The Complex Association Between Alcohol Consumption and Myocardial Infarction: Always Good for a New Paradox

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First mention of alcohol as a component of diet and communal events dates back to the 7th millennium B.C. Famous ancient savants like Hippocrates used alcohol as a solvent for herb extracts, an antiseptic, and to counteract lethargy and diarrhoea, while 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 favoured for its broad availability and lack of effective sale restrictions. In 2010, the worldwide average amount of pure alcohol consumed per person aged 15 or over was 6.2 litres per year or 13.5 grams per day. ¹ There is now solid evidence that alcohol, when consumed on a regular basis and at low volumes (up to one drink for women and two drinks for men daily), confers protection against cardiovascular disease, whereas regular amounts of more than four to five drinks daily and heavy episodic drinking have opposite effects. ²³ 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 (ADH) 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 its most favourable 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. in the current issue of Circulation delivers unique and, to some extent, surprising results. ⁵ 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 Mio, 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, 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 employs rigorous methodological 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. \(^5\)

INTERHEART’s findings are relevant and timely given that alcohol consumption is on the rise in South Asia, especially India, according to the most recent WHO report released in 2014 (Figure 1A). \(^1\) The elegant study by Leong et al. 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 \textit{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 athero- and cardio-protective consequences of alcohol consumption. In brief, alcohol in moderation favourably 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 (decrease of 30%-40%), \(^3\) and life span (decrease of 17%-18% in
The “South Asian paradox”

The beneficial effects of alcohol, however, are difficult to reconcile with INTERHEART’s observation of an elevated vascular risk among mainly moderate drinkers in South Asia. As discussed by Leong et al., genetic differences in alcohol metabolism, reflected by functional polymorphisms in the genes encoding alcohol degradation enzymes like ADH and aldehyde dehydrogenase (ALDH)-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 life-style 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 unravelled 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 based on pathophysiological considerations, wine surpassed other types of alcoholic beverages in terms of favourable short-term metabolic changes. 3,9,11,12 To date, epidemiological research has not confirmed the superiority of wine over spirits. 2 However, it must be remembered that in epidemiological work

total mortality). 3
it is challenging, if possible at all, to disentangle effects of different types of beverages in “mixed” drinkers, and drinking behaviours allocated to one type of beverage only are usually driven by cultural and regional peculiarities. The stimulating INTERHEART publication should motivate further scientific elaboration of alcohol’s preferential harm in South Asia and revive research targeting alcohol quality. Promising research foci may address unexplored areas like alcohol’s influence on the gut microbiota and metabolome, and the effects of distinct alcoholic beverages on lipid composition \(^{15}\) and \textit{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, atrial fibrillation, non-ischemic cardiomyopathy, sleep apnea, cancer (most notably of the breast and gastrointestinal tract), foetal alcohol syndrome, and liver cirrhosis. It is the third-leading cause of premature death in the US, surpassed only by smoking and overweight, and even constitutes the number one 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 USSR (2014 WHO 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 more than four alcoholic drinks in men and three in women (or \(\geq 6\) drinks unisex in an alternative analysis), consumed on a single occasion, translates into short-term harm \(^5\), fits very well with these pathophysiological considerations. Alcohol in
excess produces an immediate rise in blood pressure, a short-lived oxidative and pro-
inflammatory burst, impaired fibrinolysis, and temporary heart rhythm changes with enhanced oxygen demands.\textsuperscript{3,8-13} Briefly delayed, the platelet-rebound phenomenon creates a reversible pro-coagulant 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 why individuals older than 65 years are more susceptible to injurious effects of heavy episodic drinking in INTERHEART.\textsuperscript{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 enrolment procedure on the key findings obtained.\textsuperscript{5} Analyses of short-term effects of alcohol ingestion entail the problem that alcohol consumption in the 24 hours prior to myocardial infarction is compared with alcohol consumption in the 24-to-48-hour period prior to infarction as a picture of customary drinking pattern. Acute effects of alcohol do not strictly follow a 24-hour cut-off. 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 behaviours, and thus missed the opportunity to further deepen its findings in these respects.\textsuperscript{5} Finally, problems inherently linked to epidemiological alcohol research also apply to INTERHEART, such as recall bias and deliberate denial of alcohol intake. Realistically speaking, however, all 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 B.C.) voted for three “Kylix” cups (à 250 mL) and in one of his plays had Dionysos, 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.” Since 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 recommendations suffer from the fact that the thresholds of healthy moderation are population averages and do not necessarily reflect correct individual thresholds. 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 non-differential response error is 30%-65%, or even higher. This bias is not relevant in terms of clinical recommendations, because it strikes epidemiological 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, 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 one or two 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 B.C.). 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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**Conflict of Interest Disclosures:** None.

**References:**


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risk: observations from 52 countries in the INTERHEART case-control study. *Circulation.* 2014;120:XX-XXX.


Figure Legends:

Figure 1. A) Five-year changes in recorded per capita alcohol (15+ years) consumption, 2006-2010. B) Alcohol-attributable fractions for all-cause deaths, 2012 (in percent). Reproduced, with the permission of the publisher, from the Global status report on alcohol and health 2014. Geneva, WHO 2014.

Figure 2. Proposed mechanistic insights into athero- and cardio-protective (in green) as well as injurious (in red) effects of alcohol consumption regarding inflammation (CRP, C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10; TNFα, tumor necrosis factor alpha; ICAM-1, intra-cellular adhesion molecule-1; VCAM, vascular adhesion molecule), oxidation (LDL, low-density lipoprotein; ROS, reactive oxygen species), endothelial function (NO, nitric oxide: eNOS, endothelial NO synthase; ET-1, endothelin-1), coagulation, liver function and insulin sensitivity (HDL, high-density lipoprotein; apo A-I, apolipoprotein A-I), the heart (PKC-ε, protein kinase C-epsilon; 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 non-alcohol components of red wine (polyphenols) only are labeled with the following symbol “🍇”.
Figure 1
Insulin sensitivity↑
HDL↑
Apo A-I↑
Liver Toxicity

Preconditioning, PKC-ε↑
Heart HSP-70, HO-1, MnSOD↑
Coronary flow↑
Protection against I/R
Myocyte aldehyde toxicity
PKC-ε↓
Arrhythmia↑

Platelet reactivity↓
Coagulation↓
Fibrinolysis↑
Platelet rebound
Fibrinolysis↓

Fibrinogen↓
CRP, IL-6↓
TNFα↓, IL-10↑
ICAM 1, VCAM↑

Insulin sensitivity↑
Abdominal obesity↓
Triglycerides↑
Abdominal obesity↑
Diabetes

eNOS, NO↑
ET-1↓
Blood Pressure↓
Flow-mediated dilation↑
Blood pressure↑

Figure 2
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