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TOPIC HIGHLIGHT

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Alcohol-induced hypertension: Mechanism and prevention

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Abstract

Epidemiological, preclinical and clinical studies established the association between high alcohol consumption and hypertension. However the mechanism through which alcohol raises blood pressure remains elusive. Several possible mechanisms have been proposed such as an imbalance of the central nervous system, impairment of the baroreceptors, enhanced sympathetic activity, stimulation of the renin-angiotensin-aldosterone system, increased cortisol levels, increased vascular reactivity due to increase in intracellular calcium levels, stimulation of the endothelium to release vasoconstrictors and loss of relaxation due to inflammation and oxidative injury of the endothelium leading to inhibition of endothelium-dependent nitric oxide production. Loss of relaxation due to inflammation and oxidative injury of the endothelium by angiotensin II leading to inhibition of endothelium-dependent nitric oxide production is the major contributors of the alcohol-induced hypertension. For the prevention of alcohol-induced hypertension is to reduce the amount of alcohol intake. Physical conditioning/exercise training is one of the most important strategies to prevent/treat chronic alcohol-induced hypertension on physiological basis. The efficacious pharmacologic treatment includes the angiotensin-converting enzyme (ACE) inhibitors or angiotensin Ⅱ type 1 receptor blockers (ARBs) which have antioxidant activity and calcium channel blockers. The most effective prevention and treatment of alcohol-induced hypertension is physical exercise and the use of ACE inhibitors or ARBs in the clinic

Key words: Alcohol; Hypertension; Mechanisms; Prevention/treatment; Vascular endothelium

Core tip: This is a comprehensive review of the current mechanisms of alcohol-induced hypertension and strategies for prevention and treatment of alcohol-related hypertension. This updated review will be imperative to basic scientist in the area of cardiovascular physiology/pharmacology and clinicians in the academic, industry as well as clinics and hospitals.

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INTRODUCTION

Alcohol (ethyl alcohol or ethanol, C_2H_5OH) from fermented grain, fruit juice and honey have been used for thousands of years. Fermented beverages existed and alcoholic drinks used in early Egyptian civilization, in China around 7000 BC, in India, between 3000 and 2000 BC, in Babylon as early as 2700 BC, in Greece, and in South America[1]. In the sixteenth century, alcohol (called "spirits") was used largely for medicinal purposes[2]. At the beginning and mid of the eighteenth century, spirits was

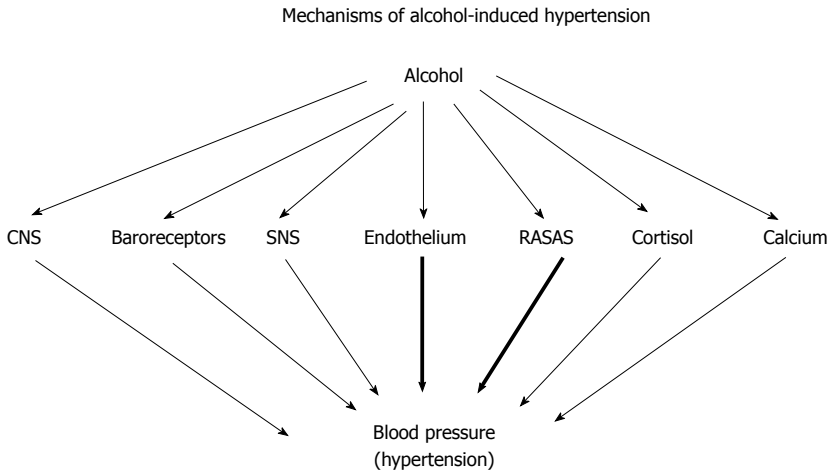

Figure 1 Mechanisms of alcohol-induced hypertension. CNS: Central nervous system; SNS: Sympathetic nervous system; RASAS: Renin-angiotensin system and aldosterone system.

