Editorial

Complex Association Between Alcohol Consumption and Myocardial Infarction

Always Good for a New Paradox

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The first mention of alcohol as a component of diet and communal events dates back to the 7th millennium BC. Famous ancient savants like Hippocrates used alcohol as a solvent for herb extracts, as an antiseptic, and to counteract lethargy and diarrhea, whereas in medieval times alcohol was well within the armamentarium of anaesthetics, sedatives, disinfectants, and diuretics. Nowadays, alcohol is no longer administered for medicinal purposes but is a frequent constituent of regular diet, favored for its broad availability and lack of effective sale restrictions. In 2010, the worldwide average amount of pure alcohol consumed per person aged ≥15 years was 6.2 L/y or 13.5 g/d.[1] There is now solid evidence that alcohol, when consumed on a regular basis and at low volumes (up to 1 drink for women and 2 drinks for men daily) confers protection against cardiovascular disease, whereas regular amounts of more than 4 to 5 drinks daily and heavy episodic drinking have opposite effects.[2,3] The J-shaped association applies to low- and high-risk individuals, the primary prevention setting, and to survivors of myocardial infarction. Sex differences are attributed to distinct gastric alcohol dehydrogenase activity and body distribution volumes.[4] Consumption of alcohol during meals on a daily basis is deemed an ideal drinking pattern, characterized by prolonged absorption and persistency, because most of its favorable effects are transient, and it blunts postprandial glucose spikes. Strictly speaking, however, the bulk of studies supporting this knowledge operate in high-income countries with little evidence available from South America, Africa, or Asia, except China and Japan.[2] In this regard, the study by Leong et al[5] in the current issue of *Circulation* delivers unique and, to some extent, surprising results. Alcohol consumers living in South Asia and the Middle East, in contrast to the rest of the world, do not enjoy protection against myocardial infarction. Inhabitants of the South Asian countries Sri Lanka, Pakistan, India, and Bangladesh (1.644 million people; 23.04% of the world population as of 2013) even faced a significantly elevated risk after adjusting for body composition, physical activity, smoking, quality of diet, and classic vascular risk factors, as well as socioeconomic and sociocultural factors.[5] INTERHEART is among the pioneer initiatives aimed at scrutinizing effects of lifestyle on human diseases on a large scale and around the globe.[6] It involves more than 27 000 individuals from 52 countries and uses rigorous methodologic standards. Early releases from this database already point to differential effects of alcohol in South Asia,[6,7] but full data have not been made available until now.[5]

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The findings of INTERHEART are relevant and timely given that alcohol consumption is on the rise in South Asia, especially India, according to the most recent World Health Organization report released in 2014 (Figure 1A).[1] The elegant study by Leong et al[5] inevitably fuels the ongoing discussion on the mechanisms linking alcohol intake and cardiovascular disease. Beyond doubt, alcohol exerts multiple effects all along the atherosclerosis process from early lesion formation to plaque fissuring and thrombus formation and directly affects heart rhythm and myocardial contractile performance.[3,8,9] Most properties proposed are dose dependent and mediated by ethanol, per se, with moderate amounts offering protection and larger quantities making the poison.

Alcohol and Vascular Disease: The Bright Side

Figure 2 illustrates current knowledge on potential atheroprotective and cardioprotective consequences of alcohol consumption. In brief, alcohol in moderation favorably affects reverse cholesterol transport, insulin sensitivity, abdominal obesity, systemic inflammation and oxidative stress, endothelial function, endogenous fibrinolysis, postprandial hypercoagulability, and platelet aggregation.[3,8–13] These effects are in part of reasonable size and may well contribute to the health benefits of habitual moderate alcohol consumption regarding coronary heart disease (decrease of 29%),[2] diabetes mellitus (decrease of 30% to 40%),[3] and life span (decrease of 17% to 18% in total mortality).[3]

The South Asian Paradox

The beneficial effects of alcohol, however, are difficult to reconcile with the INTERHEART observation of an elevated vascular risk among mainly moderate drinkers in South Asia. As discussed by Leong et al,[5] genetic differences in alcohol metabolism, reflected by functional polymorphisms in the genes encoding alcohol degradation enzymes, like alcohol dehydrogenase and aldehyde dehydrogenase-2, are unlikely to explain the paradox, because health hazards diminish in emigrants leaving South Asia.[5] Other potential explanations for the paradox are chance, unmeasured confounding, disease-modifying

