Alcohol and the Cardiovascular System
Research Challenges and Opportunities
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Bethesda, Maryland; and New Orleans, Louisiana

Excessive alcohol consumption has long been associated with cardiovascular disorders, including cardiomyopathy, hypertension, coronary artery disease, and stroke. However, recent evidence suggests that moderate alcohol intake can actually provide a measure of cardioprotection, particularly against coronary heart disease and ischemia-reperfusion injury. To explore the various dimensions of these opposing actions of alcohol, the National Institute on Alcohol Abuse and Alcoholism and the National Heart, Lung, and Blood Institute sponsored a state-of-the-art workshop on “Alcohol and the Cardiovascular System: Research Challenges and Opportunities” in Bethesda, Maryland, in May 2003. Speakers discussed the following topics: the epidemiology of alcohol and cardiovascular disease, clinical manifestations of alcohol, genetics of alcohol and cardiovascular disease, mechanisms underlying the molecular and cellular effects of alcohol, the application of new and emerging technology, and translation from discovery to therapeutic modalities of treatment. The panel concluded that future studies are needed to: 1) determine the role of genes and the environment in assessing mechanisms underlying the benefits of alcohol use and cardiovascular disease risk; 2) define the biological mechanisms underlying alcohol-induced peripheral vascular damage; 3) clarify the role of genetic variation in alcohol-metabolizing enzymes, genetic susceptibility, and pharmacogenomics in determining cardiovascular disease risk and effective treatment; 4) determine common mechanisms underlying alcohol-induced cardiovascular disease, such as oxidative stress and inflammation; 5) assess the role of insulin resistance, blood clotting, protein kinase C isoforms, and signal transduction mechanisms mediating alcohol’s beneficial effects; and 6) explore the potential of stem cells in myocardial regeneration and repair in hearts damaged by alcohol. (J Am Coll Cardiol 2005;45:1916–24) © 2005 by the American College of Cardiology Foundation

Excessive alcohol intake is a major cause of toxic cardiomyopathy in the U.S. today, yet low-level ingestion of alcohol over long periods of time appears to afford a measure of protection to the heart and vasculature against disease. The National Institute on Alcohol Abuse and Alcoholism and the National Heart, Lung, and Blood Institute convened a state-of-the-art workshop to discuss the complex interactions between alcohol and the cardiovascular system. The goals of the workshop were: to assess current information regarding the population-wide risks and benefits of alcohol consumption with respect to cardiovascular morbidity and mortality, to explore the etiologies of these relationships, and to chart a new course for future investigations into the biological basis of alcohol’s effects on the cardiovascular system. This state-of-the-art report summarizes the epidemiology, genetics, and clinical manifestations of alcohol and cardiovascular disease and presents new findings on the cellular and molecular mechanisms underlying the medical consequences of alcohol. Recommendations for research that may lead to new principles for the treatment and prevention of cardiovascular mortality associated with excessive ethanol consumption are presented.

THE EPIDEMIOLOGY OF ALCOHOL CONSUMPTION AND CARDIOVASCULAR DISEASE
Coronary heart disease (CHD) is the most common form of heart disease in the U.S. and affects approximately 13 million Americans (1). Recent epidemiologic and clinical evidence suggests that light-to-moderate alcohol consumption is associated with a reduced risk for developing CHD and ischemic stroke (IS) (2). The relationship between alcohol intake and the relative risk of developing CHD is a J- or U-shaped dose-response, where the risk is lower when alcohol consumption is light-to-moderate and is high when alcohol consumption is higher or absent altogether. “Moderate drinking” is defined as no more than one drink/day for women and two drinks/day for men (U.S. Department of Health and Human Services/U.S. Department of Agriculture Dietary Guidelines 2005). In the U.S., one drink is usually considered to be 12 oz of beer, 5 oz of wine, or 1.5 ounces of spirits. A standard drink contains 0.6 oz (15 g) of ethanol.

A meta-analysis of the relationship between moderate alcohol intake and risk of developing CHD showed that,
compared with abstinence, moderate alcohol consumption (as much as 30 g/day) is causally related to a 20% to 45% reduction in the risk of developing CHD (3). Prospective studies from several countries worldwide suggest that the beneficial effects of moderate alcohol consumption are not dependent on the type of beverage or pattern of consumption (4,5). Thus, although red wine consumption was thought to be important in the “French paradox,” it appears that it is the alcohol itself that confers the major benefit (6). The “French paradox” refers to the low mortality rate from ischemic heart disease and cardiovascular diseases displayed by French men despite a high level of risk factors, such as cholesterol, diabetes, hypertension, and a high intake of saturated fat (7). Levels of alcohol intake in excess of 120 g/day to 150 g/day significantly increase the risk of CHD, hypertension, IS, and all-cause mortality (2). However, many confounding factors, for example, socioeconomic status, lifestyle variables, and the “sick quitter” effect, may influence the relationship between alcohol and cardiovascular disease (8).

