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Cardiovascular Effects of Alcohol With Particular Reference to the Heart[1]

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FRIEDMAN, H. S. *Cardiovascular effects of alcohol with particular reference to the heart.* ALCOHOL 1(4) 333–339, 1984.—Alcohol has acute and chronic cardiovascular effects. Acutely, alcohol depresses cardiac function and alters regional blood flow. Even when withdrawn from alcohol for several days, alcoholics may still manifest evidence of left ventricular dysfunction. In some alcoholics a severe muscle disorder may ensue with the clinical features of a dilated cardiomyopathy. The concomitant presence of a thiamine deficiency or cirrhosis may produce hemodynamic changes that can obscure the clinical features of alcohol-induced heart muscle disease. Alcoholics may also develop acute myocardial infarction with patent coronary arteries; some may have cardiac arrhythmias even without other evidence of heart disease. Although epidemiological studies suggest that moderate users of alcohol have fewer coronary events than teetotalers, such studies also demonstrate a relation between alcohol abuse and hypertension and an increased occurrence of coronary disease. Thus, the injurious cardiovascular effects of alcohol must be considered when establishing recommendations for its use.

Acetaldehyde Acetate Alcoholic cardiomyopathy Regional blood flow Acute myocardial infarction Cardiac arrhythmias Cirrhosis

ALCOHOL has profound cardiovascular effects. Acutely, alcohol ingestion affects cardiac function and alters regional blood flow. Chronic alcoholism may produce severe injurious effects to the cardiovascular system. Problem drinkers are at risk for systemic hypertension, stroke and coronary events. Of particular concern is the effect of alcohol as a cardiotoxin: Unexplained heart failure may occur in alcoholics. The heart of patients with this complication of alcohol abuse is generally dilated and hypocontractile. However, even before alcohlics show such severe cardiac dysfunction, more subtle evidence of impaired left ventricular performance may be found.

The diagnosis of alcohol-induced heart muscle disease—that is, alcoholic cardiomyopathy—is made largely by association: long-standing alcohol abuse without any other cause for the heart disease. For this reason, the prevalence of alcoholic cardiomyopathy is not known. However, in hospitals where substance abuse is common, as in municipal and federal hospitals, perhaps 10–15% of patients admitted with congestive heart failure will satisfy the clinical criteria for alcohol-induced heart muscle disease. If one considers also alcohol abusers who present with concomitant valvular, coronary, or hypertensive heart disease, in whom alcohol abuse may be contributing to the heart muscle damage, the incidence of alcohol-induced heart muscle disease may approach 20–25% of cardiac admissions to these hospitals.

Although the hallmark of alcoholic heart disease is a primary muscle disorder, alcoholic heart disease may present in other ways: Tachycardias occurring in the alcoholic, even without the presence of electrolyte imbalance or an identifiable structural alteration in the heart, has been termed "holiday heart." Even more intriguing is the occurrence of myocardial infarction, indistinguishable clinically from that seen with obstructive coronary disease but occurring despite patent coronary arteries. Alcohol may also affect the heart through its actions on blood pressure and lipids. In fact, the damaging effects of alcohol on the cardiovascular system, and even perhaps its apparent protective actions, may occur through such mechanisms.

ACUTE EFFECTS

Ethanol is a myocardial depressant. Studies in isolated atrial [23] and ventricular tissue [40] have demonstrated reduced contractile function with concentrations of ethanol found with acute alcoholic intoxication. Similar observations have been made in intact animals [21]. However, the other actions of alcohol and its metabolites may obscure this effect. Alcohol [7] and its metabolites, acetaldehyde [21] and acetate [33], are potent vasodilators. Alcohol also elevates catecholamines [56].

