Chinese Journal of Physiology 52(5 Supplement): 339-344, 2009
DOI: 10.4077/CJP.2009.AMH036

Review

From Neurogenic Pulmonary Edema to Fat Embolism Syndrome: A Brief Review of Experimental and Clinical Investigations of Acute Lung Injury and Acute Respiratory Distress Syndrome

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Abstract

Acute respiratory distress syndrome (ARDS) is the most devastating form of acute lung injury (ALI) or pulmonary edema (PE). We presented the experimental studies and clinical investigations of two serious forms of ALI. Drastic and severe PE could be induced by intracranial hypertension or cerebral compression (CC). The CC-induced PE was attributed to overactivation of the medullary sympathetic mechanism. Sympathetic vasoconstriction of the systemic and pulmonary resistance and capacitance vessels caused shift of blood volume from the splanchnic vascular beds to the lung. The hemodynamic changes led to systemic and pulmonary hypertension. Consequently, left ventricular failure as evidenced by dramatic decline in aortic flow with a slow decrease in pulmonary flow resulted in pressure and volume loading in the pulmonary circulation. These changes finally produced severe alveolar flooding and sudden death. Vasodilators such as sodium nitroprusside or nitroglycerin were capable of reducing the CC-induced pulmonary pathology and hemodynamic alterations. Fat embolism syndrome (FES) is a serious clinical problem in patients suffering from long bone fractures. ARDS may develop and cause mortality. Our laboratory reported a total of 14 subjects associated with FES and died of ARDS. We also developed a simple technique to produce FES. Corn oil was mixed with distilled water to form fatty micelles. Intravenous administration of or introduction of fatty micelles in anesthetized rats or isolated perfused lungs caused severe alveolar damage. Our clinical observation and animal experimentation revealed that infusion of fatty acids caused physical phase, resulting in microvascular obstruction accompanied by pulmonary hypertension and increased capillary permeability. Thereafter, the lipases in the lung hydrolyzed the neutral fat and released free fatty acids and biochemical mediators which were toxic to the lung. Our data have suggested that nitric oxide (NO), inducible NO synthase (iNOS), phospholipase A_2, free radical and inflammatory cytokines (tumor necrosis factor$_\alpha$, interleukin-1$_\beta$ and interleukin-6) are involved in the biochemical phase of FES with ARDS. The alveolar macrophages are the major source of iNOS. Later study also found that neutrophil elastase and myeloperoxidase were elevated following fat embolism. N-acetylcysteine (an antioxidant), and NOS inhibitors such as N^{ω}-nitro-L-arginine methyl ester (L-NAME), S-methylisothiourea (SMT) or L-N^6 (1-iminoethyl)-lysine (L-Nil) were able to abrogate the FES or the fat embolism-induced changes.

Key Words: neurogenic pulmonary edema, fat embolism syndrome, acute respiratory syndrome, cerebral compression, N-acetylcysteine, inducible nitric oxide synthase

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Received: May 20, 2008; Revised: November 2, 2008; Accepted: February 18, 2009.
 ISSN : 0304-4920. http://www.cps.org.tw

Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are serious chest disorders with high mortality (10, 78). The risk factors for ALI or ARDS include head injury, intracranial hypertension (7, 18), endotoxemia (45, 56, 72, 77), infections (9, 10, 27, 38, 40, 51), air embolism (61, 76), hypercalcemia (21, 34, 39), amphetamine (41, 65), ischemia-reperfusion (36, 46, 71), phorbol myristate acetate (an activator of neutrophils, leucocytes, and macrophages) (35, 58, 75), oleic acid (13), fat embolism (40, 44, 48, 60) and other causes.

Our cardiopulmonary laboratory has carried out experimental studies and clinical investigations of ALI and ARDS with a variety of causes. In this brief review article, I draw attention to an important clinical problem of neurogenic pulmonary edema (PE) following intracranial disorders, and address the pathogenetic mechanisms of fat embolism syndrome (FES) leading to fatal ARDS. I discuss the involvement of nitric oxide (NO), inducible NO synthase (iNOS) and biochemical mediators in the pathogenesis of ALI and ARDS. Finally, I propose the possible therapeutic regimen for the lung injury induced by intracranial hypertension and fat embolism.

