The effects of alcohol on local, neural and humoral cardiovascular regulation

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Introduction
Cardiovascular actions of alcohol have long been recognized [1] and extensively studied. However, the recent recognition of an association between alcohol consumption and hypertension [2] has led to a renewed interest in the effects of alcohol on cardiovascular regulation. This article reviews the acute and chronic effects of alcohol on the cardiovascular system and discusses possible mechanisms by which alcohol consumption may elevate blood pressure.

Effects of alcohol on blood pressure, heart rate and cardiac function
Acute alcohol administration to man or animals has variable effects of relatively small magnitude on blood pressure [3]. When taken orally, an immediate pressor effect which occurs as a reflex response to gastrointestinal irritation is usually seen [1, 4–6]. In the supine position this may be followed by either a slight rise in blood pressure [5, 7, 8] usually seen with lower doses, no change [9–15], or a fall in blood pressure, usually with higher doses and at later observation times [4, 16–20]. In contrast to the variable effects on supine blood pressure, nearly all studies have shown an increase in heart rate [4–6, 8, 14, 15, 18, 20]. This probably occurs as a reflex response to preserve blood pressure after arteriolar and venous dilatation [21], or volume depletion as a consequence of alcohol induced diuresis [22]. Acute alcohol administration after autonomic blockade with propranolol and atropine causes a consistent fall in blood pressure [23, 24] and acute alcohol administration enhances the blood pressure fall in response to haemorrhage [25] and orthostasis [26]. Furthermore, acute alcohol administration causes a fall in blood pressure in persons with cardiac failure, possibly because they do not possess an adequate reserve of cardiac output to respond to the reduction in preload or afterload [27, 28].

Acute alcohol administration causes a dose dependent impairment of cardiac function in animals and man [7, 11, 12, 16, 29–35]. This effect is more readily demonstrated in isolated heart preparations [31] or with direct measurements of myocardial contractility [29, 32], which exclude the confounding effects of alcohol on the peripheral circulation. In intact animal preparations and in man, moderate levels of alcohol may have no net effect [36] or actually lead to an increase in cardiac index and apparent increase in contractility because of a reduction in afterload [15, 37]. Similarly, the measurement of changes in systolic time intervals without correction for changes in afterload may lead to an overestimation of myocardial depression at low levels of alcohol [37–39].

Less is known about the effects of chronic alcohol consumption on cardiovascular function than about the effects of acute administration. Blood pressure increases with the amount of alcohol consumed in population studies [2] and chronic alcoholics have higher blood pressures and a higher incidence of hypertension than moderate drinkers or teetotallers [40–42]. However, the pressor effect of chronic alcohol consumption has not always been observed in animals [43–45]. Chronic exposure to high levels of alcohol may lead to a progressive impairment of myocardial function and the eventual development of cardiomyopathy in both animals [43] and man [46].

Direct effects of alcohol and acetaldehyde on blood vessels
Depending upon the dose and the vascular bed studied, alcohol generally causes vasodilatation of
both arteries and veins in vivo and in vitro [21]. At concentrations ranging from 1 to 100 mmol/l alcohol inhibits spontaneous contractile activity in rat aorta, mesenteric vessels and portal veins [21, 47–49]. At low concentrations (around 1 mmol/l) alcohol potentiates vasoconstrictor responses to noradrenaline, adrenaline, vasopressin and prostaglandin F₂ [21, 47, 50]. However, at levels such as would be seen with mild intoxication in man, responses to all vasopressor substances are non-specifically impaired [21]. At very high alcohol levels (greater than 100 mmol/l) alcohol has direct vasoconstrictor effects in probably all vascular beds [21, 51]. This vasoconstriction is antagonized by calcium channel blockers [21] but not by specific antagonists of pressor hormones and neurotransmitters. In certain vascular beds such as the cerebral circulation [52], coronary arteries [53], umbilical arteries [54] and possibly the pulmonary vasculature [55] alcohol exerts direct vasoconstrictor effects at all concentrations ranging from 1 mmol/l to greater than 100 mmol/l.

