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Alcohol and the Cardiovascular System

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Ethanol has long been recognized as a toxic agent that has acute and chronic effects on cerebral and hepatic function. Over the past two decades important influences on the cardiovascular system have been either rediscovered or observed for the first time. The combined use of tobacco cigarettes and alcohol appears to increase the risk of many of these clinical abnormalities. While many individuals addicted to ethanol have subclinical abnormalities of the heart, somewhat less than a majority develop symptomatic cardiac problems. These include heart failure and arrhythmias. In addition to supraventricular arrhythmias that often normalize spontaneously, there is an increased incidence of sudden death that peaks at about 50 years of age in the alcoholic population. A significant degree of blood pressure elevation occurs in individuals who abuse alcohol. This appears to be transient and is normalized in most individuals during abstinence. The increased incidence of hemorrhagic and nonhemorrhagic stroke in middle age also appears to decline when alcohol abuse is interrupted. A preventive effect of mild to moderate drinking on coronary artery disease is, at present, equivocal, largely due to the question of appropriate controls.

(*JAMA*. 1990;264:377-381)

CHRONIC ethanol abuse can be associated with a variety of cardiovascular disorders, ranging from hypertension and stroke to heart failure and sudden death. The variability of the target organ affected clinically has been attributed to inherent properties of the cell that renders the individual tissues susceptible to chronic ethanol toxicity.

Congestive cardiomyopathy related to alcoholism has been reported as the most frequent identifiable cause of cardiomyopathy. The incidence has ranged from 21% to 32% in two series reported from referral centers,[1,2] but would be higher in situations where there is a high frequency of ethanol addiction. Moreover, a relatively high incidence of asymptomatic cardiac abnormalities, which may precede clinical decompensation, has been described.

SUBCLINICAL LEFT VENTRICULAR DYSFUNCTION

In the asymptomatic subject, a variety of techniques have been employed to establish that alcohol abuse is associated with subclinical depression of left ventricular function. Longitudinal hemodynamic studies of the alcoholic are not yet available. Current data suggest that patients without heart failure may have reduced diastolic compliance, manifested as an elevated end-diastolic pressure and diminished end-diastolic volume.[3,4] Contractility and relaxation indexes were also impaired.[4] In a chronic ethanol canine model, reduced diastolic compliance occurred without hypertrophy and before basal contractility was affected.[5] A similarity to the left ventricular responses of chronic hypertension has been noted,[6] but in the subclinical stage systolic function is generally not impaired in the hypertensive. Measured as ejection fraction[7] or velocity of filter shortening,[8] "contractility" may actually be enhanced with sustained essential hypertension.

Recently, a relatively homogenous group of subjects who were employed and living with family were assessed.[9] Detailed evaluation of their nutritional state revealed no evidence of malnutrition. Chronic alcoholism was demonstrated by radionuclide ventriculogram to be associated with dysfunction of the heart in as many as one third of chronic alcoholics, with abnormalities of skeletal muscle in almost half. The deleterious effects of ethanol were apparently dose related, and injury to the heart and skeletal muscle often coexisted.

Reversibility of the subclinical process in some individuals has been suggested during serial studies of ejection fraction by radionuclide-gated heart scans.[10] On retesting 4 to 6 months later, an improved ejection fraction occurred in those patients who were considered to have substantially reduced ethanol intake. Reduction of cardiac dilatation measured by echocardiography has also been described during abstinence,[11] but large-scale, long-term assessment of this issue is unavailable.

The cardiac status of patients diagnosed with cirrhosis is of interest because this is a group generally considered to be resistant to congestive cardiomyopathy.[12] A group of 37 subjects who had histological evidence of alcoholic cirrhosis without symptoms or signs of cardiac involvement were investigated. Two distinct patterns of left ventricular functional status were observed. More than half of the subjects had a reduced cardiac output in the basal state, and functional responses in the left ventricle were substantially depressed during increased loading conditions. In those patients with a high cardiac output, the responses to afterload increments suggested that the elevation was secondary to a diminished peripheral resistance and not related to a primary hypercontractile state.

