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Gramatté, J.; Pietzsch, J.; Bergmann, R.; Richter, T.;

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Causative treatment of acid aspiration induced acute lung injury – Recent trends from animal experiments and critical perspective

Johannes Gramatté[a], Jens Pietzsch[b,c], Ralf Bergmann[b] and Torsten Richter[a,*]
[a]*Department of Anesthesia and Intensive Care, Carl Gustav Carus University Hospital, Technische Universität Dresden, Dresden, Germany*
[b]*Department of Radiopharmaceutical and Chemical Biology, Institute of Radiopharmaceutical Cancer Research, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany*
[c]*Department of Chemistry and Food Chemistry, Technische Universität Dresden, Dresden, Germany*

Abstract. Aspiration of low-pH gastric fluid leads to an initial pneumonitis, which may become complicated by subsequent pneumonia or acute respiratory distress syndrome. Current treatment is at best supportive, but there is growing experimental evidence on the significant contribution of both neutrophils and platelets in the development of this inflammatory pulmonary reaction, a condition that can be attenuated by several medicinal products. This review aims to summarize novel findings in experimental models on pathomechanisms after an acid-aspiration event. Given the clinical relevance, specific emphasis is put on deduced potential experimental therapeutic approaches, which make use of the characteristic alteration of microcirculation in the injured lung.

Keywords: Acute respiratory distress syndrome, critical care medicine, pneumonitis, pulmonary inflammation, pulmonary blood flow, targeted anti-inflammatory therapies

1. Introduction

Aspiration is defined as foreign content entering the airway below the vocal cords [34]. It is a feared complication of general anesthesia (1/2,000–3,000 general anesthetics) or in patients with altered states of consciousness, e.g. in intensive care and emergency patients [50]. The consequences are extremely variable ranging from absence of clinical signs or presenting with signs of acute lung injury (ALI), progressing to the full picture of acute respiratory distress syndrome (ARDS) with a consecutive mortality rate about 40% [55]. Despite this, the incidence of ARDS induced by aspiration is hard to estimate, because most aspiration events happened unwitnessed. The symptoms of lung injury following aspi-

*Corresponding author: Torsten Richter, M.D., Department of Anesthesia and Intensive Care, University Hospital Technische Universität Dresden, Fetscherstrasse 74, 01307 Dresden, Germany. Tel.: +49 351 4584110; Fax: +49 351 4584336; E-mail: torsten.richter@uniklinikum-dresden.de.

ration range from a subclinical pneumonitis to severe ARDS. Nevertheless, aspiration-induced ARDS remains one of the leading causes for death associated with general anesthesia [50]. Acid aspiration (e.g. aspiration of gastric content), leads to an inflammatory reaction characterized by an early phase of alveolar epithelium damage and a delayed phase associated with neutrophilic infiltration [28]. This injury mechanism is called aspiration pneumonitis and may secondarily lead to an infectious process, caused by colonization of the aspirated content resulting in aspiration pneumonia. The incidence, epidemiology, risk factors, diagnosis and clinical management of aspiration induced pneumonitis and pneumonia was described previously [36, 50]. Consequences of aspiration are ventilation-perfusion mismatch and consecutive regional hypoxemia. It can be speculated that hypoxic pulmonary vasoconstriction (HPV), alveolar exudation and other factors like vascular geometry alteration [27] may be responsible for changes in regional pulmonary blood flow distribution over time [53]. The clinical standard treatment after an aspiration event is symptomatically, adapted on the clinical signs and the course of the illness [36, 37, 50]. Currently, there is no causative therapy of acid aspiration-induced lung injury [9]. In consequence, the purpose of this review is to summarize the aspiration-induced pathomechanisms in animal models. Additionally, a critical perspective for potential experimental therapeutic strategies of meaningful clinical relevance is given.

