European Society of Hypertension Scientific Newsletter:
Update on Hypertension Management
2004; 5: No. 22

HIGH BLOOD PRESSURE, ALCOHOL AND CARDIOVASCULAR RISK

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Introduction

More than 50 prospective population or cross-sectional studies have established a close association between regular alcohol consumption and high blood pressure (BP), consistently showing a linear dose-response relationship starting with a consumption threshold of 3 drinks per day (30 g of ethanol) (1-2). However, men who consume 1-2 drinks per day and women who drink half of this amount do not show significant changes in BP (3) or even significant reductions in BP compared to abstainers (4), suggesting that the pressor effects of alcohol may follow a "J" shape curve (5). Several aspects of the data obtained from different studies suggest a causal relationship between high ethanol intake and an increase in BP. Thus, reduction of alcohol intake lowers BP, whereas continued intake impairs response to antihypertensive treatments.

Intervention studies carried out in human subjects in order to confirm epidemiological data have shown inconsistent results with either an increase or a decrease in BP with alcohol administration, even when ambulatory BP monitoring (ABPM) was used for accurate measurement (6-7). These conflicting results may be due to differences in rate, dose, route of ethanol administration, time interval to BP pressure measurement, and, probably, psychic factors in the reported studies. However, a meta-analysis of randomized controlled trials, in which alcohol reduction was the only intervention difference between active and control treatment groups, showed a significant reduction in mean (95% confidence interval) systolic and diastolic BP of – 3.31 mm Hg (-2.52 to -4.10 mmHg) and -2.04 mmHg (-1.49 to 2.58 mmHg), respectively. These reductions in BP would be expected to result in a 6 % reduction in the risk of coronary heart disease, and a 15% reduction in the risk of stroke and transient ischemic attacks (8).

Mechanisms of alcohol-related hypertension

The differences observed in the results of previous studies suggest that pressor effects seem to be heterogeneous. Similar to the effects of salt intake on BP, when the effects of ethanol intake on BP are analyzed, two populations may be encountered, one sensitive to ethanol and another resistant to the pressor effects of ethanol. In our experience, half of the normotensive and four-fifths of the alcohol dependent patients with high blood pressure show significant changes in 24-h mean BP and may be classified as sensitive to alcohol, whereas the remaining should be considered resistant to the pressor effects of alcohol (9). The results of this study and others (10) suggest that genetic factors play an important role in the pathogenesis of ethanol-related hypertension.

Although the basis of the association between alcohol intake and hypertension has not yet been established, the following mechanisms have been proposed: 1) Activation of the renin-angiotensin-aldosterone axis; 2) Adrenergic nervous system discharge; 3) Cortisol secretion; 4) Reduction of insulin sensitivity with impairment of glucose tolerance, which may also favor fat storage and dyslipe-mia; 5) Heart rate variability; 6) Direct effects of ethanol on peripheral muscle tone, via changes in calcium or sodium transport into smooth muscle cells; and 7) Endothelial dysfunction due to ethanol that may induce changes in the relaxant capacity of the endothelium and decrease the release of nitric oxide (Table 1) (11-14).

Table 1. **Mechanisms involved in the pathogenesis of ethanol-related hypertension**

- Genetic factors
- Stimulation of the renin-angiotensin-aldosterone axis
- Abnormal sympathetic stimulation
- Increased cortisol secretion
- Reduction of insulin sensitivity with changes in glucose tolerance
- Heart rate variability
- Effects on peripheral muscle tone, via changes in calcium or sodium transport into smooth muscle cells
- Endothelial dysfunction

Some authors have also suggested that the association of alcohol and hypertension may be due to withdrawal from alcohol. However, in intervention studies, no differences in plasma adrenaline or noradrenaline values were observed when the patients did or did not receive ethanol and alcohol withdrawal syndrome were excluded. In addition, if hypertension was related to alcohol withdrawal, BP would be higher when alcohol dependent patients give up alcohol. Finally, epidemiological studies (15) have related changes in BP to obesity, cigarette smoking, coffee, tea, total cholesterol, uric acid, potassium and calcium, and experimental studies have suggested that alcohol-induced hypertension could be related to magnesium depletion. However, in intervention studies performed to evaluate the pressor effects of ethanol, no significant differences were observed in plasma ionic and metabolic parameters of chronic alcoholics between the measurements obtained when they received ethanol and when they only received the placebo. These data suggest that the short-term effects of ethanol are not related to any change in plasma hormones or ions.