A reduced systemic vascular resistance in cirrhotic subjects has been considered to be a potential basis for the relative rarity of congestive cardiomyopathy in this group of subjects. Since the majority of alcoholics with cirrhosis have a normal peripheral vascular resistance,[12] this rationale appears unlikely. As liver disease progresses, nutritional deficiences may occur that may influence the appearance of some of the components of cardiomyopathy, including synthesis and degradation of collagen in the interstitium.

A pathological counterpart to these observations has been reported in a series of 43 noncardiac cirrhotics, free of other etiologies for heart disease.[13] Widespread focal myocardial fibrosis of the heart that did not correlate closely with heart weight was noted in 22 of 43 alcoholic patients at autopsy.

HEART FAILURE

Cardiac decompensation typically occurs in men between 30 and 55 years of age who have ingested at least 80 g of alcohol almost everyday for a minimum of 10 years.[14] The physical signs of

This article is one of a series sponsored by the American Heart Association.

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cardiac decompensation found in these individuals are similar to those observed with other forms of congestive cardiomyopathy.

When cardiac dysfunction progresses to low-cardiac-output heart failure, exertional or nocturnal dyspnea is present. The latter may also be affected by diastolic dysfunction. Patients may also complain of weakness and fatigue, presumably because of the reduction in cardiac output.

Many patients with an element of cardiac decompensation will exhibit a diastolic gallop. An atrial gallop is commonly found in individuals who retain normal sinus rhythm. In the absence of heart failure, this is a useful sign of myocardial disease.[15] Cardiomegaly may be due to the primary myocardial process or secondary to mitral regurgitation related to papillary muscle insufficiency. At the bedside, the murmur of mitral regurgitation may not be readily differentiated from that of rheumatic valvular disease. Echocardiography may be helpful in making this distinction.

Since the addicted person may frequently delay seeking medical assistance for weeks or months, evidence of right-sided heart failure is not uncommon. As with other types of congestive cardiomyopathy, progression of the left ventricular dysfunction may result in secondary pulmonary hypertension and right-sided heart failure.[16] In individuals who develop more advanced disease complicated by right-sided heart failure, a pansystolic murmur may be heard in the third and fourth intercostal spaces, which is tricuspid in origin and diminishes with the amelioration of heart failure.

The electrocardiogram at this time may be relatively normal or show nonspecific changes.[17] Poor progression of the R wave across the precordium is fairly common, particularly as the disease advances. This is considered to be due to progression of ventricular pathology and conduction delay. Evidence of left ventricular and atrial enlargement is common, but left anterior hemiblock occurs in a minority of the patients, while left or right bundle-branch block appears in approximately 10% of the patients. A variety of arrhythmias may be present, including atrial or ventricular ectopic beats and atrial fibrillation. These are usually secondary to heart failure.

The hemodynamic characteristics of the left ventricle in alcoholic patients who are compensated from heart failure are considered to be similar to those of other causes, but the characteristics contrast with those described for the subclinical state. The latter patients presented with palpitations or noncoronary chest pain that was not further characterized. In these patients, left ventricular end-diastolic pressure was significantly elevated, associated with a slight reduction of end-diastolic volume, and consistent with diminished compliance.[4] In those patients who presented with shortness of breath, there was an increase of end-diastolic pressure as well and a further reduction of systolic function, as measured by ejection fraction. Although diastolic dysfunction may be a basis for dyspnea in some patients, this phenomenon was not observed in this group.

A not uncommon complication of cardiomyopathy is the development of pulmonary or peripheral arterial emboli. Systemic emboli can originate from mural thrombi in the left ventricle and left atrium. Pulmonary emboli are often associated with mural thrombi in the dilated right side of the heart or thrombophlebitis in the venous system.

ARRHYTHMIAS

A variety of atrial dysrhythmias in subjects without overt cardiomyopathy or enlarged heart but with a background of alcoholism has been described during acute intoxication. In a report of patients admitted to an emergency department, 32 separate symptomatic dysrhythmic episodes that required hospitalization occurred in 24 patients who drank habitually with superimposition of recent heavy ingestion before the arrhythmia.[18] Atrial fibrillation was the most common arrhythmia and plasma electrolyte levels were usually normal. Sinus rhythm was restored spontaneously in some patients, but the restoration usually required cardioversion or pharmacologic intervention.

