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Smeding, L.

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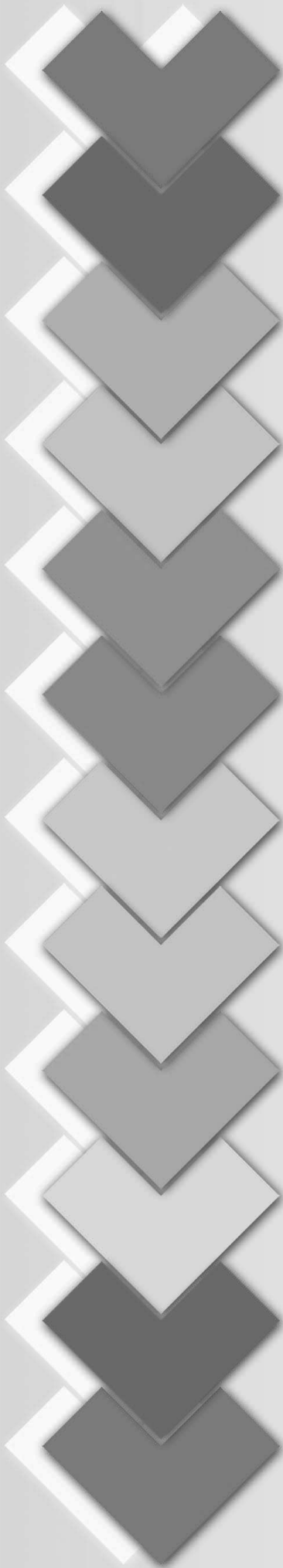
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1.

General introduction

Patients in the intensive care unit (ICU) are suffering from a variety of diseases amongst which severe sepsis, which has a prevalence in Dutch ICUs of about 30%. Severe sepsis is associated with organ failure of which myocardial and respiratory failure are most prominent and treatment may require mechanical ventilation. However, increasing evidence indicates that mechanical ventilation may have injurious effects on lungs and other organs, for example ventilation with conventional high tidal volumes was indicated to increase mortality (1). In this thesis we aim to investigate the effect of mechanical ventilation on the heart in face of yet compromised myocardial function during sepsis.

Sepsis

Severe sepsis affects millions of people around the world each year and is associated with high mortality. Sepsis is defined as the non-specific systemic inflammatory response to microbial infection and is characterized and modulated by different pro- and anti-inflammatory pathways. It may advance to severe sepsis when it is associated with acute organ failure or hypoperfusion. Finally, septic shock is diagnosed when in severe sepsis hypotension or need for vasopressors develops despite adequate fluid resuscitation (2). Table 1 summarizes the current criteria to define the different stages of sepsis. Per year, about 9,000 patients with severe sepsis are admitted at the ICU in the Netherlands (3) and in the United States an incidence of about 750,000 cases per year is reported (4). Incidence is highest in the elderly patients with 26.2 severe septic patients per 1000 persons aged ≥ 85 years (4). Almost three in four (69-78.1%) severe septic patients admitted at the ICU suffer from at least two organ dysfunctions of which respiratory failure, observed in 75% of these patients, and cardiovascular failure (51-55.4%), were most prominent (3;5;6). Adequately volume-resuscitated patients with septic shock present with a hyperdynamic circulatory state with high cardiac output (CO) and reduced systemic vascular resistance (SVR) (7-9). However, despite a high CO, which is mainly due to the lowered SVR, sepsis is often associated with myocardial dysfunction, indicated by reduced ejection fraction and ventricular contractility (9). Patients with severe sepsis have a longer length of stay, a higher requirement of organ support and a higher mortality rate compared with other patients on the ICU (5). Mortality rates are greatly varying, due to differences in, amongst others, age, treatment and organ failure, and was found to be around 50% in septic shock patients with at least two failing organs systems (5;6).