Figure 1 illustrates the myocardial depressant actions of ethanol. In anesthetized closed-chest dogs an ethanol infusion, which produced an average concentration of 199 mg/dl at 60 min, reduced left ventricular ejection fraction. As blood ethanol levels increased, further depression of left ventricular function ensued, whereas a saline infusion of a comparable volume, delivered over a similar period had no effect on

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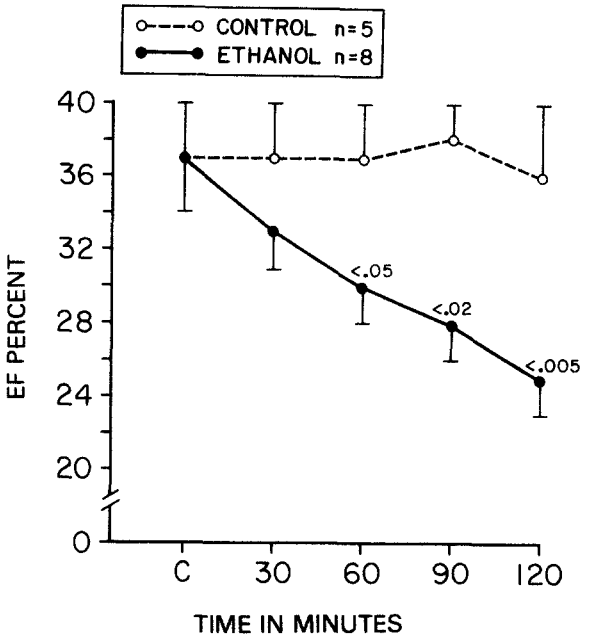

FIG. 1. Effects of ethanol on cardiac function. During an infusion of ethanol in anesthetized dogs, which produced an average concentration of 118 mg/dl at 30 min and 294 mg/dl at 120 min, ejection fraction (EF) declined. Saline (control) did not produce such a change.

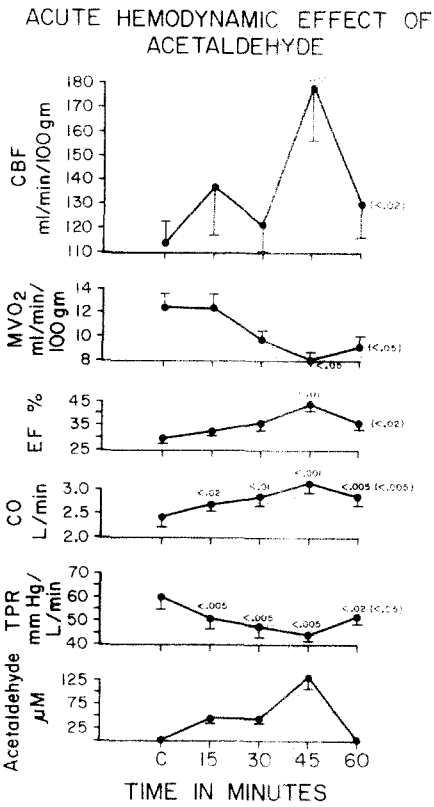

FIG. 2. Effects of acetaldehyde on hemodynamics. With acetaldehyde infusion at an average concentration of 40 μM, total peripheral resistance (TPR) declined and cardiac output increased. At 129 μM ejection fraction (EF) and coronary blood flow (CBF) increased, whereas myocardial oxygen concentration (MVO_2) declined. (Reprinted with permission from Friedman *et al. Cardiovasc Res* **13**: 483, 1979.)

cardiac function. By contrast, (Fig. 2) acetaldehyde at average blood concentration of 40 μm, a level comparable to that occurring from metabolism of ethanol under similar experimental conditions, increased cardiac output as a result of a decline in total peripheral resistance. At higher blood acetaldehyde concentrations an even greater improvement in cardiac function is shown with significant elevations of ejection fraction and further increments of cardiac output. Acetate, at clinically relevant blood levels, has also been shown to produce favorable effects on cardiac dynamics [33].

The biochemical basis for the myocardial depressant actions of ethanol is still not clear. Studies in man [44] and in experimental animals [43] demonstrate that ethanol alters lipid metabolism with a reduction in myocardial extraction of fatty acids and an increase in the extraction of triglycerides. Other metabolic changes have been demonstrated such as reduced calcium release and uptake by sarcoplasmic reticulum [51], inhibition of sodium-potassium ATP-ase of myocardial membranes [55], alteration in the interaction of the contractile proteins, actin and myosin [47], and inhibition of cardiac mitochondrial oxygenation [49]. However, these changes have been observed at ethanol concentrations substantially higher than that generally found with alcoholic intoxication in man.

