 15 Hz	≥2 cmH2O above MAP on CMV	Not stated	expansion to 8 to 9.5 ribs
Johnson	2002	Dräger Babylog 8000; SensorMedics 3100A; SLE 2000HFO	10 Hz	6-8 cmH2O	MAP increased until FiO2<0.3	ninth pair of ribs
Reempts	2003	Infant Star	Not stated	8 cm H2O if <29 weeks; 10 cm H2O if 29–31 6/7 weeks	Not stated	ninth pair of ribs
Author	**Year**	**CMV strategy**				
		Frequency	*PEEP*	*PIP*	*Tidal Volume*	*pCO2*
Thome	1999	60-80 /min	≥3 cmH2O	PIP as low as possible	Not stated	40-60 mm Hg; to 70 mm Hg after the 7th day
Moriette	2001	Not stated	4-5 cmH2O	PIP as low as possible	Not stated	40-50 mm Hg
Courtney	2002	≤60 /min	4-6 cmH2O	Not stated	4-7 ml/kg	40-55 mm Hg; 45 to 65 mm Hg if CLD
Johnson	2002	60 /min	Not stated	Not stated	Not stated	34-53 mm Hg
Reempts	2003	80 /min	4-8 cmH2O	20-30 cmH20	6–8 ml/kg	35-45 mmHg during the acute phase; up to 70 mmHg later

All trials were powered to show a relative reduction of chronic lung disease in survivors using high frequency oscillatory ventilation with a high lung volume strategy compared with conventional mechanical ventilation applying a lung protective strategy. In only one of these trials an improvement in pulmonary outcome was demonstrated that was statistically significant [14]. The inability of the last four trials to change the evidence that there was no improvement to pulmonary outcome was robust to smaller differences in effect size in a sensitivity analysis. With respect to other important clinical outcomes, intraventricular hemorrhage grade III and IV and periventricular leukomalacia, the last five trials did not result in enough evidence to draw definitive conclusions yet. Uncertainty remained as to whether high frequency oscillatory ventilation resulted in more intraventricular hemorrhage grade III and IV and/or periventricular leukomalacia.

In general, a clinical trial is undertaken to test relevant clinical treatment effects. The size of a trial is estimated by a power analysis that is based on an expected effect size and chosen probabilities for type I and II errors. However, this does not answer the question whether this new trial will be able to adjust the available cumulative evidence sufficiently to conclude that a clinically relevant effect can be refuted or accepted. By performing a sequential analysis, i.e. a sequential meta-analysis of earlier comparable trials it can be decided whether enough cumulative evidence has been gathered already to render another trial uninformative. Sequential analysis is already an accepted procedure within a trial. In this report we demonstrated that performing a sequential meta-analysis before starting three randomized trials comparing high frequency oscillatory ventilation with conventional mechanical ventilation could have resulted in a different study design aimed at investigating other more promising hypotheses (e.g. accepting smaller differences in primary outcome in the power analysis or choosing other primary outcome variables).

We think that, in addition to a power analysis, sequential meta-analysis of earlier comparable studies should be an integral part in the planning and design of new randomized trials. As we have shown in this report, the results of sequential meta-analyses can have major consequences for study design or even result in the decision to refrain from starting another trial.

Summarizing, before expanding existing experimental evidence by starting a new randomized clinical trial, it is useful to perform a sequential meta-analysis, to determine whether a treatment effect has already been convincingly established by cumulative evidence of previous trials. Sequential meta-analysis may result in decisions to change study design or even refrain from performing additional randomized trials designed to show the same objectives.

APPENDIX

Suppose k RCTs are available for a sequential meta-analysis. All RCTs compare the same experimental treatment E with a control treatment C and all have the same dichotomous outcome (event or no event). Results from the ith RCT (I=1,…,k) can be summarized in a two-by-two table (Table X).

Table X.

ith RCT	E(xperimental)	C(ontrol)	overall
event	S_{Ei}	S_{Ci}	S_i
no event	F_{Ei}	F_{Ci}	F_i
total	N_{Ei}	N_{Ci}	N_i

The proportions of events with the experimental and with the control treatment are

$P_{Ei} = S_{Ei} / N_{Ei}$ and $P_{Ci} = S_{Ci} / N_{Ci}$, respectively.

The logarithm of the odds ratio, as a measure for association between treatment and outcome, is defined as

$$\theta_i = \log\left\{\frac{P_{Ei}(1-P_{Ci})}{P_{Ci}(1-P_{Ei})}\right\}.$$

The test statistic Z_i is expressed as the difference between the observed number of events with E in the ith RCT (S_{Ei}) and the expected number under the null hypothesis of treatment equivalence.

$$Z_i = S_{Ei} - N_{Ei}S_i / N_i.$$

The statistic V_i, the variance of Z_i, is defined as

$$V_i = \frac{N_{Ei}N_{Ci}S_iF_i}{N_i^2(N_{i-1})}$$

The pooled estimate for the overall θ is equal to

$$\hat{\theta} = \frac{\sum_i \hat{\theta}_i w_i}{\sum_i w_i} = \frac{\sum_i Z_i}{\sum_i V_i}, \text{ with } \hat{\theta}_i = \frac{Z_i}{V_i} \text{ as the estimated log(OR)}$$

for the ith RCT and the weighting factor $w_i = V_i$.

An approximate 95% confidence interval for θ can be estimated by

$$\hat{\theta} \pm 1.96 \sqrt{\frac{1}{\sum_i w_i}}.$$

(For further details see References 1, 22 and 23.)

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Chapter 5.

High Frequency Oscillatory Ventilation compared with Conventional Mechanical Ventilation in Acute Respiratory Distress Syndrome: a randomized controlled trial

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ABSTRACT

Introduction

To compare the safety and efficacy of High Frequency Oscillatory Ventilation (HFOV) with Conventional Mechanical Ventilation (CV) for early intervention in Acute Respiratory Distress Syndrome (ARDS), a multi-centre randomized trial in four intensive care units was conducted.

Methods

Patients with ARDS were randomized to receive either HFOV or CV. In both treatment arms a priority was given to maintain lung volume while minimizing peak pressures. CV ventilation strategy was aimed at reducing tidal volumes. In the HFOV group, an open lung strategy was used. Respiratory and circulatory parameters were recorded and clinical outcome was determined at 30 days of follow up.

Results

The study was prematurely stopped. Thirty-seven patients received HFOV and 24 patients CV (average APACHE II score 21 and 20, oxygenation index 25 and 18 and duration of mechanical ventilation prior to randomization 2.1 and 1.5 days, respectively). There were no statistically significant differences in survival without supplemental oxygen or on ventilator, mortality, therapy failure, or crossover. Adjustment by a priori defined baseline characteristics showed an odds ratio of 0.80 (95% CI 0.22-2.97) for survival without oxygen or on ventilator, and an odds ratio

for mortality of 1.15 (95% CI 0.43-3.10) for HFOV compared with CV. The response of the oxygenation index (OI) to treatment did not differentiate between survival and death. In the HFOV group the OI response was significantly higher than in the CV group between the first and the second day. A post hoc analysis suggested that there was a relatively better treatment effect of HFOV compared with CV in patients with a higher baseline OI.

Conclusions

No significant differences were observed, but this trial only had power to detect major differences in survival without oxygen or on ventilator. However, in patients with ARDS and higher baseline OI there might be a treatment benefit of HFOV over CV. More research is needed to establish the efficacy of HFOV in the treatment of ARDS. We suggest that future studies are designed to allow for informative analysis in patients with higher OI.

Introduction

Mechanical ventilation of patients with adult respiratory distress syndrome (ARDS) may cause lung injury and, subsequently, multi-organ failure [1]. Multi-organ failure is a major cause of death in ARDS [2]. In particular, repetitive opening and closure of alveoli with significant shear forces exerted to the alveolar walls and over-distension of alveoli and small airways are thought to be main factors leading to ventilator induced lung injury. Lung protective ventilation strategies with low tidal volumes and high end-expiratory pressures are used to prevent ventilator induced lung injury [3]. In high frequency oscillatory ventilation (HFOV), extremely small tidal volumes are combined with a high mean airway pressure to prevent atelectasis and at the same time limit peak inspiratory pressures. HFOV is suggested, by some, to be the theoretically most optimal form of lung protective ventilation [4]. However, the role of HFOV in ARDS has to be established yet.

Most studies comparing HFOV with conventional mechanical ventilation (CV) have been performed in premature neonatal patients [5]. The routine use of HFOV as an elective treatment in premature neonates with respiratory distress is equivocal. In a recent paper we have argued that improvements in CV diminished the relative benefit of HFOV [6]. There is much less evidence in adult and paediatric patients. Three non-randomized prospective trials and no more than two randomized controlled trials in patients with ARDS have been published to establish the safety and efficacy of HFOV [7-11]. In these trials, the oxygenation index (OI), a cost benefit ratio of inspired oxygen times airway pressure divided by arterial oxygen pressure ([OI = FiO2 x MAP x 100] / paO2), was an important predictor of mortality.

We performed a randomized controlled trial designed to test the safety and efficacy of HFOV as a primary mode of ventilation in ARDS patients compared with CV. This study was prematurely terminated because of a low inclusion rate and the completion of a similar trial [7]. We compared survival without supplemental oxygen or on ventilator, mortality, therapy failure and crossover.

Methods

Between October 1997 and March 2001 61 patients were enrolled in a randomized controlled trial comparing HFOV with CV in patients with ARDS to detect differences in mortality, therapy failure and ventilatory support at 30 days. This study was conducted in intensive care units in London, Cardiff, Paris and Mainz. Patients with ARDS and a bodyweight greater than 35 kg were randomized to receive either HFOV or CV. ARDS was defined as the pressure of arterial oxygen divided by the fraction of inspired oxygen (paO2 / FiO2) les than 200 mmHg, radiographic evidence of bilateral infiltrates on chest X-ray and no evidence of atrial hypertension. Patients with a non-pulmonary terminal disease, severe chronic obstructive lung disease or asthma and grade 3 or 4 air-leak were excluded. Patients with FiO2 > 0.80 for 48 hours or more than 10 days of mechanical ventilation before meeting the entry criteria were excluded as well. Randomization was by a sequentially numbered computerized randomization algorithm. The allocation to treatment was concealed until study entry. This study was approved by the ethical committee board of all participating institutions and was in compliance with the Helsinki Declaration. Informed consent was obtained from next of kin of patients prior to study entry.

The general physiological targets for the two ventilator arms were similar. The oxygenation goal was to maintain an O2 saturation ≥ 88% or paO2 > 60 mmHg with a FiO2 < 0.6. The ventilatory goal was to establish an arterial pH > 7.20 and a HCO3 > 19 mmol/l while minimizing peak inspiratory pressures irrespectively of arterial carbon dioxide (paCO2). The priority in both treatment arms was to maintain lung volume by first weaning FiO2 to < 0.60 after which mean airway pressure and FiO2 were given equal priority for reduction. Patients were crossed over to the alternative ventilator in case of therapy failure: intractable hypotension despite maximum support (RR mean < 60 mmHg > 4 hours or < 50 mmHg > hour), intractable respiratory acidosis (pH , 7.20 at HCO3 > 19 mmol/l for > 6 hours), oxygenation failure (rising OI of more than two times since study entry or OI > 42 after 48 hours) and grade 4 air leak: air leak with multiple recurrences (> 4), air leak requiring more than two chest tubes per hemithorax, air leak continuing longer than 120 hours or pneumopericardium or pneumoperitoneum. Patients could be withdrawn from the study treatment for the following reasons: withdrawal of consent, weaned from mechanical ventilation, death or treatment failure after crossover.

