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.