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THE RELATIONS OF ALCOHOL AND THE CARDIOVASCULAR SYSTEM

Arthur L. Klatsky

Cardiovascular Division, Department of Medicine, Kaiser-Permanente Medical Center, Oakland, California.

CONTENTS

INTRODUCTION

Much has been learned about relations between alcohol and heart disease during more than a century of interest by investigators and clinicians. However, the clinical, epidemiologic, and physiologic evidence cannot yet be integrated into definitive concepts. Past attempts to generalize have impeded progress in understanding this subject. However, some apparent paradoxes disappear when we consider the following premises.

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1. The apparent roles of alcohol in various cardiovascular disorders are disparate. For example, the relation of alcohol to cardiomyopathy, hypertension, and the various manifestations of coronary disease has features unique to each condition.

2. The relation of alcohol to a specific cardiovascular disorder is likely to vary with the amount used.

3. Alcohol most often plays an indirect or partial role in specific cardiovascular disorders. It is best to think of alcohol as a conditioning factor or risk factor in these conditions. Although alcohol is statistically associated with some cardiovascular disorders, a cause-and-effect relation has yet to be proved between alcohol and any cardiovascular condition.

HISTORICAL REVIEW

Because there have been intellectual digressions, the history of alcohol and heart disease is worth reviewing. Some of the great clinicians and pathologists of the 19th and early 20th centuries perceived an association between the regular use of large amounts of alcohol and nonspecific heart disease. Thus in 1861 Friedreich (45) described heart enlargement associated with alcoholism, and in 1873 Walsche (155) used the term "patchy cirrhosis of the heart." The "*Münchener Bierherz*" was considered a common condition in the Bavarian capital in the late 19th century. Böllinger (17) described the entity as a nonspecific dilatation and thickening of the heart chambers and also mentioned estimates of an average annual per capita beer consumption of 432 liters in Munich (compared with 82 liters elsewhere in Germany). In 1893 Graham Steell (149) reported a series of 25 cases of alcohol-induced heart disease and stated, "Not only do I recognize alcoholism as one of the causes of muscle failure of the heart but I find it a comparatively common one." James MacKenzie (87) made similar observations in 1902 and may have been the first to use the term "alcoholic heart disease."

An epidemic of heart muscle disease due to contamination of beer by arsenic occurred in 1900 in England (53, 120, 126–128, 150). After this epidemic, Steell (150) adopted the view that the "heart condition" due to use of substantial amounts of alcohol was largely the result of arsenic. From 1900 to the late 1920s, there was general doubt that alcohol had a substantial, direct role in heart muscle disease, although Vaquez (154) strongly believed in such a relation.

From the late 1920s to about 1950, the entity "beriberi heart disease" became the dominant theme in the medical literature concerning the effects of alcohol on the heart. The general interest then rapidly turned back in the 1950s to possible direct effects of alcohol on the heart muscle, separate from

or in addition to deficiency states. The terms "alcoholic heart disease" and "alcoholic cardiomyopathy" have been increasingly used, and the existence of such an entity has become more accepted than ever before.

Since William Heberden's classical description in 1786 of angina pectoris (59), some have felt that alcohol might be beneficial in coronary disease. Heberden described subjective benefit for angina, but there is evidence (19, 132) that the subjective benefit is the result entirely of dulled perception of the discomfort. Since 1970, largely through epidemiologic studies, considerable interest has arisen in possible relations of chronic alcohol use to both hypertension and coronary atherosclerotic disease. Evidence is increasing that hypertension is more prevalent among heavy drinkers and that coronary disease is more prevalent among abstainers.

EFFECTS OF ALCOHOL ON CARDIOVASCULAR FUNCTION, BIOCHEMISTRY, AND STRUCTURE

Knowledge of the cardiovascular effects of alcohol, especially with respect to the effects of chronic alcohol use, is incomplete. Most experimental work on animals and humans has concerned the effects of acutely administered alcohol. In many instances, the results of such investigations cannot be applied directly to the relations of alcohol and chronic disorders.

Heart Rate, Blood Pressure, and Blood Vessel Tone

It has long been known that in healthy humans alcohol doses of 30–75 ml (equivalent to 2–5 ordinary drinks) produce slightly increased heart rate, blood pressure (systolic more than diastolic), and cardiac output (34, 55, 67, 123). How much these changes are direct effects of alcohol on the circulation and how much they represent indirect nervous system regulation is unclear. Overall peripheral vascular resistance changes little; blood vessels in the skin dilate (producing the familiar facial flush), but blood vessels in skeletal muscles and internal organs constrict (41). It has also long been known (34) that doses of alcohol sufficient to produce severe intoxication also produce hypotension, bradycardia, and, ultimately, death from cardiac standstill. Nervous system reflexes are believed to predominate in these effects.

