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## Ethanol and the Cardiovascular System: Friend or Enemy?

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Alcohol as an old drug and popular beverage has attracted human interest since the beginning of the recorded history. However, in all societies concurrent with alcohol consumption, scientific debates on its risks and benefits have also been generated and continue to this date ((Kloner and Rezkalla,2007). Because of the major role of cardiovascular disease (CAD) in mortality rates

(30% of all global death in 2008, according to the World Health Organization report), the association between alcohol consumption and cardiovascular system disease has attracted more attention from researchers. A large body of studies carried out over the past decades have repeatedly supported a J-shaped curve association between alcohol intake and the relative risk of developing cardiovascular system disease: it was found that at light-to-moderate levels of alcohol intake the risk was lower, but it increased at higher doses (Kloner and Rezkalla,2007 ;Lucas et al.,2005). Recent epidemiologic studies have indicated that light-to-moderate amounts of ethanol reduce cardiovascular risk by reducing blood pressure

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and suppressing smooth muscle cell proliferation (Kisters et al.,2000). Contrary to these beneficial effects, some studies have found that ethanol consumption increases the risk of hypertension and the risk of cardiovascular disease with progression of atherosclerosis (Rantakomi et al., 2009; Shirpoor et al., 2012). Recently, a meta-analysis of 34 cohort studies on more than one million subjects involving both men and women has confirmed the complex relationship between ethanol consumption and CAD. According to this meta-analysis study, drinking alcohol, up to two drinks/d (around 20 g) by women and four drinks/d by men resulted in a maximum risk reduction of 18% and 17% in them, respectively. This is while ethanol consumption of higher doses by subjects was associated with an increase in the total mortality (Di Castelnuovo et al., 2006). Given the results of the above studies, the J-shaped curve is the result of a combination of beneficial and harmful effects of ethanol intake. The ascending leg of the curve reflects an enhanced risk of alcohol-dependent diseases such as cardiomyopathy, heart failure, atherosclerosis, as well as other organ and tissue disorders. In contrast, the lowest point of the curve reflects a relatively lower risk of cardiovascular disease among light to moderate drinkers compared with the abstainers. It seems that the effects of ethanol on the cardiovascular system depend on various factors, including the drinking pattern, dose, gender, and type of the beverage. It is therefore evident that the effects of ethanol on the cardiovascular system are complex and identifying the underlying mechanisms that may explain the paradoxical effects of ethanol is highly warranted. It was less than thirty years ago that atherosclerosis was believed to be the result of lipid accumulation in the arterial wall, but a better understanding of atheroma plaque formation has led to the development of a new concept of atherosclerosis as a chronic low grade inflammatory disease of arterial endothelial cells (Hansson, 2005). When several risk factors such as dyslipidemia, hypertension, oxidative stress, inflammatory reaction, and endothelial cell disturbance are combined, they induce a gradual thickening of the arterial

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wall to form atherosclerosis plaque, which is important in the development and progression of atherosclerosis.

Through controlling the release of several vasoactive substances including nitric oxide (NO), endothelial cells play a significant role in regulation of oxidative stress, permeability of vasculature to plasma constituents, platelet aggregation, thrombosis, vascular tone, and blood pressure (Callow, 2002). It has recently been reported that chronic alcohol ingestion is associated with an increase in aortic inflammation, oxidative endothelial injury, and a decrease in the aortic endothelial NO generation system, creating the condition for the loss of vascular relaxation response and hypertension among rats (Husain et al., 2011). Moreover, the expression of the adhesion molecules on the surface of the vascular endothelium in response to the lesions is another indicator of endothelial dysfunction and an important step in the development of atherogenesis (Poston et al., 1992). Several of these factors, namely the intercellular adhesion molecule-1(ICAM-1), vascular cell adhesion molecule-1(VCAM-1), and endothelial-leukocyte adhesion molecule-1(E-selectin) have been identified in endothelial cells and in human atherosclerosis lesion cells, leading eventually to monocyte adhesion to the vascular wall and trans-endothelial migration (Poston et al., 1992). The next phenomenon sets off the formation of foam cells and cytotoxicity of vascular cells. The adherence of monocytes is a key step in this process, and occurs as a result of the up-regulation of adhesion molecules on both the endothelium and the leukocytes during the development and progression of atherosclerosis (Ross, 1999). Interestingly, our recent study results have indicated that chronic ethanol consumption leads to atherosclerotic plaque formation in wistar rats' aorta by starting pro-inflammatory and pro-atherosclerotic processes, as manifested by an increase in serum levels of C-reactive protein (CRP) and adhesion molecules (such as ICAM-1, VCAM-1, and E-selectin) and by the appearance of infiltrated monocytes in the aorta, as well as by an increase in blood pressure (Shirpoor et al., 2012). In

