EDITORIAL COMMENT

Vintners and Vasodilators

Are French Red Wines More Cardioprotective?*

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Alcoholic beverages have been consumed by numerous societies for thousands of years, their use often intertwined with religion and culture. Alcohol has both beneficial and detrimental effects on health. A beneficial effect of alcohol was first reported in 1786 by Heberden, who noted relief of angina pectoris by “spiritious cordials” (1). Using observational data, an inverse relationship between alcohol consumption and cardiovascular disease risk was initially published by Cabot in 1904 (2). Since that time, almost 100 geographic, case-control, cohort, and epidemiological studies have reported similar findings (3,4). Concurrent observations have been found in comparisons of arteriographic and postmortem coronary atherosclerosis with reported alcohol consumption. The reduction in cardiovascular risk is generally confined to middle-aged and older individuals. Somewhat less cardioprotection from alcohol is evident in women. Coronary heart disease risk decreases with increasing alcohol consumption, but hypertension, cardiomyopathy, atrial fibrillation, possibly hemorrhagic stroke, and many noncardiovascular diseases are associated with increased use (5). The combination of beneficial and detrimental effects of alcohol results in a U-shaped relationship between alcohol consumption and total mortality. The minimum all-cause mortality occurs for middle-aged and older individuals at one to three drinks per day. Although the beneficial effect of moderate alcohol use appears to be independent of the complex lifestyle confounders associated with alcohol consumption, no randomized controlled trials of alcohol have been performed with cardiovascular events as the end point.

European vs. American studies. European studies have generally found a greater reduction in cardiovascular risk associated with wine, and especially red wine consumption, compared with other alcoholic beverages. The same differential benefit has generally not been found in American studies. In this issue of the Journal, Wallerath et al. (6) report that exposure to French red wines in contrast with German red wines increases endothelial-type nitric oxide synthase (eNOS) mRNA, protein, and activity in cultured human umbilical vein endothelial cells (HUVEC) in both a concentration and time-dependent manner. This observation provides a plausible and interesting explanation for the differences in the European and American observations. The report by Wallerath et al. (6) examines the direct effects of 1%, 3%, and 10% concentrations of three German and six French wines (two each Bordeaux, Rhone, and Burgundy areas) on cultured HUVEC and HUVEC-derived EA.hy 926 cells, eNOS mRNA, protein, and activity, the latter by guaneryl cyclase stimulation functional assay. The French red wines produced significant increases (150% to 400% of control) in eNOS mRNA at 10% concentrations within 24 h and 1% concentrations after 10 days of incubation. Similar significant increases were also observed in eNOS protein expression and activity. These effects appear to be due to increases in eNOS promoter activity. No differences were observed in the effect of wines matured in oak barrels and steel tanks. Conversely, the German red wines and the equivalent ethanol concentrations produced no increases in eNOS mRNA. For this observation on different effects of wines from two regions to have clinical significance, however, it must be assumed that alcohol is indeed beneficial, that wine is more beneficial than other alcoholic drinks, and that red wine is more beneficial than is white wine. Otherwise, it is pointless to compare red wines of different origins. Whereas the first assumption is unproven, but likely, the other two assumptions are uncertain.

European observational studies have generally attributed more benefit to wine and especially red wine compared with other sources (7). Correcting for confounders is even more difficult in consideration of the type of alcohol consumed because wine drinkers tend to be less obese, to exercise more, and to drink with meals (8). These lifestyle associations, however, tend to vary from population to population, and progressive dose-response relationships with wine consumption have not been consistently observed in individual studies. In an 11-year study, Gronbaek et al. (9) followed 24,523 men and women 20 to 98 years of age according to their total and type of alcohol consumption. Although moderate wine drinkers experienced about 20% less mortality than did nonwine drinkers, subjects whose wine consumption made up from 1% to 30% of their total alcohol intake had the same mortality benefit as those who drank >30% of their alcohol as wine, suggesting the presence of confounding factors. The lower cardiovascular mortality reported in the wine-producing and -consuming countries of France, Italy, Spain, and Switzerland is not accompanied by lower overall death rates (10). This is surprising because cardiovascular mortality makes up about 40% of total mortality in developed countries.