In the CV treated group, patients were treated with time cycled pressure controlled ventilation. Respiratory rate to achieve low tidal volumes was free up to 60/minute. Maximum peak inspiratory pressure was limited to 40 cmH2O. To minimize the inspiratory pressures, an arterial pH > 7.20 was acceptable irrespectively of the level of paCO2. Positive end-expiratory pressure was advocated up to 15 cmH2O. An inspiratory-expiratory ratio up to 2:1 could be used to achieve adequate oxygenation. Otherwise, the patient was crossed over to HFOV as indicated above. More detailed ventilation procedures and methods of weaning were according to standard protocols of the investigating centres.

Patients in the HFOV group were ventilated with the SensorMedics 3100B ventilator (SensorMedics, Bilthoven, the Netherlands). A high lung volume strategy was used as has been previously described [12]. HFOV was started with continuous distending pressure (CDP) at 5 cm H2O higher than mean airway pressure (MAP) on CV and then adjusted to achieve and maintain optimal lung volume. Therefore, initially, CDP was increased until an O2 saturation > 95% was achieved. CDP was not decreased until FiO2 < 0.60 was feasible applying the general physiological targets mentioned earlier. Pulmonary inflation was checked by chest X-rays if increasing CDP did not result in O2 saturation > 88%. Frequency was initially set at 5 Hz with an inspiratory time of 33%. Delta P was adjusted according to paCO2 and chest wall vibrations. If ventilation did not improve despite a maximum Delta P, frequency could be lowered. Weaning was instigated if paO2 > 60 mmHg at FiO2 < 0.40 and suction was well tolerated by decreasing Delta P and CDP to Continuous Positive Airway Pressure level. Ventilator weaning was continued on CV according to standard protocol of the unit.

Measurements

Assessment of the principal outcomes and repeated measurements was not blinded. Principal outcomes consisted of: Cumulative survival without mechanical ventilation or oxygen dependency at 30 days, mortality at 30 days, therapy failure, crossover rate and persisting pulmonary problems defined as oxygen dependency or still being on a ventilator at 30 days. Data collection began one hour following randomization for the conventionally treated patients and at the initiation of HFOV for the HFOV treated patients. The time period on CV prior to the study, ET tube length and diameter, air leak score, Acute Physiologic And Chronic Health Evaluation (APACHE) II score at admission, arterial blood gases, ventilator settings and cardiovascular measurements, were recorded. Arterial blood gases, ventilator settings, heart rate, blood pressure and cardiac output, if available, were registered after study entry or crossover

and every eight hours for four days on the assigned ventilator. Ventilator settings and blood gases were recorded for every change of ventilator settings during the first three days of treatment.

Statistical analysis

In analyses of primary outcomes, the intention to treat principle was used. Based on a projected survival without mechanical ventilation or oxygen dependency in the control group of 25%, an increase to 51% in the HFOV group would be detectable with 106 patients (alpha of 0.05, power of 0.80) [9]. Univariate logistic regression analysis was used to calculate differences in 30 day survival without mechanical ventilation or oxygen dependency, mortality, crossover, therapy failure and incidence of supplemental oxygen dependency or mechanical ventilation at 30 days. Cox proportional hazard analysis was conducted to detect differences in mortality. The proportionality assumption was graphically tested using log minus log plots. Multivariate logistic regression and Cox proportional hazard analysis for mortality were used to adjust in case of post-randomization differences in a priori defined pre-treatment conditions (dummy variables for study site, OI, ventilatory index, APACHE II score, age and weight). Furthermore, we looked at the relation between the OI response and mortality. Average values and standard errors of respiratory and circulatory parameters were calculated for days 1, 2, 3, and 4 of the study. Significant differences between treatment groups were tested by a general linear mixed model analysis. P-values were calculated 2-sided. All analyses were conducted using SPSS 12.0.1 for Windows software (SPSS Inc., Chicago, Illinois, USA).

Results

The study was stopped prematurely after inclusion of 61 patients because

Table 1

	HFOV	CV
N	37	24
Female-male ratio	9/28 (24%)	10/14 (42%)
Mean age (years)	81.0 ± 20.5	81.7 ± 12.5
Weight	50.7 ± 17.4	55.4 ± 12.8
APACHE II score	21.1 ± 7.6	20.1 ± 9.3
Diagnosis (%)		
Trauma	1 (3)	2 (9)
Sepsis	25 (68)	13 (57)
Pneumonia	8 (22)	3 (13)
Other	3 (8)	5 (22)
Site (%)		
United Kingdom	24 (65)	15 (63)
France	7 (19)	5 (21)
Germany	6 (16)	4 (17)
Ventilation time prior to study (days)	2.1 ± 2.6	1.5 ± 1.8
Oxygenation Index	25.2 ± 13.0	18.0 ± 7.4
Ventilatory Index	33.8 ± 20.4	30.3 ± 12.5
Respiratory rate (per min)	18.1 ± 4.1	17.8 ± 4.6
Tidal volume(ml)	618.4 ± 142.6	549.7 ± 130
Tidal Volume per ideal bodyweight (ml/kg)	9.3 ± 2.2	8.4 ± 2.0
Peak Inspiratory Pressure (cmH2O)	33.1 ± 6.8	32.3 ± 5.4
Positive end expiratory pressure (cmH2O)	13.9 ± 3.8	12.9 ± 3.2
Mean Airway Pressure (cmH2O)	21.5 ± 5.4	21.0 ± 5.1
FiO2	0.84 ± 0.19	0.76 ± 0.19
PH	7.3 ± 0.13	7.3 ± 0.11
PaCO2 (mmHg)	53.5 ± 17.3	52.2 ± 11.9
paO2 (mmHg)	80.8 ± 24.1	93.3 ± 24.5
SaO2 (percentage)	90.8 ± 6.4	94.3 ± 3.1
Heart rate	109.8 ± 23.7	111.2 ± 29.5
Mean Arterial Pressure (cmH2O)	75.3 ± 13.1	72.2 ± 14.1
Central Venous Pressure (cmH2O)	13.5 ± 4.2	13.8 ± 4.9

Table 1. Patient characteristics at study entry

HFOV = High Frequency Oscillatory Ventilation; CV = Conventional Mechanical Ventilation; APACHE II = Acute Physiologic and Chronic Health Evaluation II; OI = Oxygenation Index = (FiO2*MAP*100) / paO2, where: FiO2 = Fraction of inspired oxygen, paCO2 = Pressure of arterial carbon dioxide, paO2 = Pressure of arterial oxygen, SaO2 = Arterial oxygen saturation. Values are presented as means with standard deviations.

of a low inclusion rate and the completion of another trial comparing HFOV with CV in patients with ARDS [7]. Of the 61 patients, 37 patients were randomized to receive HFOV and 24 patients to receive CV. Follow up time to 30 days was incomplete in seven patients (5 HFOV and 2 CV).

The baseline OI at study entry was higher in the HFOV group than in the CV group, 25 versus 18 (Table 1). Patients were comparable for age and APACHE II score. The youngest patient was 17 years and the oldest patient was 77 years. The female-male ratio was lower in the HFOV group than in the CV group: 0.24 versus 0.42. The majority of patients (80%) were diagnosed with sepsis or pneumonia. Prior to randomization, patients were ventilated with an average tidal volume of 9.3 ml/kg ideal bodyweight in the HFOV group and 8.4 ml/kg ideal bodyweight in the CV group. Peak inspiratory pressures were comparable for both treatment groups. In one case, the limitation of 40 mmHg for peak inspiratory pressures was violated in the CV group. There were no major differences between treatment groups in mean airway pressures or positive end-expiratory pressures. Blood gas results prior to randomization showed a lower arterial oxygen saturation and paO2 in the HFOV group compared with the CV group.

The primary outcomes are presented in Table 2. There was no difference in cumulative survival without oxygen dependency or still on mechanical ventilation at 30 days between HFOV and CV. Mortality at 30 days did not differ significantly between HFOV and CV. An important cause of death was withdrawal of treatment (10 cases in 24 deaths). None of the deaths were directly related to the assigned therapy. Figure 1 shows a nearly identical cumulative survival of the HFOV group and the CV group corrected for the baseline covariates; study site, OI, ventilatory index, APACHE II score, age and weight. The survival curves of the duration of

Table 2.

				Unadjusted		Adjusted	
	HFOV	**CV**	**P**	**OR**	**95%CI**	**OR**	**95%CI**
N	37	24					
Survival without supplemental Oxygen or on ventilator	12 (32%)	9 (38%)	0.79	0.80	0.27 - 2.53	0.80	0.22 - 2.97
Mortality	16 (43%)	8 (33%)	0.59	1.52	0.45 - 2.59	1.15	0.43 - 3.10
Circulatory failure	6	2					
Cardiac arrhythmia	3	1					
Brain death	0	2					
Withdrawal of life support	7	3					
Therapy failure	10 (27%)	5 (21%)	0.76	1.41	0.41 - 4.78	1.35	0.35 - 5.22
Hypotension	4	1					
Acidosis	1	1					
Oxygenation	4	2					
Air leak	1	1					
Cross-over	7 (19%)	4 (17%)	0.82	1.17	0.30 - 4.51	0.62	0.12 - 3.19
Supplemental oxygen or on ventilator at 30 days	9 (24%)	7 (29%)	0.96	0.96	0.26 - 3.58	0.67	0.12 - 3.84

Table 2. Primary outcomes

N = number of patients included in the analyses. Values between brackets are percentages of N except for CLD that has the number of survivors in the denominator. CI = confidence interval. OR = odds ratio unadjusted and adjusted for study site, OI, ventilatory index, APACHE II score, age and weight.

ventilation were virtually identical for the HFOV group and the CV group (data not shown). The median duration of ventilation was 20 days (± 6 SD) for HFOV and 18 days (± 5 SD) in the CV treatment group.

Treatment failure occurred in 10 patients (27%) in the HFOV group and five patients (21%) in the CV group. Seven patients (19%) treated with HFOV crossed over to CV, in the CV group four patients (17%) were switched to HFOV. Of the four patients that crossed over in the CV group two patients died and one patient was on supplemental oxygen therapy at 30 days. In the HFOV group, five patients that crossed over died and two patients were still on ventilator or needed extra oxygen. The occurrence of being on oxygen or mechanical ventilation at 30 days in survivors was equal between HFOV and CV.

Figure 1.

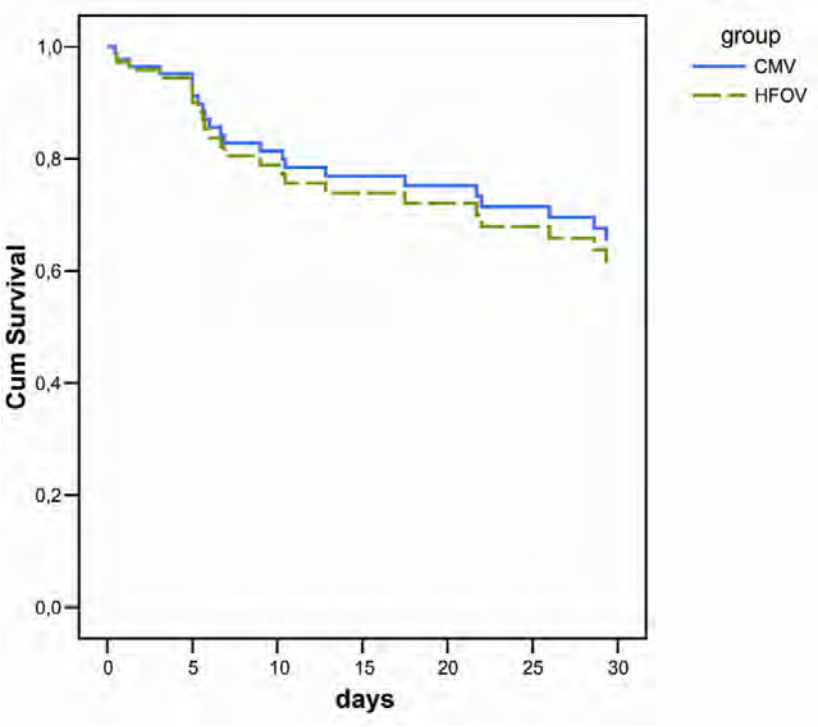

Figure 1. Cumulative mortality incidence HFOV versus CV.