2. Animal models of aspiration-induced lung injury

The main content of aspiration in humans is gastric reflux, a mixture containing a suspension of food particles and gastric acid (pH usually >1.5), contaminated with bacterial cell wall products and cytokines resulting in a substrate of high osmolarity [38]. Aspiration matter may be composed of other substances, e.g. seawater, blood, meconium, enteral nutrition given over a misplaced feeding tube, or foreign matter. There are particular animal models to examine the aspiration of seawater as a complication in an almost drawing event [32, 33] or for the meconium aspiration syndrome, a common cause of respiratory failure in neonates [12, 31, 60]. The pathophysiology and clinical manifestation is different to the acid aspiration and have therefore separated animal models. Regarding the aim of this review, two types of aspiration content applied in animal models are considered: hydrochloric acid (HCl) and HCl with particulate matter. These approaches are well established to investigate the pathogenesis and treatment options of ALI/ARDS induced by aspiration [30, 38]. The intrapulmonary instillation of HCl is a simple and reproducible way to study effects of acid aspiration in animals. The mode of acid application ranges from nebulization to direct fluid instillation. In most of the studies, HCl is instilled directly in the trachea over a breathing tube [13]. The administration of acid by a catheter located in a main bronchus can be used to create a site-specific injury in the lung [3], which may allow for intra-animal comparison. Beside the volume, the spread of the instilled acid depends on the position of the animal, the respiratory state (apnoe or ventilation), and the speed of instillation. Even with a standardized procedure inducing the injury, it remains uncertain to predict which particular functional lung region will get damaged. Therefore, it is recommended to proof adequate spreading by computed tomography. Since the studies from the 1960 s it has been known that the effects of aspiration can be augmented by increasing the amount and lowering the pH of the acid [28]. To induce a reliable lung injury in this way, the pH applied has to be lower than what is to be expected in physiological gastric content. Furthermore, the reaction to an aspiration event is more severe with the addition of particle matter [30]. The animal model of acid aspiration is recognized as a model of acute lung injury to study, e.g., pulmonary hemodynamics, deteriorations in gas exchange and initiation of inflammation, like mechanisms of neutrophil recruitment. It is used also to study new therapeutic approaches, e.g. the treatment by different ventilation strategies [38].

3. Pathophysiological aspects of aspiration-induced lung injury

In general, the time course of pathophysiological response to aspiration is biphasic [4, 28]. After the contact of HCl with lung tissue, it is assumed that proteins and the bicarbonate system buffer the acid very fast [5]. Nevertheless, an acute alteration of the airway and alveolar epithelium and capillary endothelium leads initially to significant changes in functional parameters like deterioration in gas exchange in rodents [3, 70] and increased lung compliance with the need of higher ventilation pressures [4]. The damaged alveolar-capillary membrane [17] allows the development of an intra-alveolar edema [44] with consecutive impaired gas exchange. Partial pressure of arterial oxygen decreases immediately after acid aspiration in rats [47]. Partial pressure of arterial CO_2 consecutively rises but not until the first 6 hours [3]. Early increases of plasma lactate dehydrogenase and macrophage inflammatory protein-2 are signs for tissue damage within the first hours in rats [56]. The initial phase is followed by an acute neutrophil derived inflammatory response, which is the main feature for developing ALI [61]. This includes recruitment of polymorphonuclear neutrophils resulting in increased neutrophil counts in peripheral blood within the first hour. Their activation was followed by an infiltration into the alveoli [6, 51]. The recruitment of leukocytes into the lung is not yet fully understood but comprises mechanisms like platelet-neutrophil interaction which is platelet P-selectin-dependent, in mice [69] and which is attended by neutrophil-endothelial cell adhesion [65]. The details of leukocyte sequestration were described in detail by Doerschuk [15]. Furthermore, acid-aspiration induced ALI is characterized by intrapulmonary shunting [7] as well as by an increased heterogeneity of pulmonary blood flow pattern. In a rat model of one-sided acid aspiration, the pulmonary blood flow increases in areas of aspiration directly after injury [52]. This blood flow pattern remains stable in the first hour [54]. However, after 2 hours a redistribution of pulmonary blood flow away from injured regions was observed, accompanied by a partial recovery from hypoxemia over time [53]. Histologically, the lung injury is characterized by an initial pore formation in the apical alveolar membrane immediately after acid aspiration in rodents [62]. Within the first two hours there is an increase of alveolar epithelial permeability and pulmonary vascular permeability resulting in an intra-alveolar and interstitial edema [25, 29, 40]. For the next hours (6 h up to 24 h after aspiration) an alveolar serofibrinous exudate, alveolar hemorrhage, alveolar septal thickening and parenchymal necrosis have been reported [3]. Already within the first week after injury, signs for the development of fibrosis in rats may occur [67]. In response to acid aspiration, alveolar epithelia release H_2O_2 which is NADPH oxidase 2-dependent [62]. This signaling mechanism initiates neutrophil-related inflammation and is augmented by proteases and other oxidants derived from neutrophils [29]. Severity of ALI is correlated to oxidative stress, which is a key pathway of the injury [23]. The capacity of antioxidants is relatively decreased, due to high oxidant activity in ALI [42] and by serine proteinases degrading certain superoxide dismutases [41]. Not only the oxidative stress machinery is triggered by acid aspiration, there occurs generation of oxidized phospholipids (oxPLs) in the lung, too. These oxPLs trigger the cytokine production induced by Toll-like receptor 4 [23]. The lung has a large surface area that is exposed to the aerobic environment and thus is a highly susceptible site for oxidative events, making the lipids at the air-liquid interface an "ideal" substrate for lipid modifications. The microvascular lung damage increases in hyperoxia conditions through the production of reactive oxygen species. This becomes important if mechanical ventilation with high fractions of inspired oxygen needs to be provided [43]. In bronchoalveolar lavage fluid (BALF) the tumor necrosis factor alpha (TNF-α) is increased within the first hour after acid aspiration in the rat model [13], followed by interleukin (IL)-8, IL-1β, IL-6 and IL-10 during the next hours [25]. Recent studies showed that nucleosomes and histones play a key role in proinflammatory pathways after acid aspiration; they are elevated in BALF and in the peripheral blood [70]. Beside the local consequences of acid aspiration, this type of injury induces inflammatory responses in extra-pulmonary regions which are mediated by neutrophils [57] and complement [66]. A leukocyte

