Published in final edited form as:

Crit Care Med. 2015 September ; 43(9): 2015–2016. doi:10.1097/CCM.0000000000001121.

Primed for Injury: Cigarette Smokers and ARDS

John P. Reilly, MD, MSCE and Jason D. Christie, MD, MSCE

John P. Reilly: john.reilly@uphs.upenn.edu; Jason D. Christie: jchristi@upenn.edu

Keywords

ARDS; Cigarette smoke; epidemiology

Cigarette smoking is the leading cause of preventable death in the world, resulting in 6 million annual deaths worldwide, and an estimated 10-year reduction in life expectancy in the United States [1, 2]. The detrimental effects of tobacco smoke on chronic lung diseases are well established, as well as the link between cigarette smoke and acute illnesses, such as invasive pneumococcal disease and influenza [3]. The association between cigarette smoke and the acute respiratory distress syndrome (ARDS), however, has been unclear. In experimental models, cigarette smoke increases epithelial and endothelial permeability, decreases surfactant production, alters the immune response to infection, and increases production of reactive oxidant species, all pathophysiologic mechanisms relevant to ARDS [4-6]. While not all studies have demonstrated a consistent signal [7], cigarette smoking has been identified as a risk factor for lung injury in multiple populations, including ARDS after cardiac surgery and blunt trauma [8, 9], as well as in transfusion related acute lung injury [10], and primary graft dysfunction after lung transplantation [11]. The main challenge to linking cigarette smoke to ARDS in epidemiologic studies is exposure ascertainment. Specifically, the reliance on a detailed smoking history, often provided by a patient's surrogate, leads to the potential for recall or reporting bias, potentially influencing study conclusions.

In this issue of *Critical Care Medicine*, Calfee and colleagues report the results of a study aimed at quantifying the association of cigarette smoke exposure and ARDS in patients at-risk for ARDS [12]. The authors conducted a prospective cohort study of 426 critically ill patients with precipitating risk factors for ARDS other than trauma or transfusion, including the largest at-risk populations of pneumonia and non-pulmonary sepsis. Subjects were enrolled from the intensive care unit (ICU) of Vanderbilt University Medical Center within one week of hospitalization and followed for the development of ARDS through ICU day 5. The study had several strengths including close attention to obtaining accurate smoking

Corresponding Author: Jason D. Christie, M.D., M.S., Professor of Medicine and Epidemiology, Division of Pulmonary, Allergy and Critical Care Medicine, Center for Translational Lung Biology, University of Pennsylvania, Perelman School of Medicine, 423 Guardian Drive, 717 Blockley Hall, Philadelphia, PA 19104.

Conflict of interest statements for all authors – Drs. Reilly and Christie report receiving research funding from the National Institutes of Health. Dr. Christie has also received institutional research funding from GlaxoSmithKline to study sepsis and lung injury.

Invited Editorial to accompany manuscript # CCMED-D-14-02192 "Cigarette Smoke Exposure and the Acute Respiratory Distress Syndrome"

histories, as well as history of alcohol use, another important ARDS risk factor and potential confounder [13]. In order to overcome the information bias that may result from inaccurate smoking histories, they also measured urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a validated biomarker of cigarette smoke exposure. In the overall cohort, neither cigarette smoking history nor NNAL concentration was associated with ARDS; however, within the pre-specified subgroup of 212 patients with non-pulmonary sepsis, cigarette smoking history and higher NNAL levels were both independent risk factors for ARDS. Further supporting the findings, the interaction between non-pulmonary sepsis and cigarette smoke exposure was statistically significant. Cigarette smoke exposure also appeared to confer lower mortality among patients who developed ARDS in unadjusted models; however, this finding likely resulted from confounding characteristics of smokers including younger age and less comorbidities, as the mortality findings lost significance in adjusted models.

The study conducted by Calfee *et al.* provides solid evidence expanding the ARDS risk factor of cigarette smoking to one of the largest at-risk populations, non-pulmonary sepsis [12]. Surprisingly, there was no detected association between cigarette smoke exposure and ARDS among patients with a direct lung injury (i.e. pneumonia, aspiration). This finding is surprising because cigarette smoking is a reported risk factor for several pulmonary infections [3]. As the authors acknowledge, the lack of an association between cigarette smoke and ARDS in direct lung injury may represent selection bias caused by enrolling at ICU and not hospital admission. Hospitalized patients with pneumonia may not be admitted to the ICU unless they develop respiratory failure. Exclusion of patients with milder pneumonia, who may be less likely to smoke, may mask a true association between cigarette smoking and ARDS in this subgroup. This potential selection bias may not be as significant a factor in non-pulmonary sepsis if this group was more likely to be admitted to the ICU regardless of the development of ARDS. Alternatively, the authors' findings may represent the increasingly recognized heterogeneity of ARDS, whereby different phenotypes of the syndrome possess distinct risk factors.