After restoration of normal sinus rhythm, moderate conduction delays were found by electrocardiogram during high-speed recording and were considered to be the background for the induction of acute arrhythmias. This phenomenon has been reproduced in the electrophysiology laboratory. In 11 subjects with clinical evidence of heart disease who abused alcohol, atrial fibrillation was inducible without acute ethanol administration in 4 subjects, and in an additional 4 subjects only during its use.[19] In an analysis of new-onset atrial fibrillation in 40 patients under 65 years of age, alcohol was considered to be causative or contributory in approximately two thirds of the patients.[20]

A health maintenance clinic analysis examining the prevalence of acute arrhythmias was obtained from 1322 persons who reported six or more drinks per day, as compared with 2644 subjects who reported drinking at least monthly, but less than daily.[21] Relative risk in the former was at least doubled for atrial fibrillation, atrial flutter, supraventricular tachycardia, and atrial premature complexes.

In view of the observations on the "holiday heart," it is not surprising that in the setting of patients admitted to a hospital for ethanol withdrawal, Holter monitoring revealed a relatively high incidence of atrial arrhythmias in addition to sinus tachycardia.[22] No evidence of ventricular tachycardia was observed despite isolated ectopic beats.

One explanation is that ventricular tachycardia in alcoholic patients rapidly progresses to fibrillation. Several reports from medical examiners have indicated a higher incidence of sudden death without known heart disease than previously appreciated in subjects who abuse ethanol.[23,24] The incidence of hypertrophy in this and the following study is not clear, since heart weight was not related to body mass. While this usually occurs in subjects without overt cardiomyopathy, when heart failure is present the incidence of fatal arrhythmias is not known to differ from cardiomyopathy unrelated to ethanol.

A prospective study of sudden death at the Pathology Institute in Moscow, USSR, revealed that 17% of all cases were related to alcohol abuse, predominantly in patients under 50 years of age.[25] None could be attributable to sleep apnea; inclusion in the study required that the event be witnessed and that death occur within 30 minutes of symptoms. Significant coronary disease was absent in these patients, but evidence of cardiomyopathy by light and electron microscopy was present in specimens taken within hours of death. Moreover, histochemical analysis of myocardium indicated reduction of mitochondrial enzymes, particularly succinic dehydrogenase, thought to be relatively specific for alcoholic cardiomyopathy vis-à-vis the idiopathic variety. No data were provided in terms of the relative purity of the alcohol consumed since contaminants may contribute to cardiac pathophysiology. The incidence of hypertrophy in the above three studies is not clear, since heart weight was not related to body mass.

In Sweden, registration with the temperance board was associated with increased risks of sudden cardiac death in 50-year-old men who were followed up for 10 years.[26] Moreover, men who chose not to participate in a primary prevention trial were more often registered for alcohol problems and had a higher incidence of coronary deaths. Excess mortality in nonparticipants

was largely accounted for by sudden cardiac deaths.[27-29] In addition, half of all the men in a longitudinal study of 50-year-olds in Uppsala who died suddenly were registered at the temperance board.[30]

A 5-year Finnish study of 4532 men between the ages 40 and 64 years revealed a reduced incidence of sudden death in abstainers, regardless of the presence of coronary disease. These results were true for both smokers and nonsmokers.[31] A case-control study of sudden unexpected death in women in Rochester, Minn, showed that 40% of case patients had a diagnosis of alcoholism, compared with 7% of myocardial infarction patients, and 3% of controls.[32]

In view of the uncertainties of epidemiologic studies in terms of quantification of intake and the use of other cardioactive agents, an investigation was undertaken in a canine model of chronic alcoholism in which 36% of calories was fed as ethanol.[33] The animals were maintained in a well-nourished condition. After 12 months there was an accumulation of collagen in the myocardial interstitium and abnormal diastolic compliance. This model exhibits progressive low-grade prolongation of left ventricular conduction times. Ventricular vulnerability was determined in the basal state as well as during infusion of either saline or 1.5 g/kg of ethanol over a 2-hour period. The ventricular fibrillation threshold was not significantly affected in normal control animals during ethanol infusion. In the experimental group the threshold in the basal state was reduced by 26%. Infusion of ethanol further reduced the threshold levels to a modest extent.