infiltration in the heart with necrosis in myocardium and conducting system, infiltration with lymphocytes in the liver and renal inflammation have all been seen extra-pulmonary after acid aspiration in pigs [22].

4. Current treatment options

Today the treatment of aspiration-induced ALI/ARDS remains symptomatically. Clinically, there is not a known causal therapy to reduce the severity of lung injury or even prevent the development of ARDS. The current common practice in the treatment of aspiration involves bronchoscopy to clear the airways and support pulmonary function (e.g. mechanical ventilation with positive end-expiratory pressure (PEEP), which can improve oxygenation [8, 18, 48]. PEEP has to be selected cautiously to avoid an enhancement of the inflammatory process [2]. In most cases acute aspiration of gastric content leads to sterile pneumonitis (at least initially), therefore antibiotics are not primarily indicated. In the past corticosteroids were used with the aim to reduce the development and spread of the inflammatory response to acid aspiration. However, in human studies it was not possible to demonstrate any benefit in this regard, but showed higher rates of secondary infection [35, 58, 64]. Other approaches like treating patients suffering from ARDS with intravenous β-2 agonists showed no benefits in humans as well [20].

5. Potential approaches for causative treatment of acid-induces lung injury

Several promising approaches for the development of rational treatment options have been followed by *in vitro* and *in vivo* studies (Table 1).

Surprisingly, these studies were not continued further, even though the results were promising for a beneficial effect. Therefore, it remains questionable if and to what extent these results are transferable to humans. In this context it appears of particular impact that in some of the studies under discussion the administration of the experimental treatment had been performed before aspiration as a preventive therapy [11, 24, 40, 41]. Moreover, most of the studies applied pure HCl but not particulate matter. Except for witnessed aspirations it is not easy to determine the time of aspiration. Sometimes it remains a suspicious diagnosis following some indicators, clinically e.g. dysphagia, reduced state of awareness and reflexes. These indices may be associated with chronic cough and, when exacerbating, affect asthma [50] and with findings by imaging (X-ray, computed tomography of the thorax). The assumption is, to treat aspiration as early as possible following the idea, to interrupt the inflammatory process at the initial phase. It remains not clear at which time after the aspiration event, the treatment would be useless or may later become contra-productive. It is known that strategies inhibiting neutrophil adhesion and influx in the lung, often alter host defense, leading to increased susceptibility to secondary infections [64, 65]. Another question for the causative treatment is which form of application to use. Using the systematic approach (intravenous, oral or enteral drugs) could result in adverse side effects or insufficient local concentrations. Local application per inhalationem will not necessarily lead to appropriate substance levels in the affected area due to most of it getting stuck in the upper airways [10]. However, drugs are not being able to interact with their target because of edema in alveoli or atelectasis. The mechanisms for the blood flow distribution changes after acid aspiration is though due to hypoxic pulmonary vasoconstriction (HPV) [16]. It has been shown, that nonhypoxia mechanisms contribute for perfusion redistribution in bronchoconstricted patients with asthma [27]. The assumed factors as local hyperinflation, unidentified cell signaling, alterations in local vascular impedance by changing the local vascular geometry may result of interactions not caused by HPV. These nonhypoxia-derived mechanisms may be important between aspiration-injured airways and the