Mechanisms underlying the cardioprotective effects of moderate alcohol consumption may be related to alcohol-induced changes in serum lipids, lipoproteins, blood clotting proteins, platelets, inflammatory cytokines, and insulin resistance (9). Moderate alcohol consumption has been shown to increase high-density lipoprotein cholesterol (HDL-C) by approximately 30% and is believed to account for approximately 50% of the reduced risk of developing CHD (10). The proportion of reduced risk not accounted for by increased HDL-C may be attributable to alcohol-induced increased insulin sensitivity, lower levels of inflammatory markers such as interleukin (IL)-6, C-reactive protein, and tumor necrosis factor-alpha, constituents of beverages other than alcohol, and polymorphisms among alcohol-metabolizing enzymes, which reduce toxic metabolites, primarily acetaldehyde (11,12). The pattern of alcohol consumption as it relates to clinical outcomes and changes in cardiovascular risk has been examined in the Framingham cohort (13), in which most adult men and women, approximately 80% and 67%, respectively, consume alcohol. The proportion of individuals consuming alcohol decreases with age, a trend that may relate to adverse clinical outcomes. A 24-year follow-up study of Framingham participants consuming 2 to 2.5 standard drinks/day showed that among nonsmokers, increasing alcohol intake decreased the incidence of CHD, whereas among light smokers, a U-shaped relationship was seen with increasing intake. In heavy smokers, there was no association between alcohol intake and CHD.

The relationship between alcohol intake and heart failure (HF), IS, intermittent claudication (IC), and all-cause mortality has been investigated. In a study separating nondrinkers, former drinkers, and current drinkers according to the number of drinks consumed each day, there was a decline in the crude incidence rates and HF risk from nondrinkers to moderate consumers. From moderate to heavy consumers, there is an upturn in the curve describing the relative risk of developing HF in both men and women. Data presented at the workshop and subsequently published (14) indicate little association between long-term moderate alcohol consumption and atrial fibrillation, a risk factor for stroke, among participants in the Framingham Study. However, a significant increase in stroke risk was observed among both active and former drinkers consuming more than three drinks/day.

The risk of IC in Framingham participants reveals a steady decrease in incidence with increasing alcohol intake, an effect that was more evident in men than in women and more strongly associated with wine and beer than with spirits. All-cause mortality attributable to alcohol also was analyzed in Framingham participants. In each case, people who drank heavily had an increased mortality risk compared with moderate drinkers. The findings in this cohort suggest that moderate alcohol consumption is inversely associated with risk for CHD, congestive HF, and IC. This association has been confirmed in a meta-analysis on all-cause mortality published since the workshop, which demonstrated an inverse association between light-to-moderate drinking and total (all-cause) mortality (15). The resulting J-shaped curve, with the lowest mortality risk occurring at the level of one to two drinks/day, is caused primarily by the protective effects of alcohol consumption on CHD. The relationship between alcohol consumption and CHD has been the subject of American Heart Association/American College of Cardiology science advisories (16,17), which conclude that, in the absence of proof of causality, the use of alcohol as a cardioprotective strategy is not recommended.

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<td>ADH</td>
<td>alcohol dehydrogenase</td>
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<td>ALDH</td>
<td>acetaldehyde dehydrogenase</td>
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<td>Apo</td>
<td>apolipoprotein</td>
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<td>BT</td>
<td>blood thrombosis</td>
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<td>CAD</td>
<td>coronary artery disease</td>
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<td>CHD</td>
<td>coronary heart disease</td>
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<td>DCM</td>
<td>dilated cardiomyopathy</td>
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<td>FDC</td>
<td>familial dilated cardiomyopathy</td>
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<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
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<td>HF</td>
<td>heart failure</td>
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<td>IC</td>
<td>intermittent claudication</td>
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<td>IDC</td>
<td>idiopathic dilated cardiomyopathy</td>
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<td>IL</td>
<td>interleukin</td>
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<td>IS</td>
<td>ischemic stroke</td>
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<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>MSC</td>
<td>mesenchymal stem cells</td>
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<td>NAD</td>
<td>nicotinamide adenine dinucleotide</td>
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<td>NO</td>
<td>nitric oxide</td>
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<td>PKC</td>
<td>protein kinase C</td>
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<td>ROS</td>
<td>reactive oxygen species</td>
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<td>SCD</td>
<td>sudden cardiac death</td>
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<td>TF</td>
<td>tissue factor</td>
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ALCOHOL AND THE CARDIOVASCULAR SYSTEM: CLINICAL MANIFESTATIONS

For many decades, research has shown that atherosclerosis is the principal contributor to the pathogenesis of myocardial and cerebral infarction and peripheral vascular disease. In addition to the role played by lipoproteins in atherogenesis, experimental and clinical studies have provided ample evidence for the presence of ongoing inflammation in atherosclerosis (18). Although there is no evidence of a direct effect of alcohol on inflammatory mediators influencing cardiovascular disease and stroke, effects on surrogate endpoints have been demonstrated.

