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The association between alcohol consumption and heart disease has been recognized for over a century but it was not until 1964 that this link became firmly established with the description of a cardiomyopathy attributed to alcohol abuse.[1] This alcohol-induced heart muscle disease has been shown to occur in the absence of caloric or vitamin deficiencies,[2] and it may be the most common cause of cardiomyopathy in certain populations.[3] The pathophysiology of this disorder has remained unclear, because the connection between alcohol ingestion and the reported biochemical sequelae of alcohol exposure in the heart, such as decreased fatty acid oxidation and triglyceride accumulation, has remained unknown. In 1981, direct metabolism of ethanol by myocardium was first reported with the description of fatty acid ethyl ester synthesis.[4] This metabolic pathway provides a potential molecular understanding for the manner in which heart disease is engendered by alcohol abuse, which may have important diagnostic and therapeutic implications.

Alcohol abuse principally affects the heart and cardiovascular system in four ways. First, much epidemiological evidence has recently emerged to indicate that alcohol use and abuse is associated with hypertension. Large studies from the United States,[5-7] Australia[8] and Europe[9,10] have all reported that ethanol ingestion is related to elevated levels of systemic arterial pressure. As estimated from the Kaiser Permanente Study, there is a rise of approximately 1mm Hg systolic pressure per glass of alcohol taken on a daily basis, an effect independent of other factors such as sex, age, obesity, race, smoking, and coffee use, and prevalence of hypertension in moderate alcohol users is twice that in abstainers.[5] Apart from these stud-

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ies in essentially normal people, further investigations of hypertension in alcohol abusers have indicated that there is a definite and often substantial elevation of blood pressure during and shortly after acute intoxication.[11-13] This hypertension usually disappears with hospitalization, but only if alcohol is withdrawn, which suggests that the effect is not milieu-dependent.

Although the use of ethanol is clearly associated with hypertension both in non-abusers and abusers of alcohol, numerous gaps in our knowledge exist. For example, quantitation of alcohol use by retrospective questionnaires is fraught with error and, although, sophisticated prospective techniques for assessing alcohol consumption are now available, these have not yet been applied to the effect of alcohol on hypertension.[14] Genetic factors are important in numerous alcohol abuse syndromes but, thus far, only one study has been reported to suggest that a predisposition to alcohol-induced hypertension may exist.[15] The pathophysiology of the effect is also unknown, though increases in norepinephrine metabolites after even modest ingestions of alcohol have been reported.[16,17]

A second deleterious effect of alcohol on the cardiovascular system is the association with both atrial and ventricular dysrhythmias in the so-called holiday heart syndrome, first described by Regan in 1978.[18] Given the high frequency of admissions of such patients with atrial flutter and fibrillation, one must conclude that ethanol is one of the more powerful atrial arrhythmogenic agents known. Typically, patients will present several days after a binge of alcohol consumption, rather than during the intoxicated period. This relationship has led to the suggestion that such arrhythmias may be associated with a mild withdrawal syndrome and/or be mediated via the central nervous system. Little direct experimental evidence is available, however, to assess any pathophysiological mechanism for induction of atrial dysrhythmias, though acutely ethanol infusion can prolong conduction times in both the atrium and ventricle in those patients prone to alcohol-induced dysrhythmias.[19] The occurrence of ventricular extrasystoles may be also increased in the holiday heart syndrome; however, the onset of sustained ventricular tachycardia usually heralds the development of alcoholic cardiomyopathy.

A direct and deleterious effect of alcohol abuse on the heart muscle itself is the production of a cardiomyopathic ventricle[1] after prolonged periods of exposure. Ethanol administered acutely is a potent negative inotropic agent,[20] and numerous biochemical

abnormalities of the myocardium also occur. These include diminution of fatty acid oxidation,[21] the primary fuel source for the heart, an increase in myocardial triglyceride content,[22] and impaired mitochondrial function,[23] a virtual hallmark of the prolonged alcohol abuse and development of the heart muscle disease. Elucidation of the pathophysiological mechanism of alcohol-induced heart muscle disease had been hampered by lack of demonstrable myocardial metabolism of ethanol until recently with the documentation of direct metabolism of ethanol by the heart to form a family of neutral lipids, fatty acid ethyl esters.[24] These compounds transiently accumulate in the human heart after ethanol exposure[25] and can induce mitochondrial dysfunction.[26] Thus, this pathway for nonoxidative ethanol metabolism may serve to provide a link between ethanol ingestion and development of alcohol-induced heart muscle disease.