There are suggestions of possible links between alcohol and several abnormal physiologic processes in humans that have been implicated in experimental or clinical hypertension. These tentative links include increases in renin and aldosterone (85) as well as elevation in cortisone-like hormones to produce a state resembling Cushing's syndrome (111, 112, 145).

Effects on Heart Pumping Action

GENERAL SUMMARY The effects of alcohol on heart muscle have been explored in numerous studies of normal and diseased humans, intact animals, and isolated animal heart muscle preparations. The results vary according to dose, route, duration, and frequency of administration, parameters measured, and pathologic state of subjects. Most studies indicate that alcohol in sufficient doses decreases myocardial contractility. The dose required for this effect in humans may be lower if there is clinical evidence of heart muscle disease or if the subject has ingested substantial amounts of alcohol for a long time.

ACUTE STUDIES Depressed contractility has been convincingly demonstrated in isolated heart muscle fibers exposed to alcohol (47, 146). Other studies provide evidence of depressed heart muscle contraction in anesthetized dogs (93, 116, 156, 157) and in conscious dogs (62) at blood alcohol levels of 100 mg/100 ml. Discharge of the adrenal glands and sympathetic nervous system as a compensatory mechanism has also been demonstrated (165), although other investigators (65) could not confirm this.

In normal humans, depressed contraction of the left ventricle has been found at blood alcohol levels of 75–250 mg/100 ml (93, 97). These levels could represent very mild to severe intoxication. Similar findings have been demonstrated with various indirect methods such as systolic time interval (2) and echocardiographic measurements (31, 90) at blood levels of 75–138 mg/100 ml. This decreased force of contraction was not always associated with decreased cardiac output (2, 31), leading to the suggestion that a direct myocardial depressant effect of alcohol brought compensatory mechanisms into play to preserve overall circulatory integrity. Poor correlation of the observed effects with doses of alcohol within the ranges studied (31, 67) also can be interpreted as evidence for the development of compensatory mechanisms. Still more evidence of physiologic compensation is provided by studies of near-maximal cardiac exercise performance that showed little effect of blood alcohol levels of 85–200 mg/100 ml in normal humans (16, 123).

The acute depressant effects of alcohol on heart muscle contraction may be more pronounced and may occur with smaller alcohol doses in persons with preexisting heart disease not related to drinking. A study of patients with coronary artery disease (29) led to the conclusion that "three or four whiskeys" profoundly depressed heart muscle. Similar results have been reported with doses of 60 ml of alcohol (equivalent to five 12-ounce cans of beer or 5 ounces of 80-proof whiskey) administered to volunteers with various types of heart disease (50, 51). Analogous evidence is provided by

a study of anesthetized dogs to which a standard nonpenetrating blow was given to the chest (83). Prior administration of alcohol greatly increased the mortality of the blow and decreased the performance of the traumatized heart.

CHRONIC STUDIES Deleterious effects on heart function have been shown in well-nourished mice fed large amounts of alcohol for only 7–10 weeks (20). A study of rats that received 25% of their calorie intake as alcohol showed a decrease in force of heart muscle contraction (88), but no abnormality was seen (86) in the same species given 15% of their food intake as alcohol. One study of dogs fed about one third of their calorie intake as alcohol (100) showed no functional cardiovascular abnormalities after several months, but another study (115) of dogs fed a like proportion of their calories as alcohol showed definite impairment of heart function after 18 months. Thus dose and duration of chronic alcohol use are both important in production of functional cardiac abnormalities in animals. No experiment has yet produced frank congestive failure in well-nourished animals.

There is much evidence that humans with a long history of substantial alcohol intake and without clinical evidence of heart disease often have abnormal myocardial function. This phenomenon, which is considered by many to represent preclinical heart muscle disease, has been demonstrated by physiologic studies (52, 84, 117) as well as by indirect noninvasive tests (89, 147, 166). Men may be more susceptible than women to these effects (166). A recent report (7) suggests that the functional abnormality in humans may represent primarily decreased left ventricular compliance.

Coronary Circulation

The substantial body of data showing that ethanol adversely affects heart muscle function is not paralleled by similar consistency in known effects of alcohol on the blood supply to the heart muscle (the coronary circulation). In fact, some of the experiments showing acute impairment of heart muscle contractile force (93, 117) in humans and dogs showed concomitant increase in coronary blood flow. Ganz (46) also found evidence suggesting increased coronary blood flow from acute exposure to alcohol. Nevertheless, there are experiments that suggest decreased coronary blood flow (116, 156) or no effect (138, 160). Studies of humans with coronary disease who were monitored by electrocardiograph while exercising suggest no benefit or possible worsening of impaired coronary blood flow (99, 132). It should be kept in mind that responses of normal coronary vessels to pharmacologic agents may differ from responses of diseased vessels, which have limited capacity to dilate. A recent study in dogs (44) suggests that alcohol in-

creases blood flow in nonischemic myocardium but that, in acute experimental ischemia, there is an unfavorable redistribution of myocardial blood flow.

