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Acute lung injury and acute respiratory distress syndrome: experimental and clinical investigations

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Abstract

Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) can be associated with various disorders. Recent investigation has involved clinical studies in collaboration with clinical investigators and pathologists on the pathogenetic mechanisms of ALI or ARDS caused by various disorders. This literature review includes a brief historical retrospective of ALI/ARDS, the neurogenic pulmonary edema due to head injury, the long-term experimental studies and clinical investigations from our laboratory, the detrimental role of NO, the risk factors, and the possible pathogenetic mechanisms as well as therapeutic regimen for ALI/ARDS.

1 Introduction

Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) is a serious clinical problem with high mortality.[1] In animals and humans, ALI can be induced by various causes such as brain injury,[1–4] enterovirus,[5,6] Japanese B encephalitis,[7] and coronavirus.[8,9] The risk factors for ARDS included septicemia, acid aspiration, infection, traumatic injury, fat embolism, ischemia/ reperfusion, and other caused.[1,6,8,10–18] Our cardiopulmonary laboratory has carried out experimental studies and clinical investigations on ALI and ARDS since 1973.[1–3,17,19,20] The purposes of this review article are: (1) To describe in brief the historical perspective of ARDS and ALI; (2) To draw attention of an important clinical issue of neurogenic ALI; (3) To present the experimental studies and clinical investigations from our laboratory from 1973 to 2009; (4) To elucidate the functional role of nitric oxide (NO) and other mediators involved in the pathogenesis of ARDS/ALI; (5) To define the risk factors for ARDS and ALI; and (6) To discuss the pathogenetic mechanisms and therapeutic regimen for ARDS/ALI.

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2 Neurogenic pulmonary edema

ALI or pulmonary embolism (PE) has been reported in humans and animals with intracranial disorders such as head trauma, brain tumor, intracranial hypertension or cerebral compression. Early studies in our laboratory demonstrated that acute PE of hemorrhagic and fulminant type occurred accompanying severe hypertension and bradycardia (Cushing responses) in rats following cerebral compression (CC) or intracranial hypertension (ICH). The lung pathology was characterized by intravascular congestion and disruption of pulmonary large and small vessels leading to severe alveolar hemorrhage (alveolar flooding). These changes was prevented by spinal transection, sympathectomy and sympathoadrenergic blocking agents, but was not affected by decerebration, adrenalectomy, vagotomy and atropine. These results suggest that sympathetic nervous system is pivotal in the neurogenic PE. Brain areas above the medulla oblongata and parasympathetic nervous system play little role.[2]

A series of studies was carried out to elucidate the hemodynamic events involved in the neurogenic PE. In anesthetized rats, we measured the aortic and pulmonary blood flow and used techniques of right and left heart bypass. The imbalance in the right and left ventricular output was characterized by a rapid and dramatic decline in aortic flow accompanying a gradual decrease in pulmonary arterial flow. In rats with a right heart bypass, ICH produced severe pulmonary hypertension and PE. In the left heart-bypassed rats, ICH induced systemic hypertension,

whereas no significant changes occurred in the lungs.[4] In anesthetized dogs with a total heart bypass preparation, ICH produced constriction of the systemic and pulmonary resistance and capacitance vessels.[21–24] The implications of these findings are: (1) Central sympathetic activation elicits increase in the systemic and pulmonary vascular resistance associated with decreases in vascular capacity in both circulations; (2) The major cause of volume and pressure loading in the pulmonary circulation is acute left ventricular failure resulting in a marked decrease in aortic flow; and (3) Systemic venous constriction causes a shift of blood from the systemic to the pulmonary circulation (Figure 1). A schematic representation summarizes the neural and hemodynamic consequence caused by cerebral compression (Figure 2).
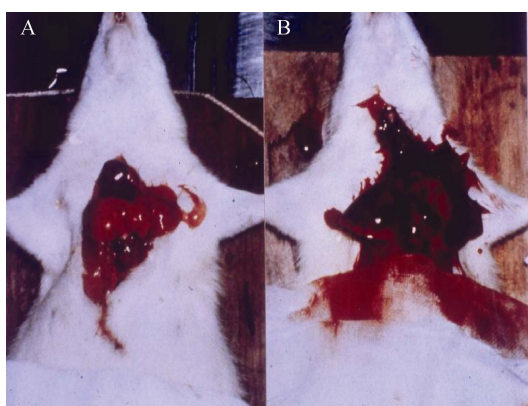

Figure 1. Gross inspection of the lungs in rats with and without cerebral compression. (A): The normal configuration of lungs from a control rat without cerebral compression; (B): After cerebral compression, there were edematous and hemorrhagic changes of the lungs. The lungs were enlarged and swollen with marked discoloration.

