Bratisl Lek Listy 2008; 109 (12)
590 – 594

REVIEW

Ethanol and cardiovascular diseases: epidemiological, biochemical and clinical aspects

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Abstract: The effects of alcoholic beverages on the cardiovascular system can take opposite forms, depending on how much of ethanol is consumed. The negative effects of alcoholism are well established. Alcoholism is a cause of cardiomyopathy, cardiac arrhythmias and hypertension. The best argument is the situation of Russian Federation where extremely high alcohol consumption caused very high ischemic heart disease and stroke mortality both in male and female population. On the other side there are also many proofs of health benefits of moderate alcohol consumption. The National Institute on Alcohol Abuse and Alcoholism in USA has completed an extensive review of current scientific knowledge about the health effects of moderate alcohol consumption: the lowest death rate from all causes occurs at the level of one drink per day. Moderate drinkers have the greatest longevity. Higher serum levels of high density lipoproteins (HDL) in moderate alcohol drinkers are associated with reduced risk for the development of atherosclerotic disease. HDL particles are believed to be antiatherogenic due to their capacity to drive reverse cholesterol transport and to antagonize pathways of inflammation, thrombosis, and oxidation *(Fig. 4, Ref. 34).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: heart disease, stroke, alcohol intake, high density lipoproteins.

Alcoholic beverages date back to the very early part of man's history. The effects of ethanol on the cardiovascular system can take opposite forms, depending on how much is consumed. The negative effects of alcoholism are well established, but there are also many proofs of health benefits of moderate alcohol consumption: "A drink a day will keep the doctor away".

Negative effects of alcoholism on cardiovascular system

Beside liver cirrhosis, psychiatric and social problems there are at least three factors increasing the risk of cardiovascular diseases (CVD) in alcoholics:
– cardiomyopathy,
– cardiac arrhythmias,
– hypertension.

Cardiomyopathy

The association between excessive ethanol consumption and the occurrence of congestive heart failure in chronic alcoholics is known for many years. Alcoholic cardiomyopathy accounts for 20 to 50 percent of all cases of cardiomyopathy in European Union (EU) and probably much more in the Russian Federation. The prevalences of binge drinking and alcohol dependence are substantially elevated in Russian males and females. There is no method enabling reliable estimation of ethanol consumption in Russia, because nobody can count hectoliters of illegally produced spirits. Nevertheles, there are some more reliable Russian and WHO data showing cardiovascular mortality and the incidence of alcoholic psychosis (1, 2). Figure 1 shows almost parallel trends in cardiovascular mortality and the incidence of alcoholic psychosis in Russia (3). Great fluctuation of data is probably explainable by deep political and economical changes in

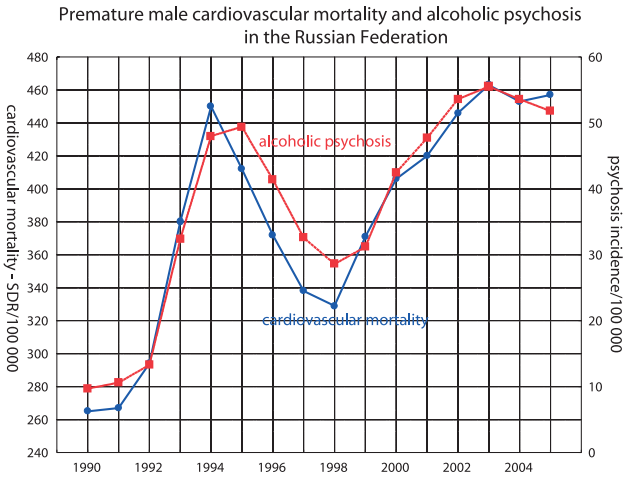

Fig. 1. Correlation of male premature cardiovascular mortality (age group 0–64 years) and the incidence of alcoholic psychosis in Russia.

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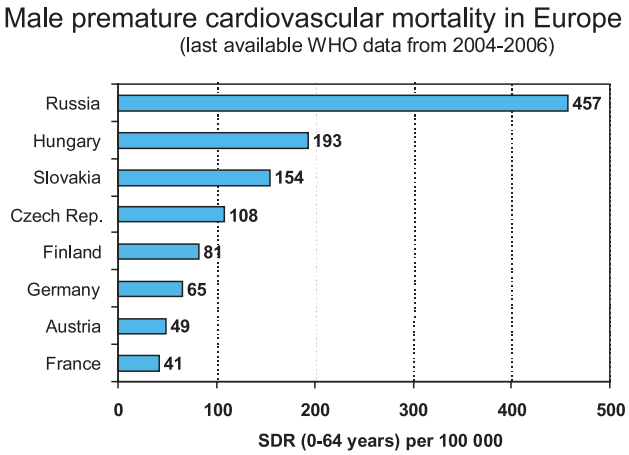

Fig. 2. Extremely high cardiovascular mortality in Russian males (age 0–64 years).