Alcohol Versus Acetaldehyde

The physiologic response to acetaldehyde, the first metabolite of alcohol, has been the subject of some investigation. In dogs, a pressor effect and an increased coronary blood flow have been demonstrated (91), but this effect was the result of secondary catechol release. In another dog experiment (44), ethanol and acetaldehyde (at levels produced by alcohol metabolism) had opposite effects upon cardiac function; alcohol depressed myocardial performance, but acetaldehyde improved cardiac performance secondary to peripheral vasodilation. Both substances appeared to increase coronary flow in this study.

Myocardial Biochemistry

Because there is no apparent metabolism of alcohol in heart muscle cells, the mechanism of possible myocardial injury in heart muscle cells presumably differs from the situation in the liver (65). Mitochondrial oxidation of fatty acids represents the major source of myocardial cell energy. In isolated heart muscle cells, alcohol inhibits fatty acid oxidation (86). In humans, blood alcohol levels of 100–200 mg/100 ml can cause leakage of mitochondrial enzymes (116, 117, 159). Furthermore, chronic alcohol administration in animals appears to reduce cardiac mitochondrial capacity to oxidize a number of other substrates (100). Chronic alcohol feeding in dogs reduces the activity of intramitochondrial isocitrate dehydrogenase and also reduces calcium binding to sarcoplasmic reticulum (119, 129, 135). An analogous effect upon skeletal muscle has been shown in human volunteers with short-term experiments (130). Because myocardial contraction requires calcium release by sarcoplasmic reticulum, this biochemical effect is likely to have functional correlates. Reduced protein synthesis (139) and altered phospholipid composition of cardiac cell membranes (114) have also been demonstrated. Additional acute effects of alcohol upon cardiac muscle cells include the inhibition of Na-K ATPase activity (164) and direct influence upon contractile proteins (109).

Effects on Heart Muscle Structure

Enlarged scarred hearts were described as early as 1861 (45) among some chronic heavy users of alcohol. A number of modern descriptions are available (3, 4, 21, 136). Grossly, the hearts show hypertrophy, dilatation, fibrosis, and mural thrombus formation. Under the optical microscope, there is variation in muscle fiber size; cellular swelling, vacuolization, fatty

droplet infiltration, and focal scarring or inflammation. These abnormalities have been observed in very heavy drinkers with no clinical heart disease evident during life (136). The coronary vessels have generally been unobstructed, but there has been a report of fibrosis in small coronary branches (39).

Electron microscopy shows evidence of damage in various ultrastructural components including mitochondria, myofibrils, intercalated discs, and the sarcoplasmic reticulum (4, 19, 21, 94). Histochemical studies show an increased accumulation of fat droplets and a decrease in oxidative enzymes. None of the gross, optical microscopic, electron microscopic, or histochemical findings are specific enough to distinguish heart muscle disease in users of large amounts of alcohol from cardiomyopathy in other persons.

Animal experiments have shown production of similar ultrastructural abnormalities with chronic feeding of large amounts of alcohol (20, 115, 141). The accumulation of Alcian blue-staining material (presumably glycoproteins) may correlate with the increased functional stiffness of the myocardium (115). The animal experiments, in which all essential nutrients were supplied, given evidence that alcohol toxicity to the heart muscle is not related to associated nutritional deficiency. However, neither gross cardiac dilatation nor congestive heart failure has yet been produced in animal experiments.

ALCOHOL AND SPECIFIC CARDIOVASCULAR DISEASES

Alcoholic Cardiomyopathy

Much of the evidence described above clearly suggests a direct myocardial toxic effect by alcohol or one of its metabolites. The existence of at least one chronic disorder due to this direct, toxic effect is widely accepted by clinical cardiologists and is usually called alcoholic cardiomyopathy, or alcoholic heart disease. The circumstantial evidence for the existence of this condition is substantial, although some (142) question it.

EVIDENCE FOR ALCOHOLIC CARDIOMYOPATHY The condition has often been reported by excellent clinicians and pathologists of the past two centuries. The reports represent various types of practices and populations (3, 4, 17, 18, 21, 37, 38, 56, 87, 106, 143, 149, 154).

