Ethyl Alcohol and the Heart

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SUMMARY

Since a significant fraction of the population are heavy consumers of ethanol, and recent postmortem studies suggest that most alcoholics have some degree of cardiac abnormality, elucidation of the basis for alcoholic cardiomyopathy is of some importance. Intoxicating amounts of ethanol depress ventricular function acutely and effect leakage of myocardial cell components.

On the basis of studies in three animal species and in man, it would appear that the cumulative effects of chronic ethanol intake can, without evident malnutrition, depress ventricular function and produce metabolic and morphologic abnormalities of the myocardium before clinical manifestations. Progression of the disease to produce heart failure, arrhythmias, or thromboembolism, separately or in combination, occurs under multiple circumstances that are not clearly defined. These would appear to include the cumulative effects without superimposed factors, an intensified drinking episode, simultaneous exposure to trace metals in excess, and occasional specific nutritional deficiency or superimposed infection. The low incidence of nutritional complications such as cirrhosis, peripheral neuritis, and delirium tremens associated with cardiomyopathy supports the view that the cardiac abnormality is commonly not dependent on malnutrition. Finally, clinical data indicate that cessation of alcohol intake will reverse the disease or interrupt its progression in many patients. Anticoagulant therapy is recommended at least during the early recovery stage.

Additional Indexing Words:
Nutrition Alcoholism, pathology Arrhythmia Electrolytes Myocardial composition Ventricular function

WHILE THE ASSOCIATION of alcoholism with cardiomyopathy is well known, the nature of this relationship has remained undefined. A recent review by Ferrans\(^1\) states that alcoholism was recognized in the last century as a cause of heart failure unassociated with nutritional deficiency. A different view emerged during the period of economic depression in the 1930's. Beriberi heart disease was commonly observed and dominated the etiologic considerations of heart disease in alcoholics. Cardiovascular manifestations often coexisted with peripheral neuritis, and the hyperkinetic nature of the circulatory disorder was evidenced by the rapid circulation time, wide pulse pressure, high cardiac output, and low peripheral resistance.

It is evident that identification of the pathogenesis of the cardiac involvement is of more than theoretical interest. If ethanol per se is the predominant etiologic factor, then major emphasis on the nutritional aspects of therapy rather than on alcoholism itself would be erroneous. During the later 1950's, three separate reports drew attention to the many cardiac patients with long-standing alcoholism without evidence, in the majority, of significant nutritional deficiency. Eliaser\(^2\) related the cardiac abnormalities seen in alcoholics to the severity and duration of the alcoholism and concluded that a significant number of alcoholics with heart failure had no vitamin deficiency or hepatic disease. Brigden\(^3\) reporting observations in 50 patients, noted the

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difficulty in obtaining a history of alcoholism, often obtained only through persistent questioning or from relatives. The diagnosis was primarily made by exclusion of other causes of heart disease, namely hypertension, coronary artery disease, cor pulmonale, and congenital and valvular disease. Heart disease apparently developed earlier in those who drank spirits rather than beer, and only 10% presented with the high-output failure of beriberi and responded to thiamine. The remaining patients presented with low-output heart failure often complicated by atrial or ventricular arrhythmias. The occupational diversity of patients with alcoholic cardiomyopathy was emphasized by Evans in that the majority of his 20 patients held executive positions.4

A male predominance has been repeatedly observed in these and subsequent series and is presumably due to the greater prevalence of alcoholism in the male; a lesser sensitivity of the female to the myocardial effects of ethanol has, however, not been excluded. An ethnic or racial predilection to alcoholism and alcoholic heart disease is more difficult to establish but has been suggested on the basis of a relatively high prevalence in the urban areas of the northeast.5 The duration of alcoholism reported by most authors is usually at least 10 years before cardiac symptoms appear. If a population sample consists predominantly of short-term addicts then a relatively small number of individuals would be expected to have clinically detectable heart disease.