Myocardial dysfunction is one of the most prevalent organ dysfunctions in severe sepsis and septic shock. The cause of sepsis-induced myocardial dysfunction is unknown but appears to be multifactorial (8-11). Cytokines that are released during sepsis, such as tumor necrosis factor (TNF)- α ,

Name	Criteria
SIRS	Two or more of the following:
	Body temperature >38.5°C or <35.0°C
	Heart rate >90 bpm
	Respiratory rate >20 breaths per minute or arterial CO ₂ tension <32 mm Hg or need for mechanical ventilation
	White blood cell count >12 000/mm ³ or < 4000/mm ³ or immature forms >10%
Sepsis	SIRS and documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection, eg, ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)
Severe sepsis	Sepsis and at least 1 sign of organ hypoperfusion or organ dysfunction:
	Areas of mottled skin
	Capillary refilling time ≥3 s
	Urinary output <0.5 mL/kg for at least 1 h or renal replacement therapy
	Lactates >2 mmol/L
	Abrupt change in mental status or abnormal electroencephalogram
	Platelet counts <100 000/mL or disseminated intravascular coagulation
	Acute lung injury—acute respiratory distress syndrome
	Cardiac dysfunction (echocardiography)
Septic shock	Severe sepsis and 1 of the following:
	Systemic mean blood pressure <60 mm Hg (<80 mm Hg if previous hypertension) after 20–30 mL/kg starch or 40–60 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mm Hg
	Need for dopamine >5 μg · kg ⁻¹ · min ⁻¹ or norepinephrine or epinephrine <0.25 μg · kg ⁻¹ · min ⁻¹ to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)
Refractory septic shock	Need for dopamine >15 μg · kg ⁻¹ · min ⁻¹ or norepinephrine or epinephrine >0.25 μg · kg ⁻¹ · min ⁻¹ to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

Table 1. Current criteria for establishment of the diagnosis of SIRS, sepsis, and septic shock. SIRS indicates systemic inflammatory response syndrome (2;10).

interleukin (IL)-1 β and IL6, and other small molecules such as nitric oxide (NO), induced by TNF α , and endothelin may affect myocardial contractility by altering calcium signaling, handling and sensitivity in the myocardium. Furthermore, activation of the endothelium induces sequestration of inflammatory cells, vascular leakage and edema and although global ischemia does not seem to occur (12),

redistribution of flow with subsequent local hypoperfusion (13;14), sequestration of cells and edema may cause local hypoxia. Moreover, these factors may not only affect myocardial function through local hypoxia, but may also affect myocardial contractility by itself. Next, an important role in myocardial dysfunction is indicated for mitochondria (15;16). Local hypoxia, inflammatory cytokines, such as TNF α , NO and other mediators may lead to mitochondrial dysfunction and damage which causes energy depletion. Reduced mitochondrial enzyme activity, inhibition of the electron transport chain activity and transcriptional changes in bio-energy proteins were shown (17). The inability of cells to use oxygen and produce adenosine tri-phosphate (ATP) is called cytopathic hypoxia and is thought to play an important role in sepsis-induced myocardial dysfunction. Finally, systemic circulating inflammatory factors, lack of ATP and increased mitochondrial damage may induce apoptosis both through the intrinsic (mitochondrial) and extrinsic (death receptor) pathway.

Acute respiratory distress syndrome

Respiratory failure is seen in about 75% of severe septic patients (3;5;6) and nearly 50% of the patients with severe sepsis will develop acute lung injury (ALI)/ acute respiratory distress syndrome (ARDS) (18). ARDS is caused by an insult to the alveolar-capillary membrane that results in increased permeability and subsequent interstitial and alveolar edema (19). The observed lung injury may result from two different pathways: a direct insult on lung cells, such as pneumonia, the most common cause of sepsis, or an indirect insult as a result of an acute systemic inflammatory response. As such, sepsis can induce ALI/ARDS through multiple mechanisms such as systemic inflammation, leukocyte activation and recruitment, neutrophil infiltration, oxidative stress and apoptosis of the lung epithelial cells (20). Indeed, sepsis was found to be one of the major causes of ARDS as rates of sepsis-induced ARDS range from 24-32% of total ARDS cases (21-23).

Important features of ARDS are severe hypoxemia with relatively high fraction of inspired oxygen (F_iO_2), decreased pulmonary compliance and bilateral pulmonary infiltrates all in the absence of cardiogenic pulmonary edema (19). Although a joint American-European Consensus Conference (AECC) on ARDS had formed definitions on ALI and ARDS (24), these definitions have been highly debated as this definition is incapable of identifying an homogeneous group of patients with similar outcomes (25). Current treatment for ARDS is supportive in nature. Patients with ARDS uniformly require MV to decrease the work of breathing and to improve oxygen transport (19).