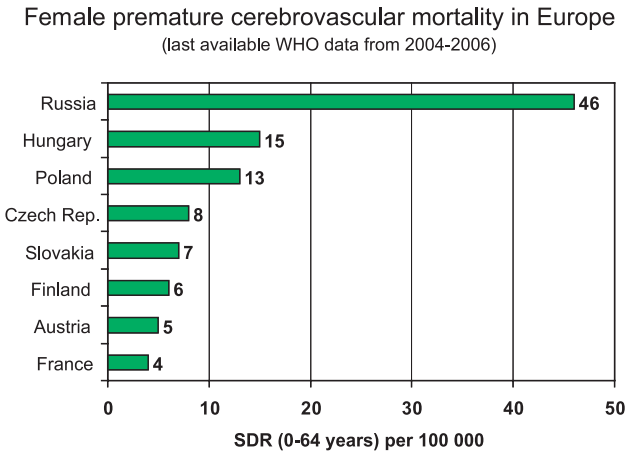

Fig. 3. Extremely high cerebrovascular mortality in Russian females (age 0–64 years).

Russa (disintegration of Soviet Union, etc). The incredible increase of cardiovascular mortality in Russia caused great decrease of male life expectancy (from 65 years in 1987 to 57.5 years in 1994).

Several mechanisms have been suggested to explain negative effects of ethanol on cardiac muscle. Alcohol has an adverse effect on the integrity and function of the contractile proteins – actin and myosin (4, 5). High intakes of ethanol reduce the oxygen supply to the cardiac muscle, interfere with aerobic heart metabolism and decrease the level of the adenosine triphosphate (ATP) in the myocardium. Alcoholism alters the permeability of the sarcoplasmic reticulum to calcium ions, and thus reduces the efficiency by which calcium activates muscle contraction.

Cardiac Arrhythmias

In chronic alcoholics electrophysiological changes in cardiac rhythm are found. Following heavy alcohol consumption acute disturbances in cardiac rhythm associated with sudden cardiac death were described. The situation in the Russian Federation is a good example. Contemporary life epectancy of Russian men is more than 20 years shorter than in Iceland and is similar as in poor developing countries (India, Ghana, Senegal, Sudan) (6). The greatest increases in mortality were in regions experiencing the most rapid economic transition, as measured by gains and losses in employment. Young men with poor education were especially vulnerable to the changes. Their deaths were more likely to be sudden, and many men who die showed little evidence of the expected coronary artery lesions. Premature male cardiovascular disease (CVD) mortality (age 0–64 years) is ten times higher in comparison to the best EU countries (1) (Fig. 2). Increased thickening of connective tissue in myocardium could provide the anatomical source of the disturbance in ventricular rhythm by impeding electrical conduction and explain ehanol-induced cardiac arrhythmias. In alcoholics, there are electrolyte disturbances, a lack of oxygen to the myocardium and disorders of neurotransmitter turnover involved in transmitting impulses from nerves to the myocardium.

Hypertension and stroke

Daily intake of three or more drinks increased blood pressure. A reduction to less than one drink per day resulted in a short-term drop in blood pressure (9, 10). One reason could be low levels of ionized magnesium in the alcoholic's blood plasma (11). Magnesium ions cause blood vessels to relax, whereas calcium ions have the opposite effect. Ethanol-induced hypertension predisposes alcoholics to intracerebral hemorrhages (12), which are associated with binge drinking. Women appear to be especially sensitive to an increased risk of hemorrhagic stroke, even at the relatively low levels of ethanol consumption. Unfortunately, the alcoholic epidemics seized both Russian males and females. The grim face of Janus (with two heads looking in opposite direction) represents the toxic effects of ethanol, broke out in extremely high cerebrovascular mortality of Russian females (Fig. 3). These mortality data form the Russian Federation are ten times higher than in Austria or France.

Increased danger of alcoholism for minorities

In USA there are great ethnic differences in drinking patterns. Heavy drinking is most prevalent among American Indians, Afro-Americans, Alaska Natives and Native Hawaiians. In Europe the prevalences of binge drinking, and alcohol dependence are substantially elevated in gypsies (Roma people). The risk of CVD is substantially higher in these minorities (13–16).