Since arrhythmogenesis is often dependent on the sympathetic nervous system, it is paradoxical that the heart at this stage of alcoholism has a diminished electrophysiologic response to catecholamine stimulation both in vitro and in vivo.[33] However, a nearly tenfold increment of plasma catecholamines was observed in the immediate postethanol period in the experimental animal. Despite a reduced dose-responsiveness, the levels of norepinephrine at the β-adrenergic receptor appear to be sufficient to increase vulnerability in vivo.

CORONARY ARTERY DISEASE

A series of epidemiologic investigations have suggested that low to moderate ethanol intake reduces the risk of coronary heart disease. However, many of these studies were not designed primarily to study the role of alcohol and often yielded equivocal information. Data collected on alcohol intake are often more limited than in a dedicated alcohol study. Most researchers rely on self-reports of alcohol consumption, which are particularly unreliable among heavier drinkers. This may be the reason why many of the population studies contain so few heavy drinkers. Verification of intake by communication with family and friends or by measurement of clinical laboratory variables is usually lacking.

To explore the significance of moderate alcohol ingestion in patients registered in a health plan, the question was asked whether nondrinkers accounted for a significantly different proportion of the myocardial infarction group. There were no significant differences in persons under the age of 64 years. Above this age, patients who did not use alcohol had a significantly higher incidence of myocardial infarction, a phenomenon particularly evident in women. There was, however, no difference in the incidence of out-of-hospital sudden death in the same population.[34]

In contrast to these findings is a prospective study of physicians who were first seen as medical students and followed up to midlife, when the influence of drinking habits on health was examined.[35] The quantity of alcohol consumed as reported by the regular drinkers in the group averaged two drinks per day. The incidence of clinical evidence of coronary heart disease was significantly higher than in nondrinkers; however, the difference was not significant when the effect of cigarette smoking was removed. Thus, moderate drinking appeared to have little or no evident effect on the health of middle-aged physicians.

Of interest is the 17-year follow-up experience of nearly 2000 white men originally aged 40 to 55 years from the Western Electric Co.[36] When mortality rates were adjusted for age only, total intake of ethanol at the level of six or more drinks per day was associated with an increased risk of death from all causes of cardiovascular diseases, coronary heart disease, or cancer. The associations between alcohol intake and death from cardiovascular and coronary heart disease failed to persist after adjustments were made for other risk factors such as smoking and blood pressure. The association between alcohol intake and mortality was generally stronger for those deaths that occurred more than 10 years after entry in the study.

Shaper and coworkers[37] found no clear relationship between alcohol intake and major ischemic heart disease events in a prospective study of middle-aged men studied for 6 years in Great Britain. Though daily light drinkers had the lowest incidence of ischemic heart disease, these individuals also had lower blood pressure and a reduced mean body mass index. The higher mortality in the zero-intake group was thought to be a result of preexisting cardiovascular disease and the transfer of such subjects from the "substantial drinking" to a "nondrinking" category. The apparent advantage of having up to five drinks daily remains equivocal.

An earlier report from Gothenburg, Sweden, had indicated that alcohol abuse was an independent risk factor for coronary death, and that this increase was limited to patients with evidence of coronary disease but without recent myocardial infarction.[25] More recently, the comparative role of cigarette smoking in the alcoholic has been evaluated.[29] Among nonalcoholic subjects the relative risk of a presumed coronary death was double that of nonsmokers. In smoking alcoholics the risk was substantially higher on multivariate analysis; both smoking and alcohol abuse were independently associated with coronary death. Among nonsmoking alcoholics the relative risk was three times that of control subjects. In smoking alcoholics this increased fourfold compared with nonalcoholic nonsmokers.