It is now pertinent to consider the prevalence of alcoholism in the general population. In view of the difficulty in obtaining reliable histories, we can assume that there is some underestimate of incidence. In a recent survey, Cahalan found that two thirds of the population used alcohol, and he divided these into four categories: infrequent, light, moderate, and heavy users. The group considered to be heavy users represented about 12% of the adult population.5 An important element in considering incidence is the variation in different regions of the country and in hospitals of a given region. With these reservations in mind, cardiac changes observed at postmortem in subjects who were chronic heavy users of alcohol are of interest.

In a recent review, 97 patients with a clinical history of excess alcohol intake were studied at necropsy.6 Diffuse interstitial fibrosis of varying severity was present in the myocardium of 90% and did not appear to be the result of vascular narrowing. Almost half had myofiber vacuolization, and nearly a third had heart weights greater than 500 g. Hypertension was unusual, but no information was provided on the prevalence of anemia, which could have an important bearing on hypertrophy. Hepatic changes, ranging from fatty infiltration to end-stage cirrhosis, did not correlate with the cardiac pathology. Death resulted from clinically obvious myocardial disease in 20% of this group, but the contribution of the cardiac alteration to mortality in the remainder was unknown. These studies suggest a high incidence of cardiac-muscle disease in alcoholics dying in a hospital but, without rigorous exclusion of nutritional factors, the primary role of alcohol can only be presumed.

In a prior study of the failing heart in alcoholics, focal areas of fibrosis were found to be associated with histochemical evidence of diffuse lipid deposition within myocardial fibers.1 Electron microscopic studies showed abnormalities of mitochondria, myofibrils, and sarcoplasmic reticulum. The structural changes in the myocardium appeared to differ from those of obstructive cardiomyopathy in that the latter demonstrates abnormal muscle-fiber size and orientation. In the hearts of patients with hypokalemic myocardial disease, isolated sarcomere units undergo degeneration in the early stages, in contrast to the heart in the alcoholic. Unfortunately, after the onset of symptoms in the alcoholic, the morphologic alterations may be diffuse and similar in appearance to those of the idiopathic variety so that the clinical utility of myocardial biopsy is limited at the present time.

The nutritional status of alcoholics today appears to have improved over that of the 1930's when approximately 100 cases of thiamine deficiency were recognized in one

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hospital during a single year. In contrast, during the past 15 years there have been few published cases fulfilling the criteria for beriberi heart disease. In evaluating ambulatory chronic alcoholics representative of the lower middle class, Neville observed a relatively low incidence of nutritional deficiency. Although 36% of calories were derived from alcohol and intake frequency approximated 80 of every 100 days, only 15% of patients had thiamine deficiency; riboflavin, niacin, and protein deficiency occurred in less than 10%. Whether a different myocardial response to chronic alcohol exists in this minority compared to the better nourished remains to be demonstrated. In this regard, blood vitamin levels assayed in hospitalized patients frequently reveal no clear difference of levels in alcoholics with or without evidence of liver disease. Blood vitamin concentrations may also be low as a nonspecific effect of chronic illness in the absence of alcoholism. Up to the present time, there have been no morphologic features of myocardial involvement that distinguish nutritional deficiency from direct cardiotoxic effects of ethanol.

To minimize the potential contributions of malnutrition in evaluating the relation between alcohol and the heart, a group of alcoholic subjects who had normal cardiovascular clinical examinations and no clinical evidence of vitamin deficiency or malnutrition were chosen for hemodynamic study. These subjects were within 5% of normal weight for age, and there was no hypoalbuminemia, peripheral neuropathy, edema, or anemia of significance. Arterial concentrations of pyruvate and lactate were normal, and the uptake of these substrates across the myocardium was also normal, which diminished the likelihood of thiamine deficiency. Documentation of at least 10 years of alcoholism was obtained, and performance of the left ventricle was studied by increasing afterload with angiotensin. The noncardiac alcoholic showed a significantly greater rise of ventricular end-diastolic pressure with minimal increment of stroke volume compared to nonalcoholic controls, so that by this standard ventricular performance of the noncardiac alcoholic was diminished. To test the contractile state of the ventricle at rest, the same group of patients was analyzed by use of the contractility index of Frank and Levinson in which the maximum rate of pressure rise in the left ventricle (MRPR) was normalized for a given preload and afterload (fig. 1). The noncardiac alcoholics showed significantly lower values than normal subjects but substantially higher values than alcoholic patients who had progressed to heart failure.