used heavily in Britain. The nineteenth century brought a change in attitudes and the temperance movement began promoting the moderate use of alcohol. In 1920 the United States passed a law prohibiting the manufacture, sale, import and export of intoxicating liquors. Current research suggests that the moderate consumption of alcohol is beneficial to the cardiovascular system and lowers the blood pressure[3-5]. A preclinical study also showed a decrease in systolic blood pressure in rats fed ethanol (1.0 g/kg) for 12 wk[6]. Moderate drinking is generally considered to be: Two drinks a day for men younger than age 65, one drink a day for men age 65 and older and one drink a day for women of any age. A drink is 12 ounces (355 milliliters) of beer, 5 ounces (148 milliliters) of wine or 1.5 ounces (44 milliliters) of 80-proof distilled spirits. Low to moderate drinking has been shown to reduce the incidence of coronary heart disease[3-5] and to increase longevity. It has clearly been a major analgesic, and one widely available to people in pain[1,2,7].

Today, alcoholic beverages are consumed regularly by most of the human societies in the world. However its abuse is a major public health problem in the world. In United States alcohol abuse affects more than 20 million individuals leading to loss of 100000 lives annually[8,9]. Chronic high dose ethanol consumption most commonly causes hepatic, gastrointestinal, nervous and cardiovascular injuries leading to physiological dysfunctions[10]. A cause and effect relationship between regular alcohol consumption and blood pressure elevation (hypertension) was first suggested in 1915 by Lian *et al*[11]. Recent epidemiological and clinical studies have demonstrated that chronic ethanol consumption (more than three drinks per day, 30 g ethanol) is associated with an increased incidence of hypertension and an increased risk of cardiovascular diseases[12-17]. The magnitude of the increase in blood pressure in heavy drinkers averages about 5 to 10 mmHg, with systolic increases nearly always greater than diastolic increases[18]. Similar changes in blood pressure were also reported in preclinical studies[19-22]. In the Framingham cohort[23,24], there was an increase of 7 mmHg in mean arterial pressure when heavy alcohol users were compared with all others. In some epidemiological studies a linear dose-response relationship has been established, sometimes starting with a consumption threshold of 3 drinks per day (30 g of ethanol)[25-33]. In others, the relationship has been nonlinear, especially in women, and some authors have speculated that ingestion of smaller quantities of alcohol may reduce blood pressure[34-38]. Only a few studies have addressed the relationship between alcohol and hypertension in the elderly, and most of them have shown a strong association between hypertension prevalence and alcohol intake[39,40]. However preclinical studies have also shown a linear relationship between blood pressure and ingestion of alcohol[6]. The molecular mechanisms and possible mediators through which alcohol causes vascular injury and raises blood pressure remain elusive. This review focuses the mechanisms implicated with alcohol-induced hypertension and the strategies to control, prevent or to treat alcohol-induced elevation of blood pressure.

MECHANISMS OF ALCOHOL-INDUCED HYPERTENSION

There are several possible mechanisms through which alcohol can raise the blood pressure as shown in Figure 1.

Central nervous system in alcohol-induced hypertension

The World hypertension League speculated that the relatively greater effect alcohol on systolic blood pressure compared with diastolic blood pressure may indicate an imbalance between central nervous system factors influencing cardiac output and the peripheral vascular effects of alcohol[41,42]. There is increasing evidence that alcohol initiates central as well as peripheral reactions which in a synergistic manner have a hypertensive action. In addition, alcohol induces an increased sympathetic outflow, most probably linked to secretion of corticotropin-releasing hormone[43]. Some investigators have suggested that the association between alcohol and hypertension is related to the temporal sequence of alcohol use and blood pressure measurement[24,44]. Since many community programs require an overnight or twelve-hour fasting period, alcohol withdrawal, albeit subclinical, may be oc-

curring. Similarly, patients may abstain or diminish alcohol intake before visiting a clinic or physician. Thus, the observed elevations in blood pressure could be due to excessive central-nervous-system excitability and adrenergic discharge associated with the withdrawal period.