CEREBRAL VASCULAR ACCIDENTS

Epidemiologic studies have indicated a positive association between the amount of alcohol consumed and the development of cerebral vascular accidents. Both acute alcohol intoxication and regular heavy drinking appear to be risk factors for primary aneurysmal and nonaneurysmal subarachnoid hemorrhage. In a prospective study of 172 patients aged 15 to 55 years presenting consecutively with primary subarachnoid hemorrhage,[38] intracerebral aneurysm was identified in 119 patients by use of a combination of neuroradiological techniques. No aneurysm was identified in the remaining 53 individuals.

Heavy drinking was twice as common in men and seven times as common in women who had sustained a subarachnoid hemorrhage than in the general population. Furthermore, heavy drinkers were more likely to have been intoxicated in the 24 hours preceding their subarachnoid hemorrhage than persons who drank less.

Several additional studies of stroke have implicated acute, heavy alcohol consumption in the evolution of this lesion in young adults.[39,40] Hypertension is a risk factor for stroke in general and it has been suggested that the relationship between alcohol consumption and stroke might be mediated via alcohol-

induced hypertension. Although the relationship between alcohol consumption and stroke has been reported to be independent of blood pressure readings,[41] transient pressure elevation prior to and during the onset of stroke has not been excluded.

Threshold levels of alcohol consumption above which the risk for stroke increases significantly have not been clearly defined. In the study by Hillbom,[38] the risk of developing a subarachnoid hemorrhage increased significantly in individuals who drank almost daily more than five drinks a day. Furthermore, prospective data in middle-aged women have suggested that moderate alcohol consumption may increase the risk of subarachnoid hemorrhage despite an apparent decrease in the risk of ischemic stroke.[42]

More important, individuals who reduce their alcohol intake have a significantly lower risk of developing hemorrhagic stroke than individuals who maintain or increase their alcohol intake.[41] This suggests that reducing alcohol intake may reduce the risk of cerebrovascular accidents, but additional prospective studies are required to confirm this observation.

HYPERTENSION

Social drinking is often associated with a small rise of systolic pressure. In subjects who habitually imbibe heavily, the rise of blood pressure may be substantial. A study was undertaken involving noncardiac alcoholics to assess the effects of inebriation and the postintoxication period on the level of arterial pressure in relation to cardiac function, as compared with recovery levels. The hypertension was not related to a high-output state, and peripheral arterial resistance was substantially elevated.[43] High plasma levels of aldosterone and renin, as well as urinary catecholamines, correlated with this vasoconstrictor response. A decline of these hormones as blood pressure spontaneously normalized is compatible with this interpretation. Whether this hormonal system is altered between episodes of active heavy drinking is not known. Moderate, habitual drinkers have normal activity of these hormones.[44]

Despite the observation that these chronic alcoholic subjects can have an acute hypertensive response to acute intoxication, the left ventricular dimensions demonstrated by echocardiography were normal in the acute hypertensives as well as in the normotensive alcoholic group.[43]

Changes in the intrinsic nerve activity of the smooth muscle of the arterial wall may affect this response. The response of the smooth muscle to adrenergic stimulation may vary with different stages of alcohol intake,[45] and an increased sensitivity to the neurotransmitter norepinephrine may have contributed to the observed rise of peripheral vascular resistance.

While reduced levels of circulating magnesium ion can elicit arterial vasoconstriction,[46] the levels of magnesium did not differ from those in the normotensive alcoholic. This does not exclude a change in smooth-muscle magnesium levels and an effect on cell calcium activity.

Whether fixed hypertension can develop in persons who have frequent vasoconstrictive responses to ethanol withdrawal is not clear. Studies of cardiac function in alcoholic patients, when carried out days to weeks after the last ethanol consumption, have shown normal arterial pressure in the preclinical state,[3] mild failure,[47] or severe heart failure after compensation.[48] In addition, the largest transient elevations of systemic arterial pressure have been reported in individuals with compensated cirrhosis,[49] which is associated with a low incidence of cardiomyopathy.

