HHS Public Access

Author manuscript

Alcohol Clin Exp Res. Author manuscript; available in PMC 2018 November 24.

Published in final edited form as:

Alcohol Clin Exp Res. 2014 February ; 38(2): 312–315. doi:10.1111/acer.12335.

Chronic alcohol ingestion and predisposition to lung 'cirrhosis'

Jesse Roman, M.D.

Departments of Medicine and Pharmacology & Toxicology, University of Louisville Health Sciences Center and Robley Rex VA Medical Center, Louisville, KY

Evidence for the existence of fermented beverages has been available for as early as the neolithic period (Patrick, 1970) and wine appeared in Egyptian pictographs around 4,000 B.C. (Lucia, 1963). Since then, our ancestors have warned about the detrimental effects of heavy alcohol ingestion and advocated moderation in its consumption. Today, we know that alcohol not only lifts the spirit, but also can lead to dramatic impairments in organ function if consumed in excess. Liver cirrhosis, associated with oxidant stress, inflammation and tissue fibrosis, is perhaps the best known consequence of chronic alcohol abuse (Beier and McClain, 2010), but the pancreas, stomach, heart, brain, and other organs may be affected as well The lung is yet another target for alcohol, but alcohol-related pulmonary changes have traditionally been ascribed to indirect consequences related to the aspiration of gastric contents or immune depression which, in the setting of impaired mucociliary clearance, may promote bacterial infection and sepsis (Molina et al., 2010; Wyatt et al., 2012).

In 1996, however, investigators found that chronic alcohol ingestion is associated with increased incidence of and mortality due to acute lung injury (Moss et al., 1996). Considering that acute lung injury carries a mortality rate of close to 40%, and that it affects an estimated 200,000 individuals annually in the U.S. alone, many of them of young age, the effects of alcohol in the lung became the focus of intense investigation. Rodents fed for 6–8 weeks an alcohol-containing diet showed increased susceptibility to lung injury induced by endotoxemia, thereby providing a suitable animal model for testing the effects of alcohol in lung (Holguin et al., 1998). Using this model, it was demonstrated that chronic exposure to alcohol is associated with profound reductions in glutathione levels in bronchoalveolar lavage fluid suggesting that, as has been found for the liver, alcohol affects the lung by inducing oxidant stress. Amelioration of acute lung injury by pre-treatment of the animals with the anti-oxidants N-acetylcysteine and S-adenosyl-L-methionine further strengthened that idea (Holguin et al., 1998). These observations, conducted over a decade ago, paved the way for subsequent studies designed to explore the defects leading to what is now termed the 'alcoholic lung phenotype' (Joshi and Guidot, 2007). In addition to oxidant stress, this phenotype in rodents is characterized by lung epithelial cell dysfunction (Downs et al., 2013), upregulation of soluble factors and cytokines (Joshi et al., 2005), disruption of normal regulatory signaling pathways (Mitchell et al., 2009), and activation of lung tissue remodeling genes (Roman et al., 2005; Lois et al., 1999). Importantly, similar decrements in glutathione content and activation of tissue remodeling have been documented in the lungs

Corresponding author: Please send comments to: Jesse Roman, MD, Department of Medicine, Ambulatory Care Building, 3rd floor, Jackson Street, Louisville. KY 40202, Tel. 502-852-5241, Fax. 502-852-6233, j.roman@louisville.edu.

of otherwise “healthy” humans chronically exposed to alcohol (Yeh et al., 2007; Burnham et al., 2007). Although the relative contribution of these derangements to the observed susceptibility to lung injury in humans and rodents in the setting of chronic alcohol exposure remains unclear, these studies clearly show that the lung is an important target for chronic alcohol ingestion.

In this issue of the Journal, Sueblinvong and colleagues extend knowledge in this area by studying the effects of chronic alcohol ingestion (20% alcohol in drinking water for 8 weeks) on the development of lung fibrosis in C57BL/6 mice induced by administration of bleomycin; an agent known to induce lung fibrosis in both humans and rodents (Sueblinvong et al., 2013). Administration of bleomycin directly via tracheal instillation or systemic delivery triggers a massive inflammatory response associated with oxidant stress and edema that is most evident a week after the insult (Mouratis and Aidinis, 2011). Afterwards, the inflammatory reaction gives way to excessive deposition of collagen and other connective tissue matrices leading to tissue fibrosis. The investigators found that collagen deposition, based on hydroxyproline content measurements, and histological fibrosis after bleomycin injury increased in the setting of chronic alcohol ingestion, and that this outcome was associated with increased production of activated transforming growth factor-β (TGFβ), a growth factor known for its ability to stimulate fibroproliferation and matrix expression, and increased expression of α-smooth muscle actin, a marker of myofibroblast differentiation. Importantly, and consistent with a role for oxidant stress, the authors found that diet supplementation with S-adenosylmethionine (SAMe), a glutathione precursor, ameliorated the production of TGFβ and the development of fibrosis.