In healthy humans, alcohol increases cardiac output [28]. With exercise cardiac output and oxygen consumption increase more than normal following the ingestion of alcohol; maximum oxygen consumption, however, remains unchanged [9]. The increment in cardiac output may be a reflection of an increase in stroke colume, resulting from the vasodilating actions of alcohol, but may also be due to an increment in heart rate [9]. By contrast, in patients with compensated heart disease the myocardial depressant actions of alcohol may be predominate and cardiac output may decrease [25]. With advanced heart failure, and intense vasoconstriction present, the vasodilating actions of alcohol may predominate, resulting in a fall in cardiac filling pressure, a modest decline in systemic blood pressure, but no change in cardiac output [26]. However, in healthy subjects, even when cardiac output increases after ethanol ingestion, systolic time intervals and ejection phase indicies may still show a depression in left ventricular function [1, 11, 52].

Even when alcohol produces no alteration in cardiac output, regional blood flow may change. Alcohol can produce at least a transient decline in brain blood flow [6,19]. This effect is most marked and persistent in the cerebellum [19]. A redistribution in splanchnic blood flow also occurs at blood ethanol levels averaging between 106 and 231 mg/dl [20,31]: As shown in Fig. 3 hepatic arterial blood flow increases, whereas pancreatic arterial blood flow declines. A more variable effect is demonstrated in the other splanchnic organs.

The effects of ethanol on coronary blood flow is a subject of some controversy. Most studies in *intact* animals, however, show an increment in coronary blood flow after an infusion of ethanol when the following conditions are satisfied: The ethanol infusion is slow, blood levels exceed 200 mg/dl, and the administration of alcohol is not followed by a fall in cardiac output [18]. Figure 4 shows a progressive increment in coronary blood flow following an infusion of ethanol in the anesthetized dog. A significant increment is

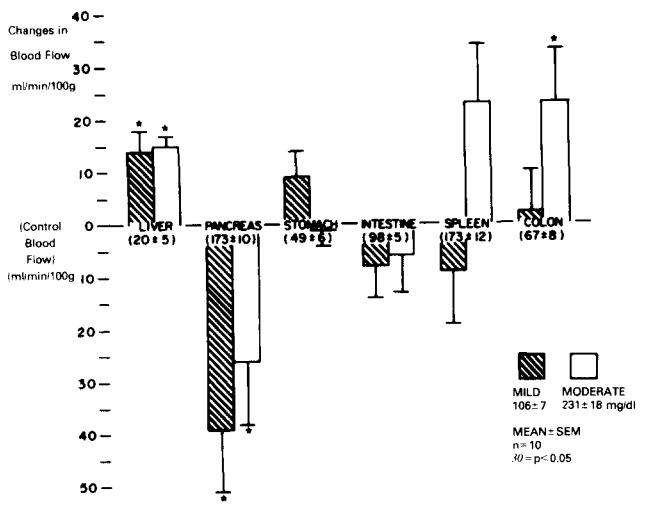

FIG. 3. Changes in splanchnic blood flow after an ethanol infusion in conscious dogs. Pancreatic flow is shown to decline as hepatic arterial flow increased. (Reprinted with permission from Friedman *et al., Proc Soc* **174:** 379, 1983.)