Neurogenic Pulmonary Edema

During the research work on pulmonary edema (PE), ALI and ARDS for more than 30 years, we found that the PE due to cerebral compression (CC) was probably the most drastic lung damage following head injury. In anesthetized rats, rapid impact of a plasticine mass into the cranium on distension of an intracranial balloon caused systemic hypertension, pulmonary arterial and venous hypertension followed by severe lung edema and hemorrhage. Histopathological examinations revealed alveolar flooding including congestion, disruption of blood vessels, endothelial damage with leakage of blood cells and exudate. The lung weight was increased 3 to 4-fold the normal value (7, 18). With respect to the central nervous system that was responsible for the pulmonary sequelae following CC, activation of a “hypothalamic pulmonary edema genetic center was implicated to be involved in the centrogenic PE (62). We found that a midcollular decerebration did not affect the CC-induced PE. A spinal transection at the cervical region abolished systemic and pulmonary hypertension, and prevented the PE induced by CC. The results indicated that hypothalamus was not involved in the neurogenic PE. Overactivation of the central sympathetic mechanism in the medulla oblongata leading to systematic vasoconstriction is the major culprit for the PE of centrogenic origin. Whether the rostral ventrolateral medulla play a specific role requires further investigation. We also found that cervical vagotomy and atropine did not affect the CC-induced systemic and pulmonary changes. Our results suggested that vagal efferent pathway was not crucial. The involvement of vagal afferents is yet to be determined.

A sintiphographic study using intravenous administration of a specific isotope, indium-113m demonstrated accumulation of blood in the lung (16). Regional sympathectomy disclosed that the splanchnic beds were the major site of systemic vasoconstriction. Direct sympathetic pulmonary vasoconstriction contributed only partly to the neurogenic PE (12, 23). Hemodynamic measurements with pulmonary and aortic flows, and with heart bypass preparations revealed that intracranial hypertension caused vasoconstriction of resistance and capacitance vessels in the systemic and pulmonary circulation. Shift of blood volume from the systemic vascular beds to the lung was the main cause of pressure and volume loading in the pulmonary circulation (11, 19). Later study further supported the intention that systemic vasoconstriction was pivotal in the genesis of CC-induced PE. Adrenal glands, bronchial circulation and pulmonary innervation played little role (20). Large dose of vasodilators such as sodium nitroprusside and nitroglycerin were capable of reducing the PE induced by CC. On the other hand, oxidant scavenger was not effective. We proposed that vasodilators might be applied clinically in case of lung injury following traumatic injury. In addition, oxidative stress was not involved in the centrogenic PE (15). Sympathoadrenergic blocking agents such as neuronal blockers, ganglionic blocking agents, norepinephrine depleter and α-adrengeric blockers were effective on the CC-induced PE (7, 18).

We concluded that activation of the medullary sympathetic mechanism results in systemic vasoconstriction of the resistance and capacitance vessels. The hemodynamic changes eventually caused acute left ventricular failure with a marked reduction in cardiac output accompanying a slow decline in pulmonary arterial flow. For more details regarding the neural and hemodynamic mechanisms and the interactions between systemic and pulmonary circulation, please refer to the following research and review articles (6, 8, 10, 14, 17, 37, 73).

Fat Embolism Syndrome (FES)

Hsu and colleagues reported a total of 18 subjects died of ARDS due to four causes, Japanse B encephalitis (6 cases), breast carcinomona with lymphangitis (2 cases), ruputure of cerebral mycotic aneurysm (4 cases), and six patients with fat embolism caused by

