

Chronic alcohol abuse and its impact on ARDS

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SUMMARY. Alcohol abuse is a comorbid variable that independently increases by about 3-4 times the incidence and severity of acute respiratory distress syndrome (ARDS) in patients at risk. Chronic overconsumption of alcohol causes oxidative stress in the lungs through its metabolism, and diminishes the synthesis and utilization of glutathione (GSH), which is a major antioxidant, resulting in impairment of the antioxidant ability of cells. The decreased concentration of GSH in the lungs leads to a variety of lung changes, including decrease in alveolar liquid clearance and increased protein leak across the alveolar epithelium, overexpression of transforming growth factor- β 1, depression of the synthesis and secretion of surfactant phospholipids by type II alveolar epithelial cells, increased apoptosis of alveolar macrophages and loss of their phagocytic ability, and dramatic alterations in connective tissue remodelling. GSH replacement by the administration of GSH precursors such as N-acetylcysteine and procysteine has been demonstrated to minimize alcohol induced injuries. More detailed studies are needed to define the mechanisms by which alcohol abuse renders the lungs susceptible to acute lung injury, in order for more specific therapeutic strategies to be developed. *Pneumon 2008; 21(4):321–326*

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome common among both medical and surgical patients, with an annual incidence in the US of 75 per 100,000. The clinical disorders commonly associated with ARDS can be divided into those leading to direct injury to the lung and those that cause indirect lung injury in the setting of a systemic process¹. Although the mechanisms responsible for the development of ARDS in patients at risk remain unclear, alcohol abuse has been shown to be an important independent variable which increases both the risk of developing ARDS, by as much as 3-4 fold, and also its severity².

Greece has been ranked 17th in the world for overconsumption of alcohol and its harmful consequences³. In the study of Moussa et al it was found that 31.8% of the Hellenic Navy training conscripts were heavy alcohol drinkers, which supports the current view that there is a trend in the Greek

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youth towards overconsumption of alcohol. This is an important finding because if the alcohol abuse can be detected and modified at an early stage, then alcohol related problems may be prevented⁴.

EPIDEMIOLOGICAL DATA CONCERNING THE RELATIONSHIP BETWEEN ALCOHOL AND ARDS

Alcohol overconsumption and ARDS were shown to be associated for the first time by Moss and his colleagues in a retrospective study on critically ill patients, in which it was found that a prior history of alcohol abuse was associated with an increase in both the incidence and the severity of ARDS (43%). Among the group of patients who developed ARDS, the in-hospital mortality was 65% in chronic alcoholics compared with 36% for non alcoholics^{5,6}.

Similar effects have been observed in patients with non-small cell lung cancer after pulmonary resection. The incidence of chronic alcohol overconsumption among patients who developed acute lung injury (ALI) following the resection was 43% compared with 7% in patients without ALI⁷. Trauma patients with a history of alcohol abuse had a higher incidence of respiratory complications⁸.

Alcohol ingestion not only is an independent risk factor for ARDS development among predisposed patients, but it also increases the incidence and the severity of multiple organ failure. In a multicentre study on patients with septic shock, the severity of organ dysfunction was estimated, using daily SOFA scores. After adjustment for other confounding factors such as gender, age and source of infection, it was found that patients with a history of alcohol abuse had higher SOFA scores than those without⁹.

MECHANISMS OF LUNG INJURY

The pathophysiology of ARDS involves multiple complex pathways and mechanisms, including the production of oxygen radicals by stimulated neutrophils and macrophages, resulting in oxidative stress¹. Alcohol metabolism in the lung through the cytochrome p450 leads to acetaldehyde production¹⁰, which in turn causes oxidative stress by oxygen radical generation, lipid peroxidation and decreased antioxidant activity¹¹.

The role of glutathione

Glutathione (GSH) is the major antioxidant for the detoxification of endogenous or exogenous oxidant radicals by inactivation, conjugation and excretion. As a result, it controls the inflammatory cascade and protects the cells¹². It is synthesized in the liver predominantly, and the lung cannot synthesize GSH de novo. Type II alveolar epithelial cells import GSH from the plasma and concentrate it intracellularly in the mitochondria, and the epithelial lining fluid (ELF). Under normal conditions, the concentration of GSH in the ELF is greater than 400μM, which is several hundred times higher than that in the plasma¹³.