Baroreceptors in alcohol-induced hypertension

Alcohol diminishes the baro (presso) reflex by interacting with receptors in the brain stem, i.e. nucleus tractus solitarii and rostral ventrolateral medulla[43]. Other investigators reported that baroreceptor reflex curves, which indicate the gain in baroreceptor reflex sensitivity, were shifted up and reduced slope in ethanol fed rats when challenged with vasoconstrictors (phenylephrine and angiotensin Ⅱ) compared with controls[45]. This findings and others[42,46,47] suggest the impairment of baroreceptor control and sympathetic system. A greater decrease in heart rate in ethanol treated rats compared with control rats during β-adrenoreceptor blockade with propranolol indicates that the ethanol treated rats had an increased sympathetic activity. An increase in sympathetic activity is consistent with impairment of the baroreceptors that, when activated, inhibit the sympathetic nervous system[45,47]. However this mechanism is implicated more likely in acute alcohol-induced hypertension.

Sympathetic nervous system in alcohol-induced hypertension

Several studies reported increased sympathetic nervous system activation and discharge of sympathetic amines after alcohol consumption[43,48,49]. Alcohol may cause hypertension by affecting the autonomic nervous system[50]. However, alterations in the sympatho-adrenal function that occur during ageing may cause older people to have a different reaction to factors triggering their autonomic system than do younger individuals[51]. The increased sympathetic outflow is expected not only to induce adrenoreceptor-mediated reactions (vasoconstriction, heart rate increase) but to stimulate oxidation reactions[43]. Direct recordings of sympathetic-nerve activity suggest that short-term alcohol ingestion in humans and both short and long-term administration of ethanol in rats stimulates sympathetic-nerve discharge[47,49,50]. Moreover, in rats the alcohol-induced increases in blood pressure and sympathetic activity is centrally mediated[47]. It is possible that alcohol may stimulate adrenals to release adrenaline, resulting in increased heart rate cardiac output and systolic blood pressure[52]. Randin *et al*[53] have also reported that alcohol induces hypertension in rats by sympathetic activation that appears to be centrally mediated. This mechanism is also likely being implicated in alcohol-induced hypertension.

Renin-angiotensin-aldosterone system in alcohol-induced hypertension

The serum levels of vasoactive substances such as renin-aldosterone have been reported to be affected by alcohol ingestion *in vivo* or ethanol *in vitro*[54-56]. Antihypertensive drugs are shown to offer protection against alcohol induced responses in cultured human endothelial cells suggesting the possible involvement of renin-angiotensin system (RAS)[56]. It has been reported that a significant increase in plasma renin activity in patients consuming heavy alcohol compared to mild or moderate alcohol consumption[55,57,58]. However other reports showed no significant in plasma renin activity after alcohol consumption[48,59]. Other studies reported an expansion of the extracellular fluid after alcohol consumption which has been shown to elevate the systolic blood pressure in rats[60,61]. Chan *et al*[60] have proposed that expansion of the extracellular fluid is the result of elevated plasma vasopressin levels and plasma renin activity, indicating increased sympathetic stimulation. Recent studies have shown a significant increased in blood and aortic angiotensin II levels after alcohol ingestion in rats[62,63]. Okuno *et al*[64] have reported prolonged elevation of serum angiotensin converting enzyme (ACE) activity in alcoholics suggests that angiotensin Ⅱ levels are elevated due to activation of ACE activity. Alcohol ingestion in dogs caused sustained RAS activation with progressive increases in plasma levels of Angiotensin Ⅱ, renin activity, left ventricular ACE enzyme activity, and left ventricular myocyte Ang Ⅱ AT1 receptor expression[65]. This mechanism is more likely implicated in alcohol-induced hypertension.

Cortisol in alcohol-induced hypertension

Certain studies have implicated the role of cortisol in alcohol-induced rise in blood pressure[66-68]. Potter *et al*[66] have reported a significant rise in plasma cortisol levels following alcohol consumption and a drop in plasma cortisol levels when alcohol intake was discontinued. Increased cortisol levels in regular alcohol drinkers may be due to direct stimulation of adrenocorticotropin hormone or potentiation of corticotropin releasing hormones by arginine vasopressin[67]. The effect of blood pressure may be due to the mineralocorticoid activity of cortisol or catecholamine hypersensitivity[68]. Alcohol stimulates the secretion of corticotrophin releasing hormone in rats[69,70] leading to stimulation of cortisol secretion[71], sympathetic stimulation and hypertension in rats. However this mechanism is implicated more likely in acute alcohol-induced hypertension.