Further evidence is the fact that long-standing use of substantial amounts of alcohol has been found in a large proportion of patients with unexplained heart disease (3, 56, 134, 143). Alexander (3) made an attempt at control. He reported that 80% of patients hospitalized at the Minneapolis Veterans Administration Hospital for primary myocardial disease were defined as

heavy drinkers compared with 28% of patients with other diagnoses admitted to the same medical service. This difference, although impressive, apparently represented a hospital population with a large proportion of substantial alcohol users. On the other hand, the proportion of alcohol users in some series of cardiomyopathy patients has been much lower; Goodwin (49) stated that "alcohol is certainly not the cause of congestive cardiomyopathy in the majority of patients."

Other evidence consists of a few well-documented case reports. Congestive heart failure developed in one well-nourished patient during a 4-month period when he ingested 12–16 ounces (390–518 ml) of Scotch whiskey daily; the clinical abnormality subsided after he ceased drinking (117). Other such cases have been reported (140); many must have been seen and not reported.

An important study (32) documented more frequent regression of clinical abnormality in cardiomyopathy patients who abstained compared with those who continued to drink.

Other indirect evidence is the documented existence of both acute and chronic peripheral skeletal muscle damage related to alcohol use (105, 129). Data concerning an association with cardiomyopathy are sparse, but a case has been reported (107). Affected skeletal muscles have shown microscopic evidence of inflammation, intercellular edema, and ultrastructural abnormalities of the mitochondria and myofibrils. These abnormalities are similar to the cardiac abnormalities seen in cardiomyopathy (105, 129).

Another example of circumstantial evidence is the observation of heart rhythm disturbances in relation to drinking (35). This phenomenon has been given the colorful name "holiday heart syndrome" (36). More serious arrhythmias are believed to be related to acute alcohol use (144). A recent case has been reported of an alcoholic patient in whom ventricular tachycardia could be provoked only after alcohol ingestion (54).

Perhaps the strongest circumstantial evidence for alcoholic cardiomyopathy are facts already cited in detail: (*a*) autopsy studies showing abnormalities in large proportions of alcoholics with no clinical evidence of heart disease; (*b*) acute and chronic interference with heart function and metabolism by alcohol; and (*c*) structural abnormalities in human and animal heart muscle cells related to alcohol ingestion.

CLINICAL FEATURES Early signs or symptoms are nonspecific electrocardiographic (ECG) changes and rhythm disturbances, often minor. The holiday heart syndrome (36) following spree drinking has already been mentioned. Nonspecific ST-T variations on the electrocardiogram, as well as arrhythmias, occur among some nonspree drinkers and regress when drinking is reduced or stopped. Evans (37) described T-wave configurations

that he considered relatively specific for early alcoholic heart disease, but others (10, 101, 108) have not often observed these "characteristic" ECG findings. The prevalence of such early nonspecific evidence of cardiac susceptibility to alcohol is unknown. The likelihood of progression to chronic myocardial disease is also unknown and probably low. However, it seems reasonable to suppose that these persons represent a high-risk group, and there is evidence that reversibility is maximal at early stages of alcoholic heart disease.

The late clinical picture, a chronic congestive cardiomyopathy, is described in several excellent reports (3, 18, 21, 102, 106, 134). Congestive heart failure, chronic rhythm disturbances, conduction abnormalities on the ECG, and a high incidence of embolic complications are characteristic. Although the development is usually insidious, a number of patients seem to have an acute onset of severe heart failure and do not come to medical attention before the late stage has been reached. Even at this point, some patients show partial regression, but many progress inexorably despite abstinence from alcohol and optimal medical therapy. Except for the relation to alcohol use, this clinical picture cannot be distinguished from chronic congestive cardiomyopathy of any cause.

DIAGNOSIS AND TREATMENT The diagnosis of alcoholic cardiomyopathy is always presumptive, since there are no specific symptoms, signs, tests, or pathologic findings. A high clinical index of suspicion and skillful interpretation of nonspecific evidence are necessary. Basically, the two necessary diagnostic features are a compatible drinking history and the exclusion of other causes of heart disease. Little is known about the minimum amount and duration of alcohol use that may lead to cardiomyopathy, but it is generally believed that very heavy drinking over many years is necessary. One investigator (78) has suggested as a criterion for diagnosis of alcoholic cardiomyopathy a drinking habit equal to or greater than 125 ml of ethanol daily for 10 years or longer. Even among very heavy drinkers, the prevalence is probably low, distinctly lower than the prevalence of liver damage. The exclusion of other types of heart disease is necessary for reasonable certainty of diagnosis, but there is no logical reason that a person might not have both alcoholic heart disease and another type of heart disease. Existence of another type of heart disease might actually predispose to heart muscle damage by alcohol.