Spectral analysis of the aortic flow and pressure wave was employed to evaluate the hemodynamics of steady and pulsatile components. In anesthetized dogs, ICH caused significant increases in characteristic impedance, pulse wave reflection and total peripheral resistance with decrease in arterial compliance and cardiac output. The ventricular work was elevated.[25] Clinical study in patients with head injury of various severities, analysis of the heart rate variability with frequency analysis revealed increased low frequency percentage, and low to high frequency ratio with decrease in high frequency. The findings indicate augmented sympathetic and attenuated parasympathetic drive. These autonomic functional changes were related to the severity of brain-stem damage.[26] These two studies further support the contention that central sympathetic

activation is involved in the Cushing pressor response and consequent hemodynamic and autonomic alterations.

3 The mediators involved in ALI and pulmonary hypertension

In 1990s, my associates and I were interested in the study of chest disorders. We developed an isolated perfused rat's lung *in situ* preparation (Figure 3). Previous method involved removing the isolated lungs from the body and placing the organ on a force-displacement transducer to record the changes in lung weight and these procedures were rather complicated and unstable. Our *in situ* preparation does not require removing the lungs. Instead, the isolated lungs were left *in situ*. The whole rat was placed in a scale platform to measure the change in body weight (BW). Since the lungs are completely isolated from the body, the changes in BW reflect the lung weight (LW) changes. The preparation can be accomplished in 15 min. We used a digital-analogue converter to transfer the weight change from the scale platform to a recorder. The LW thus could be continuously monitored during the experiment. In this model, we can obtain the lung weight gain, LW/BW ratio, the changes in pulmonary arterial, capillary and venous pressures, the microvascular permeability (capillary filtration coefficient, K_{fc}), protein concentration in bronchoalveolar lavage (PCBAL), dye leakage, and exhaled nitric oxide (NO). The concentration of nitrate/nitrite, methyl guanidine (an index for hydroxyl radical), proinflammatory cytokines [tumor necrosis factor α (TNF$_\alpha$) and interleukin-1$_\beta$ (IL-1$_\beta$)] and other factors in the lung perfusate can also be detected. Early animal experimentations investigated the pathogenesis, modulators and mediators involved in the ALI induced by phorphol, air embolism, platelets, hypoxia, ischemia/reperfusion, endotoxin [lipopolysaccharide (LPS)]. The major finding is that cyclooxygenase products of arachidonic acid, thromboxane A_2 in particular is involved in the ALI and pulmonary hypertension caused by phorbol, platelets and air embolism.[27,28] Furthermore, we found that *L*-arginine and inhaled NO enhanced the lung injury caused by air embolism, while blockade of NO synthase (NOS) with N^ω-nitro-*L*-arginine methyl ester (*L*-NAME) attenuated the ALI.[28] The result suggests that NO is also involved.

