Influence of mechanical ventilation and sepsis on redox balance in diaphragm, myocardium, limb muscles, and lungs

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Mechanical ventilation (MV), using high tidal volumes (V_T), causes lung (ventilator-induced lung injury (VILI)) and distant organ injury. Additionally, sepsis is characterized by increased oxidative stress. We tested whether MV is associated with enhanced oxidative stress in sepsis, the commonest underlying condition in clinical acute lung injury. Protein carbonylation and nitration, antioxidants, and inflammation (immunoblotting) were evaluated in diaphragm, gastrocnemius, soleus, myocardium, and lungs of nonseptic and septic (cecal ligation and puncture 24 hours before MV) rats undergoing MV (n = 7 per group) for 150 minutes using 3 different strategies (low V_T (V_T = 9 mL/kg), moderate V_T (V_T = 15 mL/kg), and high V_T (V_T = 25 mL/kg)) and in nonventilated control animals. Compared with nonventilated control animals, in septic and nonseptic rodents (1) diaphragms, limb muscles, and myocardium of high-V_T rats exhibited a decrease in protein oxidation and nitration levels, (2) antioxidant levels followed a specific fiber-type distribution in slow- and fast-twitch muscles, (3) tumor necrosis factor α (TNF-α) levels were higher in respiratory and limb muscles, whereas no differences were observed in myocardium, and (4) in lungs, protein oxidation was increased, antioxidants were rather decreased, and TNF-α remained unmodified. In this model of VILI, oxidative stress does not occur in distant organs or skeletal muscles of rodents after several hours of MV with moderate-to-high V_T, whereas protein oxidation levels were increased in the lungs of the animals. Inflammatory events were moderately expressed in skeletal muscles and lungs of the MV rats. Concomitant sepsis did not strongly affect the MV-induced effects on muscles, myocardium, or lungs in the rodents. (Translational Research 2014;164:477–495)

Abbreviations: ALI = acute lung injury; BAL = bronchoalveolar lavage; CLP = cecal ligation and puncture; CTL = control; CuZn = copper zinc superoxide dismutase; GAPDH = glyceraldehyde-3-phosphate dehydrogenase; HO-1 = heme oxygenase 1; ICU = intensive care unit; Kg = kilogram; mL = milliliters; Mn-SOD = manganese-superoxide dismutase; MV = mechanical ventilation; Nrf2 = erythroid 2-related factor 2; OD = optical density; PEEP = positive end-expiratory pressure; ROS = reactive oxygen species; RNS = reactive nitrogen species; TNF = tumor necrosis factor; VT = high tidal volumes; VILI = ventilator-induced lung injury

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AT A GLANCE COMMENTARY

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Background

Mechanical ventilation (MV), using high tidal volumes, causes lung (ventilator-induced lung injury) and distant organ injury. Additionally, sepsis is characterized by increased oxidative stress. MV may be associated with enhanced oxidative stress in sepsis, the commonest underlying condition in clinical acute lung injury.

Translational Significance

Medium-term changes in redox balance induced by high-tidal volume MV were characterized by increased oxidative stress in the lungs, whereas causing a decline of these phenomena in respiratory and limb muscles, and myocardium. Inflammatory events were moderately expressed in skeletal muscles and lungs of the MV rats. Concomitant sepsis did not strongly affect the MV-induced effects on muscles, myocardium, or lungs in the rodents.

INTRODUCTION

In intensive care units (ICU), acute lung injury (ALI) and acute respiratory distress syndrome are common conditions that cause death in patients as a result of shock and multiorgan failure.[1] In these patients, mechanical ventilation (MV) is a lifesaving strategy that may entail serious complications in lungs such as alveolar disruption and pulmonary edema,[2] a process known as ventilator-induced lung injury (VILI).[3]

Several cellular and molecular mechanisms have been involved in the development and perpetuation of VILI.[4] Inflammatory cells and proinflammatory cytokines were shown to participate in the pathophysiology of VILI.[5,6] In the lining fluid of mechanically ventilated lungs, antioxidant activity was decreased,[7] whereas malondialdehyde levels were increased.[8] Levels of nitrosative stress were also shown to be increased in the lungs of patients with ALI.[9] Moreover, in another study,[10] it was also reported that increased levels of protein oxidation and inflammation took place in lungs from rats exposed to high-tidal volume (V_T) MV. Recently, caveolin-1 was shown to play a key role in the inflammatory events and endothelial hyperpermeability taking place in the lungs during MV.[11]

In several animal models of VILI,[10,12-18] high-V_T MV of short duration was also shown to induce injury in distant organs other than the lungs. In a recent investigation from our group,[10] the diaphragm and both slow- and fast-twitch limb muscles exhibited a significant decline in oxidative stress markers and low levels of intramuscular inflammatory cell infiltration in response to high-V_T MV of very short duration (1 hour). We concluded from that study that perfusion of organs and muscles in the high-V_T rats was likely to be reduced as a result of the hypotension exhibited by the rodents after the 1-hour period of MV.[10] However, in that study,[10] we used a rather high V_T (35 mL/kg) for a very short period of time (1 hour). Whether MV using lower V_T (more clinically relevant) for longer periods of time and in a more clinically realistic context (ie, sepsis, as the most common risk factor for ALI) induces similar molecular events in muscles and organs other than the lungs remains to be answered.

Patients with respiratory failure often require MV in the context of impaired gas exchange and muscle dysfunction.[19,20] On the other hand, ICU-acquired weakness has been shown to be a serious complication leading to prolonged MV and a long stay in the ICU.[19-23] On the basis of this, the study of the effects of MV on muscle status is of great clinical relevance. Several factors such as hypoxemia, increased vascular resistance, acidosis, enhanced energy requirements, inflammation, and oxidative stress are proposed contributors to peripheral and respiratory muscle contractile dysfunction in septic patients,[24] and in animal models of sepsis and endotoxemia.[25-28] Whether MV per se may influence the underlying cellular and molecular events of poor muscle condition in models of sepsis has not been identified so far.

In the present study, we hypothesized that medium-term molecular events such as oxidative stress and inflammation may develop in the lungs and distant organs including respiratory and limb muscles of rats with and without sepsis exposed to several levels of MV. The model of VILI used in the present investigation has already been used in previous studies.[6,10,12-18,29,30] Accordingly, our objectives were to specifically explore the medium-term molecular events involving oxidative stress, antioxidant mechanisms, and inflammation in the diaphragms, limb muscles (fast- and slow-twitch types), myocardium, and lungs of healthy rats exposed to several degrees of MV for 150 minutes. The influence of 24 hours of sepsis on the same muscles and organs was also evaluated in rodents exposed to identical MV strategies.

MATERIALS AND METHODS

See the online data supplement for additional methodological details regarding animal experiments, molecular biology and statistical analyses.

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