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Preclinical and clinical studies of smoke-inhalation-induced acute lung injury: update on both pathogenesis and innovative therapy

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***Abstract*:** Smoke-inhalation-induced acute lung injury (SI-ALI) is a leading cause of morbidity and mortality in victims of fire tragedies. SI-ALI contributes to an estimated 30% of burn-caused patient deaths, and recently, more attention has been paid to the specific interventions for this devastating respiratory illness. In the last decade, much progress has been made in the understanding of SI-ALI patho-mechanisms and in the development of new therapeutic strategies in both preclinical and clinical studies. This article reviews the recent progress in the treatment of SI-ALI, based on pathophysiology, thermal damage, airway obstruction, the nuclear-factor kappa-B signaling pathway, and oxidative stress. Preclinical therapeutic strategies include use of mesenchymal stem cells, hydrogen sulfide, peroxynitrite decomposition catalysts, and proton-pump inhibitors. Clinical interventions include high-frequency percussive ventilation, perfluorohexane, inhaled anticoagulants, and nebulized epinephrine. The animal model, dose, clinical application, and pharmacology of these medications are summarized. Future directions and further needs for developing innovative therapies are discussed.

Keywords: acute lung injury, intervention, pathophysiology of lung injury, smoke inhalation

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Introduction

Smoke inhalation is often caused by fire disasters, wars, and chemical toxic gas.[1] Among these, the most common source is fire tragedies, which cause multiple organ failure (MOF) with extremely high morbidity and mortality.[2] Smoke-inhalation-induced acute lung injury (SI-ALI), a significant component of MOF in burn injury, is characterized by airway and pulmonary injury, hypoxia, and a series of serious clinical symptoms. Approximately 22% of all burn patients are diagnosed with SI-ALI, leading to at least 30% of the overall fire-associated mortality.[1,3] There are only supportive therapies for SI-ALI. Considerable effort has recently been made to develop effective and specific interventions for SI-ALI. This article provides an update on recent progress in the pathological and pharmaceutical studies of SI-ALI.

Pathological mechanisms of SI-ALI

SI-ALI can be caused by inhalation of various toxic substances [e.g. carbon monoxide (CO), nitric oxide (NO), cyanide, sulfide, benzene, malondialdehyde], particles (diameter $< 5\mu m$),[4] or thermal damage, which leads to injury of the airway and lungs directly and indirectly. These substances and particles cause laryngeal/pulmonary edema, a decrease of lung compliance, ventilation/perfusion (V/Q) disorders, and other pathophysiological characteristics, which result in cough, asthma, dyspnea, and even suffocation symptoms.[5] Although the pathogenesis of SI-ALI has not yet been fully elucidated, it has been shown that multiple inflammatory cells (macrophages, neutrophils, vascular endothelial cells, and platelets) and the release of inflammatory mediators and cytokines indirectly cause