CV =conventional mechanical ventilation. HFOV = high frequency oscillatory ventilation. Curves are estimations of cumulative risk corrected for study site, baseline OI and ventilatory index, APACHE II score, age and weight.

Ventilatory settings and blood gas results at days 1, 2, 3 and 4 of the study are shown in Table 3. Patients with HFOV were ventilated with higher mean airway pressures than patients on CV ($p = 0.03$). FiO2 was also higher in the HFOV group compared with the CV group. This difference between the treatment groups was not significant ($p = 0.33$). Results of blood gases were comparable between the two treatment groups including all patients. Patients that crossed over in the CMV group had significantly lower pH than patients who did not cross over in the CMV group (p =

Table 3

	Cross-over	HFOV No (30)	HFOV Yes (7)	CV No (20)	CV Yes (4)
		N=28	*N=7 (7 HFOV)*	*N=19*	*N=4 (4 CV)*
Day 1					
	Peak Inspiratory Pressure (cmH2O)			32 ± 4.2	35 ± 6.9
	Positive end expiratory pressure (cmH2O)			14 ± 2.1	12 ± 4.5
	Mean Airway Pressure (cmH2O)	**30 ± 5.6**[§]	**32 ± 6.3**[§]	22 ± 3.2	22 ± 6.1
	Tidal Volume per ideal bodyweight (ml/kg)			9 ± 1.7	8 ± 0.7
	Frequency (HFOV: Hz, CV: breaths/min)	5 ± 0.5	5 ± 0.9	17.3 ± 3	17.3 ± 6
	Delta P (cmH2O)	63 ± 14	70 ± 12.1		
	FiO2	0.78 ± 0.19	0.82 ± 0.12	0.68 ± 0.12	0.78 ± 0.21
	PH	7.32 ± 0.08	7.31 ± 0.11	7.34 ± 0.08	**7.22 ± 0.07**[*]
	pCO2 (mmHg)	49 ± 11.3	57 ± 13	48 ± 9	52 ± 15.8
	pO2 (mmHg)	126 ± 79.2	93 ± 37.1	98 ± 26.6	99 ± 25
	SaO2 (percentage)	95 ± 3	90 ± 10.7	96 ± 2.4	94 ± 4.5
	Oxygenation Index	26 ± 16	**31 ± 8.3**[#]	17 ± 7.5	**19 ± 11.2**[#]
Day 2		*N=27*	*N=7 (6 HFOV)*	*N=19*	*N=4 (2 CV)*
	Peak Inspiratory Pressure (cmH2O)	25 ± 6.7	36 ± 7.2	31 ± 4.5	30 ± 2.6
	Positive end expiratory pressure (cmH2O)	11 ± 1.2	15 ± 1.9	14 ± 2.7	12 ± 4.7
	Mean Airway Pressure (cmH2O)	**28 ± 6.7**[§]	**29 ± 4.3**[§]	21 ± 2.3	22 ± 9.1
	Tidal Volume per ideal bodyweight (ml/kg)	9 ± 1.6	10 ± 1.9	8 ± 1.6	8 ± 1
	Frequency (HFOV: Hz, CV: breaths/min)	5.0 ± 0.4	4.8 ± 1.1	17.4 ± 2.6	17.2 ± 1.2
	Delta P (cmH2O)	64 ± 14.5	73 ± 14.8		70 ± 13.8
	FiO2	0.55 ± 0.17	0.57 ± 0.14	0.53 ± 0.12	0.76 ± 0.20
	PH	7.36 ± 0.07	7.35 ± 0.04	7.38 ± 0.06	**7.22 ± 0.08**[*]
	pCO2 (mmHg)	45 ± 9	51 ± 8.9	46 ± 8.3	53 ± 8.5
	pO2 (mmHg)	96 ± 21	83 ± 12.4	100 ± 27	87 ± 41.8
	SaO2 (percentage)	95 ± 2.1	94 ± 1.9	96 ± 1.8	87 ± 16.1
	Oxygenation Index	17 ± 10.2	**21 ± 8.2**[#]	12 ± 3.6	**22 ± 10.5**[#]

Table 3. Ventilatory conditions

The columns represent the treatment allocation: HFOV = High Frequency Oscillatory Ventilation; CV = Conventional Mechanical Ventilation.

Table 3

		HFOV		CV	
Day 3		*N=23*	*N=7 (4 HFOV)*	*N=19*	*N=4 (2 CV)*
	Positive end expiratory pressure (cmH2O)	9 ± 3	10 ± 4.3	13 ± 2.8	11 ± 5.7
	Mean Airway Pressure (cmH2O)	**23 ± 7.1**[§]	**25 ± 6.9**[§]	20 ± 2.8	24 ± 2.3
	Tidal Volume per ideal bodyweight (ml/kg)	9 ± 1.5	9 ± 3.5	9 ± 1.6	7 ± 1.6
	Frequency (HFOV: Hz, CV: breaths/min)	5.0 ± 0.4	4.6 ± 0.5	18.8 ± 6.5	19.9 ± 5.8
	Delta P (cmH2O)	66 ± 12.4	66 ± 19.1		67 ± 0.7
	FiO2	0.46 ± 0.13	0.55 ± 0.15	0.46 ± 0.11	0.65 ± 0.26
	PH	7.39 ± 0.06	7.37 ± 0.06	7.39 ± 0.06	**7.33 ± 0.1**[*]
	pCO2 (mmHg)	45 ± 10.4	47 ± 12.9	48 ± 9	47 ± 12.6
	pO2 (mmHg)	89 ± 19.7	86 ± 46.2	91 ± 13.7	89 ± 22.4
	SaO2 (percentage)	94 ± 6.7	89 ± 14.1	96 ± 1.9	95 ± 2.4
	Oxygenation Index	14 ± 7.2	**19 ± 9.3**[#]	11 ± 3.7	**20 ± 12.3**[#]
Day 4		*N=22*	*N=7 (3 HFOV)*	*N=19*	*N=2 (0 CV)*
	Peak Inspiratory Pressure (cmH2O)	25 ± 8	31 ± 6.9	28 ± 6.9	
	Positive end expiratory pressure (cmH2O)	9 ± 4.6	11 ± 4.2	11 ± 3.2	
	Mean Airway Pressure (cmH2O)	**22 ± 7.8**[§]	**24 ± 6.2**[§]	17 ± 5.6	24 ± 3.2
	Tidal Volume per ideal bodyweight (ml/kg)	10 ± 2.4	7 ± 3.1	8 ± 2.2	
	Frequency (HFOV: Hz, CV: breaths/min)	5.0 ± 0.3	4.3 ± 0.6	17.9 ± 5.3	
	Delta P (cmH2O)	57 ± 11.4	70 ± 11.8		48 ± 14.8
	FiO2	0.45 ± 0.11	0.57 ± 0.18	0.45 ± 0.11	0.51 ± 0.12
	PH	7.42 ± 0.14	7.37 ± 0.1	7.43 ± 0.12	**7.45 ± 0.06**[*]
	pCO2 (mmHg)	43 ± 12.3	46 ± 7.5	41 ± 10.3	44 ± 11.1
	pO2 (mmHg)	85 ± 22.3	84 ± 30.5	87 ± 27.4	74 ± 23.7
	SaO2 (percentage)	89 ± 15.3	90 ± 14.1	89 ± 17.2	84 ± 20
	Oxygenation Index	12 ± 5.6	**18 ± 7.9**[#]	10 ± 4.3	**19 ± 9.5**[#]

Measurements were made day 1, 2, 3 and 4 of the study. Peak inspiratory pressure, positive end expiratory pressure and tidal volume per ideal bodyweight were measured in HFOV after crossover to CV. FiO2 = Fraction of Inspired Oxygen; paCO2 = Pressure of arterial carbon dioxide; paO2 = Pressure of arterial oxygen. Values are presented as means with standard deviations. [§] Higher mean airway pressures in HFOV compared with CV (p = 0.03)**.** [#] Higher OI in patients that crossed over compared with patients that did not cross over (p=0.07 and p = 0.05). [*] Significantly lower pH in patients that cross over in the CV group (p = 0.017).

Figure 2

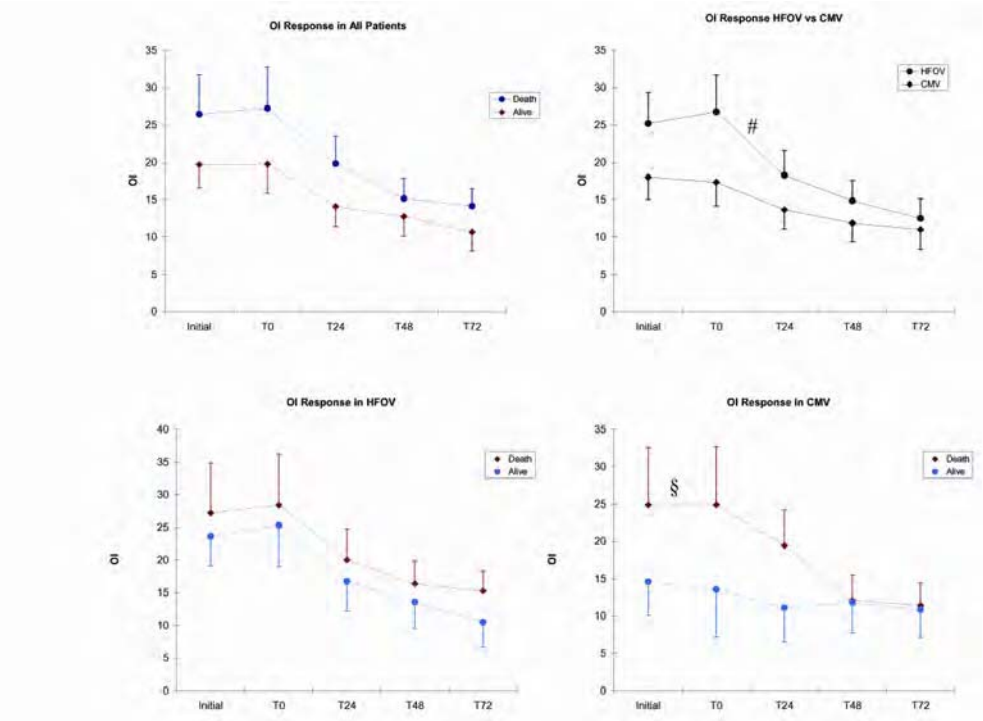

Figure 2. OI in Survivors versus Non-survivors and HFOV versus CV

OI = oxygenation index. HFOV = high frequency oscillatory ventilation. CV = conventional mechanical ventilation. OIs are presented by diamonds as means with bars as 95% confidence intervals (CI). Reported p-values for baseline OI are corrected for study site, ventilatory index, APACHE II score, age and weight. Baseline OI did not significantly predict mortality in all patients or in HFOV ($p = 0.06$ and $p = 0.41$). [§]Baseline OI was significantly different between survivors and non-survivors in the CV group ($p = 0.04$). Significant differences between OI responses were calculated by linear mixed model analyses. [#]Significant difference in OI response between HFOV and CV ($p = <0.01$). OI response did not differentiate between survivors and non-survivors in all patients or in CV and HFOV separately ($p = 0.28$, $p = 0.12$ and $p = 0.95$ respectively).