Possible beneficial effects of moderate ethanol consumption on cardiovascular system

The pleasant face of the Roman god Janus represents the beneficial effects of small doses of ethanol on cardiovascular system. The National Institute on Alcohol Abuse and Alcoholism in USA has completed an extensive review of current scien-

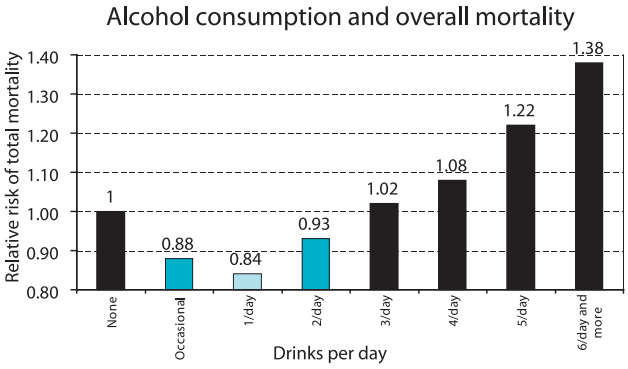

Fig. 4. J-shaped association between alcohol intake and all-cause mortality (17).

tific knowledge about the health effects of moderate alcohol consumption: the lowest death rate from all causes occurs at the level of one drink per day. The two largest of the many studies were conducted by the American Cancer Society; one included 276 800 men and the other included 490 000 men and women (17, 18). Moderate drinkers have the greatest longevity. Figure 4 shows concordant J-shaped association between alcohol intake and an all-cause mortality (17). The J-shaped distribution for total mortality is then the sum of the protective effect on CVD mortality and the detrimental effect of high levels of consumption on other causes of death. Lower CVD mortality of moderate drinkers and higher CVD mortality in heavier drinkers is the chief reason of this phenomenon. Studies from at least 20 countries in Europe, North America, Australia and Asia demonstrated a 20- to 40-percent lower CVD incidence and mortality among moderate drinkers compared to heavy drinkers or abstainers.

Light to moderate alcohol consumption (up to 1 drink daily for women and 1 or 2 drinks daily for men) is associated with cardioprotective benefits. The ethanol itself, rather than specific components of various alcoholic beverages, appears to be the major factor in conferring health benefits. What constitutes "moderate" drinking is debatable. According to the Dietary Guidelines for Americans (19) published by the US Department of Agriculture and the US Department of Health, moderate means a daily intake of one drink for women and two drinks for men. A drink was defined as one 5-ounce glass of wine (=150 ml), one 12-ounce can of beer (=350 ml), or 1.5 ounces of 40% distilled beverage (=40 ml), each of which contains about 14 g of alcohol. For Central Europe males that means daily consumption of 1.5 glass of standard 500 ml beer glass, 1 "great" wine glass (300 ml) or two "small" spirit glasses (40 ml). European authors generally describe moderation as one to three drinks per day. Women should generally consume 30 percent less than the average man. A glass of white or red wine, a bottle of beer, and a shot of whiskey or other distilled spirits all contain equivalent amounts of alcohol. Claims that wine is healthier than other alcoholic beverages have not been consistently corroborated.

The American Heart Association has reported that "More than a dozen prospective studies have demonstrated a consistent, strong, dose-response relation between increasing alcohol consumption and decreasing incidence of CHD. The data are similar in men and women in a number of different geographic and ethnic groups. Consumption of one or two drinks per day is associated with a reduction in risk of approximately 30 % to 50 %" (20). Research suggests that moderate consumption of alcohol improves cardiovascular health in a number of ways, but many of them are debatable. Thus, for instance the claim that ethanol reduces blood pressure in males is not true (21). Drinking alcohol in small doses results in dilation of peripheral veins and reduction in blood pressure but chronic consumption of alcohol leads to hypertension. Of more than 30 studies of hypertension and alcohol conducted in the past three decades revealed a relationship between increased alcohol consumption and the incidence of hypertension. The prevalance of hypertension in individuals who drink three or more glasses of alcohol per day is 3–4-times higher than it is in nondrinkers.

At least half of the protective effect of alcohol on vascular system has been attributed to the higher levels of high-density lipoprotein cholesterol (HDL-C) found among moderate drinkers (20).

Ethanol and high density lipoprotein (HDL) metabolism

In the last 20 years there is increased focus on the metabolism of high-density lipoprotein (HDL) cholesterol in an effort to reduce risk for CVD, including myocardial infarction, unstable angina, ischemic stroke, and death. Epidemiologically, high serum levels of HDL cholesterol are associated with reduced risk for the development of atherosclerotic disease. HDL particles are believed to be antiatherogenic secondary to their capacity to drive reverse cholesterol transport and antagonize pathways of inflammation, thrombosis, and oxidation (22).