The cardiomyopathy produced by ethanol clinically is a typical congestive cardiomyopathy without pathognomic features. By far the most important aspect of managing these patients is proper diagnosis because approximately 30% of patients may have reversible disease if abstention from alcohol is achieved,[27] whereas recovery without abstention seldom occurs. Diagnosis must be sought by means of historical, physical and laboratory markers of alcohol abuse, and especially application of simple interview strategies such as that employed by the four-question CAGE paradigm.[28] While detectable blood ethanol concentrations are useful, usually they are undetectable by the time the diagnosis is considered due to the short half-life of ethanol. Other specific and objective laboratory markers of ethanol exposure with longer half-lives have not been described. Thus, misdiagnoses due to patient or family denial and application of false stereotypes by the medical community may preclude the only potentially curative therapy, absention.

Although the effect of alcohol on hypertension, dysrhythmias and the contractile state of the heart are now well accepted, the suggestion that ethanol may ameliorate the degree and extent of atherosclerosis remains controversial. Several large ecological studies have demonstrated a strong negative correlation between moderate, daily alcohol consumption and coronary artery disease mortality.[29-31] Other studies have confirmed these findings,[32,33] and case control studies have reported that non-alcohol users are at greater risk for coronary heart disease than moderate alcohol consumers.[34,35] Autopsy studies have suggested that alcohol use is associated with less atherosclerosis[36] and angiographically determined

indices of coronary artery disease have been shown to be less in alcohol users than in non-users of alcohol.[37,38] Despite these suggestive findings, however, no clinical intervention trial has been conducted to demonstrate in a prospective fashion that relative risk for coronary heart disease is lowered by alcohol use. Until this reduction is shown, little definitive information is actually available concerning possible advocacy of alcohol use for this purpose.

Should such a negative correlative link exist between ethanol intake and atherosclerotic events, its mechanism is of the utmost importance. HDL-cholesterol concentration is reproducibly elevated after several weeks of ethanol consumption, with return to baseline several weeks after cessation of alcohol ingestion.[39,40] Because of the association of elevated HDL-cholesterol concentrations in other settings with diminished risks for developing atherosclerotic vascular disease, speculation has centered on the possible role of alcohol-induced elevations of HDL-cholesterol in mediating a reduction in coronary heart disease in moderate drinkers. Recent studies, however, indicate that the subfraction of HDL-cholesterol that is alcohol sensitive is HDL_3, a nonprotective fraction; HDL_2, which is associated with a decreased risk of coronary heart disease, is marginally induced by ethanol.[41] Thus, this hypothesis has been called into question. Evidence based on aortic metabolism of ethanol and cholesterol suggests that inhibition of atherogenesis by alcohol may be mediated by events intrinsic to the aorta itself: nonoxidative metabolites of ethanol found in aorta, fatty acid ethyl esters, inhibit *in vitro* cholesterol esterification catalyzed by either aortic fatty acyl cholesterol-O-acyl transferase or cholesterol esterase.[42] Interactions between lipoprotein metabolism and this alcohol product have not been studied.

In conclusion, four basic effects of alcohol on the cardiovascular system have merited serious study over the past several decades. It is now well accepted that ethanol abuse can produce a direct heart muscle disease as well as a host of atrial and ventricular dysrhythmias. Abnormalities of myocardial lipid metabolism may underlie at least some of these effects. Alcohol consumption and abuse is associated with hypertension, as assessed in numerous world-wide epidemiological studies, though the mechanism of this interaction remains to be fully elucidated. Lastly, several lines of study indicate that ethanol use on a moderate and daily basis may suppress atherogenesis, but no intervention trial has yet been performed to demonstrate that relative risk for development of coronary heart disease

can be modified by alcohol ingestion. As more details emerge concerning the molecular effects of alcohol abuse and the role of genetic influences on alcohol-induced diseases, greater understanding of the cardiovascular effects of alcohol will be gained.

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