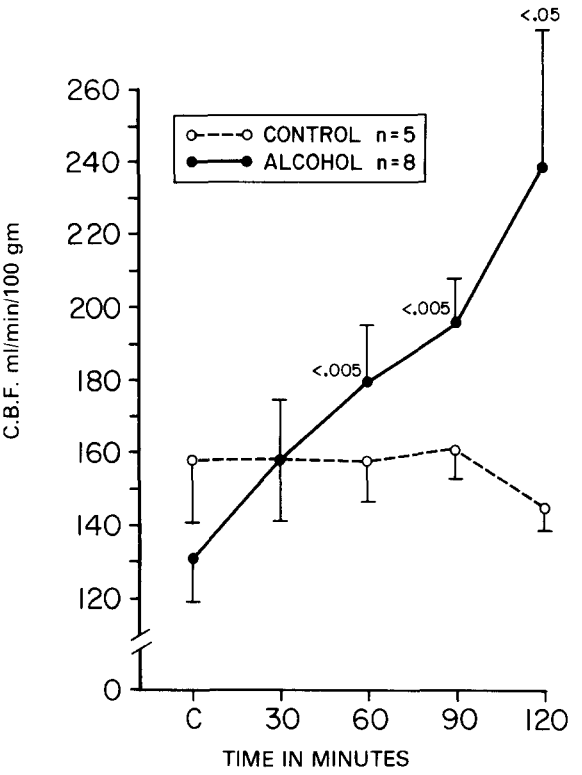

FIG. 4. Effects of ethanol on coronary blood flow (CBF). During an ethanol infusion (see Fig. 1) CBF increased; saline did not produce such a change (Reprinted with permission from Friedman *et al., Cardiovasc Res* **13:** 481, 1979.)

shown at a mean ethanol concentration of 199 mg/dl and further increases occur as alcohol concentrations rise to blood levels of 300 mg/dl. At a blood ethanol level averaging 200 mg/dl ethanol increases myocardial blood flow in a transmural fashion [18].

Since the effects of a perturbation on regional blood flow may be different with ischemia, experiments have also been done to assess the effect of ethanol on myocardial blood flow in the ischemic heart. At blood ethanol levels of approximately 200 mg/dl blood flow increased in nonischemic myocardium of the dog, whereas in ischemic myocardium there was a concomitant decline in blood flow [18]. Figure 5 demonstrates a significant increase in myocardial blood flow in nonischemic myocardium at a time when all layers in the ischemic zone declined. These experimental observations are consistent with clinical studies which have shown that patients who have coronary disease perform less well on stress testing following the ingestion of alcohol [41]. Such patients experience angina pectoris at lower levels of stress and show more exaggerated myocardial ischemia on ECG following ingestion [41].

Thus, ethanol can produce marked changes in regional blood flow in the conscious and anesthetized dog. Most studies have shown that ethanol increases myocardial, hepatic and perhaps also proximal colon blood flow [31]. Studies in the conscious dog have shown that alcohol may reduce brain and pancreatic blood flow. Anesthesia, however, may obscure some of these changes [18, 31].

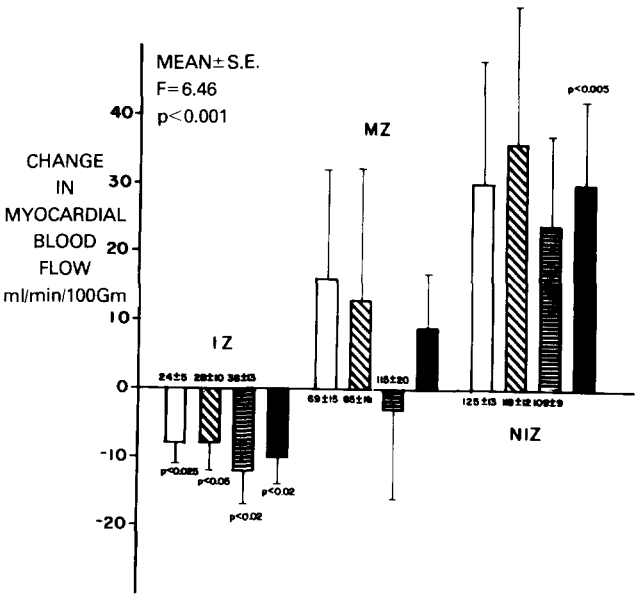

FIG. 5. Redistribution of blood flow produced by ethanol. Ischemic (IZ), adjacent to ischemic (MZ) and nonischemic (NIZ) zones, and subendocardial (white bars), myocardial (diagonal lines), subepicardial (horizontal lines) and average transmural (black bars) flows are compared. Values at base of bars indicate myocardial flow after coronary ligation; bars indicate changes produced by ethanol. (Reprinted with permission from Friedman *et al. Am J Cardiol* **4:** 232–234, 1981.)