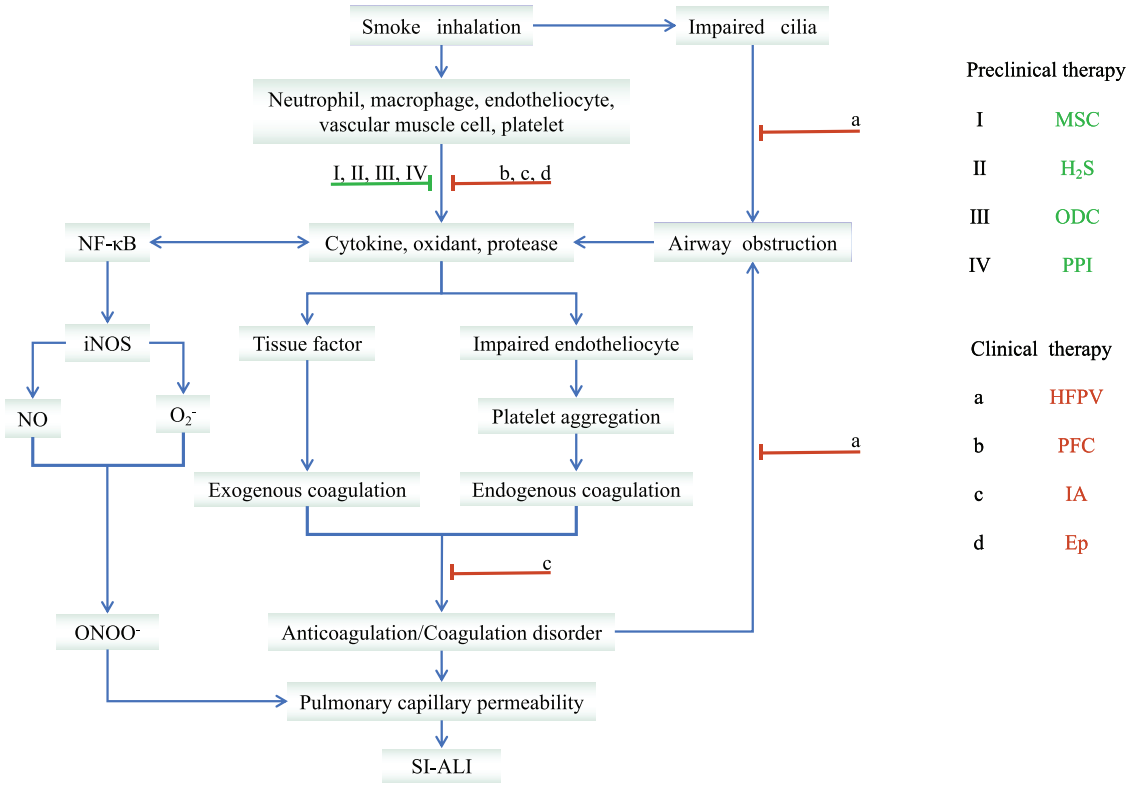

Figure 1. Pathogenesis and advanced therapeutic methods of SI-ALI.
MSC, mesenchymal stem cell; H_2S, hydrogen sulfide; NF-κB, nuclear-factor kappa B; ODC, $ONOO^-$ (peroxynitrite) decomposition catalyst; PPIs, proton-pump inhibitors; HFPV, high-frequency percussive ventilation; PFC, perfluorohexane; IA, inhaled anticoagulants; Ep, epinephrine; SI-ALI, smoke-inhalation-induced acute lung injury.

oxidative stress/antioxidant stress imbalance and an inflammatory cascade response (Figure 1).[6] In the following sections, three aspects of the pathogenesis of SI-ALI are described.

Thermal damage

Thermal damage is often caused by inhalation of steam or hot air. Gas at more than 150°C can immediately damage the respiratory mucosa, causing hyperemia, edema, and necrotic shedding. As the mucosa of the hypopharynx and epiglottis is very loose, edema easily occurs upon smoke inhalation. This results in airway stenosis, obstruction, and V/Q disorders. Meanwhile, the spread of the heat can be absorbed by the capillary blood of the nose, and some self-protective functions (such as epiglottic closure, reflex laryngeal spasm, and reflex constriction of the trachea and bronchus) can also reduce the thermal damage in smoke inhalation.[6,7] Nevertheless, thermal damage can be an important contributor to SI-ALI.

Airway obstruction

Various toxic substances and particles (diameter $<$ 5 μm)[4] can enter the alveoli and reduce the amount of pulmonary surfactant (PS), leading to alveolar atrophy and collapse.[6] The airways can also be blocked by deposited substances, which include fibers, neutrophils, bronchial epithelial cells, and mucus secretions. These materials are recruited, shed, or secreted by smoke inhalation. Meanwhile, smoke inhalation impairs the ciliary transport system, leading to material deposition and airway obstruction. Additionally, some studies have suggested that anticoagulation/coagulation disorder, which is another main cause of airway obstruction, can be caused by smoke inhalation.