Abstinence from alcohol is the mainstay of treatment. Rest, digitalis, diuretics, antiarrhythmic drugs, and other measures appropriate to the individual's clinical picture should be employed. With abstinence, the recovery rate is good in early disease. Even with advanced disease, a marked degree of recovery is possible (32, 113, 140), although there is a high death

rate from congestive heart failure, sudden death due to arrhythmias, and embolism.

RISK FACTORS AND COFACTORS Aside from the possible greater susceptibility of men (166), little is known about the reasons for individual susceptibility to alcohol's toxic effects on the heart. It seems fairly certain that alcohol itself is the major toxin, but a role for other constituents of wine, beer, or certain types of distilled spirits may exist.

The concept of synergistic toxicity to the heart by alcohol and other cofactors is supported by two well-documented historical episodes. The first was a major epidemic at the turn of the century in and near Manchester, England, due to accidental contamination of beer by arsenic (53, 120, 126–128). This episode caused a major intellectual digression in the development of the concept of alcoholic heart disease. The second occurred 65 years later in several locations in North America and in Belgium and was due to the use of cobalt as a foaming agent in beer (5, 6, 71, 92, 95, 151). In both epidemics, there was an abrupt, severe illness characterized principally by acute heart muscle failure in chronic drinkers of large amounts of beer. Those who recovered appeared able to resume their beer-drinking habit without apparent harm. The amounts of cobalt and arsenic alone were insufficient to account for the heart damage. Although no biochemical mechanisms were established, these events strongly suggest synergistic toxicity (the enhancement of the effect of one substance by the presence of another chemical).

The parallels between the arsenic and cobalt beer episodes make it likely that other metals and chemicals can act synergistically with alcohol to produce cardiomyopathy. Thus it seems reasonable that multiple factors may be involved in many instances of cardiomyopathy. Possibilities include iron, copper, and drugs with heart-damaging properties (emetine, adriamycin, and tricyclic antidepressants are a few). Furthermore, it is known that myocarditis occurs with many viral illnesses, and the possibility exists that residual heart damage acts as a cofactor in other heart muscle diseases. In fact, a synergistic link between almost any type of heart muscle impairment and alcohol is a reasonable hypothesis. A similar role of vitamin or nutritional deficiencies (e.g., selenium) may exist.

Cardiovascular Beriberi

For several decades, the concept of cardiovascular beriberi dominated thinking about the relation of alcohol to heart disease. Although the condition was well known previously, the classic detailed description by Aalsmeer & Wenckebach (1) clearly defined a clinical picture of heart failure with high cardiac output. Beriberi in persons in the Orient who subsisted

on polished rice was caused by thiamine (vitamin B_1) deficiency. Because some patients in Western countries had a similar clinical picture and responded well to thiamine, it was assumed (70) that most heart failure in heavy drinkers was caused by associated nutritional deficiencies. In the 1960s (12) and 1970s (79), high-output cardiovascular beriberi was studied by modern physiologic techniques in a few cases. These patients showed some of the highest cardiac outputs at rest ever measured. The major cardiovascular physiologic consequence of thiamine deficiency in most appeared to be dilatation of peripheral small blood vessels with the creation, in effect, of a large arteriovenous shunt. Some responded remarkably rapidly (hours to days) to thiamine, with apparent complete recovery. The clinical observations of Aalsmeer & Wenckebach were confirmed.

In Western countries, the cases presumed to represent vitamin-deficiency-induced heart failure all used large amounts of alcohol (70). It gradually became apparent that only a minority fit the rice beriberi picture. Many, if not most, had good nutritional state, responded poorly if at all to thiamine administration, and had low-output heart failure with predominant left ventricular failure (in contrast to the right ventricular failure so evident in Oriental beriberi) (158). A widely held view was that in long-standing thiamine deficiency, chronic myocardial damage occurred that no longer responded to thiamine (14, 15). One reported patient (124) demonstrated two syndromes in sequence. He first had a high-cardiac-output state that responded to thiamine, then somewhat later developed low cardiac heart failure that was unresponsive to thiamine. This was interpreted as representing beriberi followed by alcoholic cardiomyopathy.

It became the prevalent view (66) that chronic thiamine deficiency as a cause of congestive cardiomyopathy has been poorly documented but that thiamine deficiency may be a conditioning factor in some cases. Thiamine deficiency is probably, at most, a contributory factor in the "atypical" cases of beriberi. Blacket & Palmer (12) stated it well: "It [beriberi] responds completely to thiamine but merges imperceptibly into another disease called alcoholic cardiomyopathy, which does not respond to thiamine."