4 The detrimental role of NO via the iNOS isoform in the ALI/ARDS

During the summers from 2001−2003, we encountered a total of 48 children suffering from hand, foot, and mouth
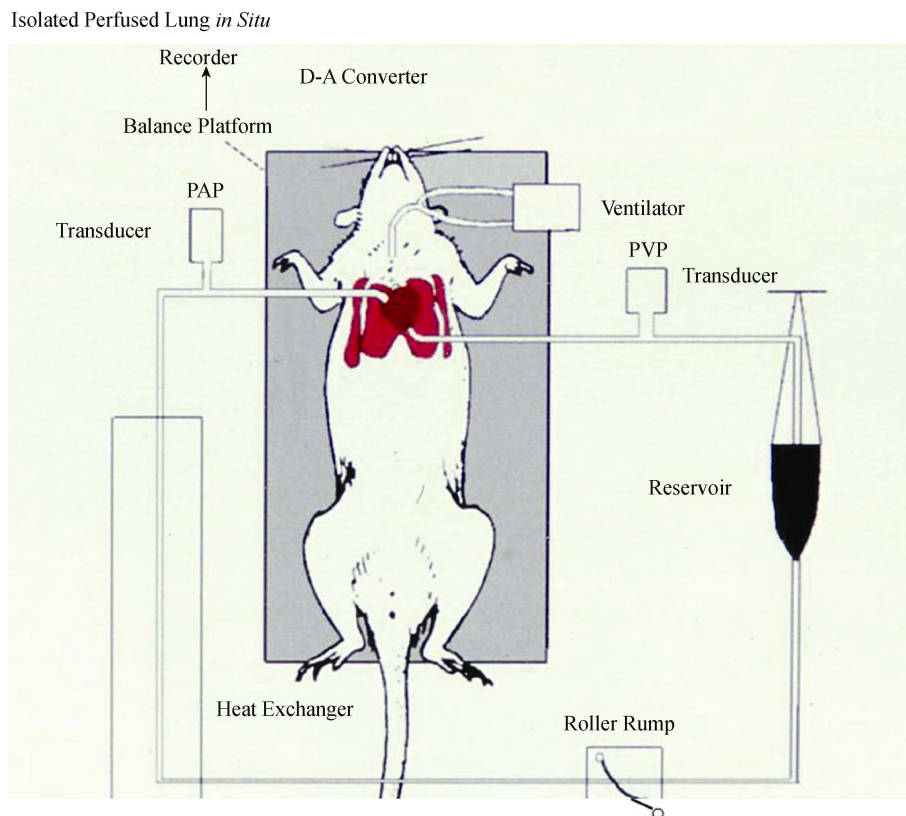
Isolated Perfused Lung *in Situ*

Figure 2.   Isolated and perfused lung *in situ* preparation. The system consists of a perfusion pump with heat exchanger and a venous reservoir. The rat is artificially ventilated. Pulmonary arterial pressure (PAP) and venous pressure (PVP) are monitored with transducers. The whole rat is placed on a balance platform to record the body weight change. Since the lung is isolated from the whole body, the change in body weight reflects the lung weight change.

disease.[6] Chest radiography on admission revealed clear lung. However, 21 out of 48 cases developed severe dyspnea, hyperglycemia, leukocytosis, and decreased blood oxygen tension. Arterial pressure (AP) and heart rate (HR) fluctuation ensued. Spectral analysis of the AP and HR variabilities showed elevation in sympathetic activity at the onset of respiratory stress. Thereafter, parasympathetic drive increased with declines in AP and HR. These children died within 4 h after the onset of ARDS. Before death, chest radiography revealed severe lung infiltration. Similar to Japanese B encephalitis, destruction of the medullary depressor area caused initial sympathetic activation. Reverse-transcriptase polymerase chain reaction (RT-PCR) found marked iNOS mRNA expression in the lung parenchyma, suggesting iNOS may also be involved in the pathogenesis of ARDS in patients with enterovirus 71 infection. Furthermore, we have reported ARDS in patients with leptospirosis.[18] In leptospirosis-induced ARDS, histochemical stain demonstrated spirochetes bacteria in the alveolar space. The pathology included alveolar hemorrhage, myocarditis,