Increased intracellular calcium and vascular reactivity in alcohol-induced hypertension

Rats treated with ethanol showed constriction of blood vessels[72] due to greater shifts in the binding of the calcium ion (Ca^{2+}) in arterial and arteriolar smooth muscle cells causes increased sensitivity to endogenous vasoconstrictors. This finding is consistent with other reports showing the shifts of the extracellular Ca^{2+} to intracellular space increase the vascular sensitivity to vasoconstrictor norepinephrine[50,61]. It is proposed that alcohol increases intracellular Ca^{2+} by (1) direct upregulation of voltage-gated Ca^{2+} channels; (2) inhibition of Ca^{2+}-adenosine triphosphatase (Ca^{2+}-ATPase) that extrudes Ca^{2+} from the cells; and (3) magnesium ion (Mg^{2+}) depletion that inhibits the sodium ion (Na^{+})-potassium

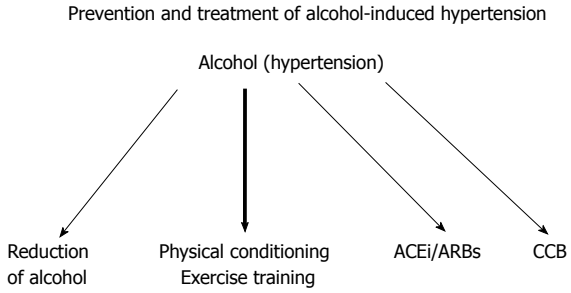

Figure 2 Prevention and treatment of alcohol-induced hypertension. ACEi/ARBs: Angiotensin converting enzyme inhibitor/Angiotensin receptor blockers; CCB: Calcium channel blockers.

ion (K^+) pump (Na^+/K^+-ATPase), causing a build up of intracellular Na^+. This reaction in turn inhibits the Na^+/Ca^{2+} exchanger, thereby increasing the intracellular calcium ion[50,61,72,73]. Chronic alcohol ingestion has been reported to induce a deficiency of blood and intracellular magnesium, which influences cellular Ca^{2+} homeostasis through attenuation of plasmalemmal ATPase activity[74]. Vasdev *et al*[75] have shown that increases in cytosolic free calcium and calcium uptake are associated with ethanol-induced hypertension in rats. Intra-arterial infusion of ethanol has been shown to reduce hand and forearm blood flow in humans[76]. This effect could be the result of a direct vasoconstriction or of a loss of endothelium dependent vasorelaxation[77]. However earlier studies in rats demonstrated no significant response of alpha-adrenergic receptor-mediated constriction of aorta after chronic ethanol ingestion in rats[45,78-80]. On the other hand, the endothelium-dependent relaxation elicited by acetylcholine was diminished in chronic alcohol-induced hypertension[77]. Our earlier study also demonstrated the role of endothelium-independent responses in the aorta of chronic alcohol treated hypertensive rats[79,80]. Inconsistencies among several reports render this mechanism of alcohol-induced hypertension less implicated.