The authors appropriately concluded that chronic alcohol ingestion renders the experimental mouse lung susceptible to fibrosis following bleomycin-induced lung injury. This is reminiscent of prior work demonstrating enhanced airways disease in the setting of chronic alcohol ingestion in the heterotropic tracheal transplantation model, a model of chronic lung rejection also characterized by upregulation of TGFβ as well as intra-airway fibrosis (Mitchell and Guidot, 2007). However, the authors refrain from extrapolating their findings to humans with chronic fibrosing disorders, perhaps considering the lack of strong clinical and epidemiological data linking chronic alcohol ingestion with increased incidence of pulmonary fibrosis. In fact, to date, other than the fibrosis observed in severe cases of acute lung injury in the setting of alcohol abuse, alcohol is not widely considered an etiologic factor in chronic fibrosing disorders such as Idiopathic Pulmonary Fibrosis. Also, it is important to note that although the bleomycin model is one of the best characterized experimental models of lung injury and fibrosis available, it does not entirely resemble the human condition in that it does not duplicate the exact histological pattern of the most common fibrosing lung disorders and it is spontaneously reversible. Importantly, pre-clinical data generated in the bleomycin model have failed to produce a safe and effective anti-fibrosis drug for use in humans (Moeller et al., 2009). These limitations, however, should not detract from the valuable information provided by these new data, which broaden our understanding of alcohol-related lung cellular dysfunction.

Several concepts should be highlighted with regard to this work. The first relates to the role of inflammation. The bleomycin model has been used to study both lung inflammation and

fibrosis since it is characterized by the development of an inflammatory reaction that occurs early (~7 days) followed by a late fibrotic phase. This and related observations support the idea that tissue fibrosis is a consequence of unrelenting inflammation, and that control of the latter would reduce fibrosis (Homer et al., 2011). Since alcohol can induce oxidant stress and stimulate the expression of pro-inflammatory cytokines, among other changes, one could argue that the enhanced fibrosis detected in the setting of chronic alcohol ingestion followed by bleomycin exposure is likely related to increased inflammation. However, the authors conducted most studies at 2 weeks after the injury. Consequently, work will be required to further explore the role of inflammation in alcohol-related bleomcin-induced lung injury.

Another important concept relates to alcohol-induced production of pro-fibrotic growth factors and how they may contribute to the development of disease. The authors documented increased expression of TGFβ and, although its causative role was not proven, intervention with SAMe, which ameliorated the injury, was associated with decreased TGFβ expression. These investigators had previously shown that chronic alcohol ingestion is associated with induction of TGFβ in lung (Bechara et al., 2005). However, alone, this is not associated with injury as traditionally described. Instead, it appears that a second hit is needed, which might result in TGFβ activation and cellular signaling. Others have found that TGFβ activation is dependent on the relative concentration of proteases and the expression of specific integrins on the surface of epithelial cells (Pittet et al., 2001), but the effects of alcohol on these and related pathways awaits further investigation.

The third concept relates to lung tissue remodeling. It has been reported that chronic alcohol ingestion induces activation of tissue remodeling in lung as determined by increased expression of matrix glycoproteins (e.g., fibronectin) and matrix metalloproteinases, collagen fragmentation, and upregulation of pro-fibrotic growth factors like TGFβ (Roman et al., 2005; Lois et al., 1999; Burnham et al., 2007; Bechara et al., 2005). Interestingly, however, this is not associated with overt alterations in lung architecture. Thus, alcohol results in relative alterations in the composition of the matrix and perhaps the production of inactive growth factors and proteases that can be activated after a second hit. This ‘pro-fibrotic’ phenotype may predispose the lung to maladaptive repair after injury, but this requires further investigation. Equally important is to identify the factors that oppose these events to prevent disease in the uninjured host.

