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The alcoholic lung disease: historical background and clinical features

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Summary. *The purpose of this review article is to prove the damage that alcohol causes to the respiratory system. We will make a brief review of alcohols history in the course of the centuries till nowadays. The problem of addiction to alcohol (alcoholism) will be examined for several countries.*

Alcohol's metabolism is another topic to be discussed parallel to its pharmacological action. In addition, alcohol's impact on the respiratory system varies from damaging the mucociliary system to the regulation of breathing and from the sleep apnea syndrome to diffusion disorders. "Alcoholic lung disease" constitutes a syndrome despite the fact that the damage of the lung due to concurrent smoking and drug use is often indistinguishable.

Introduction

Despite the fact that alcoholic beverages actually date back to Noah's era, alcohol becomes known after the discovery of distillery in the 12th century. Although it was known that during the boiling of wine it was produced an ethereal, inebriant, and flammable substance, its collection was carried out for the first time through the method of distillation – in a mixture of water – and it was called Aqua ardens (burning water) or even Aqua vitae (water of life), due to its multiple therapeutic properties. Later on, the product of the distillation of wine was named spiritus vini, meaning the "spirit of wine" or "wine spirit," while the residue of the distillation was called "phlegm." These terms were used later on to describe certain types of people, such as the "bel esprit" and the "phlegmatic" persons.

The product of the wine distillation was first called "alcohol" by Paracelsus, the Swiss physician, philosopher, and alchemist (1493–1541), from the Arabic word "alkohol" that meant "bloom" or the thinnest component of wine. However, alcohol was prepared in its clean form – without water – in 1796, through a special distillation (calcined potash or calcined lime).

The term "alcohol" is used today on the one hand in its general meaning to describe any chemical substance that derives from hydrocarbon through the replacement of the H^+ atoms by the radical OH^-, on the other hand in the special meaning, like a synonym to ethylic alcohol or ethanol, whose chemical formula is CH_3CH_2OH or C_2H_5OH. In this paper, the term alcohol is used in the latter meaning.

Alcohol is used since antiquity both as therapeutic and in order to cause inebriety. Nevertheless, the washing of wounds with wine has been known since the era of Hippocrates, as also the divinization of grapevine and wine by Ancient Greeks in the face of god Dionysus is known; or even Noah's getting drunk with wine after the cataclysm (Scripture, 1960), maybe to celebrate in this way the fact that he survived.

The reasonable daily consumption of light alcoholic beverages – such as wine (up to 300 g) and beer (up to 750 g) – does not seem to harm the human organism; not at least in an apparent way. However, chronic consumption of dense alcoholic beverages – such as brandy, ouzo, whiskey, vodka, etc. – at large quantities leads to addiction to alcohol – alcoholism – and has all the known and many probably still unknown consequences. More specifically, although the impact of alcohol on the central nervous system has been studied since the previous century, its influence on the respiratory system has recently become the object of serious studies.

The purpose of this manuscript is exactly to review the knowledge acquired in relation to the "alcoholic

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lung disease," in the framework of a more general consideration of the effects that alcohol has on the human organism.

Addiction to alcohol (alcoholism)

According to the World Health Organization, alcohol is among the addiction-causing substances and in fact among the ones that simultaneously cause physical dependence and psychic dependence, as also the opiates, the antagonist substances of opiates, the barbiturates, and the derivatives of amphetamines do. However, those who drink large quantities of alcoholic beverages do not always develop addiction to alcohol. Thus, drinkers can be divided into two groups. Those who drink periodically and can stop drinking alcoholic beverages without developing a deprivation syndrome and those who, after discontinuing drinking, present tremulousness, hallucinosis, epilepsy or rum fits, or even delirium tremens. The occurrence of such symptoms is related more to the changes of the alcohol level in blood that to its absolute value.

Alcoholism is common all around the world and in all social classes (1). However, it is more frequently met in cities and in men. In the USA, more than 10 million people have addiction to alcohol (2), while 50% of the fatal car accidents are related to the high level of alcohol in blood (3). However, alcohol consumption in the USA was 6.3 liters per person per year in 1971, while in many European countries it exceeded 10 liters (11.4 liters in Austria, 12.0 in Spain, 12.3 in Germany, 13.9 in Italy, and 16.7 in France).

Among the alcoholic beverages, those that contain the lowest rate of alcohol are beer (3–6%) and wine (8–22%), followed by ouzo, grape marc, mastic (35–48%) and finally brandy, gin, rum, whiskey, and vodka (40–55%).

During the last few years, it is noted a significant rise of alcoholism and yet among women and young people (4). For example, petty offences due to alcohol abuse in Great Britain were 71 167 for men and 4377 for women in 1971; meaning women were to be blamed for 5.8% of the offences committed due to alcohol. In 1976, this rate ascended to 8.6%. During the last decade, it is also observed alcohol over consumption in adolescents, while the first contact with alcohol is sometimes seen in preschool children (5, 6). Finally, during the last years, addiction to alcohol seems to be high among doctors (7); for example, estimation is that alcoholic doctors in the USA vary from 13 600 to 22 600, while according to (8), 1 out of 8 doctors in Georgia was, is or will become an alcoholic. The main reasons of alcoholism are social problems, anxiety, and withdrawal from the environment and sleep disorders (insomnia).

Alcohol abuse is related to a series of pathological conditions – more than 100 in total – that concern the tissues and the body organs and mainly the liver. These basic pathological conditions are malnutrition and obesity, fatty liver, alcoholic hepatitis, and liver cirrhosis (9–11), esophagitis (12), gastritis (13), enterocolitis (14), pancreatitis (15), liver cancer, cardiomyopathy (16), pulmonary infections (17, 18), polyneuritis, myelitis, encephalitis and delirium tremens (19), some blood diseases (20), etc. Mortality in alcoholics is increased, although, according to other statistics, those who drink up to 35 g alcohol per day present lower mortality than those who do not drink at all. This means that it is suggested – without it being globally accepted – that medium use of alcohol protects against cardiovascular diseases and reduces death rates due to these diseases (21).

