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Environmental Risk Factors for ARDS

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Abstract

The acute respiratory distress syndrome (ARDS) remains a major cause of morbidity and mortality in critically ill patients. Over the past several decades, alcohol abuse and cigarette smoke exposure have been identified as risk factors for the development of ARDS. The mechanisms underlying these relationships are complex and remain under investigation but are thought to involve pulmonary immune impairment as well as alveolar epithelial and endothelial dysfunction. This review summarizes the epidemiologic data supporting links between these exposures and ARDS susceptibility and outcomes and highlights key mechanistic investigations that provide insight into the pathways by which each exposure is linked to ARDS.

Keywords

Acute respiratory distress syndrome; Epidemiology; Modifiable risk factors; Alcohol abuse Cigarette smoking; Mechanisms; Future Interventions

The acute respiratory distress syndrome (ARDS) represents a significant health burden. Despite numerous efforts to identify effective treatments, few have been successful. As a result, considerable attention has now been given to the prevention of ARDS. Although many patients present with risk factors for ARDS, only a certain subset of these patients go on to develop it. While some of this phenomenon is likely explained by genetic factors, recent research has revealed that modifiable risk factors for ARDS exist as well. Alcohol use was the first major modifiable risk factor for ARDS to be identified. Significant details have since emerged over the past two decades about the mechanisms that underlie this relationship. These discoveries have spurred the search for additional risk factors. Further investigation has revealed smoking as an additional risk factor for ARDS. Although the data for this second association are newer and less developed, both of these relationships represent exciting discoveries in the quest to better understand, prevent and treat ARDS.

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Alcohol Abuse

Alcohol is one of the most commonly used and abused drugs worldwide. In the United States, nearly 20 million adults annually meet the criteria for alcohol abuse or dependence.[1,2] Alcohol is known to have numerous systemic health effects, including on the liver and central nervous system.[3] From a respiratory standpoint, alcohol abuse has long been associated with an increased risk of pneumonia.[4,5] More recently, alcohol abuse has been strongly linked in epidemiologic studies to development of ARDS in at-risk patients.

The first demonstration of an association between chronic alcohol abuse and ARDS was made by Moss et al, who retrospectively examined 351 patients at risk for ARDS.[6] In this cohort, 43% of patients who chronically abused alcohol developed ARDS compared to only 22% of those who did not abuse alcohol, with the effect most pronounced in patients with sepsis. This study was limited by its retrospective design, particularly since this design required that alcohol use history be obtained by chart review and documented history; furthermore, this study did not adjust for concomitant cigarette smoking. Encouraged by these findings, Moss et al conducted a multicenter prospective study of 220 patients with septic shock to further assess this relationship. Methodologically, this study improved on its predecessor by using the Short Michigan Alcohol Screening Test (SMAST), which has previously been validated as a screening test for chronic alcohol abuse.[7] A multivariate analysis again found that those who chronically abused alcohol developed ARDS more frequently than those who did not, 70% vs 31%, respectively.[8] These two key studies thus served as the first major evidence that alcohol use was a risk factor for the development of ARDS.

Several studies have since reinforced the relationship between alcohol use and ARDS. Licker et al examined the incidence of ARDS in 879 non-small cell lung cancer patients undergoing thoracic surgery.[9] Multivariate logistic regression found that preoperative chronic alcohol consumption was associated with increased odds of developing acute lung injury. In addition, two studies examining risk factors for transfusion-related acute lung injury (TRALI) found that chronic alcohol consumption was associated with the development of TRALI.[10,11] Gajic et al found that patients who developed TRALI were more likely to be chronic alcohol users when compared to matched controls, 36.5% vs 17.6% respectively. More recently, Toy et al found that in a multivariate model, chronic alcohol use in patients receiving blood product transfusions significantly increased the odds of developing TRALI. A later study by Gajic et al that evaluated patients 5584 patients at risk for ARDS to determine a lung injury prediction score found alcohol to be a positive risk factor for the development of ARDS.[12] These studies thus supported the prior observations and solidified the association between chronic alcohol use and ARDS (Table 1).

Although the relationship between chronic alcohol abuse and ARDS has been demonstrated numerous times, the effect of alcohol on ARDS outcomes has been less clear. Early studies that examined this relationship showed conflicting results. In a retrospective study, Moss et al found that amongst patients who developed ARDS, those with a history of chronic alcohol abuse had a significantly higher in-hospital mortality rate compared to those that did not abuse alcohol, 65% vs 36% respectively.[6] However, a follow-up prospective study that used

a more validated measure of alcohol abuse did not demonstrate any difference in mortality in ARDS patients when stratified by a history of alcohol abuse.[8]