Atherosclerosis is a diffuse disease, and its presentation varies depending upon the vascular bed in which it occurs. In the coronaries, an acute clinical event occurs by the induction of plaque rupture in lipid-rich lesions. Plaque rupture leads to thrombus formation, partial or complete occlusion of the arteries, unstable angina, myocardial infarction, and/or sudden death. Rupture of lipid-rich atherosclerotic lesions within the thoracic aorta is the cause of idiopathic or cryptogenic stroke. In comparison, atherosclerotic lesions within the carotid arteries are characteristically fibrotic and stenotic. It is likely that the force of blood against the arterial wall during systole produces dissection between the media and adventitia, causing an intramural hematoma to open into the lumen, and subsequent thrombotic stroke. Atherosclerotic lesions in the peripheral vasculature and circulation are large and stenotic but usually do not rupture. Rather, blood from patients with peripheral vascular disease who suddenly develop an occlusion has been shown to have a clotting propensity or hypercoagulable state (19). Hypercholesterolemia, inflammation, and thrombosis caused by a hypercoagulable state are part of the complex etiology of the atherogenic process. The salutary effects of moderate alcohol on coronary artery disease (CAD) are mediated in part through HDL-C; however, components of the inflammatory and thrombotic pathways, which are key factors in atherogenesis, also are influenced by alcohol (18).

The clinical manifestations of moderate alcohol on several cardiovascular outcomes are summarized in Figure 1.

High-density lipoprotein cholesterol has been shown to protect against atherosclerosis by influencing a number of steps in the initiation and progression of the disease. High-density lipoprotein cholesterol inhibits low-density lipoprotein cholesterol (LDL-C) oxidation, thus preventing uptake by macrophages, foam cell formation, and apoptosis. Transformation of macrophages to foam cells also is inhibited by secretion of apolipoprotein E, which promotes cholesterol efflux to HDL-C (20). In addition, HDL-C diminishes the formation of tissue factor (TF) and reduces the levels of metalloproteinases. In summary, increased levels of HDL-C seem to protect against the initiation of the atherosclerotic process very early on in the cascade of events by protecting against LDL-C oxidation, promoting the efflux of lipids and cholesterol from the lesion, decreasing adhesion receptor expression, and protecting against macrophage apoptosis with the attendant release of metalloproteinases and TF. Nevertheless, alcohol's effects on the components of these pathways and the processes they regulate have not been studied.

Pathologic studies suggest that the development of thrombus-mediated acute coronary/cerebral events depends principally on plaque composition and vulnerability rather than the severity of stenosis (21). Vulnerable plaques generally have thin fibrous caps and increased numbers of inflammatory cells, the products of which likely influence both plaque composition and rupture. Recent studies showing that ruptured plaques are highly enriched with a network of neovessels have suggested the novel hypothesis that neovessels within vulnerable regions of atherosclerotic lesions may play a role in plaque disruption (22). Furthermore, neovessels likely serve as a conduit for the entry of monocytes, which are known to be involved in carotid plaque hemorrhage. The major source for medial and intimal neovessels is the vasculature. Recent experimental studies have shown enhanced coronary vasa-vasorum accompanies CAD. Several studies have documented a complex interaction between neovascularization, positive vessel remodeling, and plaque disruption. Moreover, there are data to demonstrate that under hypercholesterolemic conditions, the vasa vasorum network increases dramatically, as does the density of macrophages. The effects of alcohol on plaque formation and vulnerability are not known; however, it is tempting to speculate that by increasing HDL-C or otherwise affecting HDL-C's multiple activities, alcohol may be cardioprotective.

The presence of risk factors such as diabetes mellitus type 2, hypercholesterolemia, and smoking exacerbate the progression of atherosclerotic disease and trigger atherothrombotic complications (23,24). These risk factors are all modified by alcohol. Furthermore, these observations underscore the importance of increased blood thrombosis (BT)

**Figure 1.** Clinical consequences of ethanol consumption. ADH = alcohol dehydrogenase; ALDH = acetaldehyde dehydrogenase; CHD = coronary heart disease; CV = cardiovascular; IL = interleukin.