An alcoholic has the figure of a prematurely old person, being eristic, he/she neglects the family and work, while he/she often experiences discomfort in the peptic system (burning, constipation, diarrhea) tremor of the extremes, sleep disorders, sexual impotence, etc. Whereas an alcohol's quantity of 100–150 g causes the death of nonaddicted persons, the alcoholics tolerate quantities up to 500–600 g daily. This is due to the fact that alcoholics metabolize alcohol faster, and their CNS does not become addicted. However, not all tissues become alcohol addicted. For example, liver and stomach mucosa not only do not get addicted, but they also develop progressive degeneration.

The therapeutic use of alcohol

Alcohol always was and still is one of the most valuable medicaments, with multiple applications both in therapeutics and pharmacology. In therapeutics, it has been used for massage, compresses, instillations, infusions, gargling, inhalations, or even for external use in the form of solutions, extracts, tinctures, elixirs, medical wines and acids, while in pharmacology it has registered the highest consumption, second to water.

The external/local use of alcohol was advised for the following reasons:

- For refrigeration or provocation of congestion epidermically and the prevention of decubitus;
- For perspiration of the extremes and generally of the body;
- For preparation of the breast nipples for lactation;
- For antiseptic purposes and disinfection of wounds,

bites and tools.
- For retention of capillary hemorrhages, etc;

The focal use of alcohol was done in the following forms:
- Gargles, in cases of pharyngitis, tonsillitis, gingival hemorrhage, tooth pain, etc;
- Instillations in cases of hemorrhage of the nose, the vagina, and the uterus;
- Infusions, in syringes;
- Enemas, in case of death trance;
- Inhalations, to stimulate respiration, etc.

The external use of alcohol was advised for the following reasons:
- As an analeptic-analgesic, in conditions of weakness, hemorrhages, poisoning, faints, etc;
- As antifebrile, in cases of typhus, smallpox, scarlatina, puerperal fever, rheumatisms, etc;
- As anesthetic-anticonvulsive, in surgical operations, titanic spasms;
- As sleeping draught in cases of insomnia;
- In diseases of the peptic system (vomits, diarrheas, colitis), but also as appetite stimulants for indigestions;
- In diseases of the respiratory system (bronchial asthma, abscesses, pneumonias, tuberculosis, hemoptysis);
- In diseases of the circulatory system (heart failure, faints);
- In injections for the treatment of hemorrhoids, etc.

Nowadays, alcohol is mainly used as antiseptic and as a solution of other medicaments. It is also used for skin massages and injection in the gasserian ganglion for trigeminal neuralgia. In diseases of the respiratory system, some use it – in the form of aerosol – as mucolytic as well as in order to reduce the surface tension of the tracheobronchial secretions (22).

The metabolism of alcohol

People that do not drink alcoholic beverages have alcohol in their blood at a rate of 0.002%. This alcohol is normally produced in the intestine by bacteria, such as the *Escherichia coli*, *Lactobacillus coli*, etc. (23). The destruction of the intestinal flora by antibiotics significantly reduces the indigenous alcohol in blood.

The alcohol consumed is absorbed without any change by the stomach (20%), the duodenum, and the small intestine (75%), while it is basically metabolized in the liver but also in other tissues of the body, such as the mucosa of the gastrointestinal system, the lungs, the kidneys, the brain, the spleen, etc. In total, 90–95% of the alcohol consumed is metabolized in the body, while 2–10% is eliminated without any changes through the lungs, the kidneys or even the bile, the sweat, the sputum, tears, and milk.

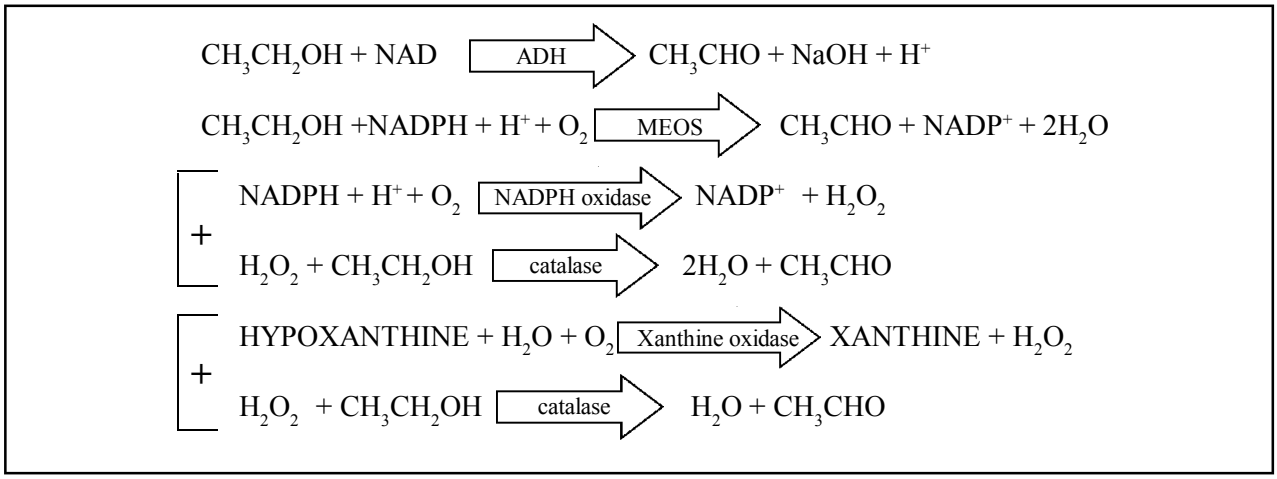
The alcohol oxidation ability is not an exclusive feature of human beings, but also of all other mammals, as well as of the insects and many plants and microorganisms. This effect is interpreted as an attempt to oxidize alcohol, which is randomly got by nature – mainly the flowers and fruits – through the alcoholic fermentation. It is characteristically referred that some species of finches (fire finch, grosbeak weaver), which are fed in autumn by the flowers of the willow trees, are possible to present even symptoms of inebriety. Nevertheless, also fish have an oxidizing system that quickly splits alcohol, even if fish have nothing to do with alcohol.