Nascent discoid HDL particles consisting almost entirely of phospholipids, apoprotein Apo A1 and small amounts of free cholesterol are formed in the liver and intestine. As these nascent HDL particles move through the circulation, Apo A1 in the HDL membrane binds with phospholipids. The free fatty acids from lecithin are transferred to the unesterified cholesterol that has been absorbed from cell membranes of vessel walls and of other tissues into the nascent HDL particle. This free cholesterol is then esterified by plasma lecithin:cholesterol acyltransferase (LCAT) and, because cholesterol esters are hydrophobic, they move to the core of the lipoprotein, causing the HDL particles to assume its spherical configuration. Cholesterol esters are transferred from HDL to apo B-containing lipoproteins by cholesterol ester transfer protein (CETP) in exchange for triglycerides. Thus, HDL particles have an important role in reverse cholesterol transport: first specific HDL subclasses function as primary cholesterol acceptors and are able to remove cholesterol from peripheral cells, and after cholesterol esterification cholesterol esters are delivered from HDL to apo B-containing lipoproteins, which are removed from the circulation by hepatic LDL-receptors. Phospholipid transfer protein (PLTP) is an important regulator of HDL metabolism. The two main functions of PLTP are

transfer of phospholipids between lipoprotein particles and modulation of HDL size and composition in a process called HDL conversion. These PLTP-mediated processes are physiologically important in the transfer of surface remnants from lipolyzed triglyceride-rich lipoproteins to nascent HDL particles. This "reverse cholesterol transport pathway" is highly dependent upon apo A-I's ability to activate lecithin:cholesterol acyltransferase (LCAT) for cholesterol to cholesterol ester conversion in the plasma.

Between the years 2005–2008 PubMed found in more than 30 studies a significant effect of alcohol intake on HDL-cholesterol (e.g. 23–29). Moderate alcohol consumption induces not only quantitative, but also qualitative changes of the HDL fractions (30). The increased lipidation of HDL found in alcohol consumers might augment the antiatherogenic effect of HDL--cholesterol increase. In addition, the phospholipid enrichment of HDL might reduce the inflammatory response of atherogenesis (30). Until now, the exact mechanism of alcohol influence on HDL metabolism is not clear. The higher HDL cholesterol associated with moderate alcohol consumption is not caused by an effect on plasma lecithin:cholesterol acyltransferase (LCAT), cholesterol ester transfer protein (CETP) and phospholipid transfer protein (PLTP LCAT, CETP or PLTP activity levels (31).

Moderate consumption of alcohol improves cardiovascular health beside its effect on HDL in a number of other ways: decreased thrombosis, increased fibrinolysis, reduced coronary artery spasm in response to stress and improved insulin sensitivity of tissues. Moderate drinkers are less likely to have type 2 diabetes than are abstainers, according to the findings of 15 different studies that followed a total of 369 862 men and women for an average of 12 years. These findings deserve a special review.

Conclusion: to drink or not to drink?

It is not easy to answer this Hamlet's question, because alcohol consumption is like a razor-sharp double-edged sword (32). Current guidelines of the American Heart Association (AHA) state that moderate alcohol consumption is beneficial for cardiovascular health, but the AHA clearly states that nondrinkers should not begin drinking alcohol in middle age due to possible counter-balancing ill consequences of alcohol consumption. Before the definitive decision prospective randomized blinded clinical trial would be important: engage a large pool of nondrinkers, half of whom would commence a moderate drinking regimen, while the other half remained abstainers. The two groups would be followed for years in a search for eventual differences in cardiovascular disease and heart-related deaths. First positive data were avaiable in 2008. King et al (33) observed that of 7697 participants who had no history of cardiovascular disease and were nondrinkers at baseline, 6.0 % began moderate alcohol consumption and 0.4 % began heavier drinking. After 4 years new moderate drinkers had a 38 % lower chance of developing CVD than did their persistently nondrinking counterparts. Those who began drinking moderately experienced a relatively prompt benefit of lower rates of CVD morbidity with no change in mortality rates after 4 years. The collected data make a strong case for the cardiac benefits of controlled drinking. Health professionals should provide balanced guidelines regarding the use of alcohol. These guidelines need to be tailored to each individual patient acording to his/her health status and educational level (34).

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Received July 2, 2008.
Accepted September 20, 2008.