another important recent study, Norouzi et al. (2015) discovered that chronic ethanol intake by rats caused an increase in the aorta wall thickness (all parts of the wall including media tunica, adventitia and intima layers) and in the aorta vascular smooth muscle cell proliferation. In addition to aorta thickness, an increase in the level of triglyceride, cholesterol, LDL, and aorta tissue Ox-LDL with no changes in the HDL and HDL/TG ratio was reported in this study to be the result of chronic ethanol consumption. Increased aorta tissue homocysteine and protein carbonyl (manifestation of oxidative stress) were also results of ethanol consumption in the study (Norouzi et al., 2015). Although previous studies, as mentioned above, have shown that chronic ethanol intake induces variations in some measures of structural and physiological changes in the cardiovascular system, the mechanism underlying the deleterious effects of heavy ethanol consumption on the development of atherosclerosis remain largely unknown. Among numerous factors important in predicting the advancement of artery atherosclerosis, Hcy and LDL are two of the most important independent risk factors for atherosclerosis and artery stiffness. Hcy exerts its atherogenic effects via promoting endothelial dysfunction, oxidative stress, VSMCs proliferation, and thrombosis (Chen et al., 2000). In the study by Norouzi et al (2015), concurrent media intima thickness, unfavorable lipid profile and oxidative stress occurrence on aorta wall were also observed among ethanol-treated animals. The relation existing between the high levels of TG and LDL and the low levels of HDL as independent risk factors for cardiovascular disease is a very well known event. Mechanistically, vascular atherosclerosis formation and progression by pathways involving inflammatory responses, oxidative stress, endothelial cell dysfunction, and foam cell formation are all induced by the elevated LDL level (Norouzi et al., 2015). Atherogenic properties of LDL are due to its composition and size. Because of its small size, LDL penetrates arterial walls and is trapped into the subendothelial space. After oxidation, the trapped LDL forms Ox-LDL (Norouzi et al.,

2015), which induces vascular wall lesion through multiple processes such as foam cell formation, vascular smooth muscle cell proliferation, growth stimulation via oxidative mechanisms, and potentiation of the mitogenic effect of angiotensin II and stimulation of MAPK (Kusuhara et al.,1997). Moreover, our recent work indicated that ethanol consumption caused aorta smooth muscle cell proliferation with dyslipidemia; increased APO-B, Apo-B/Apo-A ratio and Hcy; and decreased Apo-A, all of which are favorites for atherosclerosis formation and development (Shirpoor et al., 2013). Despite the hazardous effects of chronic ethanol exposure on cardiovascular system generally and atherosclerosis particularly, discussed briefly in the first part of this commentary, a large body of evidence indicates that light to moderate ethanol consumption is not only associated with a reduced risk of cardiovascular disease development (Lucas et al., 2005), but this effect is also noted in higher risk populations, including individuals with diabetes, hypertension, hypercholesterolemia, those who are overweight, as well as in cigarette smokers (Krenz and Korthuis, 2012). In addition, synergistic effect of low to moderate alcohol consumption with exercise demonstrated a 40-50% reduction in risk for myocardial infarction reported in men who exercised regularly for at least 30 min/day (Krenz and Korthuis, 2012). Moreover, it has been reported that the augmentation of cardio-protective effect of some food and reduction in the incidence and severity of myocardial infarction are also mediated by low to moderate ethanol consumption (Krenz and Korthuis, 2012). Several direct and indirect plausible mechanisms have been proposed as the basis for protection against or reduction in cardiovascular disease by alcohol. Among indirect mechanisms, lipids have a pivotal role in development or degeneration of atherosclerosis plaque, mainly corresponding to the levels of LDL and HDL in the blood stream. The effect of increased LDL level due to heavy ethanol consumption is discussed above. Contrary to heavy drinking, beneficial effects of low to moderate ethanol consumption mediated by increased HDL and decreased LDL levels have