Acetaldehyde, the major metabolite of alcohol, has similar direct effects to alcohol on blood vessels with the exception that in some vascular beds, such as portal vein, it produces vasoconstriction rather than vasodilation. Acetaldehyde can facilitate noradrenaline release [56] and thus the density of sympathetic innervation to a vascular bed may determine whether the net effect of acetaldehyde is vasodilation or sympathetic mediated vasoconstriction [57]. Acetaldehyde also differs from alcohol by not potentiating vasoconstrictor responses to noradrenaline, adrenaline or vasopressin at low concentrations [21]. Although the action of acetaldehyde on vascular tissue is in many ways similar to that of alcohol, the concentration of this metabolite is only 0.5% of tissue alcohol concentrations [58]. Furthermore, since acetaldehyde is oxidized at the same rate as ethanol, the metabolite does not accumulate with repeated dosing [58]. It is, therefore, probable that the cardiovascular effects of acetaldehyde are relatively unimportant compared with those of alcohol.

There is evidence that the vasodilator effects of alcohol may be a result of impaired intracellular calcium availability, and that the constrictor responses seen at low alcohol levels in some vascular beds and at high alcohol levels in all vascular beds may be due to increased calcium availability [21, 59]. Tolerance to the direct vasodilator effects of alcohol and to inhibition of vasoconstrictor responses by alcohol has been shown in rats regularly consuming alcohol for several weeks [21]. Whether tolerance also develops in vascular beds which usually respond to alcohol with vasoconstriction is unknown.

**Effect of alcohol on neural conduction**

Acute alcohol administration in vitro inhibits neurone action potentials at higher concentrations, and decreases action potential magnitude and duration [60–63]. This probably results from alcohol being incorporated into and altering the properties of the lipid layer of cell membranes [64], leading to a suppression of the inward movement of Na⁺. This effect is similar to that seen with general anaesthetics [21] and may explain the observation that acute alcohol administration inhibits electrically stimulated neurotransmitter release [65]. Alcohol can lower resting membrane potentials in vitro [60, 62, 66–68], which may explain the observation that acute alcohol increases spontaneous, in contrast to stimulated, noradrenaline release [69, 70]. It should be emphasized that these effects of alcohol on resting membrane potentials have been demonstrated only with high levels of alcohol in animal preparations. Their relationship, therefore, to the acute effects of alcohol in doses that are used in man and animals is uncertain. There is little information concerning the effects of chronic alcohol consumption on neural conduction.

**Effects of alcohol on sympathetic activity and noradrenaline metabolism**

Acute alcohol administration increases urinary noradrenaline and adrenaline excretion in both animals and man [71–79]. Although part of the increased catecholamine excretion may be a consequence of alcohol induced diuresis [75], additional evidence indicates that alcohol can acutely increase adrenal catecholamine release [80] and elevate plasma noradrenaline levels [6, 26, 35, 74, 81]. Urinary catecholamine excretion remains elevated during chronic intoxication in alcoholics [79] and during alcohol withdrawal [78, 82], although plasma noradrenaline levels appear to be unaltered by chronic alcohol consumption in man [41, 83]. Plasma noradrenaline levels [84] and dopamine-β-hydroxylase activity [42, 85] are elevated in alcoholics during withdrawal.

There is evidence from animal studies that acute alcohol administration can facilitate spontaneous, but not stimulated, noradrenaline release from central and peripheral noradrenergic neurones [68–70, 80]. This is associated with an acute reduction in noradrenaline turnover in brain and heart [86] but an increased turnover in the adrenal medulla of rats [80]. Chronic alcohol consumption increases central and peripheral noradrenaline turnover in rats [86, 87] and increases adrenal tyrosine hydroxylase and dopamine-β-hydroxylase activity [80]. However, chronic alcohol consumption may diminish the rise
in urinary noradrenaline excretion evoked by an acute dose of alcohol in man [70, 88]. Noradren-
aline turnover in animals is further increased in the first 48 h after alcohol withdrawal, after which it returns to normal [86, 87]. This corresponds with clinical signs in man suggestive of sympathetic over-
activity [42] and with an elevation of plasma nor-
adrenaline levels [84] and urinary catecholamine excretion [78, 82] during alcohol withdrawal.