Total ARDS mortality was reported around 30-58%, with incidence and mortality rates

differing between studies, mostly due to different study populations (22;23;26). Interestingly, the predominant cause of death in ARDS is not insupportable respiratory failure but sepsis and multiple organ failure, causing 33-76% of deaths in ARDS patients (22;26;27). In a cohort study of 78 ICUs in Europe, cardiovascular dysfunction was found in about 55% of the ARDS patients (23). MV, which is the most important treatment for ARDS to maintain proper gas exchange, may play a role in the development of organ failure, as increasing evidence show harmful effects, especially when high tidal volumes are used.

Mechanical ventilation

Mechanical ventilation (MV) may cause ventilation-induced lung injury (VILI), consisting of air leaks, structural disruption of membranes, decreased lung compliance and decreased surfactant function, dense pulmonary cellular infiltrates, pulmonary edema and hyaline membranes with subsequent pulmonary dysfunction (28). As such, VILI is functionally and histologically indistinguishable from ARDS (29). Historically, relatively high tidal volumes (V_t) and airway pressures were used in face of ALI/ARDS to overcome loss of lung volume by collapse of alveoli. However, these high V_t and airway pressures superimposed upon existing lung injury may create a synergistic increase in lung injury. Indeed, important mechanisms by which VILI is caused include overdistention due to the use of excessive pressures (barotrauma) or volumes (volutrauma) or by shear forces generated during repetitive opening and collapse of atelectic alveoli (atelectrauma). This atelectrauma is worsened as MV may cause surfactant dysfunction, increasing the risk of alveoli collapse (30). Moreover, when alveoli are collapsed, this will cause extra stress on adjacent alveoli as they will be stretched due to alveolar interdependence (31) and the decreased lung volume may create extra overdistention (shear stress). Next, physical forces on the cell membrane and membrane receptors may be converted into activation of intracellular signal transduction pathways, a process called mechanotransduction (29). In 2000, the ARDSnetwork showed that the use of a low tidal volume (V_t) of 6ml/kg compared to conventional volumes of 12 ml/kg decreased mortality and increased the number of ventilator-free days in ARDS-patients, indicating the clinical importance of VILI and its effect on outcome (1).

As mentioned above, ARDS-patients mainly die of sepsis and multiple organ failure indicating that inflammation may spread. In the last decade it has become clear that MV may injure not only lungs but also other organ systems. During VILI, inflammatory pathways are activated and lungs may actively excrete inflammatory mediators such as cytokines into the circulation. Increased levels of

inflammatory mediators such as TNF α , IL-1 β and IL-6 were found in the systemic circulation after ventilation with high Vt (32-36). Moreover, after disruption of alveolar membranes other soluble cell contents, such as heat shock protein (Hsp-)70, proapoptotic Fas ligand, bacteria or bacterial products, may also translocate into the blood stream (37). Once in the circulation, these mediators may reach other organs and may have adverse effects. Indeed, increased levels of multiple organ failure were shown after ventilation with conventional Vt, which correlated with inflammatory mediators plasma concentrations (38), although it is difficult to demonstrate the origin of these mediators. The release of inflammatory mediators by MV and their biological action on distant organs is called biotrauma (39).

Previous studies suggest that injurious ventilation may induce distant organ inflammation and dysfunction, particularly in the kidneys (40-46). However, only limited data are available on the effects of injurious ventilation on the heart. Positive pressure ventilation induces changes in pre-and afterload, and lung stretch upon MV may activate the vagal nerve, thereby affecting myocardial contractility (47-51), independent of VILI. Also, MV increased coronary endothelial activation shown by increased expression of carboxymethyl-lysine (CML) and increased left ventricular influx of macrophages in a chronic sepsis model (52). In addition, in an acid-aspiration-induced acute lung injury model, myocardial leukosequestration and edema formation was found, indicating that lung injury may indeed affect the heart, but this did not cause myocardial dysfunction (51). Subsequently, it was shown that lung stretch produced by positive end expiratory pressure (PEEP), with unknown effects on the lungs, may cause the release of an unidentified 'humoral agent' which decreases left ventricular contractility, possibly by depressing the Ca²⁺ATPase activity (53-55). Finally, in a model of VILI, increased expression of cyclooxygenase (COX-)1 and COX 2, enzymes that are up-regulated in inflammatory conditions, was found (44). In total, these data suggest that lung injury and MV/VILI may induce myocardial inflammation and may release mediators that can adversely affect myocardial function. Indeed, it was suggested that the inflammatory response elicited by MV and the subsequent effects on distant organs may be described as a sepsis-like syndrome (56), such that the effects of MV on myocardial function might be similar and through similar pathways as those seen in sepsis.