portal inflammation and interstitial nephritis. Antigen retrieval immunohistochemical stain disclosed iNOS expression in the alveolar type 1 cells, myocardium, hepatocytes and renal tubules. Spectral analysis of AP and HR variabilities indicated decreased sympathetic drive with increased parasympathetic activity. The changes in autonomic functions led to severe hypotension and bradycardia. Biochemical determinations suggested multiple organ damage. The pathogenesis of lung and other organ injury might also involve iNOS and NO production.[18,29] In subjects with scrub typhus, Orientia tsutsugamushi infection caused alveolar injury. Marked iNOS expression was found in the alveolar macrophages with increase in plasma nitrate/nitrite, suggesting that NO production from the alveolar macrophages accounts for the ALI.[30] The victim from rabies was a woman bitten by a wild dog. In addition to sign of hydrophobia, hypoxia, hypercapnia, hyperglycemia and increased plasma nitrate/nitrite were observed. The woman died of alveolar hemorrhage shortly after admission.[31] Recently, we encountered five cases with
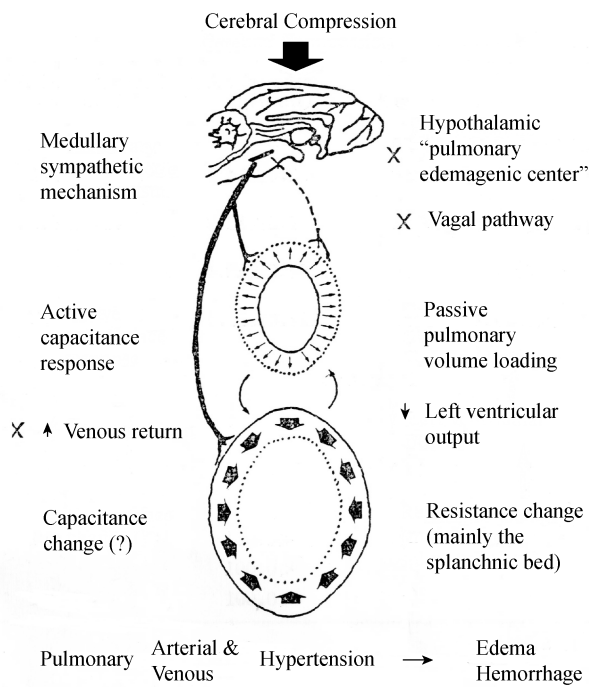
Figure 3. A schematic representation of the neural and hemodynamic mechanisms of neurogenic pulmonary edema caused by cerebral compression. Sympathetic activation from the medullary vasomotor center is the primary culprit leading to edema and hemorrhage in the lung. Hypothalamic "pulmonary edemagenetic center" is not involved. Vagal pathway plays minimal role. Cerebral compression causes sympathetic vasoconstriction of the systemic and pulmonary resistance and capacitance vessels. Resistance change, mainly in the splanchnic beds, results in dramatic decline of left ventricular output. The challenge finally produces passive volume and pressure loading in the pulmonary circulation. Severe pulmonary arterial and venous hypertension induce edema and hemorrhage in the lungs.

long-term malignancy. These subjects displayed signs of respiratory distress following an episode of hypercalcemia. Two cases died of ARDS after the plasma calcium was increased above 6 mmol/L. Search of literatures revealed that Holmes et al.[32] reported a patient who died of ARDS following a hypercalcemia crisis caused by a parathyroid adenoma. We conducted animal experiments in whole rodent and isolated perfused rat's lungs. Our results indicated that hypercalcemia (calcium concentration > 5 mmol/L) caused severe ALI in conscious rats and isolated lungs. Immunohistochemical staining showed iNOS activity in the alveolar macrophages and epithelial cells. Reverse-transcriptase polymerase chain reaction (RT-PCR) found marked increase in iNOS mRNA expression in lung parenchyma. Hypercalcemia also increased nitrate/nitrite, methyl guanidine, proinflammatory cytokines and

procalcitonin. Pretreatment with calcitonin or L-N^6 (1-iminoethyl)-lysine (L-Nil, an iNOS inhibitor) attenuated the hypercalcemia-induced changes. We proposed that hypercalcemia produced a sepsis-like syndrome. The ALI caused by hypercalcemia may involve NO and iNOS.[33,34]