0.02). This difference, however, was not found between patients who did and did not cross over in the HFOV group ($p = 0.56$). The OI, on the other hand, was higher in both patients that crossed over in the CMV group and patients that crossed over in the HFOV group compared with patients that did not cross over ($p = 0.07$ and $p = 0.05$ respectively).

Systolic arterial blood pressure and mean arterial blood pressure were higher in the HFOV treated patients compared with CV treated patients ($p = 0.06$ versus $p = 0.07$). Cardiac output was comparable between the two treatment groups (data not shown).

The OI response in all patients treated with either HFOV or CV did not differ significantly between survivors and non-survivors (Figure 2). The OI response from day 1 to day 2 was significantly larger in HFOV than in CV treated patients ($p<0.01$). Within treatment groups there was a significant difference in initial OI between survivors and non-survivors in CV treated patients, but OI response to treatment did not differentiate between survivors and non-survivors in CV treated patients. In the HFOV treated patients there was no difference in the baseline OI, nor was there a difference in OI response between survivors and non-survivors.

The results of a post hoc analysis are shown in Figure 3. Adjusted odds ratios for mortality were calculated for samples of the study population including patients with progressively higher baseline OI prior to randomization. This suggested, that in patients with a higher baseline OI, the effect of treatment with HFOV was relatively better compared with CV. OI was evaluated as an interaction term in a Cox Proportional Hazard model with treatment, age and OI as explanatory variables. The likelihood ratio test comparing the reduced (no-interaction) with the full (interaction) model showed a p-value of 0.048.

Figure 3

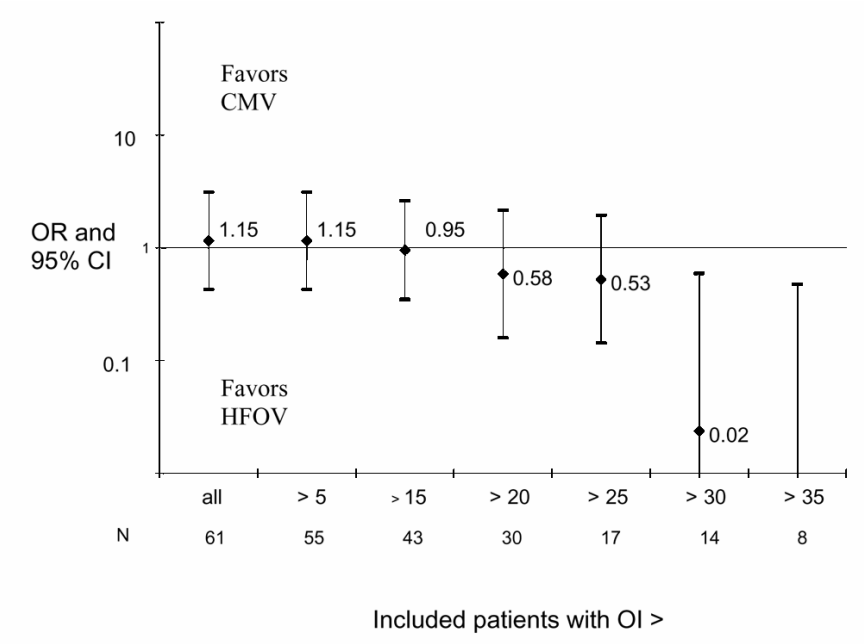

Figure 3. Post hoc analysis of the treatment effect on mortality relative to baseline OI

OI = oxygenation index. OR =Odds Ratio of mortality. CI = confidence interval. CV =conventional mechanical ventilation. HFOV = high frequency oscillatory ventilation. OI = OI. On the y-axis the OR adjusted for study site, OI, ventilatory index, APACHE II score, age and weight is presented by diamonds and 95% confidence intervals by bars. On the x-axis the different analyses are depicted including patients with increasing levels of initial OI at study entry. N denotes the number of patients in each subgroup.

Discussion

No significant differences were observed, but this trial only had power to detect major differences in mortality or survival without oxygen dependency or on ventilator. Furthermore, 11 of 61 patients were crossed over to a different treatment arm; this also, diminished the power to detect potential treatment differences. A post hoc analysis, however, suggested that in patients with a higher baseline OI, HFOV may be more effective than CV.

This trial was stopped because a low inclusion rate and the completion of another similar trial [7]. The low inclusion rate was not because of competing trials but probably due to the limited number of investigators (four centres compared with nine centres in the study by Derdak et al.). The number of patients included in the two treatment arms differed considerably. This misbalance was due to stopping the trial early. There were no protocol violations. Furthermore, baseline OI at study entry was higher in the HFOV group than in the CV group. The OI has been recognized as an important prognostic determinant of mortality [13].

HFOV was started early in the course of ARDS. Patients were ventilated on HFOV according to the open lung concept. This resulted in significantly higher mean airway pressures compared with CV ventilated patients. This mainly determined the higher OI in the HFOV group during the first days. FiO2 and paO2 values were similar between HFOV and CV patients. Potential theoretical risks of HFOV therapy, overdistension of the pulmonary system leading to barotrauma or cardiovascular compromise, packing of mucus leading to ineffective ventilation or blocking of the endotracheal tube were not encountered. None of the HFOV ventilated patients developed necrotizing tracheobronchitis.

Patients in the CV group were ventilated following a lung protective strategy targeted to minimizing tidal volumes. The tidal volumes per kg ideal bodyweight that were used in this study were higher than tidal volumes used in studies of lung protective ventilation strategies [14]. On the other hand, tidal volumes in our study were significantly lower than tidal volumes that were found to be harmful in those studies. Peak inspiratory pressures were limited to 40 cmH2O in the CV group. This restriction was violated in only one case. Nine patients were ventilated with pressures above 35 cmH2O. Furthermore, the overall mortality and survival without

mechanical ventilation or oxygen dependency at 30 days did not suggest that the ventilation treatment in the CV group was suboptimal.

The OI represents the pressure and oxygen cost for oxygenation. It has been regarded as a marker of lung injury and prognostic indicator of treatment success [15]. In CV treated patients there was a significant difference in baseline OI between survivors and non-survivors. Baseline OI, however, did not differentiate between survivors and non-survivors in HFOV treated patients. Although in some studies OI response to treatment was a predictor of outcome [7;9], we could not reproduce this relation. A possible explanation could be that fewer numbers of patients were included in our analysis. Also, we used a different time window; we compared OI on a daily basis whereas in a study by Derdak et al., OI was compared every 4 hours. In that study, OI response was maximally different at 16 hours [7]. In our study, OI response only differed significantly between HFOV and CV treated patients. This difference for the most part could be explained by the higher mean airway pressures used in the HFOV group.

A post hoc analysis suggested that baseline OI could be an important effect modifier of the relative treatment effect of HFOV compared with CV. We hypothesize that within the pressure-ventilation curve there is a safe window between under-inflation with atelectasis and shear stress and over-inflation with barotrauma [4;16]. In patients with ARDS with higher OI, this safe window possibly becomes too small for CV to prevent ventilator induced lung injury. This concept is supported by animal experiments where addition of positive end-expiratory pressure resulted in additional over-inflation contributing to ventilator associated lung injury [17]. The combination of high levels of positive end-expiratory pressure and over-distension are directly reflected in the OI. Only in patients with a higher initial OI, HFOV seemed to offer an advantage over CV. This is in accordance with observational studies that showed that better survival rates

in more severe ARDS with higher OI was associated with HFOV treatment [11;18]. In fact, HFOV has been recommended in patients who require high mean airway pressure and FiO2 exceeding 60% corresponding to an OI > 20 when paO2 ≤ 60 mmHg [12]. However, because these findings result from a post hoc analysis, they can only be regarded as hypothesis generating still to be confirmed.

Previous trials did not show a significant difference in mortality in patients with ARDS between HFOV and CV [19]. In our trial, mortality in the HFOV group was similar to mortality reported in the previous trials, but mortality in the CV group was considerably less, in accordance with the imbalance in prognostic indicators at baseline.

More evidence is needed to confirm a beneficial effect of HFOV over CV in the treatment of ARDS. Our results and those from previous trials seem promising but could depend on other criteria to select patients with ARDS that benefit from HFOV compared with CV. One of these criteria could be OI. Therefore, we believe that in future research comparing HFOV with CV as early treatment of ARDS, it is important to focus on patients with higher levels of baseline OI. As treatment differences will be smaller than our prior estimate was, larger trials are needed. We do not think that OI response can be used as an alternative outcome measurement for treatment success or failure.

Conclusion

In this study, we were not able to find significant differences in efficacy or safety between HFOV and CV as early treatment of ARDS. A post hoc analysis suggested that HFOV could prevent mortality compared with CV, in patients with a higher baseline OI. Therefore, it is important in future

studies to enable informative analysis of patients with higher baseline OI. To achieve sufficient power to detect possible important treatment differences in subgroups of patients with higher OI, larger multi-centre trials are warranted.

Appendix

Oxygenation Index = (FiO2*MAP*100) / paO2, where: FiO2 = Fraction of inspired oxygen, paCO2 = Pressure of arterial carbon dioxide, paO2 = Pressure of arterial oxygen, SaO2 = Arterial oxygen saturation.
Ventilatory index = [Peak Inspiratory Pressure (mmHg) x Respiratory rate x pCO2 (mmHg)] / 1000
Ideal body weight for male patients was calculated by: Weight = 50 + 0.91 x (height in centimetres - 152.4). For female patients by: Weight = 45 + 0.91 x (height in centimetres - 152.4)

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Chapter 6

Systematic review of determinants of mortality in high frequency oscillatory ventilation in acute respiratory distress syndrome

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Critical Care 2006; 10:R34.

ABSTRACT

Introduction

Mechanical ventilation has been shown to cause lung injury and to have a significant impact on mortality in acute respiratory distress syndrome. Theoretically, high frequency oscillatory ventilation seems an ideal lung protective ventilation mode. This review evaluates determinants of mortality during use of high frequency oscillatory ventilation.

Methods

PubMed was searched for literature reporting randomized trials and cohort studies of high frequency ventilation in adult patients with acute respiratory distress syndrome. Data on mortality and determinants were extracted of patients treated with high frequency oscillatory ventilation. Linear regression analyses were conducted to produce graphical representations of adjusted effects of determinants of mortality.

Results

Cohorts of patients treated with high frequency oscillatory ventilation from two randomized trials and seven observational studies were included. Data from cohorts comparing survivors with non-survivors showed differences in age (42.3 versus 51.2 years), prior time on conventional ventilation (4.0 versus 6.2 days), APACHE II score (22.4 versus 26.1), pH (7.33 versus 7.26) and oxygenation index (26 versus 34). Each extra day on conventional ventilation was associated with a 20% higher mortality

adjusted for age and APACHE II score (relative risk (RR) 1.20, 95% confidence interval (CI) = 1.15 – 1.25). However, this association was confounded by differences in pH (pH adjusted RR 1.03, 95%CI 0.73 - 1.46). Oxygenation index seemed to have an independent effect on mortality (RR 1.10, 95%CI 0.95 - 1.28).