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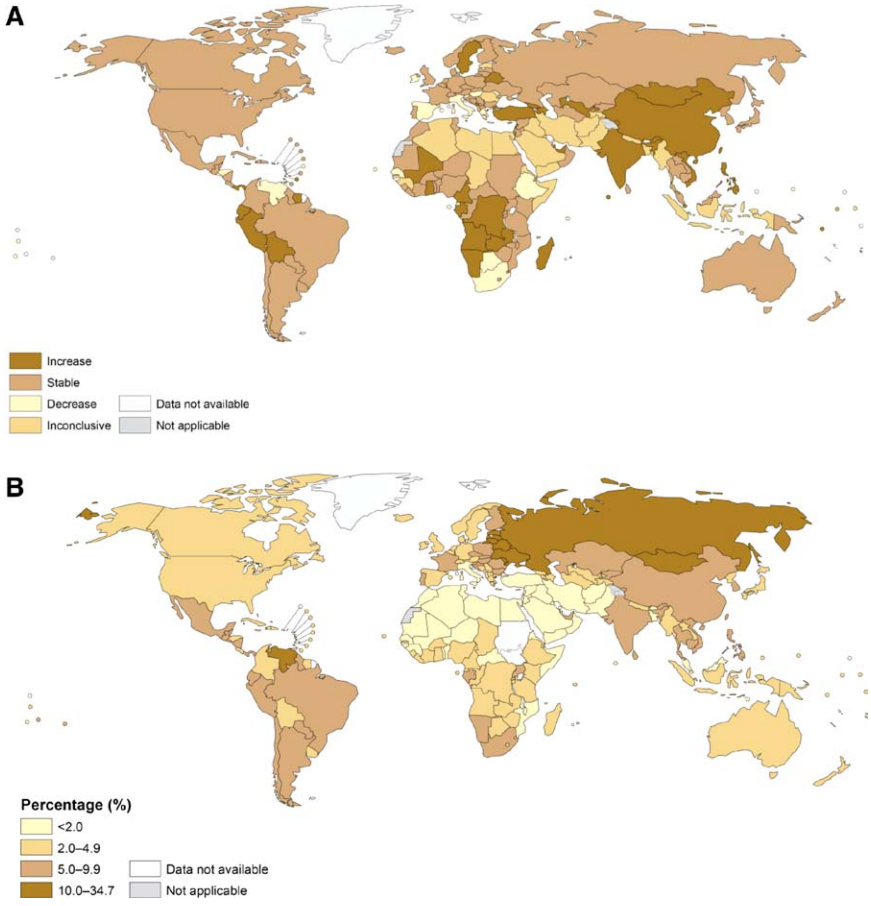

Figure 1. A, Five-year changes in recorded per capita alcohol (≥15 years) consumption, 2006 to 2010. **B**, Alcohol-attributable fractions for all-cause deaths, 2012 (in percentages). Reproduced with permission of the publisher.[1]

lifestyle and dietary peculiarities, unique drinking patterns, and the quality of alcoholic beverages consumed. Chance is abrogated by consistent evidence from another large-scale study from India.[14] Importantly, this study demonstrates that deleterious effects of alcohol are not confined to frequent binge drinking in India but extend to moderate drinkers consuming minor amounts of alcohol. Confounding may arise from the use of self-report instruments on a fundamentally different sociocultural background, but it is not immediately apparent why this should pretend harm in South Asia but not in other comparable Asian regions or countries tabooing alcohol. Nutritional modifiers of alcohol effects remain to be unraveled and hold some promise to resolve the paradox. Unique characteristics of alcohol consumption in South Asia are the globally highest proportion of unrecorded (homemade) alcohol (one half in India)[1] and the almost exclusive consumption of spirits (93.1% spirits, 6.8% beer, and 0.1% wine in India).[1,14] In small intervention trials and on the basis of pathophysiologic considerations, wine surpassed other types of alcoholic beverages in terms of favorable short-term metabolic changes.[3,9,11,12] To date, epidemiologic research has not confirmed the superiority of wine over spirits.[2] However, it must be remembered that, in epidemiologic work, it is challenging, if possible at all, to disentangle effects of different types of beverages in mixed drinkers, and drinking behaviors allocated to 1 type of beverage only are usually driven by cultural and regional peculiarities. The stimulating INTERHEART publication should motivate further scientific elaboration of the preferential harm of alcohol in South Asia and revive research targeting alcohol quality. Promising research foci may address unexplored areas, like the influence of alcohol on the gut microbiota and metabolome and the effects of distinct alcoholic beverages on lipid composition[15] and de novo lipogenesis.