In order to better evaluate the effect of alcohol use on ARDS outcomes, Clark et al performed a secondary analysis of patients enrolled in 3 ARDSnet trials: ALTA, EDEN and OMEGA, which examined the effects of aerosolized albuterol, omega-3 fatty acid supplementation and early vs delayed parenteral nutrition, respectively, in ARDS patients. Of note, all three studies were stopped early for futility. Participants enrolled in these trials (or their surrogates) completed the Alcohol Use Disorder Identification Test (AUDIT), a previously validated questionnaire [13] developed by the World Health Organization to stratify patients by level of alcohol consumption. In all, 1037 patients, representing 92% of all enrolled patients, had a completed AUDIT and were included in the secondary analysis performed by Clark et al. A multivariate analysis that adjusted for age, gender, severity of illness, history of smoking, ALI risk factor and baseline comorbidities found that a history of severe alcohol misuse was associated with an increased risk of death or persistent hospitalization at 90 days (OR = 1.78) compared to those with mild alcohol use. The authors used mild alcohol users rather than non-drinkers as the reference group since non-drinkers had poorer outcomes, thought to be due to comorbidities that discourage the consumption of alcohol. Thus, it appears likely that chronic alcohol abuse is associated with poor ARDS outcomes, though the data is less extensive for this association than for the association with susceptibility.

Mechanisms

Numerous studies have been performed both in animal models and humans in order to better understand the association between chronic alcohol use and ARDS. These studies have identified a central role for pulmonary immune dysfunction as well as alveolar epithelial dysfunction in the mechanistic link between alcohol and ARDS.

Pulmonary immune dysfunction

Both acute and chronic alcohol use can contribute to a dysfunctional pulmonary immune response. Acute alcohol use impairs neutrophil chemotaxis and function with subsequent decreased phagocytosis and bacterial killing.[14–16] Chronic alcohol use is similarly associated with altered neutrophil function and decreased superoxide production.[17] Interestingly, chronic alcohol use decreases levels of granulocyte/macrophage colony stimulating factor (GM-CSF) receptor and signaling in lung epithelium,[18,19] which has been shown to result in defective alveolar macrophage maturation.[20] The net effect of these abnormalities is an increased pulmonary bacterial burden.

In addition to its effects on neutrophils, alcohol use has a variety of effects on cytokine production in the lung. While acute alcohol use has been shown to impair production of proinflammatory cytokines such as TNF-α and IL-1β,[21] which may predispose patients to pneumonia, chronic alcohol use has actually been associated with increased levels of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, in both human and animal studies.[22–24] Recently, Burnham et al found elevated levels of CCL-5 (also known as RANTES), which is a chemoattractant for a variety of immune cells,[25] in the BAL fluid of

chronic alcoholics.[26] This increase in inflammatory cytokines appears to have a significant effect on downstream inflammation, as IL-6 was recently shown to play a key role in the pulmonary inflammatory response of alcoholic mice in a burn injury model.[25–27] This altered cytokine profile in conjunction with decreased neutrophil and alveolar macrophage function is thought to contribute to the development of ARDS in alcohol abusers.

Alveolar Epithelial Dysfunction

In addition to its effects on the lung inflammatory response, chronic alcohol use may also predispose to ARDS development by causing increased pulmonary oxidative stress and alveolar epithelial dysfunction. These effects are mediated in part via the renin-angiotensin system (Figure 1). Chronic alcohol use has long been known to increase activation of this system, resulting in elevated levels of angiotensin II in humans.[28,29] Angiotensin II may contribute to alveolar epithelial dysfunction through a variety of mechanisms, including via systemic effects on vascular tone and fluid retention as well as via localized effects such as promoting apoptosis of alveolar epithelial cells.[30] In addition, angiotensin II activates NADPH oxidase in the lung, resulting in elevated levels of reactive oxygen species.[31,32] This increase in reactive oxygen species results in depletion in alveolar levels of the key antioxidant glutathione (GSH) and increases in alveolar oxidized glutathione (GSSG), a phenomenon seen both in animal models [33] and humans who abuse alcohol.[34] Interestingly, patients with ARDS have been shown to demonstrate the same derangement with regards to pulmonary glutathione.[35,36] This alteration in glutathione results in decreased antioxidant capacity in the lung and has further been linked to decreased surfactant synthesis[37,38] and increased type II cell apoptosis.[39] Additionally, the depletion of glutathione appears to increase levels of latent TGF-β, which subsequently contributes to baseline alveolar epithelial dysfunction, manifested by increased permeability and lung edema.[40] The net result of increased activation of this pathway is an alveolar epithelium that is already dysfunctional and thus primed for developing ARDS when faced with an acute insult (Figure 2).

Future Interventions

The high prevalence of alcohol abuse worldwide and its association with ARDS present a unique opportunity to improve patient outcomes. While decreasing the prevalence of alcohol abuse remains an important goal, in addition, the unique mechanistic abnormalities involved in this relationship provide several potentially exciting therapeutic targets for alcoholic patients either at risk for or with ARDS.

One potential therapeutic intervention would be to attempt to increase glutathione levels, which play such a key role in the alveolar epithelial dysfunction observed with alcohol use. The use of N-acetyl-cysteine (NAC), a glutathione precursor, is one potential approach. In both endotoxin and microembolism rat models of ARDS, pretreatment with IV NAC attenuated lung injury.[41,42] Prior small clinical trials have shown that administration of IV NAC increases glutathione levels in patients with ARDS, although no significant improvement in outcomes was observed (ventilator free days or mortality).[43–45] However, these studies included small heterogeneous samples of patients with ARDS, rather than focusing on only those with a history of alcohol abuse. It remains unclear whether

administration of glutathione would be a successful therapeutic strategy in alcoholic patients either at risk for or who have already developed ARDS.