The initial metabolic process that alcohol goes under when reaching the liver is oxidation into acetaldehyde that is immediately metabolized into acetic acid. A small quantity of acetaldehyde enters the circulatory system and is metabolized in blood, muscles, and other tissues of the body. The acetic acid is also metabolized outside the liver into CO_2 and H_2O. Only a small quantity of the acetic acid is esterified in the liver, into acetyl-coenzyme A, which is either oxidized in the cycle of the citric acid or is incorporated into other compounds. Alcohol, labeled with radioactive carbon, is detected in ketonic bodies, fatty acids, proteins, glycerin, and glycogen.

Alcohol oxidation to acetaldehyde is mainly done by the enzyme called alcoholic dehydrogenase (ADH), while the acetaldehyde is converted into acetic acid through the enzyme aldehyde dehydrogenase, without any remarkable rise of O_2 consumption by the liver (small rise with small quantity of alcohol and reduction at large quantities). During the formation of acetaldehyde, hydrogen is transferred from alcohol to the coenzyme nicotinamide-adenine-dinucleotide (or NAD), which is converted into its reduced type, NADH NAD+2H±=NADH+H^+.

Alcohol dehydrogenase is found in small quantity in the fetal liver; however, its activity increases parallel to the age, to reach after 5 years the activity of an adult. Despite the fact that there can be great individual differences, the liver disposes of this enzyme in the double quantity of that required for the oxidation of a large quantity of alcohol that it could eliminate. Consequently, alcohol's oxidation speed does not depend as much on the quantity of the alcohol dehydrogenase as on other factors, such as the lack of NAD or the surplus of NADH. The ratio NAD:NADH depends on the process of phosphorylation in the liver; it is disturbed during the alcohol oxidation and it finally

Table. **Alcohol oxidation systems in the liver**



affects the metabolism of other substances. Apart from the alcohol oxidation with alcohol dehydrogenase, which is carried out with the protoplasm substance of the liver cells (cytosol), there are also other oxidation systems in the liver, such as the microsomal ethanol oxidation system (MEOS) – in the microsomes of the liver cells – the enzyme catalase, and a system that produces H_2O_2 (Table).

Alcohol oxidation with:

A. Alcohol dehydrogenase (ADH), nicotinamide-adenine-dinucleotide (NAD) and NAD reduced form (NADH);
B. The hepatic microsomal ethanol oxidation system (MEOS), phosphoric nicotinamide-adenine-dinucleotide of NAD reduced type (NADH) and the phosphoric nicotinamide-adenine-dinucleotide (NADP);
C. The combination of NADPH oxidase and catalysis;
D. The combination of xanthinoxidase and catalase.

During alcohol oxidation it is produced a significant amount of heat and actually 7 calories/g, while – as it is known burning produces 9.3 calories/g and hydrocarbon burning and proteins 4.2 calories/g. Thus, alcoholic beverages, which apart from alcohol also contain small quantities of hydrocarbons and other substances, cover a valuable part of calorific needs of humans, which in France are estimated up to 10% and in Germany 8%. However, in no case alcoholic drinks – even at large quantities – can cover the needs of the body in calorific substances, since their content in proteins and vitamins and inorganic salts is very low. The constant intake of large amounts of alcohol not only leads to addiction of the CNS, but also to its faster dialysis of the blood. Thus, while the metabolism rate of alcohol, in nonaddicted persons, is 7 mL – 20 m per hour – usually 8 mL/hour or 192 mL/day – in alcoholics it reaches 25 mL/hour.

Alcohol consumption develops several metabolic disorders, the main of which are:

- Hypergalacticemia and hyperuricemia;
- Incremented production of lipids and lipoproteins;
- Reduced oxidation of lipids and steatosis;
- Reduced gluconeogenesis and hypoglycemia;
- Reduction of conversion of the free fatty acids.

Finally, alcohol influences metabolism and the activity of many medicaments (cumulative or synergic effects), just like many drugs influence the metabolism of alcohol (Table 1).

Alcohol's pharmacology

Alcohol, following its absorption in the gastrointestinal system, is distributed in all fluids and tissues of the body, extracellular and intracellular, depending on their content of water. If the concentration of alcohol in the blood is considered equal to the unit (1), then its concentration in the cerebrospinal fluid is 1.15, in the urine and the sputum – 1.3, and in the brain/kidneys/ liver – 0.80–0.83. The highest concentration of alcohol in the blood is achieved after 30–120 minutes following oral intake, depending on the quantity and quality of nutrition (food rich in fat delays the absorption of alcohol). Its elimination from blood lasts 8–10 hours.

Alcohol, in the form of steam, is absorbed also by the respiratory system and actually at quantities that may even cause acute poisoning. As it is already mentioned, the alcohol absorbed is metabolized at a rate of 90–95%, while the rest is eliminated in its original form via the several excretion organs and mainly via the lungs and the kidneys. Lungs, apart from the

passive excretion of alcohol through respiration, have also the ability to metabolize and convert it into fatty acids (24), while at the same time they remove the products of alcohol from the blood, such as acetaldehyde and CO_2. The elimination rate of alcohol from the blood in a normal person is approximately 15 mg/100 mL/hour.

The most significant pharmacological activity of alcohol is paresis of the upper cerebral centers, the cortex, which starts at a concentration of 0.05% in the blood, progresses to coma at a concentration of 0.4%, and ends up to death at the level of 0.6%. An alcohol concentration in the blood between 0.05–0.1% may have no symptoms. However, the concentration of more than 0.1% creates excitation, euphoria, palaver, medium mydriasis, nystagmus, dysarthria, and ataxia; concentration more than 0.15% causes symptoms of poisoning, with acute excitation, noisy expressions, aggressiveness, greater mydriasis and dysarthria, same level of nystagmus, strabismus, and greater ataxia, while when the levels reach more than 0.2%, this causes instability in walking and fall. Alcohol concentration of 0.25% causes sleep, 0.3% – stupor, 0.4% – coma, and 0.6% – death due to respiration paralysis.

Second to the CNS, the main activity of alcohol concerns metabolism – as mentioned above – and leads to obesity but also to vitamin deficiency or even emaciation. Other pharmacological properties of the alcohol contain:

For the circulatory system: peripheral vasodilation, tachycardia or bradycardia, hypertension or hypotension, depending on the alcohol dose. A small dose causes tachycardia and hypertensions, while a large quantity – bradycardia and hypotension. The result of the peripheral vasodilation is the loss of heat and the reduction of the body temperature. These two latter facts, according to other researchers, are due to the increase of the blood flow on the skin and not to peripheral vasodilation.