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<th>Clinical Manifestation</th>
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<th>Candidate Gene</th>
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<tr>
<td>CHD</td>
<td>ADH 2*, apolipoprotein E, PONI</td>
<td>CHD</td>
<td>ADH 2*, IL-6 allele</td>
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<td>Stroke (Thrombotic)</td>
<td>ADH 2*</td>
<td>Stroke (Hemorrhagic)</td>
<td>ADH 2*, A1166C/AT1</td>
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<td>Peripheral Vascular Disease</td>
<td>ADH 2*</td>
<td>Hypertension</td>
<td>ADH 2*, CYP3A5*/3*5</td>
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<td>Ischemic/Reperfusion Injury</td>
<td>ADH 2*</td>
<td>Arrhythmia</td>
<td>ADH 2*, ACE DD allele</td>
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<td>Metabolic Syndrome</td>
<td>ADH 2*</td>
<td>Cardiomyopathy</td>
<td>ADH 2*, ACE DD allele</td>
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<td>Diabetes (CV Complications)</td>
<td>ADH 2*</td>
<td>Heart Failure</td>
<td>ADH 2*</td>
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<td>Metabolic Syndrome</td>
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in the pathogenesis of vascular diseases. Tissue factor factor is essential to the development of a hyperthrombotic or procoagulant state and has been implicated as a risk factor for the increased rate of atherothrombotic complications among diabetic, hyperlipemic, and smoker populations. Data presented at the workshop indicate that increased BT seems to be related to plasma levels of a circulating pool of activatable TF activity in diabetics and that hyperlipidemia and smoking have a significant modulatory effect on plasma levels of circulating TF and BT. Monocytes play a critical role in modulating TF activity. As an inhibitor of monocyte/macrophage activation, alcohol could indirectly decrease circulating TF and lessen thrombotic complications; however, this remains unproven.

THE GENETICS OF ALCOHOL AND CARDIOVASCULAR DISEASE

Understanding the genetic control of alcohol metabolism by the liver is essential in furthering our explanation of the mechanisms underlying alcohol-induced tissue injury, including cardiovascular disease. A number of genetic polymorphisms controlling alcohol metabolism have been identified (25). For example, a rapidly metabolizing form of alcohol dehydrogenase (ADH), the I 2*2 allele, is found in higher concentrations among many Asian and certain Jewish populations (26). The ADH I 2*2 allele has a V max of approximately 8.6 compared with the ADH 2*1 allele with a V max of 0.23. Alcohol dehydrogenase catalyzes the nicotinamide adenine dinucleotide (NAD)-dependent oxidation of ethanol to acetaldehyde. This reaction results in a redox state with increased levels of NADH and leads to triglyceride formation. Cytochrome P450 2E1, a microsomal enzyme that is highly inducible by alcohol, also promotes conversion of ethanol to acetaldehyde. However, this conversion is coupled to the generation of free radicals, reactive oxygen species (ROS), and lipid peroxidation, resulting in liver and possibly cardiac damage. Genetic variation in the activity of ADH enzymes is the basis for excess acetaldehyde accumulation, which causes facial flushing, chest pain, and profound hypotension in Asian populations (25). To prevent the unpleasant cardiovascular manifestations of alcohol intake, some individuals refrain from drinking. Thus, these genetic variations provide protection from the medical consequences of alcohol by eliciting avoidance behavior.

Acetaldehyde dehydrogenase (ALDH-2) catalyzes the oxidation of acetaldehyde to the less toxic intermediate, acetate. A defective form, ALDH2*2, is a single allelic substitution ALDH-2 Lys487 that renders the protein inactive, leading to acetaldehyde accumulation and resulting toxicities. The relative expression of ADH and ALDH contributes to circulating levels of acetaldehyde, a highly toxic compound with adverse effects on myocardial structure and function. Therefore, it is the balance between the levels of ADH, cytochrome P450 2E1, and ALDH activity that determines how much alcohol is handled in the liver and, consequently, what byproducts are delivered to peripheral tissues leading to injury.

The clinical phenotype of dilated cardiomyopathy (DCM) is an example of the interplay between genes and alcohol in the etiology of this disease. In addition to alcohol, possible causes include ischemia, infarction, hypertension, valvular disease, radiation, obesity, diabetes, tachycardia, and myocarditis. Early indications of a genetic link in DCM were derived from an observational study documenting its frequency in first- and second-degree relatives of patients diagnosed with idiopathic dilated cardiomyopathy (IDC) (27), which was defined as a left ventricular ejection fraction <50% and left ventricular end-diastolic volume dimension in the 95th percentile, excluding CAD and other known causes. Familial dilated cardiomyopathy (FDC) was defined as having a family member with the same criteria for IDC as the indexed patient. On that basis, ~20% of patients screened had FDC and approximately 90% of relatives had enlarged hearts, suggesting that IDC may have a genetic basis. These findings suggest that FDC exists with a prevalence of 20%; asymptomatic left-ventricular enlargement may be an early sign of disease.