Given the role angiotensin II seems to play in altering glutathione levels, the renin-angiotensin system also presents a potential therapeutic target for alcoholic patients with ARDS. Interestingly, some data suggests that angiotensin converting enzyme (ACE) polymorphisms that increase angiotensin II levels may affect the risk of developing ARDS and mortality. Marshall et al found that an ACE genotype that causes increased ACE activity was more prevalent in Caucasian ARDS patients compared with other ICU patients or the general population.[46] Furthermore, amongst patients with ARDS, this genotype was associated with increased mortality. A later study by Villar et al in Spanish patients did not find a similar relationship.[47] However, a recent meta-analysis by Matsuda et al of nearly 5000 patients with ARDS, including Caucasian and Asian ethnicities, found that ACE genotypes associated with increased activity were associated with an increased risk of mortality from ARDS in Asian populations.[48] These findings, in conjunction with studies in mice that show decreased ACE activity to be protective in animal models of acid aspiration and sepsis-induced ARDS,[49] make the renin-angiotensin system an intriguing therapeutic target. To date, there has been no formal evaluation of the role of ACE-Inhibitors (ACE-I) or Angiotensin-Receptor Blockers (ARB) in ARDS patients, including alcoholics. Although the utility of these agents may be limited because patients with ARDS also often have shock or renal failure, further studies would be required to determine any potential benefits.

The GM-CSF depleted state that is induced by chronic alcohol use also serves as a potential therapeutic target for patients with ARDS. Treatment of alcohol fed rats with GM-CSF has been shown to improve not only alveolar macrophage function,[19] but also decreased alveolar permeability and increased lung edema fluid clearance.[50] Likewise, elevated levels of bronchoalveolar lavage fluid GM-CSF are associated with improved mortality in patients with ARDS.[51] A Phase II trial that randomized ARDS patients to GM-CSF vs placebo showed improved oxygenation with no adverse effects.[52] However, this study as well as a larger Phase II randomized clinical trial of GM-CSF vs placebo found no improvement in outcomes such as ventilator free days, organ failure-free days or mortality.[52,53] Whether GM-CSF would improve outcomes in ARDS patients with a history of chronic alcohol use remains unknown.

Smoking

Smoking remains a global epidemic. While anti-smoking efforts in the United States continue to slowly decrease the rate of smoking amongst adults (currently 18.1%),[54] tobacco use continues to be the leading cause of preventable death both in the US and worldwide, killing nearly 6 million people annually.[55] Although many harmful effects of smoking, particularly on the lung, have been known for quite some time, the link between ARDS and smoking has been established only recently.

Early studies investing the relationship between smoking history and ARDS suggested a possible association, though the findings were inconsistent. Christenson et al studied nearly 4000 patients undergoing cardiac surgery and found in multivariable analysis that a clinical

history of being an active smoker was associated with an increased risk of developing ARDS.[56] However, this study did not address or adjust for alcohol use. A later study by Iribarren et al retrospectively studied a large cohort of patients in a single health plan network, 56 of whom went on to develop ARDS.[57] Multivariate analysis showed that a history of active cigarette smoking was associated with increased odds of developing ARDS. Interestingly, increased amounts of smoking (> 20 cigarettes per day) were associated with an even greater odds of developing ARDS. While this study did adjust for chronic alcohol use amongst patients, it was limited by its retrospective nature and the use of diagnostic coding, which detects a low prevalence of ARDS. In contrast to these positive studies, a multicenter observational study by Gajic et al of 5584 patients at risk for ARDS did not find cigarette smoking to be a predictive risk factor for developing ARDS.[12] The conflicting findings of these studies may be due in large part to reliance on smoking history. Recent studies have determined that biomarkers of tobacco use, such as plasma cotinine, are significantly more sensitive for tobacco exposure in critically ill patients compared to self-reported histories.[58]

To further investigate this possible association, Calfee et al prospectively measured plasma cotinine levels in blunt trauma patients at risk for ARDS. Additionally, alcohol exposure was measured by both clinical history and AUDIT surveys. Increasing levels of plasma cotinine were associated with an increased risk of developing ARDS. Interestingly, in a multivariate model, including adjustments for alcohol use, both active smoking as well as moderate to severe passive smoke exposure predicted the development of ARDS.[59] These findings were the first to link smoking to ARDS using biomarkers and also to identify secondhand smoke as a potential risk factor for ARDS development. If confirmed, these findings may have important public health implications, particularly with regards to public smoking bans. Despite the strengths of this study, its findings were limited by its homogenous study population, all of whom were victims of severe blunt trauma enrolled at a single center.