By contrast, Japan, with the lowest reported age-related cardiovascular mortality of developed countries (one-half that of France), has a per capita wine consumption one-sixth that of France. The beneficial effect of red wine is...
often attributed to its high levels of polyphenols, which have antioxidant, antiplatelet, and antiproliferative properties. Red wine is more commonly consumed with meals than other alcoholic beverages. Alcohol consumption at other times appears to be less cardioprotective. This finding suggests that consumption of red wine may be a specific marker for other lifestyle confounders. Alternatively, it may also represent one specific mechanism by which alcohol offers cardioprotection. Red wine (cabernet sauvignon of uncertain origin) consumption has been demonstrated to reduce the postprandial endothelial dysfunction caused by a high-fat meal (11).

American observational studies generally do not report a selective benefit from red wine. Klatsky et al. (12,13) followed cardiovascular risk in 128,934 Californians enrolled in a health maintenance organization for 13 years according to the amount and type of alcohol consumed. At eight years of follow-up, a 30% reduction in total mortality was observed in moderate drinkers, attributable to a reduction in coronary heart disease. The greatest reduction was reported for older individuals. No differences were observed according to the type of alcohol consumed. Women who drank heavily had an especially high mortality. By 13 years of follow-up, a U-shaped relationship was found between mortality and alcohol consumption. Controlling for the amount of alcohol consumed, there was no apparent benefit from any specific type of alcohol, including red wine.

In a Boston area case-control study of 340 subjects, Gaziano et al. (14) followed the incidence of myocardial infarction according to the type of alcohol consumed. Again, no significant differences were observed by type of alcohol. If there are differences between the benefit of red wine consumed in the U.S. and Europe on nitric oxide (NO) availability, the current study's observation (6) may provide a plausible explanation, assuming that American red wines do not have the same effect on eNOS that French red wines do.

**NO availability as an end point.** As in this study, NO availability has become a popular intermediate biological end point for the evaluation of the atherogenic effects of risk factors, dietary components, and drugs. Endothelial cell NO produces vasodilation and reduces platelet aggregation and also smooth muscle cell proliferation. In experimental atherosclerosis models, NO availability is inversely associated with atherosclerosis progression. Several recent clinical studies have demonstrated that human coronary and brachial artery endothelium-mediated (NO) vasodilation predicts cardiovascular event risk in an inverse fashion. All coronary risk factors are known to reduce NO availability. Cardioprotective drugs, such as statins and angiotensin-converting enzyme (ACE) inhibitors increase NO availability. These findings strongly support an inverse association between NO availability and cardiovascular risk. Does this in vitro study predict the effect of red wine on human endothelial function? Probably it does. Eight ounces of red wine daily for 30 days was found to normalize brachial artery flow-mediated vasodilation in healthy subjects given a high-fat diet, but had no effect on those consuming a low-fat diet (11). Is a nonalcoholic component of red wine responsible for this effect? Probably yes. Chou et al. (15) found that 21 ounces of American grape juice daily for eight weeks increased flow-mediated vasodilation, an index of NO availability, in subjects with coronary heart disease. Can short-term in vitro and in vivo studies of NO availability predict the atherosclerotic effects of lifestyle factors and drugs? Not reliably. This conclusion comes from examples of interventions that increase short-term NO availability, but not cardiovascular risk.