NF-κB signaling pathways and oxidative stress

Nuclear-factor kappa B (NF-κB) is a transcription-factor protein family controlling transcription, cytokine production and cell survival. Studies have shown that NF-κB is involved in the transcription of numerous proinflammatory genes, including

genes of SI-ALI-induced inflammation.[6,8–10] Soejima and colleagues demonstrated that NF-κB expression is activated by smoke particles,[8] which can increase the production and release of proinflammatory cytokines [tumor-necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), etc.]. These proinflammatory cytokines can activate NF-κB, causing the cytokines to continuously increase, forming a vicious cycle that aggravates ALI. Meanwhile, after smoke inhalation, activated neutrophils, lung capillary endothelial cells, and macrophages release a large number of proinflammatory cytokines, which then induce the synthesis of reactive oxygen species (ROS) and the production of a large amount of NO, resulting in an inflammation response.[8,9]

During inflammatory stress, accumulated NO binds to cellular superoxide, forming peroxynitrite ($ONOO^-$), a strong oxidant which can lead to damage of cells and deoxyribonucleic acid. High levels of $ONOO^-$ result in an increase of capillary permeability and hypoxic pulmonary vasoconstriction function, aggravating lung injury.[8,10]

Latest treatment progress for SI-ALI

The current supportive treatments for SI-ALI patients include oxygen therapy, airway management, fluid resuscitation, mechanical ventilation, specific detoxification[1,11,12] (for example, Alda-1 can detoxify the ALI caused by acrolein inhalation[13]), anticoagulants, β2-agonists, bronchodilators, mucolytic agents, antioxidants, and mediators of inflammation agonists.[9,12,14] If necessary, tracheotomy can be performed.[15] However, there are many side effects associated with these therapies. For example, intermittent positive-pressure ventilation can lead to barotrauma, volutrauma, and oxygen toxicity. Therefore, it is imperative to explore new treatment regimens for SI-ALI. Here, we summarize innovative therapeutic strategies targeting various pathogenic key steps (Figure 1). The therapies are divided into two groups: preclinical and clinical therapies. Preclinical therapy includes mesenchymal stem cells (MSCs), hydrogen sulfide (H_2S), $ONOO^-$ decomposition catalysts, and proton-pump inhibitors (PPIs). Clinical therapies include high-frequency percussive ventilation (HFPV), perfluorohexane (PFC), inhaled anticoagulants, and nebulized epinephrine.

Preclinical therapy for SI-ALI

Mesenchymal stem cells (MSCs). MSCs are pluripotent stem cells with the ability to self-renew and to differentiate into various cell types, such as endothelial and epithelial cells, both *in vitro* and *in vivo*. In many animal models, MSCs can be located at the site of injury and have immunosuppressive and nonimmunogenic properties.[16,17] Substantial investigation has demonstrated that MSCs are beneficial for the treatment of ALI in preclinical models, including rodents and human tissues.[17,18] In addition, different sources of MSCs, including human amnion-derived MSCs,[19] adipose-derived stem cells,[20] bone-marrow MSCs (BMMSCs),[14,21,22] and nonmuscle myosin IIA-silenced BMMSCs (NM-IIA BMMSCs),[23] were effective in SI-ALI animal models (Table 1). The results of these studies showed that the wet/dry (W/D) ratio in lungs was significantly reduced, and partial pressure of oxygen (PaO_2) and the PaO_2/FiO_2 ratio (where FiO_2 is the fraction of inspired oxygen) were significantly improved after delivery of MSCs. Furthermore, the alveolar space was wider, the alveolar septa were thinner, and the number of infiltrated polymorphonuclear leukocytes was lower compared with controls. Keratinocyte growth factor and IL-10 levels were significantly increased, and TNF-α levels were decreased in bronchoalveolar lavage fluid (BALF), suggesting the MSCs exerted anti-inflammatory effects *via* paracrine mechanisms. Although multiple paracrine factors (such as endothelial and epithelial cell growth factors, anti-inflammatory cytokines and antimicrobial peptides) secreted by MSCs play a protective role in the beneficial effects on SI-ALI,[17,18,24] our understanding of the mechanisms is still incomplete. To date, no clinical trials have been registered or reported because of the lack of information regarding source, safety, and dose of MSCs.