In addition to the aforementioned animal experimentations and clinical observations that NO production through the iNOS may be involved in the lung injury due to various causes, our research team demonstrated that endotoxemia produced in anesthetized rats by intravenous administration of lipopolysaccharide (LPS, endotoxin) provoked systemic hypotension, endothelial damage and ALI accompanied by increased plasma nitrate/nitrite and expression of iNOS mRNA, TNF$_\alpha$ and IL-1$_\beta$. The LPS-induced changes were abolished by nonspecific and specific iNOS inhibitors such as N^ω-monomethyl-L-arginine (L-NMMA), L-NAME, aminoguanine and dexamethosone.[35] This study suggested that NO/iNOS, TNF$_\alpha$ and IL-1$_\beta$ were involved in the endotoxemia-induced ALI. Generation of NO from the activated neutrophil caused alveolar injury from smoke inhalation.[36] Experiments in many laboratories using specific iNOS inhibitors and/or iNOS-knockout animals have supported the contention that NO/iNOS is responsible for the oxidative stress and endothelial damage in the ARDS/ALI caused by endotoxin, ozone exposure, carrageenan treatment, hypoxia, acute hyperoxia, bleomaycin administration, acid aspiration and other causes.[37–46] Our laboratory further provided evidence to suggest that the NO/iNOS system is involved in the pathogenesis of ALI caused by air embolism,[47] fat embolism,[48–50] ischemia/reperfusion,[51–53] oleic acid[54] and phorbol myristate acetate.[55] In these recent studies, various insults caused increase in nitrate/nitrite in plasma or lung perfusate, upregulation of iNOS mRNA in lung parenchyma accompanied with elevation of proinflammatory cytokines such as TNF$_\alpha$, IL-1$_\beta$ and IL-6. Lin et al.[56] have suggested that an increase in iNOS mRNA triggers the release of proinflammatory cytokines in septic and conscious rats. The inflammatory responses results in multiple organ damage including ALI. Inhibition of iNOS with S-methylisothiourea (SMT) or L-Nil attenuated the inflammatory changes, release of NO and cytokines and prevented the organ dysfunction and ALI.[52]

5 Risk factors and pathogenetic mechanisms

In animal experiments and clinical investigations, the risk factors causing ALI/ARDS include head injury, intracranial hypertension,[2-4,57–62] sepsis,[12,17,35,37,39,42, 44,63–66] and infections.[6–8,10–12,17,18,29–31,67] Pulmonary embolic disorders

such as fat and air embolism are less common causes.[7,15,28,47,68–70] Ischemia/reperfusion lung injury may develop as a consequence of several pulmonary disorders such as pulmonary artery thromboendarterectomy, thrombolysis after pulmonary embolism and lung transplantation.[13,51–53,71–74] Gastric aspiration occurs frequently in surgical patients under anesthesia and other causes such as blunt thoracic trauma, impaired glottis competency, and pregnancy.[73,75,76] It is one of the major causes of acute respiratory syndrome (ARDS).[77,78] Intratracheal instillation of hydrochloric acid (HCl) or gastric particles has been employed as experimental model of acute lung injury (ALI).[16,79–81] In addition, amphetamine, phorbal myristate acetate, oleic acid have been employed for the induction of ALI.[82–86] Phorbol myristate acetate (PMA, 12-O-tetradecanoyl-phorbol-13-acetate), an ester derivative from croton oil has been used to induce ALI.[65,83,86,87] Experiments *in vivo* and *in vitro* have demonstrated that PMA is a strong neutrophil activator.[87–90] Activation and recruitment of neutrophil that lead to release of neutrophil elastase and other mediators may play an initial role in the pathogenesis of ALI.[91,92] The oleic acid-induced ALI has several clinical implications. First, the blood level of oleic acid was significantly elevated in patients with ARDS.[93,94] Second, the proportion of oleic acid incorporated into surfactant phospholipids was also increased in patients with ARDS and sepsis.[95,96] These observations have provided evidence to suggest that serum level of oleic acid as a prediction or prognostic factor for ARDS.[84,93] Early studies focused on the potential toxic effects of high oxygen fractions on inspired air.[97] Ventilator-induced ALI was attributed to the deleterious effects on capillary stress due to alveolar overdistension. Cyclic opening and closing of atelectatic alveoli during mechanical ventilation might cause lung injury and enhance the injured alveoli. Recent evidence indicated that over distension coupled with repeated collapse and reopening of alveoli initiated an inflammatory cascade of proinflammatory cytokines release.[68,98–100]