Similarly, a recent study demonstrating variations in susceptibility genes and their relation to DCM in chronic alcoholics found that only a minority of subjects actually have DCM, which suggests a genetic vulnerability (28). Angiotensin-converting enzyme (ACE) genotypes were compared among patients having a similar degree of alcohol intake with no DCM. In the first group, 41 men were diagnosed with HF coupled with DCM. The control group comprised asymptomatic DCM alcoholics who were 53 years of age with at least 26 to 27 years of heavy alcohol intake (167 g/day). In patients with DCM, left ventricular ejection fraction was 34% compared with 67% in control subjects. The ACE DD allele, the genotype most common in subjects with HF, conferred an additional risk and was present in 57% of HF subjects compared with control patients. The difference in allele disposition increased the risk of HF 16-fold. This observation suggests that the ACE DD allele is associated with alcoholic cardiomyopathy. The ACE genotype data suggest that alcohol may deliver a HF pathway insult. Studies on FDC suggest that alcohol may deliver an autosomal-dominant pathway insult with incomplete penetrance. Therefore, genotyping studies have the ability to clarify the overall genetic contribution in alcoholic cardiomyopathies.

In studying the genetics of the response to alcohol, the impact of exposure to a moderate amount, where an allele may improve the beneficial effect, can be evaluated. However, that same allele at very high levels of alcohol intake may render susceptibility at the tails of the distribution. Using interindividual variation in the response to treatment paradigm, the variation in the acute or chronic response to alcohol can be evaluated. In studying an acute alcohol effect, the flushing response is a useful quantitative measure of response. A chronic response might focus on changes in the
risk for developing cardiovascular disease over time. Genetic polymorphisms specific to alcohol may contribute to different aspects of exposure and may influence the response to various treatments. Figure 1 is a summary of genes linked with alcohol's effects on the cardiovascular system.

Pharmacogenetics, the study of genetic variables designed to optimize treatment, can contribute to a better understanding of the cardiovascular outcomes of alcohol consumption. The pharmacogenetics of hypertension has several corollaries with the biomedical response to alcohol. A survey study of hypertensive patients demonstrated that a significant percentage (39%) of the cohort was unaware they had the disorder (29). Of those that were aware and being treated, most were either poorly or not controlled. Thus, the relationship among awareness, treatment, and control in hypertension must be taken into account. Similarly, the pharmacogenomics of alcohol can be considered in the context of two major areas of pharmacology. The first involves genes that influence the pharmacokinetics of the absorption, distribution, metabolism, and elimination of alcohol. The second area involves genes that influence the pharmacodynamic interaction between alcohol and its molecular downstream targets, an interface between alcohol intake and cardiovascular disease.

Genetics play an important role in determining factors influencing interindividual variation in response to drug exposure. Rare adverse outcomes are a single-gene Mendelian disorder in which a single-gene mutation renders a patient susceptible to an adverse outcome once exposure to a drug has occurred. The study of rare outcomes generally is concerned with efficacy. Most studies have involved hypertensive or cholesterol-lowering therapies. In terms of alcohol, heart disease, and genetics, it is important to define the question being asked and to design a study that will answer the question taking into account variation in short-versus long-term alcohol exposure. The field is sufficiently advanced for genetics to yield new insight into alcohol and CHD.

**MECHANISMS UNDERLYING THE MOLECULAR AND CELLULAR EFFECTS OF ALCOHOL ON THE CARDIOVASCULAR SYSTEM**

The hemodynamic effects of alcohol consumption have been recognized since the middle of the 19th century. Epidemiologic studies show that with an average intake of >2 drinks/day, a fairly consistent linear relationship exists between alcohol intake and blood pressure in a variety of populations, irrespective of race and gender. This relationship is less clear at very low levels of drinking. The Prevention And Treatment of Hypertension Study (PATHS), a randomized controlled trial, was undertaken to determine among other things, whether blood pressure is reduced by a six-month intervention to lower alcohol intake in moderate to heavy drinkers with an average duration of drinking of 37 years (30). Lowering alcohol intake by one to three drinks/day produced small, nonsignificant effects in blood pressure in this trial. Larger decreases in alcohol intake have been associated with significant reductions in blood pressure in other clinical trials. A meta-analysis study shows a net effect that is statistically significant with a three–drink/day reduction in alcohol consumption. More recently, a reduction by one drink/day in moderate-to-heavy drinkers led to approximately a millimeter of mercury reduction in blood pressure (31). Although small, this reduction represents a substantial improvement in blood pressure profile overall. This area is one that would benefit from additional research.