Alcohol and Health: The Dark Side

Harmful use of alcohol is a component cause of more than 200 disease and injury conditions,[1,3] including myocardial infarction, stroke, diabetes mellitus, atrial fibrillation, nonischemic cardiomyopathy, sleep apnea, cancer (most notably of the breast and gastrointestinal tract), fetal alcohol syndrome, and liver cirrhosis. It is the third-leading cause of premature death in the United States, surpassed only by smoking and overweight, and even constitutes the number 1 killer among men aged 15 to 50 years.[3] On a population level, hazardous effects of alcohol in aggregate may offset the beneficial ones,[1,8] and cardiovascular disease is a key contributor to alcohol-related mortality (33.4% globally).[1] Despite the intriguing novel findings for South Asia, it must be emphasized that the dimension of the problem is still greatest in the Western world and in emerging economies with rates of alcohol-related deaths peaking in the Russian Federation and successor states of the former Soviet Union (2014 World Health Organization Report; Figure 1B).[1] Figure 2 summarizes mechanistic pathways linking heavy drinking and vascular disease.[3,8] The second main finding of INTERHEART, namely that >4 alcoholic drinks in men and 3 in women (or ≥6 drinks [unisex] in an alternative

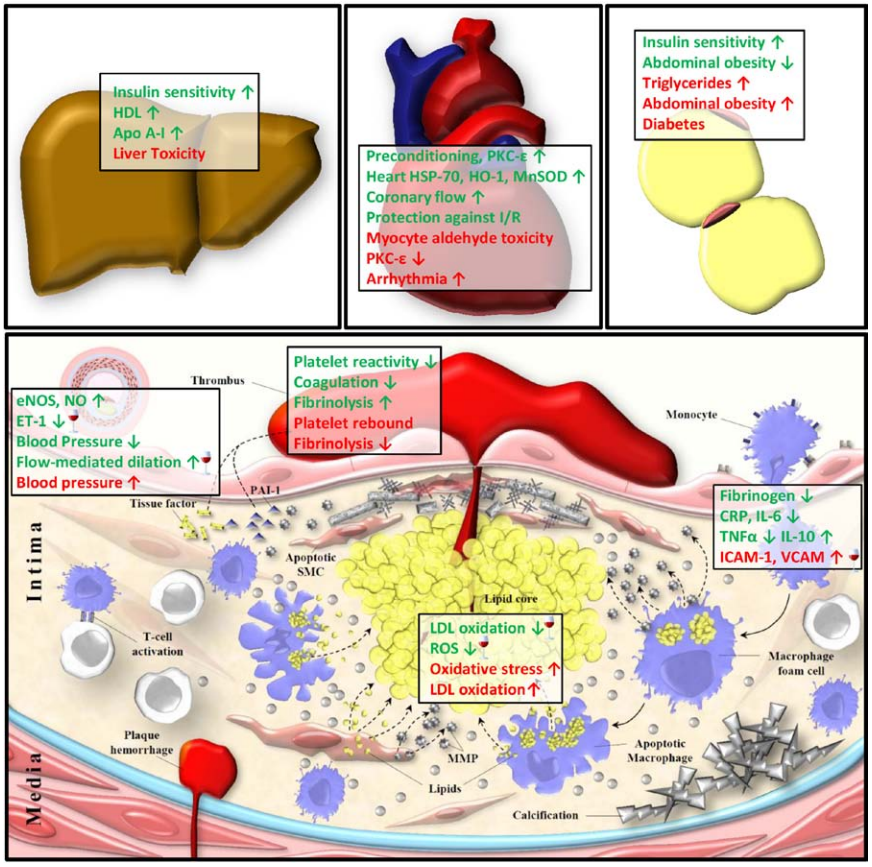

Figure 2. Proposed mechanistic insights into atheroprotective and cardioprotective (in green), as well as injurious (in red), effects of alcohol consumption regarding inflammation (CRP indicates C-reactive protein; IL-6, interleukin 6; IL-10, interleukin 10; TNFα, tumor necrosis factor α; ICAM-1, intracellular adhesion molecule 1; VCAM, vascular adhesion molecule), oxidation (LDL indicates low-density lipoprotein; ROS, reactive oxygen species), endothelial function (NO indicates nitric oxide: eNOS, endothelial NO synthase; ET-1, endothelin 1), coagulation, liver function and insulin sensitivity (HDL indicates high-density lipoprotein; apo A-I, apolipoprotein A-I), the heart (PKC-ε indicates protein kinase C-ε; HSP-70, heat-shock protein 70; HO-1, heme oxygenase 1; MnSOD, manganese superoxide dismutase), and fat tissue. Most effects refer to ethanol. Effects demonstrated for nonalcohol components of red wine (polyphenols) only are labeled with a wine glass symbol.