Since then, studies in different patient populations have provided additional evidence in support of an association between smoking and ARDS. Toy et al found that active smoking was associated with an increased risk of TRALI, after adjustment for other predictors.[11] Likewise, Diamond et al conducted a multicenter study of 1255 lung transplant patients to identify risk factors for primary graft dysfunction (PGD), a form of acute lung injury that occurs within 72 hours of lung transplant.[60] In this analysis, donor smoking was associated with increased odds of developing PGD, a finding that was robust to adjustment for other predictors. These studies add to the growing body of literature that supports an association between smoking and ARDS (Table 2).

There are limited data on the outcomes of smokers who develop ARDS. One small study examined 47 patients with ARDS and found that non-survivors were more likely to be smokers than survivors.[61] A recent study by Hsieh et al sought to better evaluate this question using 381 patients with ARDS from the ALTA and OMEGA ARDS Network randomized controlled trials.[62] Urine NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), a well validated biomarker of tobacco use with a 2 week half-life,[63] was used to stratify patients by smoking exposure status. Although active smokers were found to be

younger, with significantly lower severity of illness scores and fewer comorbidities, they had a similar severity of lung injury as measured by either the Berlin Definition or Murray Lung Injury Score, raising the possibility that smokers may be more prone to developing ARDS with a lower severity of illness. While smoking was associated with lower mortality in unadjusted analysis, a multivariate analysis that controlled for the disparities in age, comorbidities and severity of illness between smokers and nonsmokers showed no association between smoking status and 60 day mortality.

Mechanism

The mechanisms through which smoking contributes to the development of ARDS remain under investigation (Figure 3). In contrast to alcohol, there are relatively few lab-based studies explicitly evaluating the relationship between smoking and ARDS; thus, inferences about the potential mechanisms of association between smoking and ARDS must largely be extrapolated from studies on smoking's effects on the lungs in other experimental settings. With this caveat, the mechanisms linking smoking and ARDS likely involve pulmonary immune dysfunction (as with chronic alcohol use) as well as dysfunction of both the alveolar epithelium and endothelium.

Pulmonary Immune Dysfunction

Smoking impairs pulmonary immune function though a variety of pathways. Smoking has numerous direct effects on innate and adaptive immunity that increase the risk of infection.[64] These effects include impaired mucociliary function, decreased surfactant production, altered T cell responses, depressed NK cell function and decreased immunoglobulin levels.[65,66] Additionally, cigarette smoke has been shown to lower the rate of bacterial clearance by alveolar macrophages.[67–69] This decrease in bacterial clearance in turn is thought to result in an influx of neutrophils into surrounding tissues, with an associated increase in proinflammatory cytokines and an elevated proteolytic burden.[67] Furthermore, smoking promotes biofilm formation,[70] which plays a role in the increased risk of respiratory infection in smokers.[71,72] This impairment in immunity and predisposition to infection is one potential mechanism by which smoking may increase the risk of ARDS.

Alveolar Epithelial Dysfunction

Since the 1980s, studies have demonstrated increased alveolar epithelial permeability in smokers compared to non-smokers,[73] mimicking a key pathophysiologic feature of ARDS. This effect on alveolar permeability may be related to the neutrophil influx observed with smoking, though studies on this mechanistic link have reported conflicting findings. Animal studies by Bhalla et al found that reducing pulmonary neutrophils improved alveolar permeability.[74] However, in similar animal studies, Kleeberger et al found that reducing this neutrophil influx did not attenuate epithelial permeability.[75] A more recent study by Li et al also found that neutrophil depletion did not improve epithelial permeability,[76] suggesting that other mechanisms must be playing a role as well.

Since then, several studies have shown that the profound oxidant effect of smoking[77] may be one of the major contributors to the alveolar epithelial dysfunction seen in smokers. Li et

al demonstrated that intratracheal inhalation of cigarette smoke in rats resulted in decreased levels of total BAL fluid glutathione with increases in the oxidized form, GSSG.[76] In animal models, this phenomenon has been linked to increases in alveolar epithelial permeability, while increasing intracellular glutathione has been shown to ameliorate this effect.[78] These findings are remarkably similar to those seen in the setting of alcohol abuse, although the timing of the effects are different: specifically, pulmonary glutathione depletion in alcohol users appears to be more of a chronic phenomenon, while in animal models of smoking, the effect is acute, lasting only 6 hours. In an attempt to replicate these findings in humans, Morrison et al performed lung scans to measure alveolar permeability in human subjects. They found that chronic smokers had increased alveolar permeability compared to non-smokers, and that permeability increased even further after chronic smokers acutely smoked a cigarette.[79] However, unlike in animal models, this study did not find any statistically significant difference in BAL fluid glutathione levels between smokers or nonsmokers, suggesting that other mechanisms likely contribute to this phenomenon. Recent evidence shows that cigarette smoke likely disrupts tight junction integrity through an epidermal growth factor receptor (EGFR) pathway,[80,81] which could help explain the increased alveolar permeability seen in smokers. Additionally, cigarette smoke decreases the expression of the primary ion channels responsible for resolving alveolar edema,[82,83] which likely further contributes to baseline epithelial dysfunction.