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been demonstrated by previous studies (Nicolas et al., 2002). HDL has a protective effect against LDL oxidation and deleterious effects on vascular walls. The protective effect of HDL against LDL oxidation and the inverse relation between the risk for atherosclerotic events and HDL are due to the paraoxonase enzyme (calcium-dependent esterase) located on HDL (Shekhanawar et al., 2013). Paraoxonase inhibits LDL oxidation by decreasing the accumulation of lipid peroxidation products on LDL and hydrolyzing lipid peroxides in the lipoproteins. It also inhibits initiation, propagation, and aldehyde formation phases of LDL (Shekhanawar et al., 2013). Recently, results of a meta-analysis study indicated a significant association between paraoxonase, atherosclerosis, and protective effects of paraoxonase against atherosclerosis (Durrington et al., 2001). Based on the literature on the association between paraoxonase and atherosclerosis and the fact that paraoxonase level is parallel with HDL level, it can be said that low to moderate levels of ethanol induce beneficial effects on the cardiovascular system, mediated in part by an increase in the paraoxonase enzyme level located on HDL. With regard to the indirect protective effects, a meta-analysis of 42 experimental studies suggested that moderate alcohol consumption led to the inhibition of inflammatory reaction, enhancement of plasma apolipoprotein-A level, increase in plasma concentration of atrial natriuretic peptide (plays role in volume homeostasis), reduction in oxidative stress, improvement of insulin sensitivity, as well as restoration of endothelium-dependent vasodilator responses (Krenz and Korthuis, 2012). In addition, moderate alcohol consumption is identified as having anti-coagulant effects through decreasing platelet adhesiveness and plasma fibrinogen, as well as causing favorable changes in the concentration of coagulation and fibrinolytic factors (Krenz and Korthuis, 2012). Furthermore, previous studies have revealed that moderate alcohol consumption was associated with less extensive coronary atherosclerosis in high-risk patients who were undergoing coronary angiography (Femia et al., 2006). Although different epidemiologic and

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experimental studies have identified some features of low to moderate ethanol ingestion-induced protective effects on cardiovascular system, to the best of my knowledge, there have been no comprehensive studies considering details of subjects and the molecular signaling mechanisms between exposure to ethanol in low to moderate amounts and initiation of the cascade of responses leading to lowering cardiovascular system disorders and particularly anti-atherogenic properties of ethanol. Briefly, previous studies have established that molecular signals such as adenosine, bradykinin, protein kinase C, the mitochondrial  $K_{ATP}$ , NO, and MAPK, and transcription factors such as NF $\kappa$ B, as well as synthesis of de novo proteins like COX-2, heat shock protein, and some others play a role as a signaling molecule for mediating protective effects of ethanol on the cardiovascular system (Krenz and Korthuis, 2012). This information relevant to the signaling cascades of protective effects of moderate ethanol consumption provided an excellent starting point to open a window on how cardiovascular system diseases can be reduced by moderate alcohol ingestion. In the current issue of *Alcoholism: Clinical and Experimental Research*, Fitzpatrick et al. report the results of a controlled study on the effects of daily moderate alcohol intake on arterial remodeling in response to mouse carotid artery ligation. The authors had hypothesized that an increase in sonic Hedgehog signaling via regulating possible Sca1<sup>+</sup> progenitor stem cell involved in pathologic arterial remodeling followed artery ligation. Moreover, the authors reported that moderate ethanol exposure of animals' concurrent ligation led to a significant decrease in sonic hedgehog responsive Sca1<sup>+</sup> progenitor cell myogenic differentiation/expansion *in vitro* and during arterial remodeling in response to ligation injury *in vivo*. The authors concluded that sonic Hedgehog signaling regulated vascular Sca1<sup>+</sup> stem cells in the adult, and that daily moderate alcohol consumption attenuated vessel pathologic remodeling by inhibiting SHh-dependent Sca1 cell expansion. Furthermore, these data highlight resident progenitor cells as additional vascular 'targets' for alcohol. However, given the complex and mixed relationship

existing between alcohol and cardiovascular disease risk, the work sheds light on the topic of moderate alcohol protective effects since it established a molecular signaling pathway that may enable ethanol to induce its beneficial effects on artery lesion. Several questions, however, still remain to be addressed. Although a large body of studies has provided strong evidence as to cardio-protective effects of low to moderate ethanol consumption, other studies have not found any positive association between moderate alcohol drinking and heart failure (Aguilar et al., 2004; Cooper et al., 2000). In addition, although beneficial effects of moderate ethanol consumption on the cardiovascular system are now accepted, an issue can be raised that some uncontrolled perplexing lifestyle-manipulating factors may affect the subjects. Some works have suggested the fact that individuals who consume moderate amounts of alcoholic beverages display a new behavior regarding diet and exercise and that they enjoy more socio-demographic factors, which could explain the reduced risk for ischemic myocardial diseases (Mukamal et al., 2006). Moreover, some other factors such as patterns of drinking, the exact protective dose of alcohol, and type of beverage are also to be taken into account and their effects be discovered in more detail. Despite some controversy over ethanol's effects on human beings' health and cardiovascular system, results of the study by Fitzpatrick et al. will remain important to advance our understanding of molecular signaling mechanisms — those through which moderate ethanol consumption may exert its beneficial effects on the vascular wall lesion.

**Conflict of Interest:** None



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