The findings of association between cigarette smoke exposure and ARDS have two significant potential future impacts on public health. First, cigarette smoke is one of only a few known modifiable risk factors for ARDS. Given the high morbidity and mortality of the syndrome, a strong, reproducible association between smoke exposure and ARDS has significant implications towards tobacco product health policy and estimates of the costs of tobacco use on society. Second, the mechanistic link between cigarette smoke and increased ARDS risk may identify therapeutic targets for future ARDS prevention or treatment trials. Specifically, pharmacologic agents could be developed to reverse the "lung priming" effects of cigarette smoke in smokers at-risk for or who have developed ARDS. These trials could potentially be enhanced by measuring NNAL, or another biomarker of smoke exposure, for inclusion in a "personalized" trial.

Nonetheless, unknowns remain in the link between cigarette smoke exposure and ARDS. Experimental models have demonstrated several mechanisms by which tobacco smoke may prime the lung for the development of lung injury [4-6]. However, the mechanisms at play in human populations at risk for ARDS, such as those with sepsis, remain unknown. In

addition, little is known about other potential environmental risk factors that may similarly prime the lung for injury, such as air pollution. To date, no study has reported an association between components of air pollution, such as particulate matter and ozone, and ARDS; however, air pollution has also been associated with increased pulmonary inflammation, excess reactive oxidant species production, and alveolar capillary barrier dysfunction [14, 15]. Future research should include a broadened focus to environmental and other clinical risk factors that may render the lung more susceptible to injury. With a fuller understanding of the mechanisms by which environmental risk factors such as cigarette smoke increase ARDS risk, the critical care community can work towards therapies to prevent and reverse the detrimental effects in critically ill patients, possibly prior to the development of ARDS.

Acknowledgments

Copyright form disclosures: Dr. Christie provided expert testimony for various law firms (expert testimony on asbestos litigation) and received support for article research from the National Institutes of Health (NIH). His institution received grant support from GlaxoSmithKline (study of ARDS risk factors) and the NIH. Dr. Reilly received support for article research from the NIH. His institution received grant support from the NIH.

References

1. World Health Organization (WHO). Report on the Global Tobacco Epidemic. Geneva: World Health Organization; 2011.
2. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013; 368(4):341–350. [PubMed: 23343063]
3. Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med*. 2004; 164(20):2206–2216. [PubMed: 15534156]
4. Sopori M. Effects of cigarette smoke on the immune system. *Mat Rev Immunol*. 2002; 2(5):372–377.
5. Morrison D, Rahman I, Lannan S, MacNee W. Epithelial permeability, inflammation, and oxidant stress in the air spaces of smokers. *Am J Respir Crit Care Med*. 1999; 159(2):473–479. [PubMed: 9927360]
6. Schweitzer KS, Hatoum H, Brown MB, et al. Mechanisms of lung endothelial barrier disruption induced by cigarette smoke: role of oxidative stress and ceramides. *Am J Physiol Lung Cell Mol Physiol*. 2011; 301(6):L836–846. [PubMed: 21873444]
7. Gajic O, Dabbagh O, Park PK, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med*. 2011; 183(4):462–470. [PubMed: 20802164]
8. Christenson JT, Aeberhard JM, Badel P, et al. Adult respiratory distress syndrome after cardiac surgery. *Cardiovasc Surg*. 1996; 4(1):15–21. [PubMed: 8634840]
9. Calfee CS, Matthay MA, Eisner MD, et al. Active and passive cigarette smoking and acute lung injury after severe blunt trauma. *Am J Respir Crit Care Med*. 2011; 183(12):1660–1665. [PubMed: 21471091]
10. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. *Blood*. 2012; 119(7):1757–1767. [PubMed: 22117051]
11. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med*. 2013; 187(5):527–534. [PubMed: 23306540]
12. Calfee CS, Matthay MA, Kangelaris KN, et al. Cigarette Smoke Exposure and the Acute Respiratory Distress Syndrome. *Crit Care Med*. 2015 in press.
13. Moss M, Bucher B, Moore FA, et al. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA*. 1996; 275(1):50–54. [PubMed: 8531287]

14. Huang W, Wang G, Lu SE, et al. Inflammatory and oxidative stress responses of healthy young adults to changes in air quality during the Beijing Olympics. *Am J Respir Crit Care Med*. 2012; 186(11):1150–1159. [PubMed: 22936356]
15. Que LG, Stiles JV, Sundry JS, Foster WM. Pulmonary function, bronchial reactivity, and epithelial permeability are response phenotypes to ozone and develop differentially in healthy humans. *J Appl Physiol* (1985). 2011; 111(3):679–687. [PubMed: 21700892]