Clinical features

The clinical relevance of the magnitude of changes in BP after ethanol withdrawal should also be considered. In some intervention studies, the average change of 24-hour mean BP was -8.4 mmHg in the alcohol-sensitive normotensive patients and -12.5 mm Hg in the alcohol-sensitive hypertensive subjects (Fig. 1). In epidemiological studies, reductions of only 2 or 3 mm Hg in BP in the whole population have the same effect on mortality as anti-hypertensive treatment. Since the reductions of BP observed in the intervention studies after alcohol withdrawal were between two to six-fold greater than these figures, the changes should be considered as clinically relevant (9).

On the other hand, ethanol-sensitive alcohol dependent patients have shown a significantly lower left ventricular ejection fraction and a significantly greater left ventricular mass than ethanol-resistant patients (Table 2). In this respect, one may wonder whether the former group of alcohol dependent patients is more sensitive to the effects of ethanol intake on the whole cardiovascular system or whether the changes observed in ethanol-sensitive patients are secondary to a relatively higher BP than ethanol-resistant alcohol dependent patients. Since no significant differences were observed in the BP parameters, alcohol dependent subjects sensitive to the pressor effects of ethanol may also be more sensitive to the effects of ethanol on the myocardium (9). Thus, an echocardiography and/or radionuclide ventriculography should be performed in all alcoholics with ethanol-induced hypertension in order to rule out left ventricular dysfunction or dilated cardiomyopathy.

Table 2. **Clinical and laboratory data of the alcoholic patients who were classified as sensitive to the pressor effects of ethan-ol compared to those classified as resistant (non-sensitive) in a series of 35 normotensive chronic alcoholics (from ref. 9).**

	Sensitive (n = 18)	*Non-sensitive (n = 17)*
Age *y*	39.8 ± 7.1	39.5 ± 8.0
Daily ethanol intake *g*	219 ± 86	214 ± 72
TLDE *kg/kg*	21.9 ± 13.3	19.3 ± 10.7
SBP *mm Hg*	122 ± 7	121 ± 10
MBP *mm Hg*	92 ± 5	91 ± 7
DBP *mm Hg*	78 ± 6	77 ± 7
End-diastolic diameter *mm*	52.4 ± 2.7*	50.5 ± 3.5
End-systolic diameter *mm*	34.2 ± 3.0	32.8 ± 3.4
Interventricular thickness *mm*	10.4 ± 1.4	8.2 ± 0.8
Posterior wall thickness *mm*	9.8 ± 1.2	8.5 ± 0.7
Left ventricular mass g/m^2	131.7 ± 22.3	95.4 ± 17.1
Shortening fraction %	34.8 ± 3.8	35.7 ± 4.7
Ejection fraction %	52.6 ± 6.1	57.8 ± 4.9
m - cortisol *nmol/L*	451 ± 163	513 ± 155
e - cortisol *nmol/L*	206 ± 108	246 ± 138
PRA *pmol of angiotensine* h^{-1} ml^{-1}	0.68 ± 0.99	0.68 ± 0.66
Aldosterone *ng/dL*	402 ± 280	460 ± 272
ANP *fmol/mL*	18.1 ± 22.5	14.1 ± 13.4
Noradrenaline *pg/mL*	260 ± 137	246 ± 80
Adrenaline *pg/mL*	71 ± 36	61 ± 33
Insulin *pmol/L*	112 ± 71	120 ± 75
SGOT (U/L)	59.7 (15 - 357)	33.1 (9 - 101)
SGPT (U/L)	47.9 (15 - 128)	39.3 (8 - 79)
GGT (U/L)	199 (10 - 885)	116 (21 - 600)

TLDE: total lifetime dose of ethanol; SBP: systolic blood pressure; MBP: mean blood pressure; DBP: diastolic blood pressure; m: morning; e: evening; PRA: plasma renin activity; ANP: atrial natriuretic peptide; SGOT: serum glutamic oxalacetic transaminase; SGPT: serum glutamic pyruvic transaminase; GGT: gammaglutamyl transferase; *P = 0.078: P < 0.001; P = 0.010.