Alcohol and Hypertension

Strong epidemiologic evidence exists that regular use of large amounts of alcohol is associated with a substantially higher prevalence of hypertension. On the other hand, persons who use small amounts of alcohol, up to the amounts contained in one or two drinks daily, seem to fare slightly better than nondrinkers with regard to blood pressure measurements. This possible environmental link to a common serious condition is of both theoretical and practical importance.

The reports (11, 27, 30, 33, 68, 89, 96, 110, 111) of an alcohol-blood pressure link represent varied populations. By far the largest study (77) used data gathered at checkup examinations given at the Kaiser-Permanente Medical Care Program in Northern California. These data showed a statistically strong association between blood pressure and known drinking habits of 83,947 men and women of three races. After cross-classification, this relation proved to be independent of smoking, coffee use, salt use, blood group, educational attainment, and adiposity (height/weight index).

The difference in mean blood pressure in the Kaiser-Permanente study translated into a doubled prevalence of hypertension (defined as blood pressure of 160–95 mm Hg or higher) in white men and women who took six or more drinks daily compared with nondrinkers or users of two or fewer drinks daily. The doubled prevalence among the white heavier drinkers was quite similar to the findings in other studies (30, 68) in which the methods of classifying data allowed comparison.

In view of agreement among various studies, some type of association between alcohol use and blood pressure is established. However, various types of indirect association have not been ruled out. These include (*a*) psychosocial stress as an underlying factor, (*b*) a common hereditary predilection both for use of alcohol and hypertension, (*c*) other environmental factors such as dietary habits, and (*d*) alcohol withdrawal, which is associated with higher pressures in some heavier drinkers.

The blood pressure elevations among heavier drinkers, whether direct or indirect, could be a temporary effect that disappears, at least in part, with reduced drinking. The study of Du Pont employees (30) supports this possibility. On the other hand, there was a residual increase in hypertension prevalence in presumably abstinent alcoholics among the Du Pont workers. A physiologic mechanism is not established. The effects of acutely administered alcohol on blood pressure do not provide a ready explanation. Evidence is limited about pathophysiologic actions of chronic substantial drinking that could account for blood pressure elevations. In view of the uncertainty about the nature of the alcohol–blood pressure association and the absence of a proven mechanism, a causal relation has not been proved.

Alcohol and Coronary Atherosclerotic Disease

In coronary atherosclerosis, the factors involved in the production of the underlying occlusive process are not identical to those that immediately provoke symptoms or clinical events. Furthermore, present knowledge suggests that the role of alcohol should be considered separately for each of the three major clinical expressions of the condition: angina pectoris, acute myocardial infarction, and sudden death.

ANGINA PECTORIS Heberden's classic description of angina (59) included the statement that "wine and spiritous liquors afford considerable relief." Over the ensuing two centuries, it was widely presumed (82, 161) that alcohol was a coronary vasodilatator. However, studies of exercise performance ability using electrocardiographic evidence of ischemia have shown either no benefit (132) or, with doses of 65–320 ml of alcohol, decreased exercise performance ability (99). However, in contrast to the effects of other types of ingested foodstuffs, the *perception* of ischemic discomfort with exercise—anginal distress—did not occur sooner when alcohol was given.

Attempts to study coronary blood flow in relation to acutely administered alcohol have yielded conflicting findings (46, 93, 117, 138, 157, 160). Furthermore, the acute blood pressure and heart rate effects of doses of 30–75 ml of alcohol (34, 55, 67, 123) may affect the occurrence of myocardial ischemia, independent of any possible action of alcohol on the coronary circulation itself. Thus an ambiguous relation exists between alcohol ingestion and angina pectoris due to coronary atherosclerotic disease. Subjective benefit is probably not related to concurrent improvement in myocardial oxygen supply but presumably is the result of anesthetic or tranquilizing effects of alcohol.

MYOCARDIAL INFARCTION AND CORONARY DISEASE MORTALITY The relation of alcohol consumption to myocardial infarction and death from coronary disease has aroused much recent interest and some controversy. Some of the earlier population studies (26, 104) showed no association between alcohol use and major coronary events. The data were not apparently controlled for cigarette smoking, a well-established predictor of coronary events and a strong correlate of alcohol use (72, 74, 76, 137). The Framingham Heart Study reported data (153) showing a slight but statistically insignificant inverse relation (drinkers at less risk) between use of 30 or more ounces of alcohol per month and myocardial infarction, even without apparent control for smoking.

