

## Alcohol, wine, and vascular diseases: an abundance of paradoxes

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THE “FRENCH PARADOX” is usually defined as a low rate of coronary artery disease (CAD) in France despite high prevalence of the usual CAD risk traits. In 1819 Dr. Samuel Black, an Irish physician interested in angina pectoris and perceptive about epidemiologic aspects, wrote what is probably the first relevant commentary (1). Noting much angina in his Irish medical practice but little discussion of this common symptom of coronary disease in the writings of French physicians, he explained the presumed disparity by “the French habits and modes of living, coinciding with the benignity of their climate and the peculiar character of their moral affections.” It was to be 160 years until presentation of international comparison data showing less coronary heart disease mortality in wine-drinking countries than in countries where beer or liquor drinking predominates (12). Confirmatory international comparisons plus reports of nonalcoholic antioxidant phenolic compounds and antithrombotic substances in wine, especially red wine (2, 11, 14), have created great interest in this area. A 60 Minutes TV broadcast (CBS: Nov 17, 1991) attributed the lower heart attack risk in France partially to red wine. Red wine sales in the US subsequently skyrocketed in the 1990s and remain high. Whether correct or not, the public has heard the implied message.

Light drinkers have ~30% lower CAD morbidity and mortality risk than lifelong abstainers, resulting in an ~10% lower total mortality risk (3, 8, 9). Consistency in studies, relative specificity of benefit for CAD, and plausible biological mechanisms for protection by alcohol against CAD support a causal protective effect. Although there have been no randomized, controlled trials of alcohol drinking in relation to CAD outcome events, many epidemiologists now feel that there is little doubt that alcohol exerts a protective effect against CAD.

Plausible biological mechanisms (2, 3, 8, 9, 11, 14) for CAD protection by ethyl alcohol start with the compelling evidence of higher levels of protective high-density lipoprotein (HDL) cholesterol in drinkers. Analyses suggest that HDL effect explains ~50% of the alcohol-CAD benefit. This is an effect of alcohol, without specificity for wine. Antithrombotic effects, less specifically an alcohol effect, are also supported by substantial data. Less-established mechanisms for the benefit of alcohol include improved endothelial function and reduced insulin resistance. Thus any non-alcohol-related benefit from a specific beverage, such as red wine, would be additional to that from alcohol.

Support for the hypothesis that wine may be more beneficial than liquor or beer is of two major types. The first consists of international comparisons showing lower CAD mortality in wine-drinking countries (e.g., France) than in countries where beer or distilled spirits are the preponderant alcoholic beverages

(4, 12). These ecological studies relate mean consumption data to aggregate mortality. Since traits of individuals are not involved, such studies are not well controlled for confounding explanations. The second type of evidence is the aforementioned presence of potentially beneficial nonalcohol compounds in wine (2–4, 8, 9, 11, 14).

A report by Spaak et al. in the *American Journal of Physiology-Heart and Circulatory Physiology* (13) details a well-conceived and -executed experiment about acute effects of ethanol and red wine on various measures of cardiovascular physiology. These included blood pressure, heart rate, cardiac output, sympathetic nerve activity, and brachial artery flow. Since the experiments were done serially on the same persons, this afforded very nice control. The main results showed few differences between red wine and alcohol. Surprisingly, red wine, but not ethanol, attenuated brachial artery flow. Overall, the data suggested that red wine phenolics have little effect on these particular measures.

At first glance, one might presume that these data (13) should have relevance to the alcohol-CAD associations described above. However, extrapolations of this type need to be done very carefully, especially when relating acute physiological events to mechanisms for CAD development. Atherosclerotic CAD generally takes decades to develop, and mechanisms increasing risk of atherosclerosis development are not identical to those for acute CAD events. The established long-term atherosclerotic CAD risk traits [smoking, systemic hypertension (HTN), diabetes mellitus, blood lipids, etc.] are not clearly related to acute immediate vascular effects of an intervention such as alcohol.

It might be easier to postulate relations of immediate physiological vascular effects to acute CAD events, now understood as usually due to intra-arterial thrombosis upon the substrate of rupture of a vulnerable atherosclerotic plaque. However, none of the effects described by Spaak et al. (13) would logically explain the protection against acute CAD events usually seen among persons ingesting one or two drinks per day.

Acute physiological effects of alcohol might have a more direct relationship to the alcohol-HTN association, established empirically by dozens of cross-sectional and prospective epidemiologic studies (6, 10). Although this relationship has been reported in some studies at drinking levels as low as one or two drinks per day, other reports indicate a threshold relation at approximately three standard drinks per day. The alcohol-HTN relation is a subacute one, developing in days to weeks. Acute human and animal experiments show no consistent increase in blood pressure after alcohol administration, especially of moderate doses (6, 10). Much work has failed to establish a biological mechanism for increased HTN in heavy drinkers. The research has not found consistent relationships to various potential neuroendocrine mechanisms. An overactive sympathetic nervous system exists during the alcohol withdrawal state but is felt unlikely to be the explanation for the alcohol-HTN relation

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at the drinking levels seen in the studies (6, 10). The intervention in the present study (13) did not affect blood pressure immediately. While it is possible that blood pressure measurement the next morning might have demonstrated an effect, the doses of alcohol involved in the experiment may have been too small to show a relationship.

Understanding of the roles of alcohol drinking and vascular disorders has suffered from oversimplifications and intellectual diversions. There are disparities in associations of alcohol consumption to various cardiovascular conditions (9). While there are interrelationships, epidemiologic and mechanistic considerations are best analyzed separately. Known associations include 1) alcoholic cardiomyopathy from chronic heavy drinking in susceptible persons; 2) systemic HTN in some heavier drinkers; 3) a relation of drinking to higher risk of hemorrhagic stroke but to lower risk of ischemic stroke; 4) certain arrhythmias, especially among binge drinkers (i.e., the “holiday heart” phenomenon), and 5) the inverse relation of alcohol use to CAD.

Despite the title, this commentary actually deals more with “disparities,” which usually refer to differences or distinctions in nature, than with “paradoxes,” which usually refer to seemingly self-contradictory phenomena. A final disparity concerns appropriate advice by health practitioners or public health officials. One size doesn’t fit all. Individualization of advice to a concerned person needs to consider his or her specific potential risks and benefits with respect to alcoholic beverages (5, 7). In this important area, overgeneralized statements about health effects of “alcohol” and personal moral or religious beliefs should have little role in giving objective enlightened information.

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*Am J Physiol Heart Circ Physiol* 294:582-583, 2008. First published Dec 14, 2007;  
doi:10.1152/ajpheart.01387.2007

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This information is current as of December 30, 2008 .