For the respiratory system: the increase of the lungs' ventilation in a small dose and respiration paralysis in case of acute poisoning. For the peptic system: increase of secretions and appetite at concentration up to 20%, while at concentration of 40–60% – acute irritation, burning, vomiting and hemorrhage. For the endocrine glands: reduction of the antidiuretic hormone, thus increase of urination, and increase of the glucocortico-steroid and catecholamines. For the muscular system: increase of the ability for voluntary muscular work – because the feeling of fatigue is reduced – and reduction of the involuntary muscular work (produced by electric stimulation).

Moreover, alcohol suppresses the center of thirst and – in combination to the increased urination – it leads to the dehydration of the body. Finally, alcohol significantly reduces the body's defenses, leading to increase of infections.

Many of the pharmacological properties of alcohol are due not only of the alcohol itself but also to the products of its metabolism and mainly acetaldehyde, which is toxic. Thus, it has been proved that acetaldehyde – on its own or in combination with alcohol – increases the size of respiration, causes vasodilatation, and stimulates the system of the hypothalamus – pituitary gland – of the adrenal glands, while the repression of its metabolism through several drugs, such as disulfiram, metronidazole, quinacrine, sulfonylurea and chloramphenicol, causes headaches, nausea, dyspnea, and hypotension.

Finally, even the acetic acid, the product of the metabolism of acetaldehyde, can cause metabolic disorders, such as the decreased liberation of fatty acids, which is the main source of energy for the peripheral tissues. In the following chapters, there are details about the effects of alcohol on the respiratory system.

Effects of alcohol on the respiratory system

The alcohol that is not metabolized in the liver obligatorily passes through the pulmonary circulation, receiving large quantities of alcohol in the lungs, especially in alcoholic people. Thus, despite the fact that the lungs metabolize and eliminate alcohol and its products from blood (25), the possibility to present organic and functional disorders similar to those of the liver is not excluded.

The existence of a relation between alcoholic and pulmonary diseases has been noted long ago (26). However, the exact effect of alcohol on the lungs of the alcoholics is difficult to assess, since heavy drinkers are at the same time heavy smokers.

Researches that were carried out during the last decades have shown that alcohol has impacts on the respiratory system both directly and indirectly (27). The direct impact of alcohol is related to the defense of the respiratory system, the respiratory function, and some of the nonrespiratory function of the lungs and it is due to either alcohol itself or the products of its metabolism. The indirect impact is related to the collateral circulation, which is created due to the liver damage, and which is caused by alcohol itself.

Effects of alcohol on the mucociliary system and the tracheobronchial secretions

The mucosa of the tracheobronchial tree is covered by the pseudostratified ciliary epithelium, which in humans consists of 9 kinds of epithelial and 2 kinds of migrating cells. The epithelial cells are: the ciliated, the calculus, the serous, the Clara cells, the special type cells, the setaceous, the intermediate, the basal, and the Kulchitsky cells, while the migrating ones are the lymphocytes and the leukocytes.

The free surface of the ciliated cells – meaning the surface towards the lumen of the respiratory tracts – has 150–300 cilia of total length 5–7 m, which move towards the center at a frequency of 160–1500/1 mm and move the tracheobronchial secretions to the trachea. These secretions are mainly produced by the submucosal glands – approximately 6000 on the tracheobronchial tree – and the caliculus cells. The transfer rate of the tracheobronchial mucus (the mucociliary clearance) varies: 13.5–22.3 mm/min during in vivo measurements and 3.1–36.1 mm/min during in vitro measurements.

Alcohol reduces the mucociliary clearance of the respiratory tracts. Experiments that were carried out using an alcohol injection on mice and guinea pigs showed reduction of the clearance of staphylococci from the lungs of these animals (28–31). Moreover, the endoperitoneal infusion of alcohol in cats resulted in a significant reduction of the mucociliary clearance (29). This action of alcohol is respective to its level in blood, which was in general very high (0.45–1.2%) compared to the level that humans tolerate, without developing symptoms of toxicity (0.05–0.1%).

Experiments on rabbits using alcohol steam inhalation showed that the movement of the epithelial cilia of the trachea reduces when the concentration of the alcohol in the inhaled air is greater than 11 000 ppm. Moreover, experiments on cats showed that the movement of cilia and the mucociliary clearance of carbon granules are influenced only at high densities of alcohol in the blood.

The focal application of alcohol – solved at any rate in distilled water – on the cilia causes their standstill for a few seconds. A diagram of alcohol in normal saline and at a concentration up to 15% has minimal impact on the movement of the cilia, while at a concentration of 20%, it causes the immobility of the cilia both in vitro and in vivo in rabbits (30).

Regarding the tracheobronchial secretions, experiments (31) on rabbits showed that alcohol inhalation at a quantity of 1 mL/kg resulted in the reduction of their special weight by 8.7%. Taking into consideration that the respiratory system of the rabbits absorbs 1–2% of the alcohol inhaled, we conclude that out of 1 mL/kg only 0.01–0.02 mL/kg is absorbed. This means that it is a quantity that has no general action, but a local one on the mucosa, resulting in the increase of the soluble mucus of the tracheobronchial secretions. The inhalation of more than 2 mL/kg of alcohol caused an increase of the amount of tracheobronchial secretions on rabbits. The inhalation of a quantity higher than 5 mL/kg – absorption higher than 0.05 mL/kg – had apart from the local, probably also a systematic impact, while the quantity higher than 10 mL/kg caused the raise of the insoluble mucosa but also the death of 14% of the subjects-animals, within 6 hours. Following the administration of a dose of 25 mL/kg, within 6 hours, 25% of the animals died, while a dose of 125 mL/kg killed 33%. In general, half of the lethal dose of alcohol (LD_{50}) for rabbits was 204±24 mL/kg administered by inhalations and 2 mL/kg with intravenous administration. The postmortem studies on the animals showed that following the inhalation of up to 10 mL/kg, there has been a slight hyperergia of the submucosa layer. After the inhalation of 25–125 mL/kg of alcohol, it was noted the dilation of the capillary vessels and veins, edema, granular penetration, and necrosis of the mucosa and the submucosa of the respiratory tracts. The rabbits that survived more than 24 hours after the lethal alcohol dose inhalation, presented atelectasis, which was attributed to the disorder of the surfactant substance (32).

