Chapter 1

General introduction
Mechanical Ventilation and Complications

Different modes of assisted ventilation have been tried for centuries in both respiratory insufficient animals and humans. Vesalius (1514-1546) inflated animal's lungs via bellows attached to intratracheal tubes. Similar devices were used in the 1700s in resuscitation of drowning victims, but because of complications they fell into disrepute by the nineteenth century.¹ Later that century police and fire rescue units used the Pulmotor to force air into the patients lungs using facial masks during resuscitation (Figure 1).¹

Figure 1.

Complications of the Pulmotor ranged from patient-pulmotor synchrony and fighting the mask to esophageal and gastric rupture.² The most commonly known historical ventilator became subsequently known as the iron lung, a tank in which the patient was placed with the head protruding (Figure 2). Inspiration and expiration were forced using negative and positive pressures respectively.² Access to the patient was limited to portholes in the side of the tank and negative pressures could produce abdominal vascular pooling resulting in decreased cardiac output and “tank shock” in patients.³ More importantly, during the height of the Copenhagen polio epidemic a shortage of iron lungs ensued and patients were tracheotomized and bag
ventilated by medical students. Eventually, tracheal intubation and positive pressure ventilation turned out to be a far more superior method that cut mortality rates in half.


Figure 2.

**Ventilator Induced Lung Injury**

Common to all historical and present day ventilation modes and apparatus are the life-saving capacities, but also the wide range of complications of this intervention. Initial understanding of these complications was largely limited to gross air leaks induced by large transpulmonary pressures – so called barotrauma. Various other, more subtle, detrimental effects of mechanical ventilation (MV) have been identified since, largely based on studies on mechanisms of injury. These studies have established several specific ventilator-induced lung injury (VILI) mechanisms. First, regional overdistension caused by the application of local stress or pressure that forces cells and tissues to assume unnatural shapes and dimensions, also known as volutrauma. Second, atelectotrauma or low-volume injury which is associated with repeated recruitment and derecruitment of alveoli, causing abrasion of the epithelial airspace lining. Third, inactivation of
surfactant triggered by MV through lowering the amounts of organized lipid-protein structures reducing adsorption and surface tension. Fourth, interdependence mechanisms that raise cell and tissue stress between neighbouring structures with differing mechanical properties. In patients with underlying pulmonary disease such as acute lung injury or acute respiratory distress syndrome (ARDS) a number of risk factors have been identified that render the lung more susceptible to VILI. For example, surfactant dysfunction, malnutrition, infection and oxygen toxicity not only increase VILI susceptibility but also impair the lungs ability to repair the damage incurred. Furthermore, in ARDS, atelectasis and oedema are frequently present and can markedly reduce the aerated lungs’ capacity to as little of 25% of normal, a concept known as the “baby lung”. Clearly, even with low tidal volume per kg bodyweight ventilation, this reduced aerated lungs’ capacity results in increased overdistension of alveoli. The role of VILI clinically has been highlighted by several prospective studies and clinical trials in which lung protective ventilator management altered the degree of organ failure and mortality.

**Biotrauma**

Similar to any bodily reaction to injury, the lung reacts with a biological response to the aforementioned injurious effects of MV. This has been called biotrauma by Tremblay and Slutsky in 1998. Biotrauma refers to the changes in the activation and recruitment of inflammatory cells, and production of a number of inflammatory mediators which may play an important role in initiating or propagating lung injury and inflammation during MV. Supportive evidence for this concept came from experimental models ranging from mechanically stressed cell systems, to isolated lungs, intact animals, and humans. Of note, during MV, not only pro-inflammatory mediators are released into the lung, anti-inflammatory mediator levels have also been found to be increased. Neither pro- nor anti-inflammatory mediators are confined to the intra-alveolar space, but can be released into the systemic circulation by several different mechanisms; Uhlig proposed 4 different mechanisms: stress failure of the plasma membrane with subsequent release of preformed mediators and further propagation of inflammation by cytosolic compounds released from damaged cells. Loss of compartmentalization may occur when epithelial and endothelial barriers fail under stress, leading to haemorrhage and accumulation of leukocytes in the lungs. Overdistension without tissue destruction leading to activation of transcription factor nuclear factor-κB through mechanotransduction. Lastly, increased vascular pressure and sheer stress may induce mediator release, though little
experimental evidence is available. The systemic release of mediators prompted various authors to suggest a role for these mediators in the development of multiple system organ failure (MSOF).  