Hydrogen sulfide (H_2S). Oxidative stress is an important mechanism of SI-ALI, and it involves the attraction of a large number of inflammatory cells to the lung, leading to excessive ROS, which can cause oxidative stress injury to the lung.[27] H_2S, the third most important gaseous signal-transducing molecule (after NO and CO), has many biological functions. It not only functions as an antioxidant and antifibrotic agent[25] but it also has important effects on vasodilation, inflammatory responses, and endocrine and reproductive systems.[32,33] Exogenous H_2S has been demonstrated as beneficial in various diseases in animal

Table 1. Preclinical therapy for SI-ALI.

Therapy	Type	Model	Dosage	Results
MSCs	Human amnion-derived MSCs[19]	Rats	5×10^6/ml, i.v.	Reduced lung injury, lung fibrosis, CT score, and inflammation levels Increased PaO_2 and pulmonary SP-A, SP-C, and SP-D expression
	Adipose-derived stem cells[20]	Sheep	1×10^7/ml, i.v.	Pulmonary microvascular hyperpermeability was attenuated and lung edema was improved by treatment with adipose-derived stem cells after smoke inhalation
	BMMSCs[14,21,22]	Rabbits Mice	1×10^7/ml, i.v. 3×10^6/ml, i.v.	Reduced inflammation; protected lung tissue
	NM-IIA BMMSCs[23]	Rabbits	1×10^7/ml, i.v.	NM-IIA BMMSCs are more effective than BMMSCs in reduced early SI-ALI
H_2S	Sodium sulfide[25]	Mice	2 mg/kg of body weight s.c.	Reduced proinflammatory cytokines and IL-1β; increased IL-10; protected SI-ALI by anti-inflammatory and antioxidant pathways
	Sodium sulfide[26]	Sheep	Injected 0.5 mg/kg, then continuous infusion of 0.2 mg/kg/h for 24 h	Improved pulmonary gas exchange and reduced the presence of protein oxidation and 3-nitrotyrosine formation
	H_2S[27]	Rats	H_2S (80 ppm) for 6 h	Reduced iNOS expression, NO levels, and NF-κBp65 activity, and protected against the SI-ALI
$ONOO^-$ decomposition catalysts	INO-4885[28]	Sheep	Bolus 0.5 mg/kg dissolved in saline 0.01 mg/kg/h infused for 24 h	Improved pulmonary oxygenation and shunting. Decreased transvascular fluid flux and lung edema
	WW-85[29]	Sheep	Delivered into the bronchial artery with a low dose (0.002 mg/kg/h, 2 ml/h)	Decreased lung lymph flow, pulmonary microvascular permeability, lung water content, and NO levels
	R-100[30]	Sheep	Used a total of 80 mg/kg of R-100 diluted in 500 ml of 5% dextrose i.v.	Promoted gas exchange and blood oxygenation; attenuated the pulmonary arterial pressures, which prevents a fluid imbalance
PPIs	Esomeprazole[31]	Mice	30 mg/kg	Reduced markers of inflammation and fibrosis

BMMSC, bone-marrow mesenchymal stem cell; i.v., intravenous, CT, computed tomography; IL, interleukin; iNOS, inducible nitric oxide synthase; MSC, mesenchymal stem cell; NF-κB, nuclear-factor kappa B; NM-IIA BMSC, nonmuscle myosin IIA-silenced BMMSCs; NO, nitric oxide; $OONO^-$, peroxynitrite; PaO_2, partial oxygen pressure; PPI, proton-pump inhibitor; s.c., subcutaneous; SI-ALI, smoke-inhalation-induced acute lung injury; SP, surfactant protein.