Alcohol reduces the surface tension of the tracheobronchial secretions, and for this reason physicians use it to treat the acute pulmonary edema. Frothy sputum has a surface tension of 60 dynes/cm approximately. Alcohol, depending on its concentration, reduces their surface tension in the following way: 30% solution reduces the sputum surface tension to 32 dynes/cm; 50% solution reduces the sputum surface tension to 28 dynes/cm; 100% solution reduces the sputum surface tension to 22 dynes/cm.

The reduction of the surface tension of the frothy sputum turns them into a thin fluid, facilitating in this way their elimination with cough or aspiration (antifoaming action). Alcohol is used in the treatment of the acute pulmonary edema at a concentration of 30–50%, in the form of aerosol and at a quantity of 5–15 mL. In emergency cases, it is administered O_2 that passes through alcohol or even aerosol of heavy alcohol drinks, such as vodka. The reduction of the surface tension of the tracheobronchial secretions from alcohol is due to the disorder of the surfactant substance, which has half time duration, 12 hours (33).

As a conclusion, we must note that the mucociliary clearance is influenced only when the level of alcohol in the blood is very high. On the contrary, the inhalation of alcohol steams causes vasodilation and hyperemia of the mucus, reduction of the cilia movement, increase of the tracheobronchial secretions, change in their compositions, and changes in the composition of the surfactant substance. The chronic use of alcohol inhalation and especially at large quantities irritates the mucus of the respiratory tracts and causes chronic bronchitis.

Effects of alcohol on the alveolar epithelium

The alveolar epithelium consists of three types of cells: the type I alveolar cells or squamous pulmonary cells, type II alveolar cells or granular pulmonary cells, and the setaceous cells. Type I alveolar cells are epithelial, have small width (0.1–0.3 m) and cover 95–97% of the alveolus wall. Type II alveolar cells are secretive and equal or more than type I cells, but due to their cubic shape and smaller size, they cover less than 5% of the alveolus wall.

Setaceous cells are rare and depend on the setaceous cells of the respiratory tract, while their function is still unknown. A thin layer of alveolar fluid, which comprises two stratums, covers the inner surface of the alveolar epithelium. The stratum, which is located at the bottom, covers the abnormalities existing in inner surface of the alveolar epithelium and consists mainly of a tubular myelin network, while the superficial stratum is probably monomolecular. The tubular myelin made of a lipoprotein skeleton, the surfaces of which are osmophilic and rich in dissaturated phospholipid, dipalmitoyl-lecithin or dipalmitoylphosphatidyl-choline, which is linked to the superficial stratum. Dipalmitoyl-lecithin is the main component of surfactant substance, which regulates the surface tension of the alveoli in any air volume of the lungs, while it is produced and secreted from type II alveolar cells. The origination of the protein-carrying components of the tubular myelin is still unknown (34, 35).

Alcohol, apart from the direct reduction of the surface tension of the tracheobronchial secretions that it causes, also indirectly influences it, by acting on the composition of the dipalmitoyl-lecithin. Experiments on mice showed that alcohol impedes the unification of several structural components of dipalmitoyl-lecithin, such as the palmitic acid and cytidine diphosphocholine (36). However, the extent at which this action of alcohol influences the surface tension of the alveoli in vivo is still unknown.

Effects of alcohol on alveolar macrophages

Alveolar macrophages are phagocytes originating from the bone marrow and are found inside the deep stratum of the alveolar fluid. These cells move free with pseudopodiums under the phospholipid superficial stratum or are periodically linked to the inner surface of the alveolar epithelium. Some of these move towards the mucociliary stratum of the tracheobronchial tree and appear in sputum as coniophages, siderocytes, etc., but they return to the intermediate space – between the alveolus and the capillaries of the pulmonary artery – where they remain or are transferred through the lymph vessels to the cognate lymph nodes (e.g. transfer of carbon granules to the intermediate pulmonary tissue).

The alveolar macrophages have their own phagocytic activity in the alveolar fluid and this is why their vacuoles contain as much tubular myelin as dipalmitoyl-lecithin. This means that these substances originate from the wear and phagocytosis of the surfactant system of the alveolar fluid, without the reverse being excluded, meaning the production of the surfactant substance from the alveolar macrophages (37).

Foreign substances – bacteria – that enter the alveoli are fixed on the alveolar fluid, cause the migration of the alveolar macrophages, get closed in upon them and finally become idle, or get destroyed through several mechanisms. Type I alveolar cells have also the phagocytic ability.

Alcohol, even at small quantities, reduces the clearance of the airways from bacteria (38, 39). This action of alcohol is due to both the reduction of the mobility of the alveolar macrophages and the suppression of their bactericidal property. Alcohol does not seem to influence the ability of the alveolar macrophages to encircle foreign bodies.

The bactericidal ability of the alveolar macrophages mainly depends on the formation of several oxides, such as the peroxide anions, the hydroxyl roots, etc. (40). These oxides get destroyed by bacteria inside the phagosomes through the peroxidation of the lipoids of their membrane. The mother cells are protected against peroxidation through several enzymes, such as catalase. Catalase is abundantly expressed in most phagocytes and it has a double action: the catalytic and the metabolic one in several substances, such as the alcohol. Thus, a possible action of alcohol, which has not been proved yet, is the impact of the peroxidation, which is catalase dependent.

Effects of alcohol on the regulation of respiration

The impact of alcohol on the rate and width of respiration depends not only on its concentration in the blood, but also on many other factors, such as the simultaneous intake of other medicaments, especially narcotics, the coexistence of metabolic and neurological disorders, the complications in the respiratory system (introversion-driven pneumonia), etc.