A forth concept of interest relates to epithelial cell dysfunction. The importance of epithelial cell function is highlighted by prior work showing that chronic alcohol ingestion is associated with impairment in alveolar epithelial cell function (Downs et al., 2013; Brown et al., 2007). Interestingly, epithelial cell dysfunction has also been implicated in the pathogenesis of fibrosing lung disorders; epithelial cell dysfunction is considered a driver of tissue fibrosis through the production of pro-fibrotic growth factors, epithelial-mesenchymal transformation, and endoplasmic reticulum stress, among other mechanisms (Selman and Pardo, 2006).

The final concept relates to the role of oxidant stress. As described by the authors, alcohol is well known to promote oxidant stress, which has long been considered an important driver

of liver cirrhosis, and this is known to be involved in the development of the alcoholic lung phenotype (Joshi and Guidot, 2007). Similarly, oxidant stress has been implicated in the pathophysiology of acute lung injury and chronic fibrosing lung disorders but, even though anti-oxidants may someday be proven to be beneficial in the management of these disorders (Kinnula et al., 2005), currently available information does not support this and their use remains controversial.

In summary, the article by Sueblinvong and colleagues further emphasizes the lung as an important target for alcohol and points to epithelial cell dysfunction, TGFβ overproduction, and oxidant stress as key players responsible for its effects. This work reminds us of a report by Sir Dominic John Corrigan published in the early 1800s where he coined the term ‘lung cirrhosis’ while describing 5 cases of lung fibrosis (Corrigan, 1838). His intention was not to link alcohol ingestion and pulmonary fibrosis, but to highlight the similarities observed in fibrotic lung tissues and cirrhotic livers. Interestingly, however, a mechanistic link between chronic alcohol ingestion and lung dysrepair after injury has now emerged. Clearly, alcohol alone does not lead to lung fibrosis. Instead, it appears to trigger alterations in lung cell functions that might render the host susceptible to maladaptive repair after injury and lead to tissue fibrosis in chronic lung disorders and in some cases of severe acute lung injury. Considering that the etiology of Idiopathic Pulmonary Fibrosis and related chronic fibrosing lung disorders remains unelucidated, identifying factors capable of influencing tissue disrepair after injury might lead to new insights into the pathogenesis of these conditions. Furthermore, learning more about how specialized liver and lung cells recognize alcohol might unveil new potential targets for intervention. Undoubtedly, rodent models of chronic alcohol ingestion and lung injury such as the one reported by Sueblinvong and co-authors have helped advance a poorly unexplored area of investigation, but translational studies in patients are desperately needed to evaluate the implications of this work to the human condition.

ACKNOWLEGEMENT

The author thanks Dr. Rafael L. Perez for reviewing and commenting on the manuscript. This work was supported by grant AA019953 from the National Institutes of Health.

REFERENCES

Bechara RI, Pelaez Z, Palacio A, Joshi PC, Hart CM, Brown LA, Raynor R, Guidot DM (2005) Angiotensin II mediates glutathione depletion, transforming growth factor β1 expression, and epithelial dysfunction in the alcoholic rat lung. Am J Physiol Lung Cell Mol Physiol 289:L363–L370. [PubMed: 15908476]

Beier JI, McClain CJ (2010) Mechanisms and cell signaling in alcoholic liver disease. Biol Chem 391:1249–1264. [PubMed: 20868231]

Brown LA, Ritzenthaler JD, Guidot DM, Roman (2007) Alveolar type II cells from ethanol-fed rats produce a fibronectin-enriched extracellular matrix that promotes monocyte activation. Alcohol 41:317–324. [PubMed: 17889308]

Burnham EL, Moss M, Ritzenthaler JD, Roman J (2007) Increased fibronectin expression in lung in the setting of chronic alcohol abuse. Alcohol Clin Exp Res 31:675–683 [PubMed: 17374047]

Corrigan DJ (1838) On cirrhosis of the lung. Dublin J Med Sci 13:266–286

Downs CA, Trac D, Brewer EM, Brown LA, Helms MN (2013) Chronic alcohol ingestion changes the landscape of the alveolar epithelium. Biomed Res Int 2013;2013:470217 doi: 10.1155/2013/470217. [PubMed: 23509726]

Holguin F, Moss I, Brown LA, Guidot DM (1998) Chronic ethanol ingestion impairs alveolar type II cell glutathione homeostasis and function and predisposes to endotoxin-mediated acute edematous lung injury in rats. J Clin Invest 101:761–768. [PubMed: 9466970]