models, such as ischemia-reperfusion injury,[34] ventilator-induced ALI,[35] hyperoxia-induced ALI,[36] and oleic-acid-induced lung injury.[37] In previous experiments, various doses of sodium sulfide, an H_2S donor, were injected into different SI-ALI animal models such as mice and sheep (a clinically relevant large animal model). The results showed that parenteral administration of H_2S could not only significantly reduce the oxidation and nitration of proteins and the level of IL-1β (a proinflammatory cytokine), but also increase the level of the anti-inflammatory cytokine IL-10 levels in the lung tissue of SI-ALI animal models (Table 1). In addition, the histological condition of the lung was improved, and the mortality was decreased. These results suggest that H_2S could exert cellular protective effects in SI-ALI through the anti-inflammatory and antioxidant pathways.[25,26,38] Recently, Han and colleagues found that inhalation of 80 ppm H_2S for 6 h could markedly improve SI-ALI *via* reducing inducible nitric oxide synthase (iNOS) expression, NO levels, and NF-κBp65 activity,[27,39] providing information not only about the effects but also about the mechanisms behind H_2S treatment of SI-ALI (Table 1).

According to these animal experiments, H_2S administration may be effective in the treatment of SI-ALI, but it has not been applied in clinical practice. Moreover, the optimal administration route and dose of H_2S are still unclear. Thus, further studies on clinical application and safety are necessary.

Peroxynitrite ($ONOO^-$) decomposition catalysts. It is well known that oxidative stress is closely associated with SI-ALI, which can release ROS, such as superoxide, inducing a broad inflammatory response and vascular dysfunction. Superoxide is degraded by superoxide dismutase (SOD) in healthy persons. However, SOD is saturated and superoxide levels are increased in SI-ALI patients.[30,40] Excess superoxide impairs endothelial cells and reacts with NO to produce $ONOO^-$, which increases vascular permeability and causes lung dysfunction.[30,41] $ONOO^-$ decomposition catalysts are anti-inflammatory agents and have been evidenced to protect cells in a well-characterized ovine model of SI injury.[12] In preclinical studies, various $ONOO^-$ decomposition catalysts, including INO-4885, WW-85, and R-100, were administered at several doses and *via* various routes in ovine models of SI-ALI (Table 1). The results show that lung lymph flow and pulmonary microvascular permeability were decreased, lung water content and NO levels in lung tissue were attenuated, and pulmonary dysfunction was improved by the anti-inflammatory actions of these catalysts. Meanwhile, locally administered $ONOO^-$ decomposition catalysts can prevent the adverse effects of systemic administration.[29,30,38,41] These experiments have demonstrated that $ONOO^-$ decomposition catalysts might be potential therapies for SI-ALI. However, this research is still in the preclinical stage. The optimal administration route and dose of $ONOO^-$ decomposition catalysts need to be further studied, both in SI-ALI animal models and in clinical trials.

Proton-pump inhibitors. Proton-pump inhibitors (PPIs) constitute a class of antacid drugs, used for nearly 30 years to treat gastric disorders by inhibition of H+/K+ adenosine triphosphatase in cells of the stomach. However, it is little known whether PPIs have beneficial effects on extragastrointestinal diseases, especially of the pulmonary system, such as idiopathic pulmonary fibrosis (IPF)[42,43] and chronic obstructive pulmonary disease (COPD).[44] In previous studies, it was shown that PPIs directly inhibit the enzymatic activity of dimethylarginine dimethylaminohydrolase, which participates in the progress of IPF through upregulating the expression and activity of iNOS. Owing to the importance of the iNOS pathway in SI-ALI, PPIs may be a potential therapy for SI-ALI patients.[43,45] Nelson and colleagues used esomeprazole (30 mg/kg) to treat mice after lung injury for 10 days and started with prophylactic treatment at 2 days postinjury. Their results demonstrate that the dose of the drug (30 mg/kg) could be well tolerated and had beneficial effects on the SI-ALI mice, while it could not be tolerated in the prophylactic group[31] (Table 1). In summary, it is worth noting that PPIs have extragastrointestinal functions. Moreover, esomeprazole is a candidate medicine for SI-ALI, but the usage, dosage, and mechanism are still unclear, both in animal models and in clinical practice, so further studies are required.