Conclusions

Prolonged ventilation on conventional mechanical ventilation prior to high frequency oscillatory ventilation was not related to mortality. Oxygenation index was a determinant of mortality independent of other disease severity markers.

Introduction

Acute respiratory distress syndrome (ARDS) is a clinical condition that is associated with high mortality [1]. Different lung protective ventilation strategies have had an important impact on mortality in ARDS [2]. These strategies are based on the concept that there is a safe window between atelectasis and overdistension of alveoli and have been developed, therefore, with the aim of recruiting alveoli combined with avoidance of high peak inspiratory pressures and thus overdistension. A striking impact of how ventilation can affect outcome has been demonstrated by comparing high tidal volume with low tidal volume ventilation strategies, resulting in a 8.8% reduction in mortality in the latter [3]. The most extreme form of low tidal volume ventilation is represented by high frequency oscillatory ventilation (HFOV). In HFOV, a continuous distending airway pressure is applied upon which pressure waves are produced, with frequencies typically ranging from 5 to 10 Hz. To produce those pressure waves, a HFOV ventilator is equipped with a piston driven diaphragm. A power control regulates the force and distance with which the piston moves from baseline. The degree of deflection of the piston (amplitude) determines the tidal volume [4]. This results in extremely small tidal volumes and, therefore, theoretically, in avoidance of overdistension, while at the same time, application of continuous distending pressure prevents atelectasis. Thus, theoretically, these attributes make HFOV an ideal candidate for ventilation of patients with severe lung disease like ARDS [5;6].

Due to technical restrictions, the first HFOV ventilators only had the power to ventilate infants and small children. A population in which HFOV has been extensively investigated consists of premature neonates with idiopathic respiratory distress syndrome. Although numerous randomized trials have been performed, a clinically relevant difference in mortality or

pulmonary outcome compared with conventional mechanical ventilation (CV) was not established [7]. More recent studies looked at the smallest premature infants and strived to minimize time on CV in order to maximize the effect of HFOV compared with CV [8;9]. Yet, it seemed that elective application of HFOV did not influence pulmonary outcome in most premature infants with idiopathic respiratory distress syndrome [10]. Attention has been shifted, therefore, to identifying subgroups of patients that do benefit from HFOV.

In ARDS, only two randomized trials have been performed in adult patients and one in pediatric patients[11-13]. None of these trials were able to show a significant difference in mortality between HFOV and CV. Studies have also been published that investigated determinants of mortality in HFOV treated patients [14;15]. As in studies with premature neonates, selecting the proper subgroup of patients with ARDS for HFOV treatment will be a main issue in trials comparing HFOV with CV [16]. HFOV treated patients in experimental trials and in non-experimental prospective and retrospective cohort studies were evaluated to identify baseline characteristics that predicted mortality and pulmonary outcome in patients who were selected for HFOV treatment.

Materials and Methods

A literature search was carried out to identify all randomized trials of HFOV performed in adult patients with ARDS. Reports of prospective and retrospective cohort studies were separately collected using the terms: 'high frequency oscillatory ventilation', 'acute respiratory distress syndrome' and 'mortality' in PubMed and the Cochrane database. This search was updated until September 2005 with no further time limits. Literature lists of meta-analyses and articles were searched for additional

studies. To be included, prospective or retrospective studies had to report well defined cohorts of patients included over a fixed period of time and address mortality as outcome. Case reports, case series, letters and narrative reviews were excluded. Studies were evaluated regarding selection bias and loss-to follow up by C.B.

Data were extracted from HFOV treated patients in clinical trials and cohort studies of clinically relevant outcome measures, mortality incidence at 30 days in survivors, incidence of still being ventilated at 30 days, incidence of survival without being ventilated at 30 days. Baseline characteristics of these cohorts that could be associated with mortality were identified. As well as age, sex, and acute physiology and chronic health evaluation (APACHE) II score, the following quantitative variables were extracted from all studies: ratio of partial arterial oxygen pressure (PaO2; mmHg) and fraction of inspired oxygen (FiO2); time on CV prior to HFOV (days); oxygenation index (OI), which corresponds to FiO2 × mean airway pressure (MAP; cmH2O) × 100)/paO2; blood gas results (pH and pressure of arterial carbon dioxide (PaCO2; mmHg)); and ventilatory settings on CV (peak inspiratory pressure, peak end-expiratory pressure, MAP and FiO2).

Two following a priori hypotheses were formulated to explain differences in mortality rates between studies in HFOV treated patients: first, a longer duration on CV prior to HFOV causes higher mortality and second, higher baseline OI is independently associated with higher mortality in HFOV treated patients. These hypotheses have also been raised by others to explain differences between studies[17-19]. However, the association of time on CV prior to HFOV and mortality in HFOV treated patients could be confounded by covariates such as age and disease severity (APACHE II score and pH). In the relationship between time on CV and mortality, OI could be an intermediate cause (Figure 1). Intermediate cause was defined

Figure 1. Causal inference

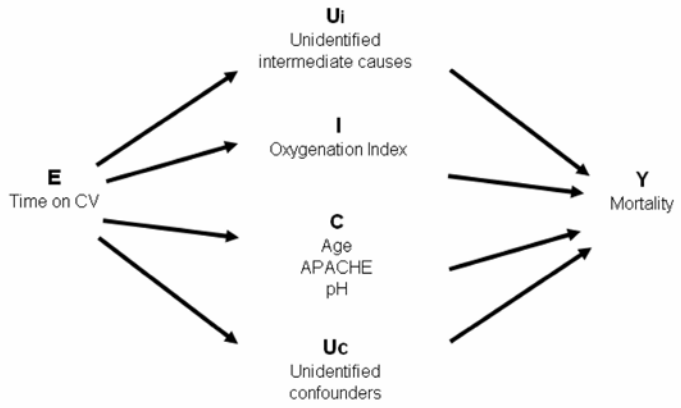


Figure 1. E = Exposure; I = Intermediate cause; C = Confounders; Y = Outcome. Theoretical causal mechanism of the association between time on CV prior to initiating HFOV and mortality at 30 days. Conditioning by oxygenation index and age and APACHE II score would block the association if no unidentified intermediate causes or confounders were present.

as a factor in a causal pathway; therefore, controlling for an intermediate cause removes the association between an explanatory variable and outcome. If controlling for a well measured intermediate cause does not remove the association, it is not an intermediate cause.

Statistical analysis

Univariate logistic regression analyses were performed to identify associations between single covariates and binary outcome (for example survival yes or no). Mean values of reported continuous covariates in survivors and non-survivors in each study were used as covariates. These analyses were weighted by numbers of survivors and non-survivors.

Linear regression analyses were conducted with mortality as dependent outcome and determinants of mortality as independent variables to create graphical presentations of crude and adjusted effects. For the dependent

variable, a linear transformation of incidence of death was calculated by taking the natural logarithm of incidence of death divided by incidence of survival. The weight of an individual study was determined by the inverse of the variance of that study.

Multivariable linear regression was used to deal with possible confounding factors of the association between hypothesized causal factors (see Materials and Methods) and outcome. Furthermore, we explored in these models whether associations between hypothesized causal factors and outcome could be explained by possibly intermediate factors. To that end we investigated whether inclusion in the model of such intermediate factors would indeed attenuate the association between hypothesized causal factors and outcome, which we will refer to as 'blocking of the effects'.

All analyses were conducted using SPSS 12.0.1 for Windows software (SPSS Inc., Chicago, Illinois, USA).

Results

Using the search term 'high frequency oscillatory ventilation' 693 articles were found. Limiting the search to studies of adults, only 76 articles were left. Of these 76 articles, 2 were randomized trials and 7 observational cohort studies; 3 of these 9 studies were retrospective studies [14;20;21] and 6 were prospective studies [11;13;15;17;18;22]. Prospective studies contributed 83% of the total weight to our analyses. Nine cohorts of HFOV treated patients from two randomized trials and seven observational trials were included in the regression analyses[11-15;17;18;20-22].

Differentiated data on survivors and non-survivors in HFOV could be

Table 1. Comparison of survivors and non-survivors treated with HFOV

	Survival No = 60 Mean	*Yes = 33 Mean*	*OR Crude*
Age	51.2	42.3	1.14
APACHE II	26.1	22.4	1.12
TimeCV	6.2	4.0	1.38
pH	7.26	7.33	0.74*
PaCO2	54.6	43.8	1.07
PAF	91.8	94.8	0.90
OI	34.0	26.0	1.05
PIP	36.7	34.1	1.61
PEEP	14.5	13.9	1.09
MAP	24.0	22.9	1.81
FiO2	0.90	0.84	1.05*

Table 1. OR = Odds Ratio; TimeCV = Time on CV prior to HFOV (days) ; paCO2 = Pressure of arterial carbon dioxide (mmHg); PAF = Pressure of Arterial oxygen (mmHg) / Fraction of Inspired Oxygen; OI = Oxygenation Index ; PIP = Peak Inspiratory Pressure (cmH2O); PEEP = Peak End-Expiratory Pressure (cmH2O); MAP = Mean Airway Pressure (cmH2O); FiO2 = Fraction of Inspired Oxygen. Values are presented as pooled means of studies weighted by number of patients. *OR per 0.01 unit change.

extracted from eight studies [11;13-15;17;18;20-22]. Pooled comparison of survivors with non-survivors in the observational studies showed differences in all covariates (Table 1). Crude odds ratios (OR) for mortality were calculated for covariates separately. The crude OR for time on CV was 1.38. However, patients that did not survive were also more severely ill (APACHE II score 26 versus 22, pH 7.26 versus 7.33 and OI 34 versus 26).

Coverage of determinants of mortality was complete for age, APACHE II score and OI in seven studies (Table 2). Only five studies supplied both time on CV, pH, PaCO2 and OI. The results from weighted multivariate linear regression analyses of mortality incidence in HFOV treated patients are graphically depicted in Figure 2. Adjusting for age and APACHE II

score increased the effect of prior time on CV on mortality by 23% per day (relative risk (RR) 1.23, 95% confidence interval (CI) 1.01 - 1.49 and RR 1.35, 95%CI 1.12 – 1.63, for crude and adjusted, respectively). Addition of OI to the model with age and APACHE II score, resulted in a decreased effect of 20% increase in mortality per day on CV (RR 1.20, 95%CI 1.15 - 1.25).

However, the association of time on CV with mortality almost disappeared when adjusting for pH (RR 1.03, 95%CI 0.73 - 1.46). On the other hand, adjusting for PaCO2 did not diminish the effect of time on CV (RR 1.28, 95%CI 1.20 – 1.36). The association of OI with mortality was less influenced by adjusting for pH (RR 1.10, 95%CI 0.95 - 1.28). Figure 3 and 4 show the relative contributions to mortality by days on CV prior to HFOV and OI adjusted by different levels of baseline pH. Data on pH could be extracted in only five studies, therefore, a full model with time on CV, age, APACHE II score, pH and OI could not be fitted.