Cerebrospinal fluid noradrenaline and 3-meth-
oxy-4-hydroxyphenylethylene glycol (MHPG: a nor-
adrenaline metabolite) levels are also increased in man during alcohol withdrawal [89–91], suggesting an elevation of central, as well as peripheral, nor-
adrenergic activity. Part of the increase in adrenal tyrosine hydroxylase and dopamine-β-hydroxylase activity after chronic alcohol consumption is dependent upon the integrity of the adrenal nerves, indicating that some of the increased adrenomedul-
lar activity is of central origin [80].

Repeated administration of alcohol to rats de-
creases α-adrenoceptor numbers measured by radioligand binding techniques in brain and liver [92, 93]. This may represent down-regulation as a consequence of increased noradrenergic activity or a specific effect on cell membrane structure [93]. Similarly, α2-receptor-mediated changes in insulin and growth hormone release are attenuated in chronic alcoholics [94]. However, the effect of alco-
hol on β-receptors is less clear. Acute alcohol administration has been reported to lower β-
adrenoceptor binding in the hearts and brains of rats [95] and to either elevate [95] or not alter [96] cardiac and central β-receptor levels during alcohol withdrawal. Elevated β-receptor numbers during alcohol withdrawal is contrary to what would be expected to accompany an increase in noradrenergic activity and associated α-receptor down-regulation. Sellers et al. [97] have suggested that increased central β-receptor responsiveness leads to the ele-
vated sympathetic outflow during alcohol withdraw-
al, and have demonstrated that the centrally active β-blocker propranolol can prevent the rise in urinary noradrenaline excretion during alcohol withdrawal.

Alcohol may also alter the metabolism of nor-
adrenaline in some tissues. An increase in the ratio of urinary MHPG in vanillylmandelic acid (VMA) has been observed after acute alcohol administra-
tion in man [79, 98, 99], suggesting a shift from oxidative to reductive metabolic pathways. This may occur because of an alteration in intracellular redox potential and an increase in the ratio of NADH to NAD. However, a similar alteration in MHPG:VMA ratios was not observed in rat brain [86], consistent with observations that intracellular redox potentials change after acute alcohol admini-
stration in liver but not in brain [100]. Since the majority of noradrenaline released from noradren-
ergic neurones is metabolized to 3,4-dihydroxy-
phenylethylene glycol after re-uptake [101], these acute effects of alcohol on urinary MHPG and VMA are of uncertain significance.

Effects of alcohol on the renin–angiotensin system

Acute alcohol administration in man and rats causes either a fall [102] or no change [103] in plasma aldosterone levels over the first few hours, followed by a rise [102, 104]. Plasma renin activity is elevated during the hangover phase after acute alcohol administration [102] and possibly during the phase of intoxication when plasma aldosterone levels are elevated [105]. The rise in plasma renin activity after acute alcohol administration may be purely secondary to hypovolaemia [3]. The observa-
tion that plasma aldosterone levels were elevated before a rise in plasma renin activity [102] may indicate that a part of the increase in plasma aldo-
sterone levels occurs because of an early rise in plasma ACTH, which is also responsible for elevated plasma cortisol levels [106]. Plasma renin activity and aldosterone levels appear to rise with chronic alcohol consumption in man, and return to normal about 48 h after withdrawal [41, 85]. This may be a consequence of increased sympathetic activity associated with chronic alcohol consump-
tion and withdrawal or a response to hypovolaemia [3, 85]. However, there is evidence that chronic alcoholics become isosmotically overhydrated rather than volume depleted [107].

Effects of alcohol on plasma vasopressin (AVP)

Alcohol causes an acute suppression of AVP secre-
tion, which is responsible for the diuresis that follows acute alcohol consumption [22, 108, 109]. After alcohol levels reach a maximum, and during the hangover phase, plasma AVP levels rise above control values, probably in response to volume depletion [108]. Plasma AVP levels are also ele-
vated after chronic alcohol consumption and during alcohol withdrawal [85]. The observation that chronic alcoholics are isosmotically overhydrated [107] suggests that AVP levels are inappropriately elevated. It has been suggested that this may be a contributory factor to blood pressure elevation during chronic alcohol consumption [110]. How-
ever, although AVP is a potent vasoconstrictor in some vascular beds, elevation of plasma AVP levels to the concentrations observed in alcoholics does not appear to increase blood pressure [111, 112].
Effects of alcohol on plasma cortisol and ACTH

Acute alcohol administration increases plasma cortisol levels in man, probably via an effect on the pituitary or hypothalamus leading to increased ACTH release. Plasma cortisol levels are also elevated after chronic alcohol consumption and during alcohol withdrawal. Plasma cortisol levels have been shown to correlate positively with blood pressure in both drinkers and non-drinkers and with blood pressures in alcoholics during alcohol withdrawal. The significance of these relationships between plasma cortisol levels and blood pressure are at present uncertain. It is possible that cortisol is elevated as a result of raised ACTH levels rather than cortisol levels, because of ACTH-stimulated mineralocorticoid secretion or a direct effect of ACTH on blood pressure.