Experiments on dogs showed that large quantities of alcohol could lead to death due to respiratory insufficiency (41, 42). More specifically, an alcohol concentration in blood ranging between 40 mg/100 mL and 400 mg/100 mL causes reduction in the respiration rate and of the lungs' ventilation, which ends up to apnea at the concentration of 450–760 mg/100 mL. Moreover, the attack with alcohol at the cerebral stem of a cat causes its death due to respiration discontinuance (43).

Death due to respiratory insufficiency is also observed in humans, when the concentration of alcohol in the blood reaches approximately 500 mg/l00 mL (44), while incidents of apnea are reported even in a child that presented poisoning from alcohol. However, humans present respiratory arrhythmia even due to medium alcohol doses (45, 46). Concentrations higher than 350–450 mg/l00 mL are capable of incrementing the PCO_2 and acidosis (pH reduction). These findings highlight the perception that when the level of alcohol in the blood is lower than 300 mg/100 mL, the respiratory insufficiency in alcoholics shall be attributed to other factors and mainly to the intake of other medicaments or the aspiration of vomits.

The intravenous infusion of alcohol (up to 44 g) as an anesthetic – in 300 women that were submitted to minor gynecological operations – resulted in the reduction of the pulmonary ventilation in only 9 of them, which had been simultaneously administered opiates, while, according to other laboratory studies, the alcohol concentration in the blood up to 120 mg/l00 mL not only does not reduce the pulmonary ventilation, but it is even possible to raise it (47).

A study of 6 patients with chronic refractory pneumonopathy, who received an alcoholic solution per os and whose maximum concentration in the blood reached 137 mg/100 mL, showed that small to medium quantities of alcohol increase the intake of O_2 – elimination of CO_2 (increase of metabolism) and reduce the pH of the arterial blood (metabolic acidosis), without influencing the frequency of breaths, the gases of the arterial blood (PO_2 and PCO_2), the frequency of the heart function, and the arterial pressure. Therefore, alcohol – at small, medium doses – even in patients suffering from chronic refractory pneumonopathy that have no hypercapnia, does not cause hypoxemia and alveolar hypoventilation, but only metabolic acidosis. However, studies that were carried out using more sensitive methods showed that the same quantities of alcohol reduced the sensitivity of the respiratory center in hypoxemia and hypercapnia (48). This phenomenon, meaning the reduction of the sensitivity of the respiratory centers due to alcohol, without the parallel reduction of the pulmonary ventilation and O_2 in the arterial blood, shall be attributed to the compensating action of the metabolic acidosis, which increases the alveolar ventilation and the sensitivity of respiration in hypoxemia. Other possible explanations include the reduction of the sensitivity of the respiratory centers, but not also the severe disorder of their functionality, the stimulation of respiration from CO_2, which is produced during the metabolism of alcohol or even the lack of the absolute correlation between the sensitivity of the chemoreceptors and the pulmonary ventilation. However, independently to the nonsuppressive impact of alcohol – in small and medium quantities – on the respiratory centers, its consumption and mainly by patients suffering from chronic refractory pneumonopathy shall be governed by great caution, due to the other harmful impacts on the mucociliary clearance, the function of the alveolar macrophages and the alveolar epithelium, the efficiency of the myocardium and the pulmonary circulation, as well as on the reflective cough, which alcohol suppresses (49). This does not mean that alcohol does not have a beneficial impact on patients with dyspnea.

Many people suffering from refractory pneumonopathy stated that alcohol alleviated dyspnea, a fact that many researchers verified (50, 51). The beneficial impact of alcohol in cases of dyspnea is not due to the suppression of the respiratory centers, but the increase of the FVC (52). Actually, the latter authors, following a study on 26 patients with acute poisoning from alcohol, suggested the increase of β-endorphins in their plasma (46.0±2.9 μg/mL compared to 26.5±2.8 μg/mL of the control groups), which suppress and affect the respiratory centers just as opiates do (53).

Effects of alcohol on the respiratory regulation during sleep

It is well documented that sleep is not a homogenous phenomenon. Contemporary studies on sleep, using electroencephalogram (EEG), electro-oculogram (EOG), and electromyogram (EMG), show that

sleep biologically progresses in two phases: the phase of the nonrapid eye movement (or NREM) and the slow waive sleep or quiet sleep or synchronized sleep and the phase the rapid eye movements (REM), the active sleep or paradoxical sleep or even desynchronized sleep.

The first stage, the non rapid eye movement, is divided into four (I, II, III, IV) smaller stages, described by quiet sleep and a slight decrease of the muscular tone, while the second stage, the one of the rapid eye movements, is described by great frequency and small width waves in the EEG, rapid and conjugate ocular movements in the EOG, loss of the muscular tone in the EMG, great fluctuations of the neurophytical functions (respiration, heart rate), and activation of the genitalia. This means that the second stage of sleep is more like the conditions prevailing during alertness. During sleep, even in asymptomatic people, respiration disorders and reduction of the Hb saturation in O_2 are noted (54). Respiration disturbance may be apnea (discontinuance of respiration through the mouth and nose for more than 10 s) or hypopnea (reduction of the respirations' width, the incoming air flow, and the saturation of Hb in O_2) (55).

Alcohol – even at medium doses – is known to cause EEG disorders during sleep (56–58) as well as snoring, which is due to the refraction of the upper respiratory tracts, and it is accompanied by a significant reduction of Hb.

Alcohol administration had the following results:

- Increase of the desaturation episodes of Hb, their greater duration and a great reduction of Hb;
- Increase of the apnea and hypopnea episodes as well of their duration;
- Increase of desaturation episodes of HbO_2 and their duration.

The importance of the respiratory disorders and the reduction of Hb saturation in O_2 during sleep, after the administration of alcohol, may be low in normal people. However, in patients with chronic respiratory insufficiency and night respiratory disorders, which affect the heart function, alcohol consumption may deteriorate an overlaying pulmonary hypertension or an arrhythmia, having fatal consequences.

Effects of alcohol on the infusion of gases in the lungs

The measurement of the pulmonary infusion capacity with carbon monoxide (DLco) in alcoholics presents some special problems. More specifically, the measurement of DLco in some automatic devices that count DLco using the Fuel Cell method, gives small significantly lower than the chromatographic method, when alcohol has been consumed in advance (even with elixirs or gargles). Thus, the false low values of DLco may lead to false conclusions (59).