Table 1
Potential approaches for causative treatment of acid-induces lung injury

Anti-inflammatory approaches	Ref.
Blocking initial pathways	
• N-acetyl-heparin neutralizes extracellular histones which seem to be major pro-inflammatory mediators in acid induced ALI	[63, 70, 71]
• Intra-alveolar polyethylene glycol (PEG)-catalase avoids increased ROS in the peri-alveolar microvascular endothelium which is a first pro-inflammatory signaling	[62]
Blocking pro-inflammatory cytokines/pathways	
• Activated protein C (APC) blocks elevation of TNF-α, IL-6 and neutrophils; IL-8 antibody improves survival of rats after acid aspiration	[19, 25]
• Angiotensin-(1–7) reduces cellular infiltrate and improves oxygenation and pretreatment with angiotensin-converting enzyme 2 extenuates ALI after acid aspiration	[24, 68]
• Pentoxifylline, a phosphodiesterase inhibitor, reduces acid induced ALI in rats by blocking TNF-α and other pro-inflammatory cytokines	[47]
• JTE-607, a multi cytokine inhibitor, attenuates ALI induced by acid aspiration in rats	[26]
• K76, inhibiting the complement pathway, ameliorates the increase of TNF-α and subsequent neutrophil sequestration in rats	[66]
Inhibition of neutrophils	
• Lidocain suppresses superoxide anion generation and neutrophil respiratory burst, and, furthermore, inhibits neutrophil chemotaxis, migration and adhesion	[14, 46]
• Blocking platelet P-selectin with antibodies resulted in reduced platelet-neutrophil interaction and consequently an attenuation of ALI	[69]
• Binding of neutrophils to endothelial surface and migration into the airways is inhibited by using monoclonal antibodies to adhesion molecules like anti-CD18	[65]
• Mice with exposure to low dose exogenous CO after acid aspiration show less neutrophil counts in bronchoalveolar fluid	[45]
• Inhibiting thromboxane receptor-mediated platelet-neutrophil aggregation ameliorates acid aspiration-induced ALI	[21, 69]
• Ellagic acid and dexamethasone reduced neutrophil recruitment	[11]
Anti-edema approaches	
• Dopamine enhances fluid reuptake from the alveolus by stimulating sodium channels and Na-K-ATPase activity	[1, 59]
• Dexamethasone enhances alveolar fluid clearance by stimulating Na-K-ATPase activity after acid aspiration in rats leading to improved paO_2	[59]

surrounding mechanical environment as well. Taking advantage of the fact, that pulmonary blood flow (PBF) in injured areas is increased right after acute aspiration [52], applying drug-carrying microspheres (or drug-microparticles) intravenously, may be promising instead and should be investigated further. Microspheres of a certain diameter (e.g. containing of human albumin) are degradable and do not alter the vascular resistance. These microspheres could contain anti-inflammatory drugs to block initial proinflammatory pathways like neutrophil recruitment at the injured regions. Otherwise, to prevent spreading of inflammation to primary unaffected lung areas [4] it might be effective, to apply microspheres carrying a different drug when PBF is redistributed away from the injured regions (e.g. 2 h after aspiration in rats [53]). The ongoing high rate of aspiration with the consecutive potential for increased mortality needs to be addressed in further studies.

6. Summary

Targeted therapy, administrated intravenously, has the potential to combine the positive effects of anti-inflammatory and anti-edemateous therapy in damaged regions - preventing the development of ARDS [39, 52]. Therefore, perfusion distribution needs to be studied [49] to get more knowledge about the pulmonary microcirculation after an aspiration event in humans.

Declaration by authors

The authors declare that they have no competing interests. The publication was written in accordance with the ethical guidelines of Clinical Hemorheology and Microcirculation.

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