**Acute Kidney Injury**

In patients suffering from respiratory insufficiency major initial physiological abnormalities are often pulmonary in origin. However, patients who go on to die of their acute illness usually die of MSOF including acute kidney injury (AKI) rather than from hypoxemia alone. Figure 3 shows several mechanisms through which MV can contribute to MSOF. Evidence for the effects of cytokines released during MV comes from studies by Ranieri and colleagues in patients with ARDS. These patients were randomly allocated to one of two different MV strategies. The patients that were ventilated with a protective strategy had significantly lower plasma cytokine concentrations and significantly less organ failure compared to patients in the control group.
Results of the ARDS Network study showed that mortality and plasma interleukin-6 concentrations were lower in the protective ventilation group than in the control group.\textsuperscript{18} It is not clear however, which factor or factors are responsible for exerting toxic effects on distal organs. In addition to cytokines, bacterial translocation and effects on gas exchange and cardiac output may also potentially contribute to MSOF.\textsuperscript{7,35,38} AKI is an early manifestation of MSOF and has a prevalence ranging from 4\% to 16\% and high mortality rates.\textsuperscript{39-43} A 2005 multinational, multicenter study of 29,269 critically ill patients showed 1,738 (5.7\%) had AKI during their stay in the intensive care unit. Of these patients with AKI, 60.3\% died.\textsuperscript{44} Of all patients with AKI, 75\% required MV, additionally MV showed to be an independent risk factor (odds ratio 2.11) for hospital mortality.\textsuperscript{44} In sepsis with MSOF, including AKI and ARDS requiring MV, mortality rates of more than 80\% have been reported.\textsuperscript{39,45} Besides being an independent risk factor for mortality in patients with AKI, MV is also an independent risk factor for the development of AKI. Studies showed a two to twenty-fold increased risk of developing AKI when patients were mechanically ventilated.\textsuperscript{46,47} Although the pathophysiologic mechanisms of AKI has been the focus of many studies, the role of MV in the development of AKI has been scarcely addressed.

**Aim and Outline of the Thesis**

This thesis focuses on the role of MV in the development of AKI. Specific aims of this thesis are the identification of pathophysiologic mechanisms that may lead to AKI during MV. The injurious effects of MV on the lung may depend on the type of underlying pulmonary pathology, with subsequent consequences for a systemic reaction and possible effects on organs distant from the lungs. Therefore, the second aim is to study the effects of different MV strategies in different types of lung injury. The third aim is to study the effects of MV on the kidney in animal models of healthy and diseased lungs. The last aim of this thesis is to identify potential therapeutic targets, thereby also further delineating the renal effects of MV.

The outline of this thesis is as follows: little is known about the potential mechanisms through which MV leads to AKI. Chapter two describes the results of an extensive search of the literature that identified different mechanisms through which MV can lead to AKI. In Chapter three we describe the potential effects of mediators, released during mechanical ventilation, on the kidney. Both chapters two and three also provide a framework for future research. Different MV strategies, i.e. high and low tidal volume ventilation, may have different effects on the lungs.
during direct and indirect lung injury. In Chapter four we hypothesize that the effects of MV on lung injury and mediator release depend on the underlying type of lung injury, the effects being most profound after high tidal volume during direct lung injury. MV of healthy lungs may also have effects on the kidney through the systemic release of inflammatory mediators. Effects on the kidney may involve renal blood flow. In Chapter five we hypothesized that upregulation of systemic inflammation in response to a lung-injurious ventilatory strategy ultimately results in kidney dysfunction mediated by local effects on renal vasculature. MV induced AKI during sepsis may involve MV induced renal apoptosis. In Chapter six we studied the effects of high tidal volume MV in septic rats on systemic inflammation and endothelial cell activation. Additionally, we hypothesized that MV causes renal apoptosis and decreased kidney function. In Chapter seven poly(adenosine diphosphate-ribose) polymerase (PARP)-1 is identified as a potential therapeutic target. We investigated the effects of pharmacological inhibition of PARP-1 on pulmonary inflammation and apoptosis kidney function during MV. Chapter eight further explores the effect of PARP-1 on the kidney. We tested the hypothesis that renal blood flow and endothelial, functional and tissue changes in kidneys during MV aggravated lung injury, is caused, in part, by activation of PARP. Finally, Chapter nine provides the conclusions and a general discussion of this thesis. This chapter ends with future perspectives on MV and AKI.
References

Introduction