Figure 2. Linear regression analysis of mortality and time on CV

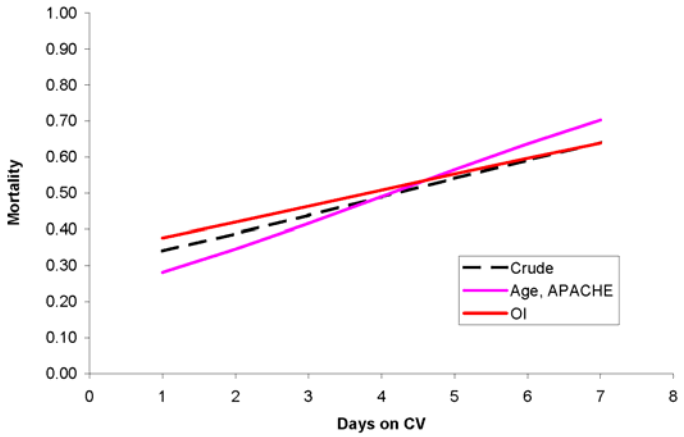


Figure 2. Interupted line: crude analysis. Purple line: linear regression adjusted for age and APACHE II score. Orange line: linear regression adjusted for oxygenation index.

Discussion

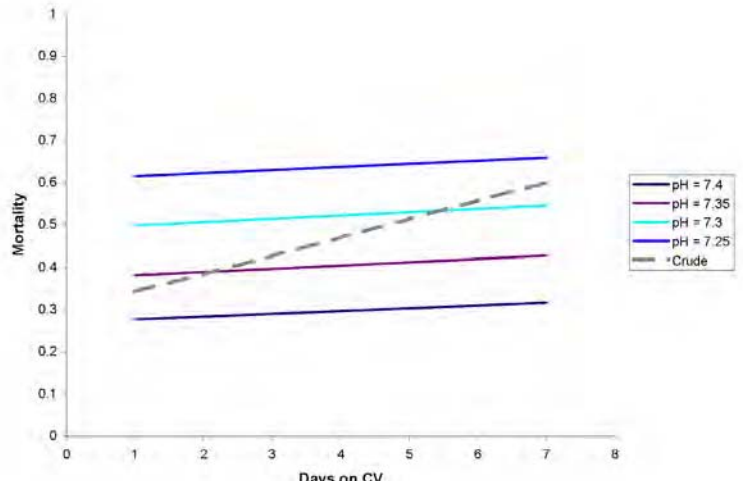
The combined evidence from the randomized trials and observational research of cohorts of HFOV treated patients shows that the association of prior time on CV before initiating HFOV with mortality was confounded by differences in pH between survivors and non-survivors. Furthermore, adjusting prior time on CV by OI as an intermediate cause did not block the effect of prior time on CV. OI, on the other hand, was associated with mortality, independently of age, APACHE II score and pH.

In this review, we combined observational evidence of an additional randomized trial with a previously reported trial and prospective and retrospective cohort studies. A priori, two hypotheses that could explain the association between length of ventilation on CV and OI, a marker of pulmonary disease severity, with mortality in HFOV were formulated. Quantitative data were available for two important possible confounders, age and APACHE II score, in seven published cohorts and pH and PaCO2 were reported for five cohorts.

Bias inherent to observational research could not be excluded. Selective reporting was not considered to be a major problem, however, because HFOV in adult patients was a relatively new treatment without strong prior beliefs or expectations on the side of the investigators. Missing patients that were treated with HFOV in retrospective analyses was unlikely as well, as this kind of treatment is easily recognized, also in retrospect. Bias due to misclassification and loss to follow up were regarded unlikely in the specific intensive care settings the studies took place. Most determinants consisted of laboratory measurements or ventilatory settings that were not likely to be influenced by observer or recall bias.

There was not enough information to assess possible confounding by other

Figure 3 and 4. Linear regression of Time on CV and OI on Mortality adjusted for different levels of pH



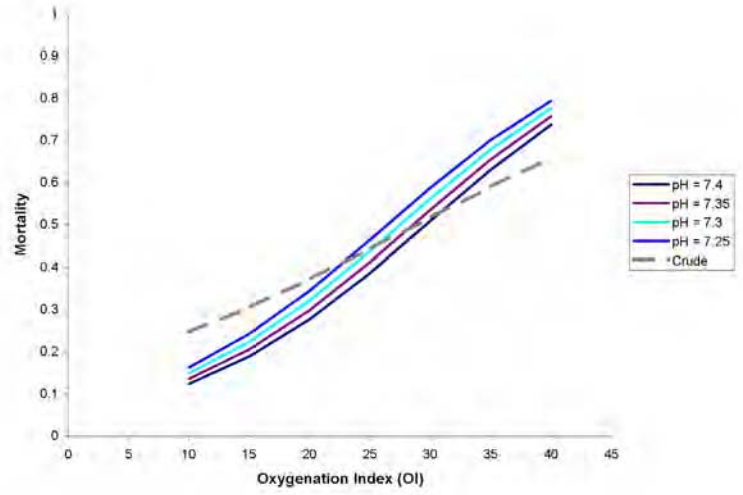


Figure 3 and 4. Interupted line: crude analysis. Colored lines: linear regression adjusted for pH.

Table 2. Linear regression analysis of determinants of mortality in HFOV

Study	*Year*	*Mort*	*Vent*	*Surv*	*NoPat*	*Age*	*Sex*	*APACHE II*	*TimeCV*	*pH*	*PaCO2*	*PAF*	*OI*	*PIP*	*PEEP*	*MAP*	*FiO2*
Fort	1997	0.53			17	38.0	0.5	23.3	5.0		44.7		47.8	54.3	18.3		
Claridge	1999	0.20			5	36.6	2.6	28.7	6.0								
Mehta	2001	0.67		0.33	24	48.4	8.3	21.5	5.7		55.1	98.9	32.5	36.7	14.5	24.3	0.78
Derdak	2002	0.37	0.43	0.36	75	48.0	0.5	22.0	2.7	7.37	44.0	114.0	24.0	39.0	13.0	22.0	0.71
Andersen	2002	0.31			16	38.0		26.6	7.0	7.30	62.2		27.4	35.1	11.6		
David	2003	0.43			42	49.0	0.7	28.0	3.0	7.33	57.0	94.0	23.0	35.0	15.0	24.0	1.00
Mehta	2004	0.62	0.53	0.18	154	47.9	56.6	24.0	5.7	7.28	53.2	91.2	31.4	36.1	14.0	24.1	0.86
Cartotto	2004	0.32			25	42.4			4.9			97.0	26.8				
Bollen	2005	0.43	0.19	0.46	37	50.7	14.3	21.1	2.1	7.30	53.5		25.2	33.1	13.9	21.5	0.84

Table 2. Mort = mortality incidence at 30 days; Vent = ventilation at 30 days; Surv = Survival at 30 days without ventilation; NoPat = Number of Patients; TimeCV = Time on CV prior to HFOV (days) ; PaCO2 = Pressure of arterial carbon dioxide (mmHg); PAF = Pressure of Arterial oxygen (mmHg) / Fraction of Inspired Oxygen; OI = Oxygenation Index ; PIP = Peak Inspiratory Pressure (cmH2O); PEEP = Peak End-Expiratory Pressure (cmH2O); MAP = Mean Airway Pressure (cmH2O); FiO2 = Fraction of Inspired Oxygen. Values are presented as pooled means of studies.

covariates and residual confounding could not be excluded. Furthermore, this meta-analysis was restricted to baseline characteristics. Sequential evolution of determinants over time may be more powerful to predict mortality. However, APACHE II score, pH and OI have been shown to be strongly related to mortality [1]. The OI represents a cost benefit ratio of ventilatory conditions and PaO2 yield and is, theoretically, a more sensitive indicator of pulmonary condition than the PaO2/FiO2 ratio. The inverse relation of mean airway pressure and FiO2 with PaO2 would render it less susceptible to specific ventilatory settings that were used. Stratified results from the trial by Bollen and colleagues with baseline OI lower or equal to 20, or baseline OI above 20, changed the effect of HFOV on mortality compared with CV [11]. This could indicate that level of OI determined which patients had the greatest benefit from HFOV.

The association of time on CV with increased mortality adjusted for age and APACHE II score has been reported by several other authors [13;15;17;18]. The proposed mechanism would be through lung damage caused by CV. As we have shown, this hypothesis is not supported by the evidence in our analysis. As we argued, if the association between time on CV and mortality arises through damage to the lungs caused by CV, we expect that conditioning for OI as a marker of lung injury would explain this association by blocking the effect, that is by adjusting for OI as an intermediate cause the association of time on CV with mortality would disappear. However, adjusting for OI did not influence the association between time on CV and mortality. A possibility could be that OI was not an appropriate marker of the intermediate causal pathway and that unidentified intermediate determinants of lung damage remained.

Moreover, the association of prolonged time on CV before initiating HFOV treatment and increased risk of death disappeared by adjusting for pH. It could be argued that pH was an intermediate causal factor. However,

adjustment for PaCO2 did not influence the association with time on CV and mortality, suggesting that respiratory acidosis due to worsening pulmonary function caused by prolonged CV treatment was not the explanatory mechanism. Studies that presented time on CV as a causal factor of worsening prognosis adjusted the effect for APACHE score and ventilatory settings but not for pH [17;18]. Only a retrospective study by Mehta and colleagues mentioned time on CV as a predictor of mortality independent of age, APACHE II score and baseline pH [14]. The strength of the effect and whether the association was weakened by the adjustment were not mentioned.

HFOV is a promising candidate for influencing mortality in ARDS patients. Research has demonstrated remarkable differences in mortality related to ventilation. These differences could be mainly attributed to ventilation strategies. There is now less discussion about the current optimal ventilation strategies in CV and HFOV [23]. The challenge seems to be to select the appropriate patients that benefit from HFOV compared with CV [16;24]. Predicting mortality has proven to be difficult because of the heterogeneous nature of ARDS. Yet, ventilatory strategies have shown a constant treatment effect independent of predisposing clinical conditions [24]. In a recent publication of a randomized trial, it was hypothesized that level of OI could determine which patients would receive a relative benefit from HFOV compared with CV [11]. This might oppose a more elective approach in which patients with ARDS are put on HFOV as quickly as possible to avoid prolonged ventilation on CV rather than waiting until a certain level of OI has been reached, as has been suggested [18]. However, the reviewed evidence presented in this report does not support that early HFOV in ARDS would be more beneficial but that patients should be stratified by OI in future HFOV trials.

Conclusion

Prolonged ventilation on CV prior to HFOV was not related to mortality. OI was associated with mortality independently of other disease markers and could be important for selecting ARDS patients that benefit from HFOV.

List of Abbreviations,

ARDS = Acute respiratory distress syndrome

HFOV = High Frequency Oscillatory Ventilation

IRDS = Idiopathic Respiratory Distress Syndrome

CV = Conventional mechanical Ventilation

OI = Oxygenation Index = FiO2*MAP*100) / paO2, where FiO2 = Fraction of inspired oxygen, MAP = Mean Airway Pressure (cmH2O) and PaO2 = Pressure of arterial oxygen (mmHg)

OR = Odds Ratio

RR Relative Risk

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Chapter 7.

General discussion and future perspectives

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General discussion and future perspectives

This thesis was conducted to determine whether or not high frequency ventilation offers clinically relevant benefits over Conventional Mechanical Ventilation (CMV). Five clinically relevant research questions were formulated to evaluate evidence pertaining to high frequency ventilation in premature neonates with infant respiratory distress syndrome (IRDS) and high frequency ventilation in children or adults with acute respiratory distress syndrome (ARDS). Four meta-analyses were conducted and one multi-center randomized trial was analyzed that supplied the following answers:

1. Does elective use of high frequency ventilation in premature neonates with IRDS result in better clinical outcome than conventional mechanical ventilation?

No, the use of high frequency ventilation with a high lung volume strategy as a primary mode of ventilation in premature neonates with IRDS did not result in significantly better survival without chronic lung disease compared with CMV with a lung protective ventilation strategy (Chapter 2) [1].