In spite of the risk factors and causes, the pathophysiology of ARDS/ALI has generally considered to be initiated by formation of alveolar edema (even hemorrhage) that is enriched with protein, inflammatory cells or red blood cells. After damage of alveolar-capillary barrier, impairment of gas exchange occurs, with decrease in lung compliance and increases in dispersion of ventilation and perfusion and intrapulmonary shunt. Hypoxia, reduction in arterial oxygen partial pressure to fraction of oxygen in inspired air PaO_2/FiO_2, hypercapnia ensued despite ventilation with high oxygen.[1,2,67,68,101,102] In addition to the potential toxic

effects of NO and free radicals, certain chemokines, cytokines, neutrophil elastase, myeloperoxidase and malondialdehyde have been shown to be associated with several types of ARDS/ALI.[50,54,55,91,103–105] The balance between proinflammatory and anti-inflammatory mediators is regulated by transcriptional factors mainly nuclear factor-$_K$B (NF-$_K$B).[106] Pulmonary fluid clearance and ion transport are important factors to determine the extent of lung edema. Regulator factors include cystic fibrosis transmembrane conductance regulators, sodium-and potassium-activated adenosine triphophatase (Na^+-K^+-ATPase), protein kinases, aclenylate cyclase, and cyclic adenosine monophosphate (cAMP).[12,29,107,108]

6   Possible therapeutic regimen

The treatment of ARDS/ALI is difficult and complex. Several review articles and monographs have addressed the issue of possible therapeutic regimen. The modalities include extracorporeal membrane oxygenation, prone position, mechanical ventilation with appropriate tidal volume and respiratory pressure, fluid and hemodynamic management and permissive hypercapnic acidosis.[68,100,109–119]

Other pharmacological treatments are anti-inflammatory and/or antimicrobial agents to control infection and to abrogate sepsis, adequate nutrition, surfactant therapy, inhalation of NO and other vasodilators, glucocorticoids and other nonsteroid anti-inflammatory drugs, agents that accelerate lung water resolution and ion transports.[68,102,120–124] Although most animal experimentations on these pharmacological options showed favorable results, the effectiveness and outcomes in clinical studies or trials were conflicting.

Beta agonists to facilitate water removal and ion transport have been shown to be promising. These agents may also stimulate secretion of surfactant and have no serious side effects. There were several reports on the pharmacological and molecular actions of beta agonists, surfactant and vascular endothelial growth factor and related molecules as well as angiotensin-converting enzyme (ACE).[107,125,126]

7   Nonpharmacological and pharmacological therapeutic for ALI and ARDS from recent studies in our laboratory

In addition to the experimental studies and clinical investigations on the pathogenesis of ALI/ARDS, our laboratory has carried out several experimentations on the therapeutic regimen for this serious disorder. In conscious rats, regular exercise training attenuates septic responses

such as systemic hypotension, increases in plasma nitrate/nitrite, methyl guanidine, blood urea nitrogen, creatinine, amylase, lipase, asparate aminotransferase, alanine aminotransferase, creatine phosphokinase, lactic dehydrogenase, TNF_α, and IL_β. Exercise training also abrogates the cardiac, hepatic and pulmonary injuries caused by endotoxemia.[124] Insulin exerts anti-inflammatory effects on the ALI and associated biochemical changes following intravenous administration of lipopolysaccharide (LPS).[127] Propofol (2,6-diisopropylphenol) has been commonly used for sedation in critically ill patients.[128] This anesthetic has rapid onset, short duration and rapid elimination.[129] Propofol protects the anesthetized rats from ALI caused by endotoxin.[65] In conscious rats, oleic acid results in sepsis-like responses including ALI, inflammatory reactions and increased in neutrophil-derived factors (neutrophil elastase, myeloperoxidase and malondialdehyde), nitrate/nitrite, methyl guanidine, inflammatory cytokines. It depresses the sodium-and potassium-activated ATPase, but upregulates the iNOS mRNA expression. Pretreatment and posttreatment with propofol alleviates or reverses the oleic acid-induced lung pathology and associated biochemical changes.[54] Pentobarbital, an anesthetic agent commonly used in experimental studies and a hypnotic for patients improves the pulmonary and other organ functions following LPS administration. It also increases the survival rate.[15] A later study by Yang *et al*.[130] further revealed that pentobarbital suppressed the expression of tumor necrosis factor$_\alpha$, which might result from decrease in the activities of nuclear factor-κβ and activator protein 1 and reduction in expression of P38 mitogen-activated protein kinase. *In vivo* examination of cytotoxic effects of LPS disclosed that LPS caused multiple organ dysfunctions. These changes were attenuated by pentobarbital. Pentobarbital also reduced the cell aptosis caused by deforoxamine-induced hypoxia. Nicotinamide or niacinamide (compound of soluble B complex) abrogates the ALI caused by ischemic/reperfusion or endotoxin by mechanism through inhibition on poly (ADP-ribose) synthase or permerase cytoxic enzyme and subsequent suppression of iNOS, NO, free radicals and proinflammatory cytokines with restoration of adenosine triphosphate ATP.[48,53] *N*-acetylcysteine, an antioxidant and cytoprotective agent with scavenging action on reactive oxygen species and inhibitory effects on proinflammatory cytokines ameliorated organ dysfunctions due to sepsis in conscious rats.[131,132] In a similar endotoxin-induced ALI model, we found that *N*-acetylcysteine improved the LPS-induced systemic hypotension and leukocytopenia. It also reduced the extent of ALI, as evidenced by reductions in lung weight changes, exhaled NO and lung pathology. In