Since the noncardiac alcoholics were believed to exhibit findings related primarily to chronic alcohol toxicity, the acute effects of ethanol were studied at two dose levels, 6 and 12 oz of Scotch administered over 2 hours. At the larger dose, a substantial significant rise in left ventricular end-diastolic pressure occurred with a modest decline of stroke output, reverting toward control after alcohol feeding was interrupted. The 6-oz dose did not produce significant change in either end-diastolic pressure or stroke output. It is apparent from this and other studies that the acute hemodynamic response to ingested ethanol may vary depending on dose, duration of administration, and time of measurement, as well as the hemodynamic state of the patient. In contrast to these findings in noncardiac alcoholics, the alcoholic patient with heart failure may have a greater sensitivity to the 6-oz dose. Figure 2 illustrates

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**Figure 1**

\[ MRPR = \text{maximum rate of pressure rise in the left ventricle; } MIP = \text{maximum isometric pressure; } 2\tau = \text{circumferential fiber lengths.} \]  
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These observations during the ingestion of 6 oz of Scotch in an alcoholic patient with cardiac decompensation reveal a depressant effect on the left ventricle at a dose that has no effect in the nonalcoholic.

Figure 2

However, the duration of chronic ethanol intake required to produce persistent abnormality of heart-muscle composition is unknown.

Figure 3

These are observations in a single, well-nourished patient receiving daily Scotch, which resulted in evidence of heart failure. The failure regressed without medical treatment after interrupting alcohol intake. (Reprinted from J Clin Invest, by permission.)

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In a discussion of pathogenesis, the role of magnesium ion must be considered. Primary magnesium deficiency does produce cardiac lesions in immature experimental animals, but unequivocal disease in adults is difficult to demonstrate although secondary potassium loss could have important consequences. In chronic alcoholic patients magnesium deficiency may be present and is readily corrected. How early in the disease hypomagnesemia appears and whether it interacts with ethanol to produce cardiac malfunction or arrhythmias in adults remain to be explored.

The fact that ethanol can diminish ventricular function acutely does not signify that chronic disease will necessarily result from habitual use. To test the thesis that cumulative effects of ethanol over a period of time may result in cardiac abnormality despite adequate nutrition, a well-compensated patient was fed ethanol as Scotch for a period of 5% months at a daily dose of 12–16 oz. After an interval of 6 weeks (fig. 3), resting heart rate began to rise and there was prolongation of circulation time and elevation of venous pressure without evidence of malnutrition. After 4 months, a ventricular gallop rhythm appeared, which persisted until ethanol was interrupted. Subsequently, without specific cardiac therapy, there was spontaneous restoration to normal.

A major role of ethanol in the production of left heart failure in this subject was substantiated by the gradual reversion of the cardiocirculatory abnormality after alcohol ingestion was interrupted. This observation supports the thesis that the myocardial disease is reversible at certain stages if intake of ethanol is discontinued as has been the experience in several studies of ambulatory patients.

In view of the variables that can obscure the pathogenesis of human disease, we have undertaken a study in dogs receiving 40% of their calories from ethanol for a period up to 3 years. These animals were maintained on normal protein with supplementary vitamins. Left ventricular function during afterload testing was found to be depressed but there was no heart failure presumably because a longer ingestion period is required, as judged by experience in man where 10–15 years of alcoholism is common before heart failure is seen. In assessing left ventricular conduction, His-Q time by the electrode catheter technique showed a 30% prolongation in the alcoholic animals compared to that in controls. QRS duration was prolonged by nearly 50%.