In a population study well controlled for smoking and other established coronary risk factors (43), there was a statistically significant inverse relation of alcohol use and heart attack among members of the Northern California Kaiser-Permanente Medical Care Program (73). A slightly inverse, but not statistically significant, relation between drinking and sudden cardiac death (42) was also found in the Kaiser-Permanente study. The inverse drinking-coronary relation was slightly progressive up to users of six or more drinks per day, although the largest difference in coronary risk was the difference between nondrinkers and users of two or fewer drinks daily.

In a study of Japanese men in Honolulu, a statistically significant inverse relation was found between drinking and both myocardial infarction and coronary mortality (13, 167).

A report from the Boston Collaborative Drug Surveillance Program (148) showed a slight inverse relation between alcohol use and nonfatal myocardial infarction. Another recent study in Boston (60) showed an inverse relation between alcohol use and death from coronary disease. In a later report (61), the relation was shown independently for users of beer, wine, or distilled spirits. A second study from the Kaiser-Permanente Medical Care Program (72, 75) showed a significantly lower hospitalization incidence and mortality for coronary disease among drinkers than among nondrinkers.

On the other hand, a number of studies (23, 30, 33, 137, 163) among problem drinkers or alcoholics have presented data showing a higher risk of myocardial infarction or coronary death among these persons. Among these studies, several (30, 33, 137) are comparisons between groups not controlled for important coronary risk factors, including smoking. Only one, a study of Swedish Temperance Board Registrants (163), showed a statistically significant increased risk of both nonfatal myocardial infarction and coronary death with control for smoking and other coronary risk factors.

Thus, most of the population studies suggest that drinkers suffer fewer major coronary events, whereas the studies of alcoholics show the opposite. It is possible that large amounts of alcohol have effects in coronary disease quite different from those of smaller amounts, but other explanations for this discrepancy are more likely. There are two possible explanations for a spurious association in the population studies. First, former drinkers, a subset of the nondrinkers in several of the studies, may be at especially high coronary risk. Second, there may be indirect association through ethnic factors, psychological traits, or other unknown risk factors. Explanations for a possible spurious association between very heavy drinking and coronary events include: (*a*) An indirect relation of very heavy drinking and coronary events through established coronary risk factors (e.g. hypertension and smoking) is almost certain. (*b*) An indirect relation may exist through other possible risk factors, such as psychosocial stress, which could be related to both heavy drinking and heart attack. (*c*) A possible erroneous diagnosis of coronary disease among alcoholics who die of other cardiac conditions, such as alcoholic cardiomyopathy, may also be made.

In the first half of this century, there were a number of reports (22, 64, 81, 103, 162) of an apparent inverse relation between chronic substantial alcohol use and atherosclerotic disease, including coronary disease, diagnosed at autopsy. However, this was dismissed by some (103, 131) as a statistical artifact because the premature deaths of many alcoholic persons

might preclude the development of atherosclerotic vascular disease. Recent work by Barboriak and colleagues (8, 9) showed that, among 900 patients examined by coronary arteriography, drinkers had significantly less atherosclerotic occlusion than nondrinkers, although the drinkers smoked more. Recent experimental data (28) concerning monkeys fed 36% of their calorie intake as alcohol indicate that alcohol at this level apparently reduces the development of experimental coronary atherosclerosis.

POSSIBLE EXPLANATIONS FOR THE INVERSE ALCOHOL-CORONARY DISEASE RELATION The emergence of a plausible mechanism for a protective effect of alcohol in coronary disease increases the possibility that such an effect exists. The mechanism is based on the observation that alcohol raises high-density lipoprotein (HDL) cholesterol levels in blood (25, 63, 80, 122). Elevated HDL is inversely related to coronary atherosclerotic disease (24, 48, 121) and may have a protective role by aiding in removal of cholesterol from the body or by retarding the formation of atherosclerotic plaques. The effect of alcohol in raising HDL levels is generally proportional to the amount regularly taken (63). Alcohol-induced HDL elevations decrease in days to weeks when drinking is stopped (63, 80). There is evidence that the site of action of alcohol's influence on HDL is the liver; some integrity of liver function is needed, as evidenced by the fact that some persons with acute, severe alcohol hepatotoxicity have very low HDL levels (80, 133). At ordinary levels of alcohol use, it has been suggested (152) that alcohol facilitates HDL production by facilitating influx of triglyceride-carrying lipoproteins to the liver cells.

Alcohol may also protect against major coronary events by a mechanism other than prevention of atherosclerotic occlusion. Although this has not been studied extensively, evidence for such an action has been reported (57). Such protection might be mediated by inhibition of platelet aggregation (58).

Alcohol and Other Cardiovascular Diseases

STROKE A positive relation between drinking and stroke incidence has been reported (13, 24, 69, 72). The relation is stronger for hemorrhagic than for thrombotic stroke (13, 72) and is felt to be not entirely explained by the association of both drinking and stroke with hypertension. A bleeding tendency due to alcohol has been implicated (13) as a possible additional explanation.