addition, *N*-acetylcysteine diminished the LPS-induced increases in nitrate/nitrite, TNF_α, and IL_β[64] In isolated lungs, *N*-acetylcysteine attenuated the ALI caused by phorbol myristate acetate.[86] In a recent study, we reported that posttreatment with *N*-acetylcysteine prevented the ALI caused by fat embolism.[50] Our series of experimental studies provided results in favor of *N*-acetylcysteine. The conflicting results and practice guidelines from clinical studies in the recommendation of *N*-acetylcysteine in critically ill patients[133,134] were commented and analyzed by Molnár.[135] The clinical application of results from animal studies requires further investigations.

8   Summary

ARDS or ALI is a serious clinical problem with high mortality. The risk factors leading to ALI/ARDS include head injury, intracranial disorders, sepsis and infections. Pulmonary embolic disorders such as fat and air embolism are less common causes. Ischemia/reperfusion lung injury may develop as a consequence of several pulmonary disorders such as lung transplantation. Gastric aspiration occurs frequently in several conditions such as anesthesia, trauma and pregnancy. The ventilator-induced ALI has been attributed to the deleterious effects on capillary stress due to alveolar overdistension. In experimental studies, phorbol myristate acetate and oleic acid have been employed to induce ALI.

The pathogenesis of ARDS/ALI is complex. Experimental studies and clinical investigations from our and other laboratories have indicated the detrimental role of nitric NO through inducible NO synthase (iNOS). Activation and recruitment of neutrophils that lead to release of neutrophil elastase, myeloperoxidase, malondialdehyde and pro-inflammatory cytokines may play an initial role in the pathogenesis of ALI/ARDS.

The possible therapeutic regimen for ALI/ARDS include extracorporeal membrane oxygenation, prone position, fluid and hemodynamic management and permissive hypercapnic acidosis *etc*. Other pharmacological treatments are anti-inflammatory and/or antimicrobial agents, inhalation of NO, glucocorticoids, surfactant therapy and agents that facilitate lung water resolution and ion transports. Adrenergic beta agonists are able to accelerate lung fluid and ion removal and to stimulate surfactant secretion. There are reports on the actions of vascular endothelial growth factor and related molecules as well as angiotensin-converting enzyme.

Our laboratory has reported experimental studies on the effectiveness of several regimen for ALI/ARDS. In conscious rats, regular exercise training alleviates the endotoxin-

induced ALI. Propofol and *N*-acetylcysteine exert protective effect on the ALI causes by endotoxin, oleic acid and phorbol myristate acetate. We have also provided evidence that insulin possesses anti-inflammatory effect. Pentobarbital is capable of reducing the endotoxin-induced ALI and associated changes. In addition, nicotinamide or niacinamide (soluble B complex) abrogates the ALI caused by ischemia/reperfusion or endotoxemia. These nonpharmacological and pharmacological therapeutic strategies require further investigations for clinical application.

Acknowledgment

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