Endothelium and oxidative stress in alcohol-induced hypertension

Imbalance of specific endogenous vasoconstrictor such as angiotensin Ⅱ, endothelin-1 and nor-epinephrine and vasodilator nitric oxide (NO) may also play an important role in alcohol-induced hypertension. Alcohol stimulates the release of endothelin 1 and 2 from vascular endothelium in a dose dependent manner[81]. Alcohol also increases the angiotensin Ⅱ levels in the blood and vessels[62,63]. Endothelin 1 and 2 as well as angiotensin Ⅱ are known to be potent vasoconstrictors of the blood vessels[63,81]. Angiotensin Ⅱ stimulates superoxide production via AT_1 receptor, by activating NADPH oxidase in the vascular wall[82,83]. Superoxide productions through NADPH oxidase activation ($p22^{phox}$ expression) has been demonstrated in rats made hypertensive with angiotensin Ⅱ infusion[84]. Chronic ethanol ingestion induces hypertension which is correlated with elevated tissue angiotensin Ⅱ levels, and activation of NADPH oxidase activity causing endothelial injury in rats[62,79,80]. It is possible that alcohol ingestion raises the blood pressure by decreasing the vasodilators such as NO in the vascular endothelium either due to inhibition of endothelial nitric oxide synthase (eNOS) or inflammatory/oxidative injury to the endothelium. Earlier studies have also shown that chronic ethanol consumption either interferes with NO production or release of NO from endothelial cells[80,85-87]. The diminished NO bioavailability may either be related to reaction with superoxide anion to form peroxynitrite radicals[88] or oxidative inactivation/uncoupling of eNOS by ethanol-induced free radicals[80,89,90]. The production of NO in the endothelium is critically dependent on the function of eNOS which is regulated by vascular endothelial growth factor[91,92]. Alcohol inhibits the enzyme that converts arginine into NO[93] as well as eNOS protein expression[80]. In the endothelium, depletion of NO production or NO reaction with superoxide anion to form toxic peroxynitrite radical which causes endothelial injury, impairment and hypertension in alcohol treated rats[20-22,62,80,94]. Recent studies have shown that chronic ethanol ingestion induces hypertension which was related to increased aortic inflammation, elevated angiotensin II levels, induction of NADPH oxidase causing endothelial injury, depletion of antioxidants, down-regulation of endothelial NO generating system and impaired vascular relaxation in rats[6,19-22,62,80]. This mechanism is most likely implicated in chronic alcohol-induced hypertension.

PREVENTION AND TREATMENT OF ALCOHOL-INDUCED HYPERTENSION

There are few strategies for the control, prevention and treatment of alcohol-induced hypertension as shown in Figure 2.

Studies have shown that a reduction in alcohol intake is effective in lowering the blood pressure both in hypertensives and normotensives and may help to prevent the development of hypertension[12,41,95,96]. Heavy drinkers who cut back to moderate drinking can lower their systolic blood pressure by 2 to 4 mm of mercury (mm Hg) and their diastolic blood pressure by 1 to 2 mmHg. Heavy drinkers who want to lower blood pressure should slowly reduce how much they drink over one to two weeks.

Another non-pharmacological prevention and treatment of alcohol-induced hypertension is physical conditioning or exercise training. There is a physiological basis for effect of physical conditioning on chronic alcohol-induced hypertension in a rat model. Exercise increases the utilization of oxygen in the body and up-regulate the antioxidant defense system in the cardiovascular system[97-100]. Exercise training also generates NO in the cardiovascular system by induction of nitric oxide synthase[19,79,90,101]. Recent studies have shown the beneficial role of physical training in the control of blood pressure in humans[97,98,102,103] and experimental animals[79,90,104,105]. Physical inactivity and overweight trigger hypertension[106,107] whereas; regular physical activity has been shown to decrease the BP and body weight[102,103]. Stud-

ies have shown that physical conditioning is beneficial in lowering the BP through suppression of weight gain in chronic ethanol treated hypertensive rats[19,79]. Physical conditioning attenuates the chronic ethanol-induced hypertension by augmenting the NO bioavailability and reducing the oxidative stress response in rats[19,79,108].

PHARMACOLOGICAL TREATMENT OF ALCOHOL-INDUCED HYPERTENSION

There are no definite clinical data available on the efficacy of specific drugs in the treatment of alcohol-induced hypertension. Randin *et al*[53] have reported that dexamethasone (2 mg per day) in human suppresses the acute alcohol-induced hypertension. It is suggested that ACE inhibitors/angiotensin Ⅱ receptor type 1 (AT_1) blockers, because of their ability to increase the cardiac output in patients with alcohol-induced cardiomyopathy will be useful in the treatment of alcohol-induced hypertension. Cheng *et al*[65] have shown that angiotensin Ⅱ type 1 receptor blockade prevents alcoholic cardiomyopathy in dogs. The calcium channel blockers, because of the probability of the involvement of calcium in the development of alcohol-induced hypertension, may also likely be the drug of choice for the treatment of alcohol-induced hypertension.

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