2. What factors determine the relative treatment effect of high frequency ventilation compared with CMV?

The use of surfactant, application of a high lung volume strategy in high frequency ventilation and a lung protective ventilation strategy in CMV were the most important factors that determined the relative treatment effect of high frequency ventilation compared with CMV (Chapter 3).

3. Is there enough evidence to establish whether or not high frequency ventilation confers clinical benefit over CMV, or do more clinical trials need to be performed?

Yes, when elective use of high frequency ventilation is compared with CMV in premature neonates with IRDS, there is sufficient evidence that high frequency ventilation does not result in less mortality or chronic lung disease compared with CMV (Chapter 4).

4. Is high frequency oscillatory ventilation as safe and effective as conventional mechanical ventilation in adults with ARDS?

The multi center randomized trial did not generate enough evidence to conclude that high frequency oscillatory ventilation (HFOV) was as safe and effective as CMV in adult patients with ARDS (Chapter 5) [2]. However, a post hoc analysis suggested better survival with HFOV compared with CMV in patients that had an initial oxygen index greater than 20 before initiating HFOV.

5. What factors determine mortality in adult patients with ARDS treated with HFOV?

Important determinants of survival in HFOV treated patients with ARDS were the oxygenation index (OI) and pH. Prior time on CV before HFOV was initiated was not independently associated with survival (Chapter 6) [3].

Studies in premature neonates

A substantial number of trials have been performed to demonstrate better pulmonary outcome in high frequency ventilation compared with CMV. The striking finding in this thesis was that differences in pulmonary outcome were mainly dictated by differences in the ventilation strategies that were applied rather than by the type of ventilator. Improvements in the

ventilation strategies applied in CMV and use of surfactant caused more favorable outcome in premature neonates with IRDS over time (Chapter 2) [1]. The most important determinants that influenced relative effect measures of high frequency ventilation compared with CMV in randomized trials with premature neonates with IRDS in the post surfactant era were use of a high volume ventilation strategy in high frequency ventilation treated patients and use of lung protective ventilation strategies in CMV.

Based on experimental studies, it was argued that possibly in smaller and more premature neonates with more advanced stages of IRDS, high frequency ventilation could demonstrate distinctively clinically better results than CMV [4;5]. Secondly, prolonged duration of ventilation on CMV prior to start of high frequency ventilation, could already cause enough lung damage to offset the relative treatment effects of high frequency ventilation [6;7]. These arguments have been used to motivate the design of two large multi-center trials of high frequency ventilation compared with CMV [8;9]. However, these hypotheses could not be substantiated by the meta-regression analyses presented in Chapter 3. Inclusion of more premature neonates and restricting duration of CMV prior to high frequency ventilation did not have a significant effect on the relative treatment effect of high frequency ventilation compared with CMV. A sequential meta-analysis of studies that compared the most optimal high frequency ventilation using a high lung volume strategy with the most optimal application of CMV using a lung protective strategy showed evidence of equality between the two treatments in pulmonary outcome after one study performed. Yet, four more studies were performed subsequently, which were designed to show the same magnitude of effect difference between high frequency ventilation and CMV (Chapter 4).

Studies in adult patients

Two randomized trials were performed in adult patients comparing HFOV with CMV in the treatment of adult respiratory distress syndrome (ARDS) and only one trial was performed in pediatric patients with ARDS [2;10;11]. In this thesis we reported one of the trials in adult patients [2]. This trial was not powered to show a difference in mortality between HFOV and CMV treated patients. In a post hoc analysis, baseline oxygenation index (OI) seemed to modify the relative treatment effect. OI is defined by the percentage of inspired oxygen multiplied by the mean airway pressure divided by the partial arterial oxygen pressure. The OI represents the pressure and oxygen cost of oxygenation, actually a cost benefit ratio, and may be regarded as a marker of pulmonary disease [12;13]. This suggested that in patients with lower OI, i.e. with a minor degree of pulmonary disease, there was no difference between HFOV and CMV. However, in patients with higher baseline OI, HFOV was more favorable compared with CMV. In patients with the highest baseline OI it was irrelevant for survival whether HFOV or CMV was used, i.e. the respiratory condition was too serious to be treatable by either HFOV or CMV.

This is in line with the concept that a safe window exists between atelectotrauma and volutrauma [14]. Once this safe window becomes too small, because of progression of pulmonary disease, to accommodate tidal volumes used in CMV, high frequency ventilation would be the most favorable solution [14;15]. On the other hand, observational studies of HFOV in adult patients revealed that prolonged ventilation on CMV prior to initiating HFOV was associated with higher mortality. This would preclude the use of HFOV as a rescue treatment that could involve longer periods of CMV before initiating HFOV. In a meta-regression analysis of observational data of cohorts of adult patients with ARDS treated with HFOV, potential predictors of mortality were assessed. Duration of CMV

prior to HFOV adjusted for differences in APACHE score and pH, was not independently associated with higher mortality. Adjusting by OI as a possible intermediate mechanism of higher mortality caused by prolonged ventilation on CMV, did not block the effect of duration on CMV on mortality. Therefore, prolonged ventilation with CMV did not seem to be a causal factor in determining mortality in HFOV.

Clinical versus experimental research

A large body of experimental evidence in animals indicates that high frequency ventilation is superior to CMV in preventing ventilator induced lung damage [4;16-23]. Meta-analysis of randomized trials comparing high frequency ventilation with CMV in premature neonates with IRDS failed, however, to establish a clinical benefit of high frequency ventilation over CMV [24]. Although the injurious effect of increased tidal volume, as found in animal experiments, were convincingly replicated in clinical trials comparing CMV with use of low versus high tidal volumes [25;26], the effects of other ventilator parameters, such as use of high positive end-expiratory pressure to open the lung and thus prevention of atelectotrauma, remain clinically controversial [27]. Complementary to experimental animal research clinical epidemiologic research provides an integrated assessment of all these mechanisms that cause ventilator induced lung injury (VILI). Therefore, favorable outcomes that could be predicted from experimental research are not necessarily always confirmed by the more complicated setting of clinical epidemiologic research. The elective use of high frequency ventilation in premature neonates with IRDS seemed to be an example of high expectations based on animal research that could not be reproduced to the same extent in human clinical research. Observational research, however, was suggestive of HFOV as early rescue treatment in adult and pediatric patients with ARDS [28-33].

Meta-analytic techniques

This thesis illustrates the pivotal role of meta-analysis in clinical epidemiologic and experimental animal studies. Different meta-analytic techniques were used to answer the different research questions posed in this thesis. Classical meta-analysis is used to enhance the precision of estimates of treatment effects. If all studies would be more or less homogeneous and point to a common effect estimate, the mere conduct of a meta-analysis would in fact add little to the overall scientific opinion about the relative effectiveness or lack of effectiveness of a treatment. However, in case of heterogeneity between studies, different techniques of meta-analysis can provide additional scientific insights about relative treatment effects. Just pooling in case of significant heterogeneity between studies is not appropriate [34].

First, this thesis showed the use of cumulative meta-analysis to track changes of the cumulatively pooled estimate of the relative treatment effect over time. In cumulative meta-analysis data are pooled each time a new study is added to the previously pooled estimate [35]. This enabled the identification of specific sources of heterogeneity between studies comparing high frequency ventilation with CMV. Subsequent stratification of those trials by the identified sources of heterogeneity was used to obtain more homogeneous pooled effect estimates. However, meta-analysis of randomized trials is observational research with trials as unit of analysis. As such, it will be subject to all sorts of bias inherent to observational research [36]. Thus, despite stratification, residual confounding can remain when covariates that are related to the stratification variable are associated with the relative outcome measures as well. For example, suppose a specific ventilation strategy would lead to a more favorable result with

high frequency ventilation compared with CMV, but at the same time smaller birth weight would also cause a more favorable result with high frequency ventilation, stratification by ventilation strategy alone could be confounded by differences in birth weight. Therefore, not only stratified meta-analyses have been conducted in this thesis but also the technique of meta-regression analysis has been used. Meta-regression analyses allows for adjustment by multiple covariates that differ between trials. Thus more unbiased estimates could be obtained of the relative importance of those differences between trials on the relative effectiveness of high frequency ventilation compared with CMV. Finally, a relatively new technique of sequential meta-analysis has been used in this thesis [37;38]. To be of value, a new randomized trial should add to current knowledge. Assessing whether clinical equipoise was present at the start of a new trial should be general research practice. With sequential meta-analysis the overall significance level alpha (type I error) is preserved, thus preventing a cumulative alpha by multiple testing and increasing type I error. Therefore, to determine whether enough evidence is gathered either to reject the null hypothesis of treatment equipoise or to accept the null hypothesis, sequential meta-analysis is the most appropriate approach. Sequential meta-analysis was used to critically assess each separate contribution of additional trials comparing high frequency ventilation with CMV in premature neonates. Thereupon, it was concluded that four of five consecutive trials were performed, powered to demonstrate the same effect as the first trial was powered to show, after the first trial already had demonstrated the lack of such effect.

Future research

The main challenge for future research to determine whether or not prevention of VILI is more effective with high frequency ventilation than

CMV will be to identify patients in which VILI cannot be avoided by CMV [39;40]. Particular attention should be paid to the ventilation strategies used in the different treatment arms [14]. The timing of initiating HFOV as the experimental treatment as opposed to CMV in the course of ARDS is considered to be critical to find a beneficial effect of HFOV [41]. While some investigators favor an early introduction of HFOV in treatment of ARDS [33], the study presented in this thesis does not support this view (Chapter 6). A possible clinical indicator to select patients that could benefit from HFOV, is the oxygenation index. A subgroup analysis of the randomized trial presented in this thesis showed an increasing benefit of HFOV over CMV in patients with higher oxygenation indexes [2]. Therefore, future studies should be stratified according to this clinical indicator.

Conclusions

Sequential meta-analysis is imperative to assess whether or not the existing evidence justifies a new trial. New trials should not be started without this critical assessment and should be designed according to the evidence as analyzed by sequential meta-analysis.

Lung protective ventilation strategies and selecting the appropriate ventilation goals can prevent ventilator associated lung damage.

The type of ventilator, high frequency or conventional, has less weight in determining pulmonary outcome as long as appropriate ventilation strategies are used. High frequency ventilation remains an alternative treatment modality that should be reserved for patients with advanced lung disease.

Future research should be directed at identifying patients in which the safe window to ventilate is too small to be treated safely or safely enough by CMV. In those patients high frequency ventilation will probably offer a distinct clinically significant improvement over CMV.

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Summary

An abundance of experimental and clinical evidence indicates that mechanical ventilation can cause ventilator induced lung injury (VILI). Particularly in preexistent pulmonary disease, injurious effects of mechanical ventilation are amplified. Primary mechanisms leading to VILI are volutrauma, i.e. use of large tidal volumes resulting in over-distension, and atelectotrauma, i.e. repetitive closing and opening of alveoli, causing shear stress. Ideally, mechanical ventilation should supply enough airway pressure, even in the end-expiratory phase of breathing, to prevent collapse of the lungs. On the other hand, inspiratory pressures should be limited to prevent overdistension. High frequency ventilation combines these features. In high frequency oscillatory ventilation (HFOV), a specific form of high frequency ventilation, a membrane causes pendulant movement of air with a frequency typically ranging from 5 – 10 Hz. These small tidal volumes are superimposed on a continuously distending pressure. The combination of these small tidal volumes at very high frequencies with a high continuously distending airway pressure should prevent volutrauma and, at the same time, atelectotrauma.