It would appear that this intermittent peripheral arterial response may commonly be unassociated with clinically significant heart disease. Although transient pressure elevations are not considered to give rise to myocardial disease,[50] if substantial elevations do occur in advanced subclinical heart disease, one cannot entirely exclude a potential role for this phenomenon in the pathogenesis of congestive cardiomyopathy in chronic alcoholism.

The incidence of chronic essential hypertension in those who abstain for a year is similar to that in age-matched controls (approximately 10%[50]). Essential hypertension in the active alcoholic appears less responsive to antihypertensive agents.[51]

DIAGNOSIS

In ascertaining the etiology of cardiomyopathic disease, denial or inaccurate information may make the history of alcohol abuse difficult to obtain. Repeated episodes of social disturbance or trauma are suggestive. A positive history is of practical importance since the heart disease may be reversible or progression delayed in patients who abstain from alcohol. Although there are no specific cardiovascular markers, plasma enzymes utilized in the diagnosis of liver injury may be helpful. Recently a serum assay of desialated transferrin has been shown superior over other tests.[52] The elevated serum levels are highly specific for this addiction, with good sensitivity for about 10 days after the last use of alcohol.

In terms of cardiac enzymes, creatine phosphokinase and lactic dehydrogenase concentrations have been examined. No diagnostic changes in these isoenzymes have been detected in the presence of subclinical cardiac abnormalities or frank heart failure. Moreover, circulating heart antibodies as detected by immunofluorescent methods have not been detectable in patients with alcoholic cardiomyopathy.

In examination of biopsy specimens from patients or autopsy tissue preparations, distinctive features have been lacking in alcoholism with alcoholic heart disease, as compared with results in those with other causes of congestive cardiomyopathy. Early in the prefailure stage there would appear to be dilatation of the sarcoplasmic reticulum and the undifferentiated portion of the intercalated disk,[53] but these events apparently are obscured at later stages when considerable myocytolysis may be seen. Increased amounts of fibrous tissue may appear as an increase in the interstitial collagen component or replacement of myocardial fibers. Decreased concentrations of mitochondrial enzymes, particularly succinic dehydrogenase, have been reported to distinguish the alcoholic from idiopathic cardiomyopathy.[25]

Skeletal muscle is a readily available tissue for biopsy in identification of the alcoholic, and its examination has been underutilized. Atrophy of striated muscle fibers has been reported particularly of the type 2B fibers, which regulate anaerobic metabolism.[54] Complicating endocrine diseases that might similarly affect muscle fiber were absent.

TREATMENT AND REVERSIBILITY

The salient feature of long-term management for all of the cardiovascular consequences of alcoholism is abstinence, which has been associated with a decline in the incidence of stroke and hypertension.[51] As with other addicted persons, long-term participation in group therapy is strongly encouraged.

In a 4-year follow-up study of patients presenting with cardiac decompensation, almost one third were found to have apparently maintained abstinence.[55] The majority of these had an improved or unchanged cardiac status, with a 9% mortality. However, 20% of those who allegedly abstained deteriorated in cardiac status. Presumably at certain stages of the disease, the pathogenetic mechanisms may continue unabated despite traditional pharmacologic management. Mortality was 54% in

those who remained actively alcoholic.

During the first episode of low-output heart failure, if the patient has been only briefly symptomatic with modest cardiomegaly and limited pulmonary congestion, he or she may be treated initially by diuretics to correct the volume overload; bed rest is also advised. The use of angiotensin-converting enzyme inhibitor has improved survival in patients with heart failure due to a variety of causes[56] and presumably would be useful for this specific etiology. Vasodilator therapy also has been shown to improve survival in patients with heart failure.[57] This study included a subset with alcoholic cardiomyopathy, but the outcome in these individuals was not separately described.

Digitalis can be particularly helpful in the control of atrial fibrillation or sinus tachycardia and contributes to the management of congestive heart failure in advanced stages of the disease. Although long-term bed rest has been suggested as perhaps aiding in management,[58] the most important feature of institutionalization is the enforced abstinence from alcohol.

The research reported here has been supported by grant AA242 from the National Institute of Alcohol Abuse and Alcoholism and the New Jersey Heart Association, New Brunswick.

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