Clinical therapy for SI-ALI

High-frequency percussive ventilation. High-frequency percussive ventilation (HFPV) is a type of oxygen supply that is used simultaneously with a variety of airflow techniques, allowing for direct alveolar ventilation with small tidal volumes by

Table 2. Clinical therapy for SI-ALI.

Therapy	Patients	Application	Results
HFPV	HFPV ($n = 92$) Conventional mechanical ventilation ($n = 130$)[51]	HFPV combined with other reagents (inhaled bronchodilator, heparin, N-acetylcysteine, humidification)[9,49–51]	Improved oxygenation, cleared pulmonary secretions, and decreased iatrogenic injury
PFC	PFC treatment group ($n = 12$) Control group (received conventional treatments) ($n = 11$)[52]	Intratracheal instillation[52,53]	Reduced early inflammatory mediators, modulation of immune microenvironment, and improved oxygenation, alveolar compliance, and lung function
Anticoagulants	Experimental group ($n = 16$) Control group ($n = 14$)[54]	Inhaled anticoagulants (UFH, heparin, ATs, tPA)[54,55]	Decreased airway fibrin deposition and obstruction and improved oxygenation and ventilation
Epinephrine	Experimental group ($n = 8$; received standard of care plus nebulized epinephrine) Control group ($n = 8$;[56] received standard of care)	Nebulized epinephrine[56–58]	Reduced the airway blood flow and mucus secretion by vasoconstriction in smoke-inhalation-injured lungs; increased ventilation

For other studies of HFPV, please see references 9,48,49, and Table 2 of reference 78; for other specific experimental data of anticoagulants, please refer to Table 2 of reference 60; for other studies of epinephrine, and preclinical studies that lay the foundation for clinical application, please see references 72,74.
AT, antithrombin; HFPV, high-frequency percussive ventilation; PFC, perfluorohexane; tPA, tissue plasminogen activator; UFH, unfractionated heparin.

using a combination of convective and oscillatory shocks. This mode of ventilation was developed by Bird in the early 1980s and was initially applied to acute respiratory failure after burns and inhalation of smoke.[46] HFPV can be manipulated by high-frequency jet ventilation, high-frequency oscillation ventilation, and high-frequency flow interruption.[9,47,48] HFPV has pressure support and oxygen supply at low oxygen concentrations compared with traditional mechanical ventilation.[9] The PaO_2 increases rapidly and the incidence of oxygen poisoning is low. The lung compliance, PaO_2/FiO_2, and V/Q mismatch are improved by HFPV, and airway obstructions are also removed. Additionally, HFPV favors gas exchange, which not only protects the affected lungs, but also reduces ventilator-associated pneumonia and mortality compared with conventional mechanical ventilation (Table 2). Evidence supporting the efficacy of this technique, however, remains deficient.[9,47,49] Clinical experience shows that drying or bleeding of the tracheal mucosa occurs when using HFPV for a long time. Furthermore, HFPV may lead to ventilation failure, serious complications, and bronchial damage, because of the long dilation time of the small airways without enough humidification. Hence, humidification is essential in HFPV after smoke inhalation.[49] About 53% of burn centers use these ventilation devices to treat SI-ALI;[9] in much research, HFPV is combined with other treatments to improve the therapeutic effect. For instance, it can be combined with inhaled heparin, bronchodilators, and N-acetylcysteine. Moreover, Japanese clinicians have used both bronchoscopy and repeated bronchoalveolar lavage to remove tracheal pseudomembranes and other debris during HFPV treatment, producing remarkable effects in the treatment of SI-ALI.[50]

As HFPV improves oxygenation, clears pulmonary secretions, and decreases iatrogenic injury, it has become an effective method of emergency treatment for SI-ALI patients.[46] However, the safety, effectiveness, and optimal application strategies of HFPV have not yet been fully

evaluated in clinical applications, so these need to be further studied in order to treat SI-ALI patients effectively.