Endothelial and Platelet Dysfunction

The damage caused by cigarette smoke on the lungs is not limited to the alveolar epithelium. Smoking also causes vascular endothelial injury and alters endothelial function, a key pathophysiologic change that is also seen in ARDS. Early animal models demonstrated that cigarette smoke increases pulmonary endothelial permeability.[84] Since then, further study has confirmed that cigarette smoke increases lung vascular permeability and worsens LPS-induced lung edema.[85,86] Interestingly, the increased endothelial permeability observed with exposure to cigarette smoke seems to be at least in part mediated by increased levels of reactive oxygen species in the lung and furthermore is attenuated by NAC.[85,86] This increase in ROS seems to have a number of downstream targets including inhibition of Rho A[85] and activation of mitogen-activated protein kinases (MAPK)[86] that ultimately result in changes to the cytoskeleton resulting in endothelial barrier dysfunction. It is notable that reactive oxygen species seem to play a key role in both the epithelial and endothelial dysfunction caused by smoking.

Like endothelial dysfunction, to which it is closely linked, platelet dysfunction has long been noted to be a characteristic feature of ARDS.[87,88] Patients with ARDS have been observed to have increased procoagulant and decreased fibrinolytic activity in the alveolar lining layer and microvasculature.[89] These abnormalities promote pulmonary fibrin deposition[90] and can result in microthrombi in small vessels, as pulmonary arterial thrombi and distal filling defects of the microvasculature have been detected in patients with ARDS.[91] These factors likely contribute significantly to gas exchange abnormalities seen in patients with ARDS.[87] Cigarette smoke has been noted to have similar effects on platelets. Both active and passive smoking have been observed to increase platelet activation, predisposing to thrombus.[92] Additionally, platelet activation also results in damage to the endothelium, which can result

in vasoconstriction, further prothrombotic and proinflammatory states and cell proliferation in the vessel walls.[92] Interestingly, the effects of second hand smoke on endothelial and platelet dysfunction are approximately 90% of those of active smoking.[92] Thus, the effects of cigarette smoking on platelets likely plays a key role in contributing to endothelial dysfunction, which may further predispose smokers to ARDS.

Future Directions

Because the mechanistic links between smoking and ARDS are less well-defined than those between alcohol and ARDS, the identification of potential targeted therapies is more challenging. One potential area of intervention is the increased oxidative stress caused by cigarettes, which seems to play a key role in both the alveolar epithelial and endothelial abnormalities associated with smoking. Given that chronic alcohol use seems to further affect the antioxidant system and frequently co-exists with cigarette smoking in patients, the antioxidant system becomes an even more exciting source for potential intervention. As mentioned previously, studies that examined the use of NAC to replenish the antioxidant system did not show any improvement in outcomes in patients with ARDS. However, this specific population, which may have decreased antioxidant function at baseline, may merit further study. Furthermore, it may be useful to assess the effect of treating this population with NAC while they are at risk for lung injury, as opposed to afterwards once the inflammatory response is well-established. Further investigation is clearly needed to better understand the relationship between smoking and ARDS in order to identify additional potential therapeutic targets. Meanwhile, continued public health interventions, such as anti-smoking campaigns and public smoking bans, may help decrease the burden of smoking associated ARDS.

Air Pollution

Air pollution has been associated with a variety of adverse health outcomes, including all-cause mortality.[93] This phenomenon is thought to be driven primarily by an increase in cardiorespiratory events. Several epidemiologic studies have shown that air pollution is associated with an increased risk of myocardial infarction and cardiovascular disease mortality.[94–97] The association between air pollution and respiratory mortality is less clear, with some studies showing an increase in respiratory mortality,[93,98,99] while other studies have found no such relationship.[100–102] Although the association between air pollution and respiratory mortality is not entirely clear, air pollution has been associated with respiratory morbidities including increased susceptibility to airway infection[103] and decreased lung function.[104] However, there are no epidemiologic studies that examine the relationship between air pollution and ARDS.

Despite the lack of epidemiologic studies involving a possible association between air pollution and ARDS, there are several reasons to hypothesize that such a relationship may exist. First, cigarette smoke and ambient air pollution share many of the same compounds, such as ozone and particulate matter < 2.5 μm ($PM_{2.5}$). Given that cigarette smoke has previously been shown to be a risk factor for ARDS,[11,56,57,59,60] it is plausible that air pollution may pose a similar risk. Second, air pollution and its constituents have been

associated with changes in the lung that mimic those of ARDS. Studies in humans demonstrate that air pollution is associated with increased pulmonary inflammation, oxidative stress[105] and endothelial dysfunction[106] while ozone exposure has been associated with increased epithelial permeability.[107] These findings suggest that like cigarette smoke, air pollution may prime the lung to develop ARDS by causing increased baseline inflammation as well as epithelial and endothelial dysfunction. However, additional studies are needed to better examine the potential relationship between air pollution and ARDS in humans.