Other factors that greatly influence the DLco in alcoholics are the coexisting anemia and smoking (most alcoholics are also heavy smokers). According to (60), in a study of 20 alcoholic patients, it was suggested a reduction of the DLco by more than 70% of the normal value, in 12 out of them. However, a corrected DLco as for the anemia was found reduced only in 4 patients, while the corrected value as for smoking (61) was found normal in all of them. According to the authors, the DLco disorder in alcoholics is due to smoking and an underlying anemia. The histological examination of the lungs in an alcoholic did not show pachynsis of the capillary alveolar membrane.

Another factor that influences the DLco in alcoholics is the frequent aspiration pneumonias, which reduce the values for months. Non-smokers, having pneumonias in the medical history, have DLco lower by 8% than those who never suffered from pneumonia, while the same difference in smokers reaches 12% (62).

Chronic liver diseases and acute pancreatitis – frequent among alcoholics – also influence the DLco and actually the liver diseases at a frequency up to 20% (63). Acute pancreatitis is possible to cause respiratory insufficiency, due to the possible pancreatic enzymes circulating in the blood. Independently to the factors mentioned above, alcohol seems to affect DLco greatly and actually its reduction.

In a study on 23 alcoholic patients that had presented symptoms in the respiratory system (dyspnea, chronic bronchitis), lower values of DLco in 14 (61%) of them, which were proportionate to the quantity of alcohol they had consumed, were reported (64). Actually, DLco remained reduced even after the separation of the impacts that smoking, pneumonias, and liver cirrhosis have on its values. According to the authors, alcohol either has the same level of harmful impacts on lungs or it increases the sensitivity of the lungs to smoking. DLco seems to reduce even after an on-time-off consumption of alcohol (65).

Finally, the increase per minute of the blood volume and the blood flow in the pulmonary circulation, caused by alcohol, is possible to provoke the raise of DLco that can cover for its reduction due to another cause.

The mechanism through which alcohol reduces the

DLco in alcoholics varies. Apart from smoking, anemia, aspiration pneumonia, cirrhosis, and pancreatitis, the toxic impact of alcohol on the lungs is also possible, which corresponds to the liver damage and the endoplasm network of mitochondria of heart cells or even the participation of the hyperlipidemia – caused by alcohol – in the DLco disorder.

Another possible explanation for the reduction of DLco in alcoholics is the change in the blood distribution from the lungs to the periphery. This means that it is a secondary result of the hemodynamics action of alcohol.

The most probable explanation for the impact of alcohol on DLco is its immediate action on it and more specifically the transfer of CO from the capillary alveolar membrane. It is known that many medicaments, among them probably alcohol, impede the diffusion of CO and probably by extension of O_2 too – to the capillary alveolar membrane. The mechanism of this action seems to be liked to the commitment of the cytochrome P450, which is probably used as a carrier of CO or O_2.

Effects of alcohol on the pulmonary circulation

Although since the begining of the century, there have been suspicions that alcohol causes pulmonary hypertension (66, 67), the case was systematically studied just a few years ago.

Studies that were performed using catheterization mainly of the right heart in human subjects suggest that alcohol does not increase pressure in the pulmonary circulation (68–70). However, these studies do not mention values of the gases in the arterial blood, while the concentration of alcohol in the blood is approximately 50 mg/100 mL.

Effects of alcohol on the resistances of the airways

Alcoholics often present an increase in the resistances of the airways, which is however attributed mostly to smoking and the several complications on the respiratory system (chronic bronchitis, pneumonias).

A spirometric study on 70 alcoholics conclude that FEV 1% (percentage of the maximal expiratory volume of air in the first second of the maximal expiration capacity) is lower by 1 SD than the normal value, in half of them (71).

Another study of 23 alcoholic patients presenting symptoms in the respiratory system (dyspnea, chronic bronchitis) found that only 1 had normal respiratory function. The rest 22 presented reductions in one or more parameters of the lung ventilation capacity (TLC, VC, RV, and FEV) and DLco, relevant to the amount of alcohol that had been consumed. More specifically, 13 subjects (60%) had decreased flows of inspired air, 12 (52%) decreased DLco, and 18 (80%) both. Based on the high frequency of ventilation disorders in the alcoholics' lungs, the authors conclude that not only smoking shall be responsible for these disorders, but also alcohol that causes chronic refractory pneumonopathies (72).

Apart from the chronic influence of alcohol on the resistances of the respiratory tracts and the mechanism of respiration, what is also important, is its direct impact on the bronchi. There has been a conflict of opinions on this matter, which still stands. This means that although alcohol has been efficiently used to treat bronchial asthma, alcoholic drinks are probable to cause bronchial spasm or asthma crisis.

Many papers – most of them quite old – suggest that alcohol, when administered per os (73, 74) or intravenously (75, 76), has beneficial impact or even cure asthma crises. However, other papers – more recent – suggest that alcoholic drinks cause bronchial spasm to those suffering from asthma (77) or even to nonasthmatic patients who deal with hypersensitive respiratory tracts (78).

Based on these findings, the authors conclude that the mechanism of the direct bronchial spasm in the case of their patient was not the cholinergic tract or the basophile cells of the tissues and the immunoglobulin IgE, but other intermediate substances with vasomotor and bronchomotor activity and a small life circle. Vasomotor disorders after the intake of alcohol are known and quite often (79, 80), but they are rarely followed by bronchial spasm.

There is another interesting case of the combination of vasomotor and bronchomotor phenomena, in a man aged 23 years, following the consumption of beer or alcohol (81). The abovementioned patient, who was not an alcoholic, did not suffer from liver, heart, or pulmonary disease and was not a smoker, though had a history of bronchial asthma in his childhood (sensitivity to dust and animal hair), after drinking beer or alcohol 95% in apple juice, he would present rubeosis on the face, nasal refraction due to hyperemia, a retrosternal feeling of contraction, and severe bronchial spasm. The administration of alcohol intravenously or by inhalations caused smaller degree bronchial spasm with rapid restitution. The preventive administration of isoprenaline or sodium cromoglycate did not have a repressive impact on bronchial spasm, while the administration of atropine, acetylsalicylic acid, cyproheptadine, and chlorpheniramine had some results. There were also other asthmatic persons in the

patient's family, presenting similar symptoms after drinking alcohol. Based on the findings, the authors conclude that the mechanism of the bronchial spasm after consuming alcohol is not the increase of prostaglandins (failure to prevent it with acetylsalicylic acid), histamine (failure of sodium cromoglycate and chlorpheniramine), or serotonin (failure of cyproheptadine), but the liberation of many intermediate substances, which act as a "concert" as well as their gender predisposition.