Intratracheal instillation of perfluorohexane (PFC). Perfluorohexane (PFC) is a group of perfluorinated compounds. PFCs are a liquid breathing medium, consisting of the elements carbon (C) and fluorine (F), with moderate-to-high gas solubility, high release rates, low surface tension, high bulk quality, good volatility, and good histocompatibility.[59] These have been applied for the improvement of pulmonary ventilation in infants with acute respiratory distress syndrome (ARDS) since the 1970s.[60] PFC is useful in treatment of ALI in various forms, including liquid ventilation, partial liquid ventilation, intraperitoneal injection, and high-frequency oscillatory ventilation treatment.[61–64] However, due to their high cost and low efficiency, the use of these methods is very limited. In 2017, Ding and colleagues explored intratracheal instillation of PFC on the basis of conventional treatment.[52] In this method, 15 ml of PFC was instilled into the endotracheal tube every 12 h, and subsequently, Ambu Bag-inspired oxygen was used to ensure the even distribution of PFC in the lung. The authors found the number of neutrophils and the levels of the inflammatory cytokines IL-6, IL-8, and TNF-α in BALF were decreased by the PFC treatment after 3 days,[52] while the proportion of phagocytic cells had increased, consistent with previous experiments[53] (Table 2). However, these inflammatory cytokines were not significantly diminished in the plasma after PFC treatment. These results suggest that intratracheal instillation of PFC may be beneficial to reduce local inflammation in the lungs, but it does not improve the systemic inflammatory response. Nevertheless, the severity of the injuries of burned patients was significantly improved after PFC treatment, and intratracheal instillation of PFC improved the effects of conventional treatments of SI-ALI.

Intratracheal instillation of PFCs can treat SI-ALI by reducing early inflammatory mediators, modulating the immune microenvironment, and improving oxygenation, alveolar compliance, and lung function. However, its application in patients remains very limited due to high volatility, low atomization efficiency, and high cost. In the future, it will be necessary to improve the effectiveness and to reduce the cost of PFC treatment of SI-ALI.

Inhaled anticoagulants. Anticoagulants include unfractionated heparin (UFH) and low-molecular-weight heparin.[65] Anticoagulants have been widely used as prevention and treatment approaches for thrombosis in the treatment of cardiovascular diseases. UFH is currently increasingly applied to extravascular spaces, such as by local administration and intrapulmonary application. Inhalation of smoke causes endothelium-derived inflammatory responses, which lead to subendothelial coagulation, fibrin deposition, and structural remodeling. Following these responses, airway obstruction and pulmonary edema can occur, which result in a series of clinical symptoms. Inhaled anticoagulants have anti-inflammatory effects and can improve lung injury by decreasing airway fibrin deposition and obstruction[54,55] (Table 2). A large number of preclinical experiments have indicated that inhaled anticoagulants, including UFH (5000 or 10,000 IU), antithrombins (ATs; 290 U), and tissue plasminogen activator (tPA; 1 or 2 mg) were effective in SI-ALI animal models whether applied alone or in combination.[55,66–69] In clinical experiments, low (5000 IU) and high (10,000 IU) doses of inhaled heparin improved oxygenation and ventilation, and reduced lung injury measurements such as the W/D ratio and histopathological scores. This suggests that inhaled heparin is safe and may be effective in patients with SI-ALI.[65,70–74] Moreover, a high dose of UFH (10,000 IU) + N-acetylcysteine + salbutamol administered every 4 h significantly promoted pulmonary function and decreased mortality in patients with SI-ALI.[54,55] Hadjiliadis and colleagues found that using a UFH dose from 50,000 IU to 400,000 IU was safe and feasible for the treatment of SI-ALI. Thus, nebulization of anticoagulants for the lungs allowed higher doses, enhanced therapeutic efficacy, and decreased the risk of systemic bleeding compared with intravenous administration.[61] In conclusion, nebulized or aerosolized anticoagulants and antithrombotic drugs, including heparin, heparinoids, ATs, and fibrinolytics could be used to treat SI-ALI. Although the usage of inhaled anticoagulants can improve survival rates for SI-ALI patients, relevant cases and systematic reviews are still insufficient.[75] Moreover, the dosage and therapeutic drugs used vary. Further clinical investigations are needed to research the optimal therapeutic dosage and to find more efficient anticoagulants.