Conclusion

Significant progress has been made since the search for environmental risk factors for ARDS began nearly two decades ago. Chronic alcohol use and smoking have been identified in numerous studies to independently increase the risk of developing of ARDS and potentially affect the outcomes of patients who go on to develop the disease. These findings have important implications for public health and for ARDS prevention. Additionally, scientific studies have yielded tremendous insight into many of the mechanisms involved in the relationship between chronic alcohol use and ARDS, and numerous potential viable therapeutic targets have been identified that may enable clinicians to better treat chronic alcohol users with ARDS. Mechanistic studies into the relationship between smoking and ARDS are less developed and represent an important area for future investigation. Future studies are also needed to define the overlap or potential synergy between these two exposures, since smoking and alcohol use often coexist in patients. Finally, further epidemiologic study is needed to determine if there are additional environmental factors, such as air pollution, that may also be associated with an increased risk of developing ARDS.

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KEY POINTS

- Multiple observational studies have demonstrated that chronic alcohol use is a risk factor for the development of ARDS.
- Alcohol use may promote development of ARDS via increased angiotensin II, producing increasing oxidative stress which creates baseline alveolar epithelial dysfunction and primes the lung for developing non-cardiogenic pulmonary edema.
- Although less studied than alcohol use, cigarette smoke exposure also appears likely to be a risk factor for ARDS.
- Cigarette smoke may prime the lung to develop ARDS by creating baseline epithelial and endothelial injury, likely through direct exposure to powerful oxidants contained in cigarettes.

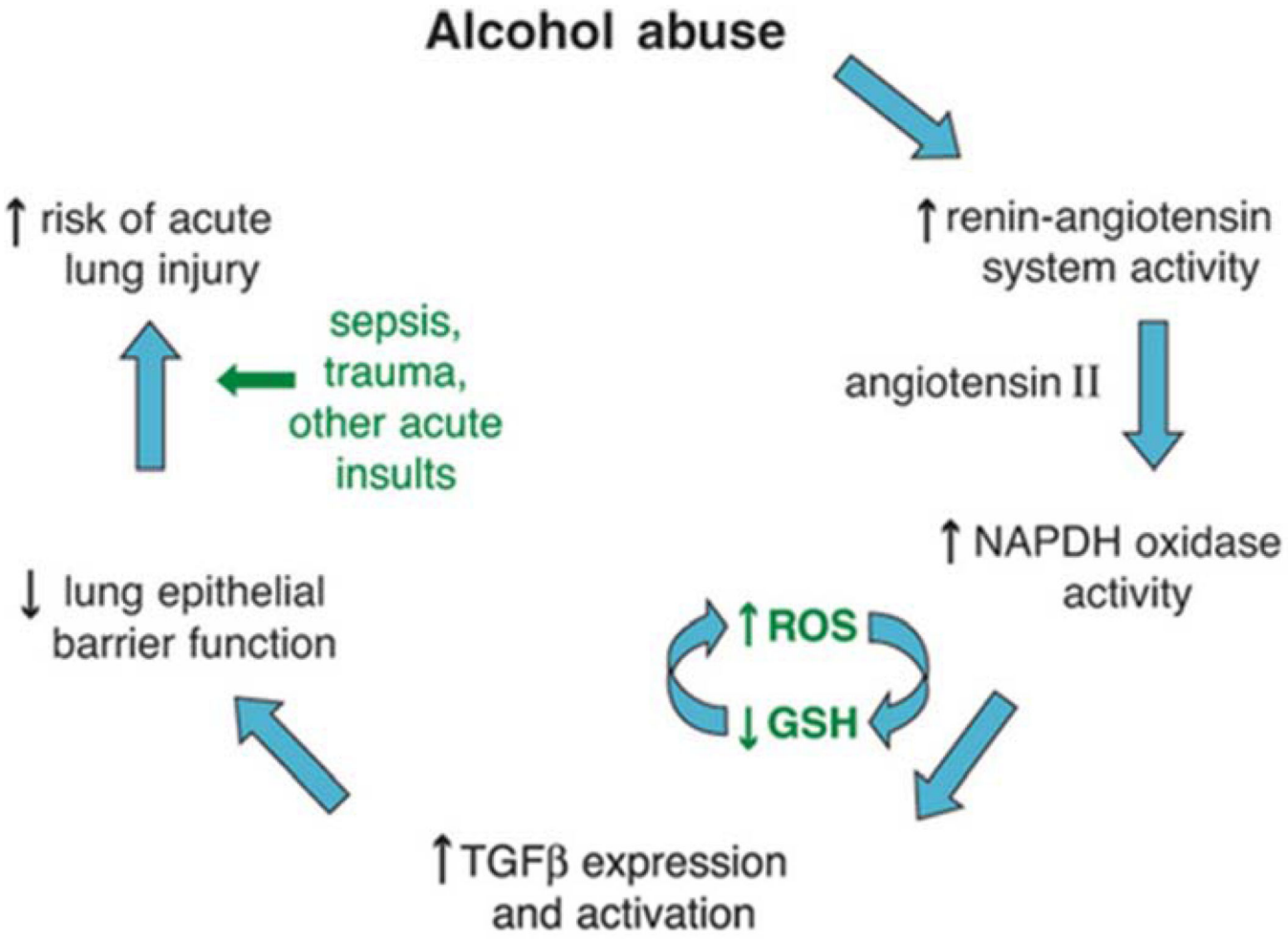

Figure 1.