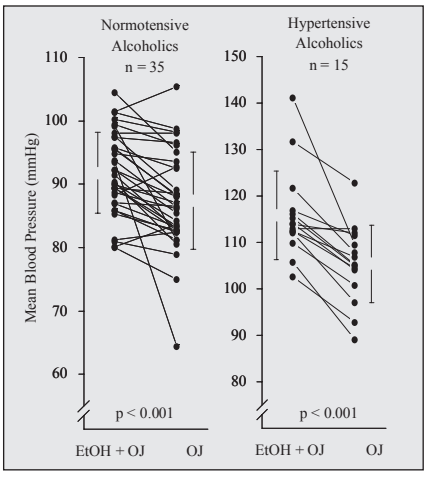

Figure 1. Mean blood pressure (MBP) values measured by 24-h ABPM during intake of 150 g of ethanol mixed with orange juice (day 1) and during orange juice alone intake (day 3). More than half of the normotensive alcohol dependent subjects and most of the hypertensive alcohol dependent subjects showed a significant reduction in mean BP between days 1 and 3. EtOH + OJ: ethanol mixed with orange juice; OJ: orange juice alone. The summary statistics are represented by the mean (open circles) and one standard deviation up and down of the mean (vertical lines up and down the mean) of the MBP with and without ethanol. P values correspond to comparisons between MBP for each subject obtained with (EtOH + OJ) and without (OJ) ethanol intake (paired t-test) (from 9).

Alcohol intake in the management of hypertension

The first step in the management of hypertension in alcohol dependent patients should be to give up ethanol (7). In most of these patients BP will reduce to normal values within the following days and they will not need pharmacological treatment. Because of the high prevalence of myocardial dysfunction and dilated myocardiopathy among chronic alcoholics, angiotensin converting enzymes inhibitors, angiotensin II receptor antagonists and/or beta blockers are commonly used to treat these patients. However, the rapid reduction of BP on cessation of alcohol intake makes close monitoring of BP and pharmacological treatment necessary during the first month of abstinence. Non-alcohol dependent patients with hypertension should limit their alcohol consumption to two drinks or fewer per day, and weekly intake should not exceed 14 standard drinks for men and nine standard drinks for women (16).

Alcohol and risk of cardiovascular disease

Several epidemiological studies have observed that alcohol has a biphasic cardiovascular effect which depends on the dose of alcohol ingested. At low to moderate doses, alcohol has a favourable (protective) impact on cardiovascular outcome (17-19). Patients who have one to two glasses of alcohol per day had fewer myocardial infarctions and an improved survival. This information suggests that low to moderate consumption of alcohol improves cardiovascular risk and this benefit exceed the risk of hypertension and heart failure. However, it is equally important to recognize the serious adverse effects due to high alcohol ingestion. With chronic high-dose alcohol intake, there is a direct relationship to elevated BP. In addition, prolonged exposure to alcohol increases the likelihood of developing congestive heart failure, liver disease and other ethanol-related diseases (20).

Conclusions

Many prospective population and cross-sectional studies have shown a highly significant association between the consumption of three or more alcoholic drinks per day and hypertension. The mechanisms of the ethanol-induced hypertension have been related to genetic factors (sensitivity to the pressor effects of ethanol) and changes in sympathetic modulation, cortisol, the renin-angiotensin system, insulin sensitivity and endothelial activity. Many patients with ethanol-induced hypertension also show other toxic effects of alcohol on the cardiovascular system such as left ventricular dysfunction and/or dilated cardiomyopathy. The goal in the treatment of ethanol-induced hypertension in chronic alcoholics is to give up alcohol. However, non-dependent patients may limit their ethanol intake to two drinks per day in men and one drink per day in women, since several studies have suggested that these doses of ethanol may exert a protective effect on the development of atherosclerosis and cardiovascular morbidity and mortality.

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