AORTIC AND PERIPHERAL VESSEL ATHEROSCLEROSIS There is little epidemiologic evidence to suggest a relation to alcohol use (72).

NONCORONARY ATHEROSCLEROTIC DISEASE An unusual form of angina pectoris, known as Prinzmetal variant angina, is widely believed to be related in some patients to reversible spasm of large coronary vessels (125). Although alcohol has been reported to be one of the pharmacologic agents that can induce this phenomenon (40), the association has not been widely observed.

Regan (118) reported a number of cases of myocardial infarction among alcoholics with no evidence of atherosclerotic or thrombotic occlusion. He postulated a mechanism of external constriction of coronary vessels by scarring due to alcoholic cardiomyopathy. Myocardial infarction without atherosclerosis is a poorly understood event that also occurs occasionally in nonalcoholics (125).

OTHER CONDITIONS Substantial alcohol use has been reported to be associated with a higher incidence of venous conditions (72) such as phlebitis and varicose veins. Heavy maternal drinking is associated with congenital anomalies of the heart (septal defects and patent ductus arteriosus) in offspring (98).

Table 1 summarizes the disparate relations of alcohol use and cardiovascular conditions. A recent report on hospitalization incidence in a large number of persons with various alcohol habits (72) demonstrated this disparity in a single cohort. The heaviest drinkers fared worst because of a higher risk of hypertension, stroke, congestive failure, arrhythmias, venous conditions, and cardiomyopathy. Moderate drinkers (two or fewer drinks per day) fared best with respect to overall incidence of hospitalization for cardiovascular causes. Nondrinkers fared substantially worse than the moderate drinkers, primarily because of a higher incidence of coronary heart disease. Hospitalizations for coronary events showed a pattern distinctly different from that for any other cardiovascular condition, with nondrinkers at significantly greater risk.

PUBLIC HEALTH ASPECTS OF ALCOHOL AND CARDIOVASCULAR DISEASES

The American public, aware of advances in knowledge in the alcohol-cardiovascular area, expects sound advice based on current knowledge, although it is probably easier to counsel individual patients than to formulate general pronouncements. Most health professionals would probably agree on a few basic facts: (*a*) There is substantial evidence that use of large amounts of alcohol carries heavy medical and social risks. The medical risks include cardiovascular and noncardiovascular disorders. (*b*) The threshold dose for possible harmful effects of alcohol is not known and probably varies from person to person. (*c*) Many persons should not drink at all—those

Table 1 Disparate relations of alcohol and cardiovascular conditions

	Apparent relation to use of alcohol	
	Small amounts	Large amounts
Beriberi	None	None (cause is thiamine deficiency)
Alcoholic cardiomyopathy	None	Direct myocardial toxicity in susceptible persons
Arsenic (As) beer drinkers' disease	None	Synergistic myocardial toxicity of As, alcohol
Cobalt (Co) beer drinkers' disease	None	Synergistic myocardial toxicity of Co, alcohol
Hypertension	None or slightly inverse (less hypertension)	Direct (more hypertension)
Atherosclerotic coronary	Inverse (less disease)	Conflicting evidence
Stroke	?	Direct (stronger for hemorrhagic than thrombotic stroke)
Venous conditions	None	Direct

with a history of a drinking problem or at special risk of a drinking problem, those with certain medical illnesses, and those with idiosyncratic reactions to alcohol.

The majority of US adults use alcohol in amounts that could be defined as moderate (76). These persons can be reassured that their drinking habit carries no known detrimental cardiovascular effects and may in fact place them in the most favorable risk category for overall cardiovascular disease incidence. With respect to alcohol use in relation to specific conditions, the following guidelines seem reasonable to the author.

1. Persons with chronic congestive heart failure or major arrhythmia problems should be extremely cautious about use of alcohol (no more than one drink per occasion).

2. Up to two drinks a day seems safe for hypertensive patients or persons at special risk of hypertension. Three or more drinks a day (35 ml or more of alcohol) probably increases the risk of hypertension.

3. Drinking before exercise is dangerous to patients with angina pectoris. Drinking before exercise is probably unwise for all persons.

4. Although a protective effect has not been proved, the evidence is mounting that use of alcohol is associated with a slower rate of development of coronary atherosclerotic occlusion and a lower incidence of myocardial infarction. There is more epidemiologic evidence for this possible benefit at low to moderate levels of drinking (up to 30 ml of alcohol per day). At higher levels of drinking, the possible protection from coronary disease may be attenuated and, in any case, is outweighed by other cardiovascular risks.

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