In the short-term, hormone replacement therapy (HRT) increases NO availability in postmenopausal women, but only transiently (16). Moreover, there are both beneficial and adverse vascular effects of HRT. Whereas HRT increases high density lipoprotein (HDL) cholesterol and decreases low density lipoprotein (LDL) cholesterol, HRT also increases coagulation, triglycerides, and some markers of inflammation (C-reactive protein). Recent large randomized HRT trials have shown null to adverse effects on cardiovascular risk despite the short-term benefits to NO availability. In a similar fashion, several studies of antioxidant vitamins have demonstrated short- and intermediate-term increases in NO availability, but the consensus of large clinical studies is a null effect on cardiovascular risk. Other factors may play a role in this discordance, including the rapidity of vitamin-free radical interaction and the entrance into cells. The lack of cardioprotection in the antioxidant vitamin trials reduces the likelihood that the clinical benefit from other antioxidants, such as red wine polyphenols, can be predicted from their short-term eNOS effects. Short-term NO availability may suggest long-term cardioprotection, but it is not an absolute index. Experimental evidence supports this discordance. Neither French red wine nor Austrian red wine polyphenol extract reduces the progression of atherosclerosis in mature apolipoprotein (apo) E-deficient mice (17). Interestingly, neither does alcohol.

Does the current vascular biological study replicate in vivo conditions? The answer is probably not. The direct incubation of endothelial cells in dilute concentrations of wine eliminates the in vivo effects of gastrointestinal absorption and processing of the unidentified substance(s) responsible for increased eNOS expression. Were the concentrations of wine physiologically relevant? Although the beneficial substance(s) are not clearly identified in the current study, Leikert et al. (18) found that a polyphenol extract from French red wine increased NO synthase expression. The current investigators have also suggested that the polyphenol is resveratrol (19). Although the volume of distribution of the polyphenols is not clear, the concentrations of red wine employed may not have been physiologic. The observed dose responses suggest that to increase eNOS requires 10% short-term wine concentrations and 1% long-term concentrations. If the volume of distribution for the beneficial substance(s) were body water,
this would be equivalent to drinking at least 3500 cc of wine acutely and 350 cc of wine perhaps daily. Although the latter amount is compatible with sobriety, as noted above, Gronbaek et al. (9) found a clinical benefit from wine at much smaller levels of consumption. Thus, the current study’s (6) dose response and observational studies do not precisely agree.

What are the likely mechanisms by which alcoholic beverages confer cardioprotection? Considerable data support a beneficial effect of alcohol itself. Individuals with a genetic polymorphism associated with slower alcohol metabolism derive more cardioprotection per drink than do those with faster metabolism (20). Alcohol raises serum HDL cholesterol due to increased apo A-I and apo A-II production, without affecting HDL catabolism (21). Both larger and smaller HDL particle size fractions are increased.

The consumption of two drinks daily increases HDL cholesterol about 10% to 15%, although there is large individual subject variation in response. Alcohol also decreases LDL cholesterol modestly. As with other sugars, alcohol increases triglycerides, sometimes dramatically. The atherogenic effect of this increase is unknown. Alcohol reduces the hemostatic parameters of platelet aggregation, fibrinogen, and Lp(a), and increases the fibrinolytic parameters of plasminogen and tissue plasminogen activator (tPA) (22). The acute consumption of two drinks reduces platelet deposition in an exteriorized venous shunt by 60% to 70% for approximately 6 h, persisting even after blood alcohol levels return to baseline (23). C-reactive protein (CRP), a nonspecific marker of inflammation, has a U-shaped relationship with alcohol consumption (24). In a study of 1,801 men and women 18 to 88 years of age, minimum CRP occurred with an alcohol intake of two to four drinks daily. Red wine may have specific anti-inflammatory and antiproliferative effects. The acute administration of red wine reduces the increase in nuclear factor-κB (NF-κB), responsible for promoting the expression of several inflammatory genes, resulting from a high-fat meal (25). This effect was not observed for vodka. This observation and the study of Cuevas et al. (11) suggest that red wine may be especially beneficial in populations consuming high-fat diets, a hypothesis that cannot be tested in in vitro studies.

Conclusions. Finally, it is tempting to latch onto a single important pathophysiological process, such as short-term NO availability, to understand a complex intervention of uncertain benefit, of which red wine is a good example. The recent sobering experiences with hormone replacement and antioxidant vitamin therapy suggest that the red wine story may be as complex as a classic vintage.

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REFERENCES