fracture of the femur and tibia (32). Clinical observation, biochemical determination and autopsy findings of these six victims with FES and ARDS indicated thrombocytopenia, dyspnea, cyanosis and increases in non-esterified fatty acid, cyclic guanosine monophosphate (cGMP), 5-hydroxytryptamine (serotonin) and nitrate/nitrite. Microscopic examination revealed severe alveolar hemorrhagic edema and fat droplets in the lung. In this clinical report, we first proposed that nitric oxide (NO) might be involved in the pathogenesis of FES (40). We continued to collect subjects suffered from FES. Kao *et al*. (48) reported eight cases died of ARDS due to FES following crash injury resulting in fracture of tibia, femer, combined fracture of both long bones and multiple fracture of pelvic bones. In addition to the six cases reported in 2003 (40), we have collected a total of 14 subjects associated with FES. We presented the clinical, biochemical and pathological features more in details. The particular manifestation of these 8 subjects was that they expired within 2 h after admission soon following the crash injury. Chest radiographs showed clear lungs on admission. Pulmonary infiltration developed at 1 h and became severe at 2 h. There were progressive acidosis, hypoxia and hypercapnia. Biochemical examinations discoverd increases in plasma phospholipase A2, nitrate/nitrite, methyl guanidine (an index of hydroxyl radical) (57), tumor necrosis factor, interleukin-1_β and interleukin-10. Before death, measurement of pulmonary arterial pressure (PAP) with a Swan-Ganz catheter revealed severe pulmonary hypertension. The average PAP = 41 ± 5 mmHg was much higher than the normal range of 12-17 mmHg (40). On autopsy, gross inspection disclosed a heavy lung. The average lung weight 1432 ± 24 g was 3 to 4 times the normal value (350-450 g). Histopathological examinations of the lung, brain and kidney revealed severe alveolar edema and hemorrhage with fat droplet and fibrin thrombi depositions in lung tissue. Special fat stains with Oil red, Sudan Black and Sudan III showed fat droplets in different colors inside the pulmonary, cerebral and renal arteriolar lumen. Fat droplets were also observed in the renal glomeruli and cerebral capillaries. Although the development of ARDS suggests the lung is the major target organ resulting from intravasation of fatty acids. Renal lesions were found in two cases (25.0%) and cerebral involvement in five cases (62.5%) compared with all subjects (8 cases, 100%) with lesions in the lung. In addition to the finding that the plasma nitrate/nitrite was elevated, immunochemical staining demonstrated marked iNOS in alveolar macrophage. The clinical investigations advanced our understanding on the pathogenesis of FES. Phospholipase A_2, NO, free radicals and inflammatory cytokines contributed to the genesis of ARDS associated with FES. NO might be detrimental to the lung and other organs. The major source of NO was the alveolar macrophage.

According to Talbot and Schimitsch (74), the first human case of post-traumatic fat embolism was described by Zenker in 1862 in a patient with a serious crash injury. Fat droplets were found in the pulmonary capillaries. FES due to circulatory fat emboli has been thereafter recognized as a clinical problem. (29, 40, 48, 63, 74, 79). Peltier (66, 67) proposed that the neutral fat was embolized after bone fracture and caused capillary obstruction (the initial phypical phase). The lipases in the lung hydrolyzed the neutral fat and released free fatty acids and chemical mediators, which were extremely toxic to the lung (the chemical phase). Although our and other clinical investigations have provided information with respect to the chemical mediators such as phospholipase A_2, platlet-activating factor, NO, cyclooxygenase products, and inflammatory cytokines in pathogenesis of FES (40, 48, 49, 69), the ultimate mechanisms in the pathogenesis of FES associated ARDS are yet to be determined.

Several experimental models have been employed to simulate or to produce fat embolism. The methodologies include glucorticorticoid administration to induce osteonecrosis (32), polymethylmethaacrylate (bone wax) injection with vertebroplastasty (1), intramedullary nailing (5, 70), and intravenous triolein and/or oleic acid (50, 64, 80). We recently developed a simple technique to produce intravasation of fat embolism. Pure corn oil (0.2 ml) was mixed with the same volume of distilled water to form fatty micelles. The micelles were administered intravenously in anesthetized rats or added into isolated perfused lungs. The introduction of fatty micelles reproducibly and consistently induced fat embolism. The lung pathology was similar to that observed in clinical subjects (40, 48).