Nebulized epinephrine. Smoke inhalation causes tracheal bronchospasm, increases mucus secretion, forms casts, and augments airway blood flow. Increased airway blood flow plays an important role in SI-ALI, as it results in lung edema, pulmonary vascular permeability,[76] and subsequent pulmonary dysfunction. Epinephrine, a nonselective adrenergic receptor agonist, leads to vasoconstriction by α_1-receptor stimulation and induces bronchodilation by β_2-receptor stimulation. Thus, nebulized epinephrine can reduce airway blood flow and mucus secretion by vasoconstriction in smoke-inhalation-injured lungs. Meanwhile, it also increases ventilation through bronchodilation.[56,57] A classic study found that nebulized epinephrine was safe and effective in a typical SI-ALI ovine model. Nebulized epinephrine not only limited pulmonary vascular permeability to water and protein but also attenuated airway blood flow and improved lung function.[57,58] Furthermore, the investigators who obtained these findings also performed a pilot clinical trial to test the safety of nebulized epinephrine in SI-ALI patients (aged 7–19 years) in 2017. Nebulized racemic epinephrine (2.25% solution, 0.5 ml in 3 ml of saline administered every 4 h for 7 days) was safe and did not have any adverse effects on children with SI-ALI. Epinephrine is inexpensive, exists in powder and liquid forms, and is easily aerosolized.[56] That study suggested that nebulized epinephrine is effective in patients with smoke-inhalation injury. Given the limitations of age, duration, and starting time of the clinical trial, follow-up studies should focus on the age range, best initiation time, and optimal dosage (Table 2).

Conclusion

Despite the fact that much progress has been made in SI-ALI patients, morbidity and mortality remain high, and the pathophysiology of SI-ALI is extremely complicated. The damage from toxic and harmful gas, oxidative stress, the interaction between cytokines and inflammatory mediators, and activation of the NF-κB signaling pathway all participate in the development of the disease. A large number of drug experiments have been conducted *in vivo* in order to prevent the occurrence of further damage from the various pathophysiological processes. Nevertheless, the above methods have been applied in clinical practice only on a small scale, and the safety of the drugs and inconsistency between experimental results are the main problems at present. Most of the new therapies are still in the animal experimental stage. Future therapeutic studies should focus on (a) molecular and gene therapy in SI-ALI, such as blocking the NF-κB signaling pathway in specific target cells and specifically inhibiting the expression of a target protein, (b) applying MSCs in ALI/ARDS, and (c) regenerative medicine and bioengineering.[9] In addition, it has been shown that vitamin E,[11] puerarin,[77] melatonin, prostate E-1, PS[78] and other drugs can prevent and treat SI-ALI.[13] Continuous intravenous infusion of low doses of arginine vasopressin is also effective in reducing oxidative stress-induced lung injury.[39] Meanwhile, early treatment remains the key to reducing mortality and improving prognosis. The inconsistent effects of certain therapies might be due to the diverse dose, delivery route, therapeutic duration, severity of patients, and complementary interventions. The development of better treatment strategies for this intractable disease still requires investigation. Currently, there is no particularly effective treatment for SI-ALI. In recent years, the research focus is on the secretion of exosomes by stem cells, which may become an innovative and effective therapy, and we look forward to its in-depth study.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Supplemental material

Supplemental material for this article is available online. The reviews of this paper are available via the supplementary material section.

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