Potential mechanism by which alcohol primes the lung for Acute Respiratory Distress Syndrome. *From Kershaw et al, Alcoholic Lung Disease. Alcohol Res Health. 2008 Sep; 31(1):66–75; with permission.*

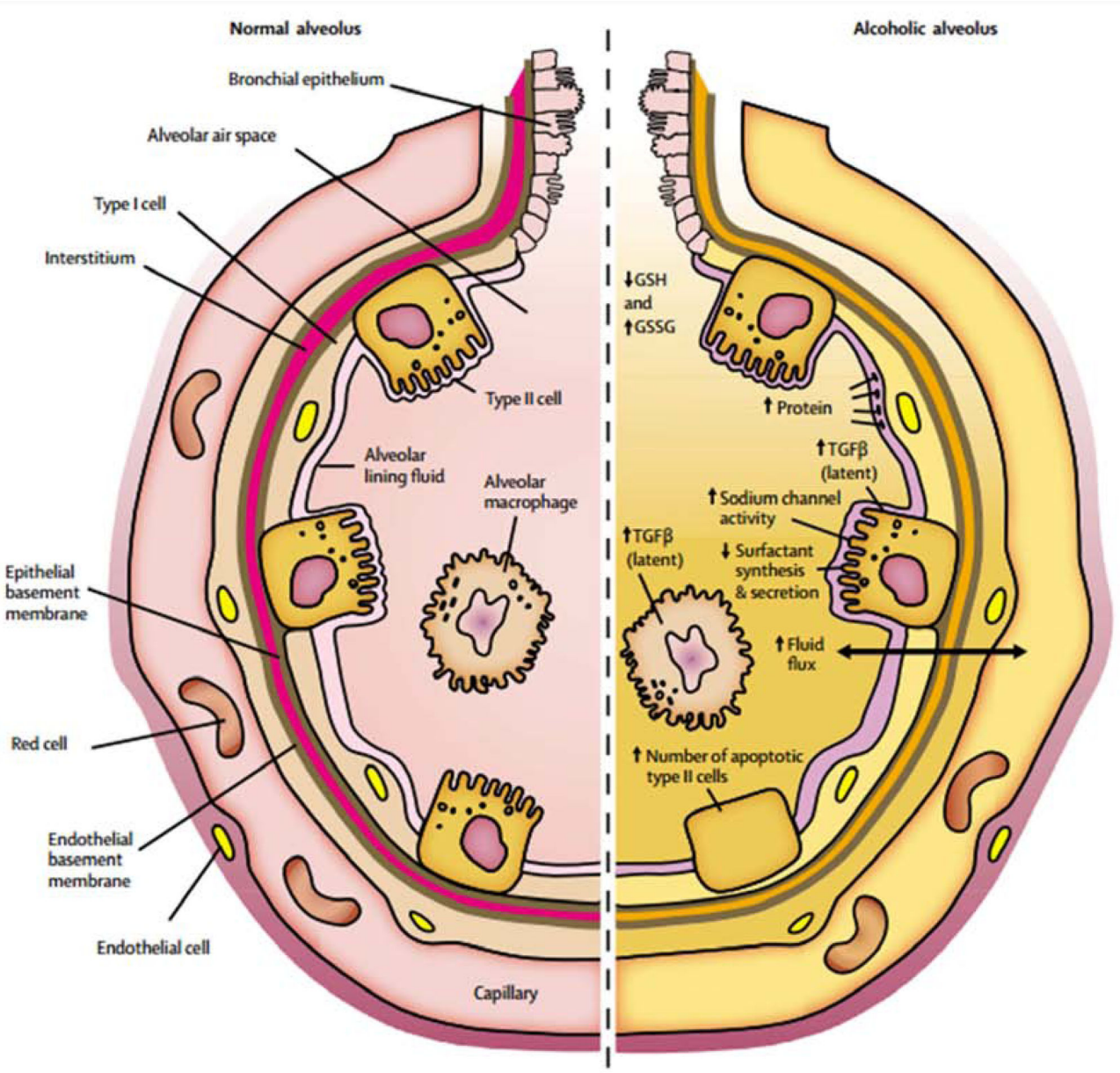

Figure 2.

Baseline dysfunction in the alcoholic alveolus.

From The Lancet, Vol. 368, Marc Moss & Ellen Burnham, Alcohol abuse in the critically ill patient, 2231-42, 2006, with permission.