analysis), consumed on a single occasion, translates into short-term harm,[5] fits very well with these pathophysiologic considerations. Alcohol in excess produces an immediate rise in blood pressure, a short-lived oxidative and proinflammatory burst, impaired fibrinolysis, and temporary heart rhythm changes with enhanced oxygen demands.[3,8–13] Briefly delayed, the platelet-rebound phenomenon creates a reversible procoagulant state and vulnerable period. Moreover, heavy drinking interferes with the absorption, metabolism, and action of several drugs used in cardiovascular prevention and may prompt irregular or delayed pill intake, which further amplifies risk. The enhanced burden of atherosclerosis and more common alcohol–drug interferences provide a plausible explanation as to why individuals aged >65 years are more susceptible to injurious effects of heavy episodic drinking in INTERHEART.[5]

Some Notes on Limitations

Limitations of the INTERHEART study are the case–control design with control recruitment from hospitals, the general community, and visitors or relatives of the index patient. Subsidiary analyses, however, argue against a meaningful influence of this heterogeneous enrollment procedure on the key findings obtained.[5] Analyses of short-term effects of alcohol ingestion entail the problem that alcohol consumption in the 24 hours before myocardial infarction is compared with alcohol consumption in the 24- to 48-hour period before infarction as a picture of customary drinking pattern. Acute effects of alcohol do not strictly follow a 24-hour cutoff. Still, this comparison is more robust than the approach commonly used in case–crossover studies, namely using self-reported long-term consumption as a reference. Finally, INTERHEART did not record alcohol quantities, types of alcoholic beverages, or previous drinking behaviors and thus missed the opportunity to further deepen its findings in these respects.[5] Finally, problems inherently linked to epidemiologic alcohol research also apply to INTERHEART, such as recall bias and deliberate denial of alcohol intake. Realistically speaking, however, all of these limitations are unlikely to invalidate the key findings of INTERHEART.

Some Thoughts About Thresholds and Moderation

The dispute surrounding the optimal quantity of alcohol that should be consumed has a history almost as long as the history of alcohol itself. The Greek poet Eubulus (375 BC) voted for 3 Kylix cups (≈250 mL), and in one of his plays had Dionysus, the god of wine, say, "Three bowls do I mix for the temperate: one to health, which they empty first, the second to love and pleasure, the third to sleep. When this bowl is drunk up, wise guests go home." Because it was customary at that time to dilute wine in a ratio of 1:2 or 1:3, Eubulus's view comes close to current guidelines. However, all of the recommendations suffer from the fact that the thresholds of healthy moderation are population averages and do not necessarily reflect correct individual thresholds.[8] Actually, intestinal degradation, absorption, metabolism, and blood clearance of ethanol are all subject to high interindividual variability. Accordingly, one is well advised to consider thresholds an uppermost limit. On the other hand, alcohol consumption is underreported by

self-estimate, as evident from comparisons of prospective diet records and tax incomes (alcohol sales), and the nondifferential response error is 30% to 65% or even higher.[16] This bias is not relevant in terms of clinical recommendations, because it strikes epidemiologic studies and the routine setting equally.

Summary and Implications

Overall, men and women consuming alcohol in moderation face a lower risk of myocardial infarction, stroke, congestive heart failure, diabetes mellitus, and death in many high-income, emerging, and developing communities. The current publication from the INTERHEART study, however, casts doubts on whether this is a universal finding that is valid around the globe. Most guidelines explicitly do not advise starting alcohol consumption for the purpose of cardiovascular prevention but instead recommend limiting alcohol intake to quantities below or equal to the thresholds of 1 or 2 drinks in women and men daily, respectively. They advise abstention in heavy drinkers only, but the current INTERHEART findings suggest extending this recommendation to South Asians en bloc. Heavy habitual or episodic drinking, on top of its long-term hazards, may be a short-term trigger of myocardial infarction already at amounts well below the conception of binge drinking.

"In vino veritas," said the Greek lyric poet Alkaios of Mytilene (630 BC). The full truth regarding the complex interplay between alcohol consumption and vascular disease, however, remains a well-guarded secret. The INTERHEART study in this issue of *Circulation* is another step in deciphering the truth, and the South Asian paradox is a valuable starting point for new research.

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Disclosures

None.

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