Sudden cardiac death (SCD) accounts for ~60% of deaths attributable to heart disease in the U.S. today. Ventricular arrhythmias are the leading mechanism underlying acute and chronic cardiac pathologies, including ischemia, myocardial infarction, and cardiomyopathies. However, aside from anecdotal accounts, there is a dearth of information about the relationship of alcohol to cardiac arrhythmia and SCD. One study postulated that as many as 5% to 50% of SCDs were attributed to alcohol (32). Limited data are available on alcohol consumption in most patients suffering cardiac pathologies; thus, the role of alcohol as a cofactor is likely to be underestimated. Heavy drinkers have an increased relative risk of SCD compared with those who are not heavy drinkers (33). Potential mechanisms that could account for these observations are: increased QT interval leading to ventricular tachyarrhythmia, electrolyte abnormalities, sympathoadrenal stimulation, and decreased vagal input. Although alcohol is likely involved in SCD under certain circumstances, the multiple pathways involved and how signals are transduced into alterations in gene expression are not known. Figure 1 summarizes the clinical manifestations of excessive alcohol on several cardiovascular outcomes.

Excess alcohol consumption over the course of long periods is associated with an increase in oxidative stress, which may account for some adverse effects on the cardiovascular system. There is evidence that alcohol-induced increases in ROS impair myocyte calcium handling and mechanical function (34). Sources of alcohol-stimulated ROS production have not been fully defined but may involve mitochondrial cytochrome p450, xanthine oxidase, and NADPH oxidase (35). In vitro, ROS causes myocyte hypertrophy, altered gene expression, and apoptosis, raising the possibility that ROS plays an important role in alcohol-induced myocardial remodeling and HF. Although in vitro studies may elucidate the role of ROS in mediating the effects of alcohol on cardiac myocyte phenotype, studies in animal models of alcohol excess will be required to clarify the role of ROS in myocardial remodeling in vivo. An understanding of the role of ROS in alcoholic cardiomyopathy and SCD may suggest new strategies that involve the use of antioxidants or inhibitors of signaling cascades activated by ROS for the treatment of these prevalent clinical conditions. The effects of alcohol on mitochondrial-
induced apoptosis and myocardial remodeling may be mediated by affecting the permeability transition pore through a free radical–dependent pathway. During chronic alcohol exposure, the sensitivity of the mitochondrial membrane to permeabilization by calcium and the Bcl-2 family of proteins was increased, resulting in a proapoptotic phenotype. Calcium accumulation in the mitochondria (instead of leaving the mitochondria through the usual physiological pathways) triggered caspase activation and the apoptotic cell death pathway. Low levels of hydrogen peroxide or ROS may act as a hypertrophic signaling mechanism in myocytes, and higher levels, although not dramatically higher, activate apoptotic signaling pathways.

The vascular endothelium may mediate many of ethanol’s effects. The endothelium plays a pivotal role as a sensor, transducer, and integrator of signaling processes regulating vascular homeostasis. Endothelial dysfunction predisposes to premature clinical events, including CHD, stroke, and peripheral arterial disease. Few studies have examined the role of alcohol as a factor in endothelial dysfunction, yet the endothelium is a target for harmful substances such as ROS, oxidized lipoproteins, and advanced glycation end-products. Recent findings indicate that alcohol directly regulates endothelial cell genes involved in inflammation, vessel patency, and cell adhesion. Treatment with low concentrations of ethanol promotes endothelial cell survival, whereas apoptosis occurs at higher levels (36). The reaction between superoxide and nitric oxide (NO) is also germane. Produced by endothelial cells, NO diffuses to underlying smooth muscle and causes vasodilatation. The loss of NO that occurs in the reaction with superoxide deprives vascular smooth muscle cells of NO. Additionally, the reaction produces the oxidant peroxynitrite, which can lead to cellular damage. One of the major sources of oxygen–free radicals is vascular NAD(P)H oxidase. The effect of alcohol on these and other reactions involving the generation of ROS within the vasculature is unknown. Using newly developed markers of endothelial dysfunction would facilitate studies on the effects of alcohol and link changes in gene expression to functional alterations (37).

Mechanisms proposed to explain the beneficial effects of moderate alcohol on cardiovascular variables include an increase in HDL-C, favorable effects mediated by alterations in protein kinase C (PKC), and a reduction in the inflammatory response. High-density lipoprotein cholesterol is an important factor for maintaining appropriate concentrations of LDL-C in vascular and other cells throughout the body. Additionally, HDL-C reduces adhesion molecule expression, inhibits oxidation of LDL-C, reduces thrombosis, and inhibits migration of inflammatory cells into the endothelial space. Acting principally through apolipoprotein (Apo)A1, HDL-C also may have a direct antioxidant effect. Moderate alcohol intake is associated with an increase in ApoA1, the major HDL-C carrier protein. The synthesis and secretion of ApoA1 by human liver cells and hepatoma cells in culture is stimulated by alcohol. In vivo studies also demonstrate increased transport rate of ApoA1 and ApoA2 in response to alcohol (38). The dose effects of ethanol and potential mechanisms of action are shown in Figure 2.