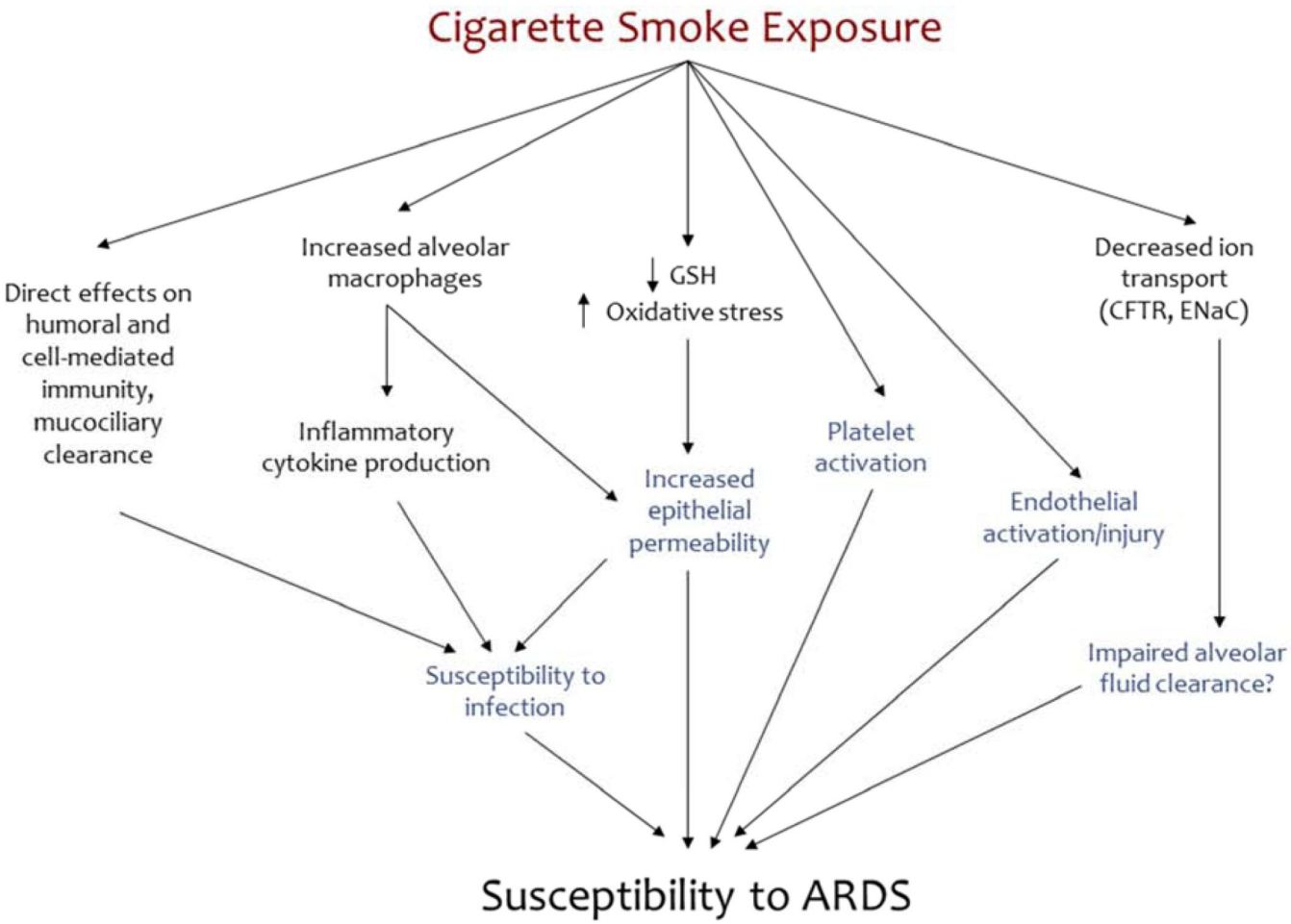

Figure 3.
Mechanisms through which smoking may prime the lung for ARDS

Table 1

Studies evaluating the relationship between ARDS and alcohol use

Author	Year	Study Size	Odds Ratio (history of alcohol abuse vs no abuse)	P value
Moss et al[6]	1996	351	1.98*	< 0.001
Moss et al[8]	2003	220	3.70	< 0.001
Licker et al[9]	2003	879	1.87	0.012
Gajic et al[10]	2007	148	**	0.006
Gajic et al[12]	2011	5584	¶	0.028
Toy et al[11]	2012	253	5.90	0.028

* Relative Risk

** No odds ratio or relative risk reported. 27 of 74 patients with acute lung injury had a history of alcohol abuse vs. 13 of 74 in matched controls.

¶ No odds ratio or relative risk reported. 44 of 377 patients with acute lung injury had a history of alcohol abuse vs. 289 of 5,207 in patients without acute lung injury.

Table 2

Studies examining the relationship between smoking and ARDS

Author	Year	Study Size	Odds Ratio (active smokers vs nonsmokers)	P value
Christenson et al[56]	1996	3,848	2.01*	< 0.001
Iribarren et al[57]	2000	121,012	2.85 (< 1 pack/day)* 4.59 (≥ 1 pack/day)*	< 0.05 <0.05
Gajic et al[12]	2011	5,584	**	NS
Calfee et al[59]	2011	144	2.77	0.01
Toy et al[11]	2012	253	3.40	0.02
Diamond et al[60]	2013	1,255	1.80	0.002

*Relative Risk

**No odds ratio or relative risk reported. 107 of 377 patients with acute lung injury had a history of active smoking vs. 1,239 of 5,207 in patients without acute lung injury