CHRONIC EFFECTS

For more than 100 years an association of alcohol abuse and the development of heart failure has been known. However, until 30 years ago, alcoholic cardiomyopathy, as we now recognize this disorder, was confused with beriberi heart disease. While both conditions may be characterized by the presence of circulatory congestion, in beriberi heart disease the left ventricular contraction is normal and even

hyperdynamic, whereas in alcoholic cardiomyopathy the left ventricle is dilated and hypocontractile.

Alcoholic cardiomyopathy is a primary disease of the heart muscle in which nutritional factors do not appear to be a causative factor. In the United States it is a disease seen largely in black men. In most American reviews of this subject [12, 36, 37] between 85 and 90% of patients are black. The average age of patients with this disorder is 40 years, although patients as young as 21 [37] or as old as 72 [10] have been reported to have this disease. The onset of the disease may be insidious with breathlessness as the predominant early complaint. Clinically, alcoholic cardiomyopathy is not different from other congestive, dilated cardiomyopathies. Such patients have congestive heart failure, low cardiac output, cardiac conduction abnormalities, arrhythmias and thromboembolic complications. Some patients may have typical angina pectoris, even though coronary arteries are generally patent.

In the early stages of the disease, the patients appear to be well-nourished. However, as the disease advances and cardiac cachexia ensues, such patients show marked inanition. The malnutrition observed in such patients is generally a consequence of the disease rather than its cause. The physical findings of patients with alcoholic cardiomyopathy are not different from those with other forms of dilated cardiomyopathy: Low blood pressure, signs of cardiac failure and the findings of a dilated heart are usually present.

In alcoholic cardiomyopathy the heart exhibits four chamber dilatation and biventricular hypertrophy [3,36]. While marked left ventricular hypertrophy may occasionally be present, generally the increased left ventricular thickness is not out of proportion to that expected for the ventricular dilatation. The presence of mural thrombus, found in 50% of patients at autopsies, is responsible for the frequent occurrence of pulmonary and systemic embolism [3, 10, 36]. Coronary arteries are generally widely patent, although intramyocardial branches may show varying degrees of vascular and perivascular fibrosis [15]. Myocardial fibrosis may also be found. Ultrastructural changes include an increase in the number, presence of swelling and alteration of the structure of mitochondria [4]. Sarcoplasmic reticulum swelling, myocardial fibril damage and an increase in glycogen and fat content are also pathologic features [5,29].

Although structural, mechanical and metabolic abnormalities have been demonstrated following prolonged administration of alcohol in several animal studies, the features of alcoholic cardiomyopathy have not been replicated experimentally. Prolonged administration of alcohol to rats [49a] dogs [42,48] and monkeys [53] have resulted in ultrastructural changes. In these experimental models, swelling of mitochondria, intercalated discs, and the transverse tubular system, and damage of myocardial fibrils have all been demonstrated. Histochemical studies in dogs after prolonged administration of alcohol with a nutritionally adequate diet demonstrate a mucopolysaccharide-like substance in the myocardium [42]. Increased cardiac accumulation of fat, in the form of triglycerides and cholesterol, has also been described. The ultrastructural changes are associated with marked metabolic abnormalities. Diminished intramitochondrial enzymes, reduction in myocardial ATPase, reduced mitochondrial oxygenation, diminished myocardial calcium content, and a reduction of calcium uptake and binding by sarcoplasmic reticulum have all been described [48]. Thus, experimentally, chronic alcohol administration can produce myocardial changes similar to those found in alcoholic cardiomyopathy: altered myocardial lipid metabolism, inhibition of mitochondrial respiration and enzyme activity, and impaired intracellular calcium uptake and binding. However, the full-blown features of alcoholic cardiomyopathy have not yet been reproduced.