Homer RJ, Elias JA, Lee CG, Herzog E (2011) Modern concepts on the role of inflammation in pulmonary fibrosis. Arch Pathol Lab Med 135:780–788 [PubMed: 21631273]

Joshi PC, Applewhite L, Ritzenthaler JD, Roman J, Fernandez AL, Eaton DC, Brown LA, Guidot DM (2005) Chronic ethanol ingestion in rats decreases granulocyte-macrophage colony-stimulating factor receptor expression and downstream signaling in the alveolar macrophage. J Immunol 175:6837–6845 [PubMed: 16272341]

Joshi PC, Guidot DM (2007) The alcoholic lung: epidemiology, pathophysiology, and potential therapies. Am J Physiol Lung Cell Mol Phy 292:L813–L823

Kinnula VL, Fattman CL, Tan RJ, Oury TD (2005) Oxidative stress in pulmonary fibrosis: a possible role for redox modulatory therapy. Am J Respir Crit Care Med 172:417–422 [PubMed: 15894605]

Lois M, Brown LA, Moss IM, Roman J, Guidot DM (1999) Ethanol ingestion increases activation of matrix metalloproteinases in rat lungs during acute endotoxemia. Am J Respir Crit Care Med 160:1354–1360. [PubMed: 10508828]

Lucia Salvatore P. A History of Wine as Therapy. Philadelphia, PA: J. B. Lippincott, 1963

Mitchell PO, Guidot DM (2007) Alcohol ingestion by donors amplifies experimental airway disease after heterotopic transplantation. Am J Respir Crit Care Med 176:1161–1168 [PubMed: 17717204]

Mitchell PO, Jensen JS, Ritzenthaler JD, Roman J, Pelaez A, Guidot DM (2009) Alcohol primes the airway for increased interleukin-13 signaling. Alcohol Clin Exp Res, 33:505–513 [PubMed: 19120067]

Moeller A, Ask K, Warburton D, Gauldie J, Kolb M (2009) The bleomycin animal model: a useful tool to investigate treatment options for idiopathic pulmonary fibrosis? Int J Biochem Cell Biol 40:362–382

Molina PE, Happel KI, Zhang P, Kolls JK, Nelson S (2010) Focus on: alcohol and the immune system. Alcohol Res Health 33:97–108 [PubMed: 23579940]

Moss M, Bucher B, Moore FA, Moore EE, Parsons EE (1996) The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 275:50–54 [PubMed: 8531287]

Mouratis MA, Aidinis V (2011) Modeling pulmonary fibrosis with bleomycin. Curr Opin Pulm Med 17:355–361 [PubMed: 21832918]

Patrick Charles H. Alcohol, Culture, and Society. Durham, NC: Duke University Press, 1952 Reprint edition by AMS Press, New York, 1970.

Pittet JF, Griffiths MJ, Geiser T, Kaminski N, Dalton SL, Huang X, Brown LA, Gotwals PJ, Koteliansky VE, Matthay MA, Sheppard D (2001) TGF-beta is a critical mediator of acute lung injury. J Clin Invest 107:1537–1544 [PubMed: 11413161]

Roman J, Ritzenthaler JD, Bechara R, Brown LA, Guidot D (2005) Ethanol stimulates the expression of fibronectin in lung fibroblasts via kinase-dependent signals that activate CREB. Am J Physiol Lung Cell Mol Physiol 288:L975–987 [PubMed: 15653713]

Selman M, Pardo A (2006) Role of epithelial cells in idiopathic pulmonary fibrosis: from innocent targets to serial killers. Proc Am Thorac Soc 3:364–372 [PubMed: 16738202]

Sueblinvong V, Kerchberger VE, Saghafi R, Mills ST, Fan X, Guidot DM (2013) Chronic alcohol ingestion primes the lung for bleomycin-induced fibrosis in mice. Alcoholism: Clin Exp Res

Wyatt TA, Sisson JH, Allen-Gipson DS, McCaskill ML, Boten JA, DeVasure JM, Bailey KL, Poole JA (2012) Co-exposure to cigarette smoke and alcohol decreases airway epithelial cell cilia beating in a protein kinase Cε-dependent manner. Am J Pathol 181:431–440. [PubMed: 22677421]

Yeh MY, Burnham EL, Moss M, Brown LA (2007) Chronic alcoholism alters systemic and pulmonary glutathione redox status. Am J Respir Crit Care Med 176:270–276. [PubMed: 17507544]