Chronic ethanol ingestion diminishes GSH synthesis and utilization by different enzymes. Studies on rat models showed that ethanol ingestion dramatically decreased GSH levels in the lung tissue, the alveolar ELF and the mitochondrial pools of type II alveolar epithelial cells^{14,15}. In otherwise healthy alcohol-dependent individuals, the GSH concentration in the ELF was decreased by approximately 80% compared with that in subjects without a history of alcohol abuse. Apart from the decreased levels, a large part of the GSH was found to be in the oxidized state (9.8% compared with 2.8% in non-abusers, which suggests increased utilization of GSH)¹⁶. As a consequence, the antioxidant ability of the cells is impaired and the accumulation of reactive oxygen species leads to chronic oxidative stress, which renders cells more susceptible to other toxic agents. In the rat model the incidence of acute lung injury was decreased by GSH supplementation prior to endotoxin administration. This indicates that the basic mechanism of acute lung injury in alcoholics is mediated

TABLE 1. Mechanisms of pulmonary injury following chronic alcohol ingestion

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- Decreased production and use of glutathione (GSH)
 - Impaired alveolar-capillary permeability
 - Increased apoptosis of type II alveolar epithelial cells
 - Increased expression of transforming growth factor-β1 (TGF-β1)
 - Increased levels of angiotensin II
 - Decreased production and activity of surfactant
 - Increased apoptosis of alveolar macrophages
 - Increased NO production and oxidative stress
 - Alteration in the composition of the pulmonary extracellular matrix
-

through GSH depletion¹⁵.

The cause of decreased GSH concentration in alveolar ELF in the case of excessive alcohol intake is multifactorial. With chronic alcohol abuse, hepatic GSH synthesis is decreased even in the absence of cirrhosis. Additionally the enzymes that use GSH for peroxide detoxification (GSH peroxidase and GSH S-transferase) are also decreased¹¹. As mentioned above, the lungs cannot synthesize GSH and must import it from plasma. In this way decreased pulmonary GSH concentration is indicative of diminished plasma concentration¹⁷, which results in impairment of alveolar epithelial cell function.

Dysfunction of the alveolar barrier

One of the most important functions of the alveolar epithelial cells is their ability to form a tight barrier, which is necessary for the normal function of alveoli. In the case of alcohol abuse this ability is lost¹⁸. The monolayer derived from type II cells which were isolated from ethanol-fed rats had a greater macromolecule leak than that from control-fed rats. This abnormality was associated with decreased alveolar liquid clearance and increased protein leak across the alveolar epithelium. When ethanol-fed rats had their diet supplemented with procysteine, a precursor of GSH, they had the same degree of protein leak as control-fed rats, and their type II alveolar cells formed a tighter monolayer¹⁹.

Studies on the effects of alcohol abuse on pulmonary alveolar-capillary permeability in humans suggest a subclinical defect in alveolar epithelial barrier permeability. A twofold increase in protein concentration was observed in the fluid lining the alveolar space of individuals with alcohol abuse compared with control subjects without a history of alcohol abuse¹⁶. In a study in which the radioaerosol ^{99m}Tc-DTPA was delivered via nebulization in individuals with a history of alcohol abuse, it was found that the half-life of ^{99m}Tc-DTPA was significantly shorter, indicating increased alveolar-capillary permeability²⁰.

However, the fact that otherwise healthy alcoholic humans do not have pulmonary oedema under normal conditions is due to increased expression of Na-K ATPase, which is located in the apical aspect of epithelial cells and is responsible for the active transport of sodium and water from the alveolar space²¹.

In acute lung injury the epithelial surface is denuded. The key to repair of the alveoli is the proliferation and differentiation of alveolar type II cells into gas-exchanging type I cells²². When GSH availability in the mitochondria of those cells is decreased, type II alveolar epithelial

cells are sensitized to inflammatory mediator-induced apoptosis in vitro and in vivo, and specifically to tumour necrosis factor (TNF- α) which is a major inflammatory mediator²³. If repair by type II alveolar cells is delayed, injury will be exacerbated through continued alveolar leak, continued neutrophil and fibroblast migration and activation, and accelerated collagen deposition by proliferating fibroblasts. Finally, all of these mechanisms culminate in increased mortality¹⁵.

The role of transforming growth factor- β 1 (TGF- β 1) and angiotensin II

Bechara et al suggest another mechanism for alcohol-induced increased alveoli permeability due to low levels of GSH in the alveoli. GSH deficiency induces increased expression of transforming growth factor- β 1 (TGF- β 1)²⁴. This factor is a cytokine which mediates in alveolar epithelial barrier dysfunction in the alcoholic lung during lung injury²⁵. Chronic alcohol ingestion increases the expression of TGF- β 1; the majority of TGF- β 1 protein is in the latent form, but can be activated in the alveolar air space during endotoxaemia²⁴.