In relation to the mechanism of the bronchial spasm, following the intake of the alcoholic drink, Pepys (82) suggests that some patients suffering from endogenous asthma are possible to present bronchial spasm after consuming an alcoholic drink but not also after the administration of alcohol, thus acting like allergic with exogenous allergy, characterized by conviviallergy. The same researcher suggests that patients with asthma or rhinitis are possible to present, after consuming alcohol, eosinophil cells in the nasal secretions or even blood.

Finally, in their comment on the paper by Gong et al. (1981), wonder why the intravenous administration of alcohol causes lighter bronchial spasm than the interior administration of the apple juice mixed with alcohol, while they speculate that the causes of bronchial spasm in the latter case are the conservative substances of the juice (sulphur dioxide) or colorants (tartrazine). However, they do not exclude the possibility that bronchial spasm was caused by an irritating impact of alcohol on the vagus nerve (83).

As far as the combination of the face rubeosis and the bronchial spasm is concerned, this syndrome is lately reported also in diabetics and nondiabetic patients (84, 85), while since it is lifted with naloxone – a competitive antagonist to opiates – it is speculated that it is due to the substances that have opiate activity.

The indirect effect of alcohol on the respiratory system

Alcohol may indirectly influence the respiratory system. The outcome of the hepatic damage, which is mainly observed in the liver cirrhosis, is pillar hypertension, the development of collateral circulation between the pillar vein and the inferior and superior vena cava, and the formation of arachnoid vascular anastomosis (spiders) in the lungs.

The collateral circulation in liver diseases causes shunt of the venous blood towards the arterial – the veins and arterial shunt – which in very advanced cases is probable to reach 30% of the blood volume. The shunt of the venous blood towards the arterial, in combination and the reduction of DLco, are responsible for hypoxemia, which is observed in chronic liver diseases.

The blood shunt from liver is possible to influence the activation or inactivation of some vasodilation substances – amines and polypeptides – that circulate in the systematic circulation and to cause pulmonary hypertension. The 5-hydroxytryptamine (serotonin), which is removed from the endothelium cells of the pulmonary circulation, increases in the large circulation in case of collateral communication, while it is not excluded that the conversion of angiotensin I into angiotensin II is influenced correspondingly.

Pulmonary circulation is also influenced in liver diseases, in the sense of a disturbance of the lungs' ventilation – perfusion relation. This means that the vasodilation of the pulmonary artery branches, which occurs in case of hypoxemia to maintain the said relation stable, is not released in patients with chronic liver diseases. Consequently, the conclusion is that the several liver diseases caused by alcohol. with the disturbance of the blood flow on the axis of the intestine – liver – lungs, is possible to influence the pulmonary circulation and cause hypoxernia in the peripheral blood, having the respective consequences.

Alcoholic lung disease

The daily consumption of a small quantity of alcohol is a medical recipe according to the popular philosophy, as "Two drinks a day keep the doctor away!" However, the chronic use of large quantities of alcohol on a daily basis is definitely followed by high frequency of chronic pneumonopathies, such as chronic bronchitis, pulmonary emphysema, pulmonary fibrosis, and possibly bronchiectasis. These chronic pneumonopathies are usually attributed to malnutrition, frequent infections, gastric content aspiration, and excessive smoking in alcoholics. And it is absolutely certain that these factors can cause chronic pneumonopathies in alcoholics. However, there is no doubt that alcohol also affects the respiratory system directly and more specifically the mucociliary clearance of the respiratory tracts, the function of the ciliary epithelium and the capillary macrophages, the regulation of respiration in agitation and even more during sleep, the pulmonary circulation, the resistances of the respiratory tracts, and finally the gases of the arterial blood and pH. Moreover, there is no doubt that alcohol influences the respiratory system also indirectly, with the damage it causes to other organs and mainly the liver, the heart, and the nervous system.

The assessment of the actual damage that alcohol

causes on the respiratory system is – as above mentioned – a difficult task, since it is implicated with the damages caused by smoking and the potential use of other narcotic drugs. However, the data that exist up to today speculate, if not the total responsibility, at least the participation of alcohol in the occurrence of chronic pneumonopathies (86), while at the same time they justify the existence of a special syndrome in alcoholics, which is described as the "alcoholic pneumonopathy" or "alcoholic lung disease" (87).

Summary

This review article summarizes the influence of alcohol on the respiratory system, its deleterious effects on mucociliary system, alveolar cells, and alveolar macrophages. Regulation of breathing, diffusing capacity of the lungs, pulmonary circulation, and airway resistance are more emphasized. It is concluded that alcohol may be responsible for some chronic pulmonary diseases in alcoholics or even for a specific alcoholic lung disease.

Alkoholinė plaučių liga. Istorinė apžvalga ir klinikiniai požymiai

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Raktažodžiai: alkoholis, plaučiai, istorija, fiziologija.

Santrauka. *Straipsnio tikslas*. Apžvelgti alkoholio žalą kvėpavimo sistemai. Trumpai apžvelgiama alkoholio istorija iki šių dienų. Apžvelgiamas skirtingų šalių gyventojų polinkis į alkoholizmą.

Alkoholio metabolizmas – kita tema, aptariama lygiagrečiai kartu su jo farmakologiniu veikimu. Alkoholio poveikis kvėpavimo sistemai yra skirtingas – nuo kvėpavimo takų gleivinės pažeidimo iki kvėpavimo reguliacijos, nuo miego apnėjos sindromo iki difuzijos sutrikimų. Alkoholinė plaučių liga yra sindromas, nors rūkymo ir vaistų vartojimo sukelti pažeidimai labai dažnai neatskiriami.

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