Even before heart failure ensues, alcoholics completely withdrawn from ethanol may shown evidence of impaired cardiac function [22,50]. Of interest, are observations that suggest a relationship of such cardiac dysfunction with systemic hypertension [22]. In this study [22] 66 chronic alcoholics were investigated 4–5 days following admission for detoxication, when none showed features of withdrawal, none were receiving medication, and none had findings or history of clinical heart disease, but 1/3 demonstrated systemic hypertension (a blood pressure of $\geq$160/90 mmHg) sometime during their hospitalization. Alcoholics tended to have high heart rates but normal cardiac output. Even though there were no clinical features of heart failure in this population, normotensive and hypertensive alcoholics showed abnormal systolic time intervals. Hypertensive alcoholics, moreover, showed more abnormal findings than the normotensive group. Both groups of alcoholics had elevations of left ventricular wall stress, with an exaggerated stress to mass ratio. However, the ratio of wall stress to the endsystolic volume, which is an index of contractility, was elevated in hypertensive alcoholics. Thus, chronic alcoholism resulted in an increased left ventricular wall stress with an abnormality of systolic time intervals; yet cardiac function was maintained by an augmentation of contractility, probably mediated by the increased plasma catecholamines observed in chronic alcoholics, especially during periods of alcohol withdrawal. The exaggerated abnormalities in the hypertensive subgroup suggest that alcoholic-associated hypertension may be a cause of cardiomyopathy or perhaps a marker for those at risk of developing this disorder.

The clinical, hemodynamic, and pathological features of alcoholic cardiomyopathy can be distinguished from the cardiac finding of three other conditions associated with alcohol abuse: Quebec beer-drinkers' cardiomyopathy [39], cirrhosis [17], and beriberi heart disease [32]. Quebec beer-drinkers' cardiomyopathy [39] appeared as an epidemic in heavy beer drinkers during the mid 1960's. This disorder had the features of a congestive, dilated cardiomyopathy. Presence of polycythemia, cyanosis, large serious cavitiy effusion, and an exceptionally high early mortality rate of 42%, distinguished this disorder from typical alcoholic cardiomyopathy. The disease disappeared when cobalt, which had been put in beer to stabilize the foam, was removed.

Beriberi heart disease [32] is characterized by a hyperdynamic circulation. Generally, central venous pressure is elevated, cardiac output is increased, and signs of circulatory congestion are present. As the disease progresses, a fulminant form, so-called shoshin beriberi may ensue which is characterized by cyanosis, lactic acidosis and, in advanced cases, vascular collapse. Thiamine deficiency can be inferred in such patients by the finding of reduced red blood cell transketolase activity, an enzyme in the hexose monophosphate shunt requiring thiamine phosphate as cofactor, or by hemodynamic responsiveness to thiamine: Cardiac output declines and total peripheral resistance increases after the administration of thiamine. Although a high cardiac output is typical of beriberi heart, normal and occasionally even reduced cardiac output may be seen with advanced disease or when alcoholic cardiomyopathy is concomitantly present. Of interest, in patients with both car-

diomyopathy and beriberi heart disease the administration of thiamine, by reversing the vasodilation, may worsen the heart failure [46].

Cirrhotics may also show features of hyperdynamic circulation [17]. However, cardiomegaly, left ventricular hypertrophy, and perivascular fibrosis may be observed on autopsy [34]. In an echocardiographic study of 20 biopsy-proven cirrhotics whose findings were contrasted with those of matched subjects, left ventircular end-diastolic volume, ejection fraction, velocity of circumferential fiber shortening, left ventricular wall stress and heart rate were found to be significantly greater in cirrhotics, whereas total peripheral resistance was lower. These findings were unrelated to the presence of anemia. Moreover, in patients with ascites or hepatic encephalopathy, the findings of a hyperdynamic heart was exaggerated. Whether the findings in cirrhotics are related to the presence of arteriovenous shunts or to still undefined relations with neurohumoral factors is not clear. Recent observations, however, indicate that cirrhotics with reduced sodium excretion, such as that observed in those with ascites, are most likely to show elevated levels of plasma norepinephine [8]. Patients in hepatic coma also have marked elevations of norepinephrine and substance P, a potent intestinal vasodilator [30]. These recently discovered findings are consistent with the view that the hyperdynamic state in cirrhotics is related at least in part to elevated neurohumoral substances. It should be noted, however, that cirrhotics may demonstrate an abnormal response to dynamic stress [24], afterload stress [44] or a volume challenge [2]. Furthermore, in a given patient the findings of cirrhosis or beriberi, or even both, may coexist with alcohol-induced heart muscle disease.

