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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