Protection of myocardial tissue from a lethal ischemic event by previous exposure to sublethal ischemic insults has been termed ischemic preconditioning (39). Epidemiologic studies showing that low-to-moderate alcohol consumption reduces CHD raised the possibility that ethanol might confer cardiovascular benefit by acting as a preconditioning agent. Evidence from human and animal studies has supported this concept. Both acute and chronic moderate alcohol consumption mimic classic cardiac preconditioning and protect against ischemia-reperfusion injury, as evidenced by reduced infarct size and decreased hypoxia–induced cell death. The mechanism of benefit involves the PKC family of isoforms, particularly PKC-δ and PKC-ε, both of which are activated by myocardial ischemia. Whereas PKC-ε aids the myocardium in resisting ischemic damage, PKC-δ actually participates in the process of myocardial damage.

Ethanol shares many of the same signal transduction pathways and effector molecules that have been implicated in conventional and/or pharmacologic preconditioning. For example, just as mitochondrial ATP-sensitive potassium channel (K$_{ATP}$) opening has been identified as the putative effector of classic cardioprotection, so too are K$_{ATP}$ activation and opening required for ethanol-induced cardioprotection (40). Agents that specifically inhibit opening of these K$_{ATP}$ channels (41) abrogate ethanol-induced preconditioning. Moderate alcohol consumption increases expres

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**Figure 2.** Dose effects of ethanol consumption and potential mechanisms of cardiovascular response. CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; ICAM = intercellular adhesion molecule; IL = interleukin; LDL-C = low-density lipoprotein cholesterol; PKC = protein kinase C; VCAM = vascular cell adhesion molecule; VEGF = vascular endothelial growth factor.
PKC-ε knockout mice are resistant to ischemic preconditioning and unresponsive to the cardioprotective effect of alcohol. The diabetic rat is another model in which PKC has been shown to mediate the beneficial effects of alcohol. In diabetic animals, alterations in PKC are associated with a decrease in cardiac function as determined by echocardiography and invasive hemodynamic measurements. Alcohol consumption (4% v/v) in diabetic animals prevented the decrease in cardiac function and produced an up-regulation of PKC-α, -δ, and -ε, similar to levels in nondiabetic animals (43).

Other data presented at the workshop bolster the hypothesis that more than one pathway is involved in mediating cardioprotection. Sphingosine-1-phosphate and ganglioside GM-1 enhance cardiomyocyte protection via a PKC-independent pathway. A better scientific foundation is needed to understand the molecular events underlying the various forms of preconditioning before this knowledge can be translated into the development of therapeutic compounds. Whether alcohol is unique in its mode of action or is a surrogate probe of cardioprotective signaling pathways is not known. Studies of how alcohol mediates cellular protection can uncover innate (homeostatic) cell survival and repair mechanisms. These observations highlight potential therapeutic targets for protection against CHD that will not require ethanol ingestion, given concerns regarding adverse effects of even moderate amounts of alcohol on other organ systems and the risk of addiction.

Alcohol is a well-known immunosuppressant involving both innate and acquired immune responses (44). It also has anti-inflammatory properties that are likely mediated through changes in cytokine profiles and cell signaling pathways. Recent data have shown that acute alcohol may exert beneficial effects on the vascular system by suppressing production of proinflammatory cytokines such as tumor necrosis factor-alpha and IL-1 by cells of the immune system (45,46). This reduction in cytokine production is associated with a decrease in phosphorylation of IκBα, which is required for the translocation of NF-kappa-B and the transcription of proinflammatory cytokines. Alcohol increases macrophage production of IL-10, which has a strong anti-inflammatory effect. Furthermore, alcohol consumption is associated with a decrease in neutrophil migration and suppression of phagocytosis. Although alcohol has both immunosuppressive and anti-inflammatory properties, any beneficial effects, for example, on heart and vascular endothelium, may be offset by increased susceptibility to infections.