The increased expression of TGF- β 1 and diminished GSH concentration in the lung tissue in alcohol abuse are due to angiotensin II²⁴, through its receptors on type II alveolar epithelial cells²⁶. It is already known that chronic ethanol ingestion increases plasma levels of angiotensin II²⁷ through activation of the renin-angiotensin system, which could explain the association between alcohol abuse and hypertension observed in alcoholics²⁸. One potential mechanism for this is direct conversion of angiotensinogen to angiotensin I by metabolites of ethanol (i.e., acetaldehyde)²⁹. In rats the administration of angiotensin-converting enzyme inhibitors maintained GSH levels within the alveolar space of ethanol-fed rats at the same levels as those in control rats. It also prevented excess TGF- β 1 expression in the lung tissue of ethanol-fed rats. In addition, dietary supplement with procysteine normalized TGF- β 1 expression. All these findings suggest that angiotensin II-induced GSH depletion is required for angiotensin II-mediated induction of TGF- β 1²⁴.

Depression of synthesis and dysfunction of surfactant

A further dysfunction of type II alveolar epithelial cells caused by alcohol abuse is the depression of synthesis and secretion of surfactant phospholipids³⁰ and decrease of their ability to maintain surfactant in its active form during conditions of stress, such as sepsis³¹. This dysfunction can

be rescued by the administration of GSH precursors, such as N-acetylcysteine and primarily procysteine, which increase GSH levels in the mitochondrial pool and in this way preserve the amount and function of surfactant in the alveoli³⁰.

Increased macrophage apoptosis

Finally, chronic alcohol abuse results in increased macrophage apoptosis by up to 85%, which can be reversed through the addition of the GSH precursor procysteine. GSH depletion from alveolar macrophages leads macrophages to chronic oxidative stress, and in turn to loss of their phagocytic ability³². This results in defects in lung immunity, with the increased susceptibility of alcoholics to infections³³, and also to decreased clearance of inflammatory cells- mainly neutrophils- that migrate into the airspace during ARDS. All of these effects can further exacerbate lung injury¹.

Increase in NO

The increased expression and activity of NO synthetase and the production of oxygen and nitrate reactive species following chronic ethanol ingestion contribute to the increased oxidative stress in lungs through angiotensin II mechanisms. This oxidative stress "primes" the lung for exaggerated response to inflammatory insults, and subsequently leads to further increase of oxidative stress. The administration of ACE inhibitors can inhibit this mechanism, adding a target for the prevention and treatment of lung injury that develops in the event of chronic alcohol ingestion³⁴.

The impact of alcohol on lung remodelling after lung injury

Every acute or chronic lung injury is associated with dramatic alterations in connective tissue remodelling. The control of connective tissue remodelling is very important since changes in this process lead to alterations in lung structure, with subsequent effects on disease outcome³⁵. As the newly deposited extracellular matrix interacts with lung cells, any alterations in its composition may influence cellular functions such as migration, adhesion, proliferation, differentiation and cytokine expression³⁶.

Alcohol can activate connective tissue remodelling by altering the content and composition of the pulmonary extracellular matrix. It is possible that this altered matrix, through its interaction with lung cells, contributes to the susceptibility to acute lung injury³⁷, a theory which

derives support from the similar action of alcohol and its metabolite-acetaldehyde on the liver, where increased deposition of the extracellular matrix glycoprotein fibronectin in the perivenular areas is observed³⁸. A study was therefore made of whether chronic ethanol ingestion results in activation of lung tissue remodelling similar to that demonstrated in the liver. It was found that rats fed with ethanol for 6 weeks showed: 1) increased expression in the lung of the pro-fibrotic molecule TGF- β 1, which participates in lung tissue remodelling after injury, and increases the permeability of alveolar epithelium, 2) increased expression and deposition of fibronectin, which is an extracellular matrix component capable of stimulating the proliferation of fibroblasts and the production of proinflammatory cytokines³⁶, and 3) increased activity of metalloproteinases-2 and -9, which are matrix-degrading enzymes^{37,39,40}.

Although tissue remodelling is considered to be a late consequence of the inflammatory response after lung injury, recent evidence suggests that it is activated very early after injury⁴¹. Considering that lung injury induced by alcohol can occur in the absence of clinical expression, early detection may lead to the identification of subjects with increased susceptibility to the development of acute lung injury⁴².

CONCLUSIONS

In conclusion, alcohol abuse is a comorbid variable that independently increases the incidence and severity of ARDS in patients at risk. The basic mechanisms are decrease in the availability of the antioxidant GSH and alteration in the lung tissue remodelling after lung injury. GSH replacement has already been demonstrated to prevent or at least minimize alcohol induced lung injury, particularly in combination with agents capable of controlling tissue remodelling. More detailed studies are needed to define the mechanisms by which alcohol abuse renders the lungs susceptible to acute lung injury, in order for more specific therapeutic strategies to be developed.

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