Outline of the thesis

Sepsis, and other infectious diseases, can cause myocardial dysfunction and increase the need for MV. However, in face of pre-existing lung injury, MV may cause VILI which may subsequently affect myocardial function. As this may already be compromised in sepsis, VILI may act as a second hit on the

heart. In this thesis, we aim to investigate the additional effect of lung-injurious MV and VILI on sepsis-induced myocardial dysfunction.

We first focus on sepsis-induced myocardial dysfunction. Although many studies were performed to examine the functional changes in the heart during sepsis (for review (7-11;15)) many findings such as elevated serum levels of cardiac proteins, autopsy findings of myocardial immune cell infiltration and edema, suggest structural, i.e. histological, changes in the heart. In **chapter 2** we review these changes and try to assess their potential role in the development of myocardial dysfunction. Subsequently, in functional studies as well as in autopsy reports mitochondrial changes are reported in the heart during sepsis. Therefore, in **chapter 3** we study mitochondrial involvement in sepsis-induced myocardial dysfunction in an acute model of lipopolysaccharide (LPS)-induced peritonitis. LPS is a major component of the outer membrane of gram-negative bacteria that can be recognized by the immune system and elicit an inflammatory response. It is therefore often used in sepsis-models. After intraperitoneal injection of LPS, peritonitis and subsequent endotoxemia develops, such that this model can mimic sepsis after an abdominal infection (3;5). We investigate myocardial function and mitochondrial injury, function and biogenesis 2 and 4 hours after intraperitoneal LPS-injection, and hypothesized that with myocardial dysfunction during sepsis may be associated with impaired mitochondrial function, mitochondrial injury and activation of mitochondrial biogenesis. In **chapter 4** we try to unravel some of the molecular events that may play a role in the development of mitochondrial dysfunction in the heart during sepsis. It was previously found that molecular and functional changes in the heart during sepsis may, in part, be mediated through down-regulation of the transcription factor proliferator-activator receptor gamma coactivator (PGC) 1α (17). This transcription coactivator plays a key role in mitochondrial metabolism and biogenesis and in chapter 4 we use the drug resveratrol, a polyphenol which is mostly known as a constituent of red wine (57) to prevent its down-regulation and thereby potentially prevent the mitochondrial dysfunction and injury observed in the heart during sepsis. In this chapter we use a more chronic model with cecal ligation and puncture (CLP) to induce peritonitis and sepsis. In this model the cecum is punctured which creates a more gradual inflammatory response and thereby mimics a more clinical relevant situation.

Subsequently, we study the effects of lung-injurious MV and VILI on myocardial (dys-)function. In order to investigate this, we first review the hemodynamic effects of MV. Upon MV, in contrast to spontaneous breathing, intrathoracic pressures increase, which may cause alterations in cardiac

loading and function. In **chapter 5** we describe the effects of heart lung interactions during MV in several clinical settings and diseases, in order to better understand the circulatory changes that occur after institution of MV.

After this review, we perform experimental studies, to investigate the effect of lung-injurious Vt and VILI on sepsis-induced myocardial dysfunction. As severe sepsis mostly originated from respiratory failure or abdominal infection (3;5) we use both a peritonitis-model and a pneumonia-model. Subsequently, we ventilate with a so-called lung-protective strategy (1;58) and a lung-injurious strategy with high Vt (35;59) to induce VILI. In **chapter 6** we study the effects of MV with high Vt on myocardial (dys-)function in a LPS-induced peritonitis model. As ventilation was shown to cause endothelial activation in the heart (52) and injured lungs induced inflammation in liver vascular endothelial cells (60), we hypothesize that endothelial activation and myocardial edema formation may be altered by VILI, with adverse effects on myocardial function. In **chapter 7** we use a model of LPS-induced pneumonia and ventilate again with injuriously high Vt. As previous studies have shown inflammation in distant organs after VILI following pneumonia or acid aspiration we hypothesize that myocardial inflammation may be induced by VILI with a subsequent aggravating effect on myocardial function.

Finally, **chapter 8** provides a general discussion and summary of our findings.

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