We used this simple technique to induce ALI in anesthetized rats and isolated lungs. The corn oil fatty micelles significantly increased lung weight, protein concentration in bronchoalveolar lavage and exhaled NO. The insult also caused severe pulmonary hypertension, and increased microvascular permeability. In addition, it increased the nitrate/nitrite, methyl guanidine, tumor necrosis factor$_\alpha$, and interleukin-1_β in plasma or lung perfusate. In the lung, the levels of neutrophil elastase and myeloperoxidase were significantly elevated. FE upregulated iNOS mRNA expression in the lung parenchyma. Post-treatment with N-acetylcysteine abrogated these changes induced by FE. The results indicated that FE caused ALI accompanying biochemical changes and iNOS upregulation. Post-treatment with N-acetylcysteine was effective to alleviate the pathological and

biochemical changes caused by FE (60). In isolated lungs, the FE-induced lung injury, biochemical changes were attenuated by pre-treatment with non-selective NOS and selective iNOS inhibitors such as N^{ω}-nitro-L-arginine methyl ester (L-NAME) or [L-N^6(1-iminoethyl)-lysine] (L-Nil), while exacerbated by pre-treatment with NO donors such as sodium nitroprusside (SNP) or S-nitroso-N-acetylpenicillamine (SNAP). The results suggest that NO production through the iNOS isoform plays a detrimental role in the FE-induced ALI (44).

With respect to the detrimental role of NO in ALI/ARDS, early work by Wang *et al*. (77) provided evidence that NO release *via* the iNOS system was responsible for the ALI caused by endotoxin. Our and other laboratories have suggested that NO release is the major or initial event in the pathogenesis of ALI caused by viral, bacterial and other infections (8, 9, 37, 38, 47), ischemia-reperfusion (46, 71), lipopolysaccharide administration (2, 22, 45, 56, 68), phorbol myristate acetate (58), fat embolism (44, 48, 60), air embolism (61), burn or smoke inhalation (28, 43), ozone exposure (42), carrageenan treatment (25), acute hypoxia (2), high tidal volume ventilation (31, 33), and other causes. We recently demonstrated that iNOS inhibition with S-methylisothiourea (SMT) or L-N^6-(1-iminoethyl)-lysine) (L-Nil) effectively attenuated the endotoxin-induced ALI in anesthetised rats and isolated rat's lungs (72). The NO release and iNOS upregulation may trigger inflammatory changes and cytokines release that lead to alveolar damage in the lung (59). There is also evidence for lung endothelial and alveolar epithelial damage in ALI/ARDS that may be the result of oxidative stress (4, 30, 52, 55). Nitrogen oxide species including NO, nitrate (NO_2^-) and nitrate (NO_3^-) are important markers of oxidative stress (3, 24, 26, 33). NO reacts with superoxide ion to form peroxynitrite, which is extremely toxic to the lung (4, 24, 33, 54).

In contrast to the detrimental role of NO in ALI/ARDS, several studies have demonstrated the protective effects of NO. NO scavenges reactive oxygen species and free radicals that are generated during oxidative stress (23, 45, 54, 55). NO causes vasodilation of pulmonary microcirculation, which allows for increased perfusion of tissue beds (14, 52). A recent clinical analysis reported that higher urine NO was associated with better outcomes in patient with ARDS (53). It is possible that NO exerts effects of damage and protection in different types of ALI/ARDS. NO may also be a double-edged sword during the course of ALI/ARDS.

In conclusion, we have addressed the pathogenetic mechanisms of ALI and/or ARDS due to intracranial hypertension and fat embolism. The detrimental role of NO generation through the iNOS isoform may be the main and initial event leading to pulmonary inflammation and damage. Our experimental studies and clinical investigations may be applied to clinical application in the therapeutic regimen for the lung injury or respiratory distress syndrome following head injury, intracranial disorders and/or fat embolism. N-acetylcysteine, L-NAME, SMT, and L-Nil can be effective in the treatment of FES/ARDS. The clinical application requires further investigation.

Acknowledgments

Most studies were supported by the National Science Council, Tzu Chi University. The authors are grateful to Prof. H.S. Fang and Prof. C.Y. Chai (Academia Sinica) for their encouragement, and to several coworkers who have participated in the animal experiments and clinical investigations.

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