Alcohol and calcium metabolism

Arkwright et al. found a positive correlation between plasma ionized calcium levels and blood pressure in drinkers but not in teetotallers, and have suggested that chronic alcohol consumption induces changes in vascular smooth muscle membrane transport that makes intracellular free calcium levels and vascular tone dependent upon the prevailing extracellular calcium concentrations. Previous studies have reported either elevated or lowered plasma calcium levels in hypertensives compared with normotensives, but have not described the drinking habits of the groups studied. It is possible that the discrepancies between these studies are due to differences in the proportion of drinkers present. Previous epidemiological studies have shown a weak positive correlation between plasma calcium and blood pressure. It is possible that this association is a result of the effects of chronic alcohol consumption on cell membrane calcium exchange, and that the association would have been more apparent if drinkers and non-drinkers had been considered separately.

Conclusions

Acute alcohol administration appears to impair cardiac and vascular smooth muscle contractility in animals and man, producing a tendency for blood pressure to fall. This may be aggravated by hypovolaemia after an alcohol induced diuresis. In the healthy, intact organism, the tendency for blood pressure to fall is compensated by an increase in heart rate and cardiac output, and may be manifested only in the erect position. The increase in plasma noradrenaline that follows acute alcohol administration appears to be largely unrelated to the acute haemodynamic changes, and alterations in plasma renin activity and aldosterone levels are probably a result of hypovolaemia.

In contrast to the acute effects of alcohol, chronic alcohol consumption causes a rise in blood pressure in man. However, this has not always been observed in rats, suggesting species variation. The haemodynamic mechanisms that underlie alcohol-associated hypertension have not yet been investigated, and the relative contributions of changes in cardiac output and vascular resistance are unknown. Several mechanisms could be involved in the pressor effect of regular alcohol consumption. There is strong evidence in animals and in chronic alcoholics that repeated alcohol administration and alcohol withdrawal leads to an increase in sympatho-adrenomedullary activity. This probably results from a combination of an enhanced sensitivity of peripheral noradrenergic neurones and an increase in neural outflow from the central nervous system. It is, therefore, possible that alcohol-related hypertension is predominantly neurogenic. Elevated plasma renin activity in chronic alcoholics during alcohol withdrawal may also result from an increase in sympathetic activity. However, it has not been possible to demonstrate increases in indices of sympathetic or renin-angiotensin system activity in moderate drinkers compared with controls, or in hypertensives while regularly drinking alcohol compared with a period of abstaining from alcohol. This may reflect a lack of sensitivity of the techniques used to measure sympathetic and renin-angiotensin system activity.

Alcohol may raise blood pressure by increasing ACTH release. This could explain the correlation between plasma cortisol levels and blood pressure in drinkers (and non-drinkers) and in chronic alcoholics undergoing alcohol withdrawal. However, the mechanism underlying such an association is obscure, as cortisol is not known to elevate blood pressure. It is possible that elevated ACTH levels after alcohol raise blood pressure through direct or mineralocorticoid effects, and that the association between blood pressure and cortisol levels is fortuitous.

Further possibility is that chronic alcohol consumption induces adaptive changes in membrane transport, leading to an increased sensitivity of all excitable tissue. An altered vascular permeability to calcium, as suggested by Arkwright et al., could lead to a generalized increase in vascular reactivity and explain the correlation between plasma free calcium levels and blood pressure in...
drinkers. An increase in the sensitivity of excitable
noradrenaline metabolites in the central nervous
peripheral noradrenaline turnover that follows
increase in metabolites of other neurotransmitters
consumption
system does not appear to be accompanied by an
on local, neural and humoral cardiovascular regula-
the chronic effects are less certain. In particular, the
rise in blood pressure remain to be determined.

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