TRANSLATION: FROM DISCOVERY TO THERAPEUTIC MODALITIES OF TREATMENT

Dilated cardiomyopathy and congestive HF are final common consequences of cardiac toxicity caused by numerous insults, including excessive alcohol exposure (47). The mechanisms by which alcohol causes cardiac damage remain unknown, but there is emerging evidence implicating oxidative stress, at least in part. Although current HF therapies have clinical benefits, none brings about repair or replacement of damaged myocardium. The traditional paradigm of the heart as a terminally differentiated organ unable to undergo repair and regeneration has been modified largely because of the work of Beltrami et al. (48) demonstrating that human cardiac myocytes are capable of mitosis after myocardial infarction. Since then, transplanting progenitor cells into the heart, a procedure known as cardiomyoplasty, stimulating endogenous precursor cell homing to the heart, and myocardial treatment with growth factors involved in cardiac repair, represent promising new treatment strategies. Among potential cellular sources used in cardiomyoplasty, mesenchymal stem cells (MSCs) derived from bone marrow are emerging as a leading candidate. Kraitchman et al. (49) have shown in a swine model of myocardial infarction (MI) that MSCs can be transplanted by intramyocardial injection with robust engraftment and differentiation into a myocyte-like phenotype. Neovascularization, improved left-ventricular function, and decreased remodeling were observed after the delivery of MSCs within two weeks of MI. Other cells, including satellite cells of skeletal muscle origin, also have been used for cellular cardiomyoplasty. It is tempting to speculate that cardiac progenitor cells, in addition to their role in post-MI repair, may offer a valuable treatment strategy for toxic and metabolic cardiomyopathies. Panel members noted that the study of the effect of alcohol on endogenous cardiovascular repair mechanisms and on the potential of exogenous stem cell-based therapies for cardiomyopathy is in its infancy. Many of these studies await the development of better animal models of alcoholic cardiomyopathy. Ultimately, the goal of such research would be to translate observations regarding the sustained benefits of moderate alcohol consumption into therapeutic approaches for protection against CHD that do not require ethanol ingestion.

SUMMARY OF RESEARCH RECOMMENDATIONS

Epidemiology of alcohol and cardiovascular disease:

- Determine the proportion of reduced CHD risk due to moderate alcohol consumption not accounted for by increased HDL-C
- Determine the potential benefits of alcohol in individuals who may be at increased risk (genetic and environmental) of developing cardiovascular disease
- Confirm the influence of beverage type and/or patterns of drinking on the relationship between alcohol consumption and the risk of developing CHD
- Additional studies on the relationship between alcohol intake and all-cause mortality (given that any protective
effect of alcohol may be offset by noncardiovascular mortality)

Genetics of alcohol and cardiovascular disease:

• Genotyping studies that define the overall genetic contribution to the development of alcoholic cardiomyopathy and alcohol-induced cardioprotection
• Assess the role of genetics in influencing interindividual variation in the cardiovascular response to alcohol exposure
• Characterize the genes involved in susceptibility to cardiomyopathies and how these are altered by alcohol
• Studies on genetic variance of alcoholism and associated biomedial consequences including cardiovascular disease
• Genes influencing the pharmacodynamic interaction between alcohol and its downstream molecular cardiovascular target

Mechanisms underlying the molecular and cellular effects of alcohol:

• Gene expression fingerprinting to identify the multiple pathways associated with alcohol’s effects on the development and progression of cardiomyopathies, hypertension, and hemorrhagic stroke
• Clarify the role of oxidative stress in alcohol-induced cardiovascular disease including both local and systemic effects such as those involving endothelial dysfunction
• Studies clarifying the molecular mechanisms underlying alcohol’s pro- and anti-inflammatory properties; likewise studies that clarify whether alcohol’s antithrombotic action may account for its protective effect
• Comprehensive approaches on the effect of alcohol on atherosclerotic plaque formation, composition, stability, rupture, thrombotic tendency at the site of vulnerable plaque, and vessel remodeling; effect of alcohol on lipoprotein metabolism and HDL-C effector function
• Determine whether the cellular targets and molecular events underlying classic preconditioning are the same or different than those mediating ethanol-induced cardioprotection; define the role of mitochondria in alcohol-induced cardioprotection

Translation: from discovery to therapeutic modality of treatment:

• Fundamental studies of the effect of alcohol on stem cell biology and endogenous cardiac repair mechanisms as well as translational approaches to assess whether exogenous stem cell-based therapies are a viable option for alcohol-induced cardiomyopathies
• Translational studies of agents that mimic alcohol’s protective effects as a potential therapeutic approach to cardiovascular disease

A randomized trial of alcohol intake and cardiovascular disease prevention. Because of a reluctance to randomly assign individuals to alcohol consumption who are naive to alcohol, such a trial would likely be conducted in drinkers who are high risk (e.g., postmyocardial infarction) and randomly assigned to continue moderate drinking or to abstain. Support for such a study comes from a recent report of a lower incidence of HF in light-to-moderate drinkers with left ventricular dysfunction after MI (50).

SPEAKERS


Moderators: Drs. Ray Hershberger, Douglas L. Mann, and Gordon Huggins.

NOTE

On the basis of an assessment of the evidence, the National Institute on Alcohol Abuse and Alcoholism recently has published a formal position paper on the health risks and potential benefits of moderate alcohol consumption that includes the area of cardiovascular disease (51).

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REFERENCES

Lucas et al.
Alcohol and the Cardiovascular System