ACUTE MYOCARDIAL INFARCTION

Alcohol abuse has been associated with the development of acute myocardial infarction in patients with patent coronary arteries [38,45]. Regan and coworkers [45] believe that this disorder is a toxic cardiomyopathy, based upon their findings of increased glycoprotein and perivascular fibrosis in the hearts of patients who succumbed with this condition. In a recent report, Moreyra and coworkers [38] observed acute myocardial infarction after a heavy alcoholic binge in two young patients (ages 18 and 22 years) with patent coronary arteries. Also, there are reports of Prinzmetal's angina, a disorder produced by coronary spasm, in which episodes could be casually related to alcohol ingestion [16]. Thus, although the mechanism for myocardial infarction in the alcoholics with patent coronary arteries has still not been determined, and a toxic cardiomyopathy or small vessel disease remain tenable possibilities, coronary spasm could be the cause. Studies with ergonovine, a substance used to provoke coronary spasm, have not been reported in alcoholics. In dogs, however, I have found that ethanol at blood levels greater than 200 mg/dl did not alter the effects of ergonovine on myocardial blood flow (unpublished observations).

It is also possible that myocardial infarction in alcoholics may be due to obstructive coronary disease in which there has been rapid spontaneous dissolution of the thrombus. Such spontaneous thrombolysis has in fact been described in man following acute myocardial infarction. An alternative hypothesis is reactive vasospasm. Since experimentally, at least, alcohol can produce coronary vasodilation, it is possible that acute myocardial infarction may be related to reactive vasospasm occurring as ethanol disappears from the blood. Such a mechanism has been suggested for angina pectoris found in munition workers after withdrawal from chronic exposure to nitroglycerin.

CARDIAC ARRHYTHMIAS

Although cardiac arrhythmias would be expected as a complication of alcoholic cardiomyopathy, at times paroxysmal tachycardias may occur in alcoholics without evidence of left ventricular dysfunction. Timothy Regan's group [14] has termed this disorder "holiday heart," because it generally occurs after episodes of binge drinking. The cause for these arrhythmias is generally not clear. Occasionally, the arrhythmias may be due to hypokalemia or hypomagnesemia.

Ethanol and its metabolites at clinically relevant blood levels however have minimal direct electrophysiological effects [23,54]. Shortening of the action potential duration in isolated rat atria at blood levels of 440 mg/dl [23] and a similar change in the action potential of isolated canine cardiac Purkinje fibers with ethanol levels between 100 and 300 mg/dl have been reported [54], but these findings are not likely to account for arrhythmias in alcoholics. By contrast, there have *even* been reports that suggest an antiarrhythmic effect of alcohol [35].

However, in several recent studies [13,27] of patients with the "holiday heart," arrhythmias could be elicited with programmed electrical stimulation after administration of alcohol. The mechanism whereby alcohol exerts these arrhythmogenic effects was not determined. Whether this action is a direct one, or perhaps related to elevations of catecholamines, will require further investigation.

In conclusion, alcohol abuse is associated with a severe form of heart muscle disease. It has also been related to acute myocardial infarction in young patients with patent coronary arteries. In some people alcohol provokes cardiac arrhythmias. Epidemiological studies have shown that moderate users of alcohol have fewer coronary events than teetotalers, but they have also shown a relation between alcohol abuse and hypertension and an *increased* occurrence of coronary events. Clinical and experimental studies have demonstrated that alcohol depresses cardiac function, especially in hearts with already reduced cardiac performance, exerts unfavorable effects on blood flow in the ischemic heart, and reduces blood flow to the brain. Thus, from the standpoint of its cardiovascular effects, alcohol should be used only in moderation and patients with heart disease should perhaps abstain from it entirely.

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