Although animal studies clearly showed less pulmonary damage using high frequency ventilation compared with conventional mechanical ventilation (CMV), clinical trials in premature neonates with infant respiratory distress syndrome (IRDS) were less unequivocal. In a cumulative meta-analysis, it was shown that, over time, CMV treatment improved, diminishing the relative treatment benefit of HFOV (Chapter 2). It seemed that use of surfactant and ventilation strategies, used both in high frequency ventilation as well as in CMV, had the largest impact on pulmonary outcome. Other differences between clinical trials, which could explain the heterogeneity in relative treatment effects of HFOV compared with CMV,

did not influence the relative treatment effect as much as ventilation strategies and use of surfactant did (Chapter 3). Enough evidence has been generated, in randomized trials, to conclude that elective use of high frequency ventilation in premature neonates with IRDS offers no clinically relevant benefits over CMV. Moreover, in a sequential meta-analysis it was demonstrated that the first of four trials already showed a lack of clinically benefits of HFOV on pulmonary outcome (Chapter 4). In other words, the other three trials, although they were intended to do so, did not contribute to the cumulative evidence regarding the clinical efficacy of HFOV compared with CMV on pulmonary outcome.

In adult patients with acute respiratory distress syndrome (ARDS) there is less clinical evidence. Two randomized trials in adult patients and one randomized trial in pediatric patients with ARDS suggested less mortality with use of HFOV. Particularly in patients with higher oxygenation index, HFOV could result in better outcome compared with CMV (Chapter 5). The oxygenation index can be regarded as a cost benefit ratio defined by percentage inspired fractional oxygen pressure times mean airway pressure divided by partial arterial oxygen pressure. Higher oxygenation index indicates more severe pulmonary disease. Thus, in patients which have more advanced disease, HFOV possibly results in less mortality and better pulmonary outcome than CMV. This could imply that HFOV should be used as rescue therapy rather than as an elective treatment immediately from the start of ARDS. Prolonged prior ventilation on CMV before initiating HFOV, however, was associated with higher mortality in observational studies. In a meta-regression analysis of cohorts of HFOV treated patients, it was found that this association disappeared when corrected for differences in pH and APACHE II score (Chapter 6). This suggested that prolonged ventilation on CMV, prior to HFOV, is no causal mechanism of mortality in ARDS. Therefore, it seems justified that future

research should be primarily directed at selecting patients with higher oxygenation index to show better outcome with HFOV.

In general, we strongly advocate the use of sequential meta-analysis to critically assess the possible contribution to existing evidence in the planning of an additional trial. Although HFOV combines appealing aspects of lung protective ventilation, i.e. small tidal volumes and higher mean airway pressures, recent advancements in conventional ventilation seem to have compensated for these benefits of HFOV. Only patients with more severe lung disease should be targeted for HFOV as rescue therapy in future research.

Nederlandse samenvatting voor niet-ingewijden

Bij kunstmatige beademing wordt door een beademingsmachine via een buis in de luchtpijp lucht in de longen geblazen. De longen zelf bestaan eigenlijk uit talrijke microscopisch kleine longblaasjes, waar uiteindelijk zuurstof wordt opgenomen en kooldioxide wordt uitgescheiden. Een overvloed aan experimenteel en klinisch bewijsmateriaal wijst erop dat kunstmatige mechanische beademing longschade kan veroorzaken. In het bijzonder bij al bestaande longaandoeningen kunnen de nadelige gevolgen van mechanische ventilatie worden versterkt. De primaire oorzakelijke mechanismen die tot beademingsgerelateerde longschade leiden zijn volutrauma, d.w.z. dat bij gebruik van grote teugvolumes overrekking van de longblaasjes ontstaat, en atelectotrauma, d.w.z. dat door het herhaaldelijk dichtvallen en weer openen van longblaasjes, trek-en-rek-spanning schade veroorzaakt. Een Hoge Frequentie Oscillatie beademingsmachine is een apparaat dat zorgt voor een constante ademweg druk en waarbij door middel van een membraan lucht in trilling wordt gebracht. Hoge frequentie oscillatie beademing (HFOV) combineert uiterst kleine teugvolumes bij zeer hoge frequenties met een hoge continue ademweg druk, waardoor overreking en het dichtvallen van longblaasjes kan worden voorkomen en daarmee, theoretisch, ook longschade.

Hoewel dieronderzoeken duidelijk minder longschade toonden bij gebruik van HFOV vergeleken met de gangbare conventionele mechanische beademing (CMV), waren klinische onderzoeken in te vroeg geboren zuigelingen met ademhalingsproblemen minder eenduidig. Wanneer resultaten van verschillende onderzoeken statistisch bij elkaar worden genomen tot een gezamenlijk resultaat wordt dit een meta-analyse genoemd. Zo'n meta-analyse kan ook cumulatief worden verricht. Het resultaat van de eerste onderzoek in een rij van onderzoeken wordt dan als

uitgangspunt genomen. Het daaropvolgende onderzoek wordt dan door middel van een meta-analyse samengevoegd met het resultaat van het eerste onderzoek. Het gezamenlijk resultaat van die twee onderzoeken vormt dan het tweede punt. Vervolgens wordt weer opnieuw in een meta-analyse een onderzoek toegevoegd zodat een samenvoeging van drie onderzoeken wordt verkregen. Deze procedure wordt herhaald tot alle onderzoeken in de meta-analyse zijn opgenomen. Met het toevoegen van het laatste onderzoek aan de analyse wordt een uitkomst verkregen dat overeenkomt met het resultaat van een klassieke meta-analyse. Het hele beloop van resultaten van het eerste onderzoek tot het gezamenlijke resultaat van alle onderzoeken heet dan een cumulatieve meta-analyse. Indien de onderzoeken in chronologische volgorde in de cumulatieve meta-analyse zijn bijeengevoegd kunnen veranderingen worden waargenomen die zijn ontstaan in de loop van de tijd. Zo blijkt uit een cumulatieve meta-analyse in dit proefschrift dat de verschillen tussen HFOV en CMV in vergelijkende onderzoeken steeds kleiner zijn geworden. Het kleiner worden van de verschillen wordt met name veroorzaakt door verbeteringen van de CMV. Een belangrijke oorzaak in de verbetering van de CMV lijkt te liggen in veranderingen van het beademingsbeleid. In de loop van de tijd werden in vergelijkende onderzoeken van HFOV versus CMV patiënten met CMV beademd met kleinere teugvolumes en een hogere ademhalingsfrequenties. Daarmee werd ook in de CMV behandelde patiënten steeds beter overrekking van de longblaasjes voorkomen en daarmee ook door beademing veroorzaakte longschade. Uiteindelijk zal daardoor bij het merendeel van de te vroeg geboren zuigelingen het niet uit maken of HFOV of CMV apparatuur gebruikt wordt. De manier waarop de apparatuur gebruikt wordt is een belangrijker factor die de uiteindelijke uitkomst bepaalt.

In het verlengde van de cumulatieve meta-analyse die leidde tot de conclusie dat er geen klinische voordelen zijn van HFOV vergeleken met

CMV is een analyse verricht om te bepalen na hoeveel onderzoek deze conclusie al duidelijk was. Dit is gedaan door een statistische techniek genaamd sequentiële meta-analyse. De term sequentieel slaat op het feit dat in de analyse steeds informatie wordt toegevoegd tot het punt dat voldoende informatie is verzameld dat ofwel de conclusie rechtvaardigt dat de ene behandeling beter is dan de andere behandeling of dat er geen verschil is tussen twee behandelingen. In de sequentiële analyse verricht in dit proefschrift bestond de informatie uit de vergelijkende onderzoeken van HFOV versus CMV bij te vroeg geboren zuigelingen met ademhalingsproblematiek. In de laatste 5 onderzoeken werd zowel bij de HFOV behandeling als bij de CMV behandeling de optimale beademingsstrategie gebruikt. Dat wil zeggen dat specifiek overrekking van longblaasjes werd voorkomen door het gebruik van kleinere teugvolumes in CMV en het dichtvallen van longblaasjes werd voorkomen door het gebruik van een hogere beademingsdruk in HFOV behandelde patiënten. De sequentiële meta-analyse toonde aan dat al na één onderzoek voldoende informatie was verzameld om te stellen dat HFOV en CMV gelijkwaardig aan elkaar zijn, mits de juiste beademingsstrategieën worden gehanteerd.

HFOV is ook bij oudere patiënten onderzocht. Bij volwassenen en kinderen met het klinisch beeld van acute ademhalingsproblemen dat kan optreden bij ernstige aandoeningen kan mechanische beademing moeizaam verlopen en kan als gevolg van de beademing bijkomende longschade ontstaan. Met name bij deze categorie van patiënten is ook onderzoek gedaan met HFOV. In een vergelijkend onderzoek bij volwassenen met HFOV gepresenteerd in dit proefschrift leek het voordeel van HFOV boven de CMV af te hangen van de ernst van de ademhalingsproblemen. Bij patiënten met een lichtere mate van acute ademhalingsproblematiek was geen duidelijk verschil tussen HFOV en CMV. Bij meer ernstige longproblemen leek HFOV wel te resulteren in een betere uitkomst dan

CMV, terwijl bij de ernstigste gevallen een slechte uitkomst niet kon worden vermeden zowel door HFOV als door CMV.

Concluderend is in dit proefschrift aangetoond dat HFOV als algemene behandeling bij ademhalingsproblemen bij te vroeg geboren zuigelingen geen duidelijke voordelen biedt boven CMV. Bij volwassen patiënten met het klinisch beeld van acute ademhalingsproblematiek lijkt het relatieve voordeel van HFOV, vergeleken met CMV, af te hangen van de ernst van de acute ademhalingsproblematiek. Verder onderzoek zal zich moeten richten op de selectie van de juiste patiënten categorieën waarbij speciaal HFOV beter is dan CMV. Echter alvorens aanvullend onderzoek wordt gedaan, is de sterke aanbeveling van dit proefschrift om een sequentiële analyse te verrichten om te bepalen of niet reeds voldoende informatie is verzameld in gelijkwaardig voorafgaand onderzoek.

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Curriculum vitae

The author of this thesis was born the 7th of December 1965 in Aalst-Waalre, the Netherlands. After he graduated from the Gymnasium at the Menso Alting College in Hoogeveen in 1984, he started Medical School at the University of Utrecht in 1985. In 1994 he obtained his Medical Degree. From 1994 until 1996 he fulfilled his military service in the Dutch army as a medical resident in the Tjongerschans hospital in Heerenveen. Experience in research was acquired by working as a research physician for the 'Stichting Cardiologische Research' in Rotterdam. This was followed by a residency Cardiology at the University Medical Centre St Radboud in Nijmegen. In January 1998 he started his training in paediatrics at the Catharina Ziekenhuis in Eindhoven under supervision of dr. Waelkens. From 2000 on, he has been working at the Wilhelmina Children's Hospital of the University Medical Centre Utrecht under supervision of prof. dr. J.J. Kimpen. A fellowship in pediatric intensive care under supervision of prof. dr. A.J. van Vught was started January 2003 and finished June 2005. Currently he is working as a member of staff of the pediatric intensive care of the Wilhelmina Children's Hospital.

During his medical training, the author of this thesis became increasingly interested in evidence based medicine and epidemiology. This resulted in a Master's degree of the Erasmus University Rotterdam in Clinical Epidemiology in August 2005. Furthermore, he has been involved in the design and development of several software applications for the pediatric and neonatal intensive care unit and hospital pharmacy.