Accumulation of lipid in the form of triglyceride, reminiscent of the human studies, was detected on chemical analysis. An abnormal distribution of electrolytes was also observed with a significant reduction of $K^+$ concentration, most evident in the endocardium. Since alterations of this cation have been related to ventricular arrhythmias, it is noteworthy that about 15% of the animals experienced sudden death apparently unrelated to high blood ethanol levels. In view of the fact that a previous investigation in the rat indicated a marked tendency to arrhythmias in chronic alcoholic animals, it is of interest that sudden, unexpected death has been observed with relatively high incidence in a group of young adult alcoholics in Baltimore. This young adult group had fatty livers as the principal pathologic finding and appeared to have characteristics similar to the alcoholics noted previously who had physiologic evidence of cardiac malfunction. Ventricular fibrillation, a frequent cause of sudden death, is strongly suspected under these circumstances. Complementary information is derived from a study of outpatient alcoholics in Oslo in whom an increased incidence of sudden cardiac deaths was observed.

Burch has recently reported that feeding ethyl alcohol daily to mice for as short as 7–10 weeks resulted in ultrastructural abnormalities in the myocardium despite adequate nutrition. Thus in three different species chronic ethanol ingestion has been found to produce deleterious effects on cardiac conduction, rhythm, function, and structure apparently independent of nutritional deficiency. It should be added that intensification of the cardiac response to ethanol appears to occur when combined with excess of trace metals such as arsenic or cobalt. In patients taking large quantities of beer containing cobalt,
heart failure marked by a rapid downhill course was frequently observed. Survivors who resumed drinking beer that did not contain cobalt apparently recovered and were asymptomatic. This experience points out the potential role of chemicals which, when combined with ethanol, may produce heart disease in the alcoholic. The contributory role of malnutrition or superimposed infection in precipitating the cardiac episode has been suspected but not as clearly implicated. In addition it is not unusual for a recent episode of intensified drinking to be associated with precipitation of heart symptoms.

Detection of cardiomyopathy in the preclinical stage in the noncardiac alcoholic would be ideal, but at present most subjects are seen after the onset of cardiac symptoms. As a group these patients are younger than the average coronary patient and exhibit nonspecific findings. As exemplified by the patient in figure 3, sinus tachycardia and a third heart sound gallop rhythm are frequent findings and may exist with only mild effort limitations. Commonly, however, some degree of orthopnea and effort dyspnea will be present. Physical findings consistent with low-output heart failure usually include a narrow pulse pressure, prolonged circulation time, increased venous pressure, pulmonary rales, and cardiac enlargement. These abnormalities usually become intensified after the first episode of heart failure.

Occasionally palpitation is the major complaint, presumably due to arrhythmias. Atrial fibrillation has been observed during alcoholic episodes, with regression after abstinence. Although sinus tachycardia associated with ventricular premature beats has been suggested as an important clue to the diagnosis of alcoholic cardiomyopathy, this combination is seen in other forms of heart disease. Abnormalities of repolarization are the rule, but the sinus or cloven-shaped T waves originally described by Evans are infrequently found and appear to be related to muscle damage rather than etiology. While no specific abnormalities of the electrocardiogram have been established, the absence of a septal Q in an alcoholic has been suggested as grounds for considering this diagnosis. Conduction changes are observed in about one third of alcoholics and have included varying degrees of A-V block and left or right bundle-branch block.

Therapy varies with the stage of disease. If an abnormality of ventricular function is demonstrable on physiologic testing prior to clinical evidence of heart disease, then therapeutic intervention should begin at once. In addition to the evidence cited above for such an abnormality, two other studies of alcoholics without evident heart disease have also detected reduced ventricular function during stress testing. If noninvasive measurements prove sufficiently sensitive, the feasibility of early diagnosis and therapy will be improved. The key to treatment at all stages involves persuasion to complete abstinence. The alcoholic with cardiac abnormality may be approached effectively as an individual rather than in group therapy, since several reports of individual treatment have described regression of disease after prolonged abstinence.

After the onset of clinical manifestations, traditional antiarrhythmic agents, electroshock, digitalis, and diuretics are used as needed. Close observation during drug usage is advised in view of the electrolyte abnormalities which may exist or appear readily in patients with moderate to advanced disease. Since thromboembolism from endocardial thrombi is a prominent feature, occurring in as many as 80% of individuals, anticoagulation is an important intervention. Finally, where facilities are available, prolonged bed rest can reduce the size of excessively dilated hearts and contribute to control of alcohol intake.

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