EDITORIAL

Is alcohol anti-inflammatory in the context of coronary heart disease?

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Although the cardioprotective effect of alcohol has been primarily explained by its effect on blood lipids and platelets, could an anti-inflammatory mechanism be involved?

A number of human studies have reported a lower rate of cardiovascular disease among moderate alcohol drinkers than among abstainers.[1–5] Even in very small amounts (one drink (approximately 12–15 g of pure ethanol) per week in certain studies), alcohol appears to be protective, which is quite difficult to explain through the ''alcohol–lipid–haemostasis'' theory. In fact, the protective effect of alcohol has been primarily explained by an effect on blood lipids (increase in high density lipoprotein (HDL) concentrations) and platelets (decreased aggregation) resulting in a reduced rate of coronary artery obstruction.[6–8] Other mechanisms are probably involved. For instance, recent clinical studies have shown that moderate drinking may improve the early outcomes after acute myocardial infarction and prevent sudden cardiac death,[9–11] suggesting a direct effect of ethanol on the ischaemic myocardium.

Another possibility, as suggested by the article by Zairis and colleagues in this issue of *Heart*,[12] is that alcohol may protect against coronary heart disease (CHD) through an anti-inflammatory mechanism. Indeed, many scientists regard coronary atherosclerosis as a product of chronic arterial wall inflammation,[13] and a growing body of evidence from animal and human studies indicate that ethanol has a direct and profound effect on inflammation.[14] Furthermore, population based studies have shown that inflammation markers such as C reactive protein (CRP) predict future CHD complications even better than all other biomarkers, including low density lipoprotein (LDL) cholesterol.[15] However, in the absence of randomised trials aimed at reducing CRP, no cause–effect relation can be ascertained. CRP was shown to be predictive of post-angioplasty restenosis, but statins (which were claimed to reduce CRP in several studies) failed to reduce restenosis rates. This example again underlines that a risk marker (or predictor) should not be assimilated to a causal factor.

Knowing that no prospective long term randomised trial with alcohol is feasible, the next question is whether there are biological data, experimental (animal) studies, or human studies to support the hypothesis that drinking alcohol may have an anti-inflammatory effect, accounting for its cardioprotective properties.

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BIOLOGICAL AND EXPERIMENTAL STUDIES

In a recent review, Stewart summarised current knowledge in that field.[14] As early as 1938, scientists reported that alcohol may inhibit leucocyte function. Later, in 1963, leucocyte motility was shown to be decreased by the presence of ethanol in donor blood, and throughout the 1970s a number of researchers continued to study the effects of ethanol on human cell lines involved in immune responses. Several laboratories also studied the effects of ethanol on a variety of inflammatory mediators in animal models. While most studies indicated an inhibitory effect of low dose ethanol on these mediators, including NF-κβ and various cytokines, some showed that the interactions of ethanol with a diet high in unsaturated fats possibly led to an increased expression of pro-inflammatory mediators. It was also reported that free radicals and antioxidants may modify the effects of ethanol on these mediators. However, it is important to remember that the vast majority of these studies dealt with high doses of ethanol, because the workers in question were usually looking for the toxic effect of heavy alcohol drinking rather than for the protective effect of moderate drinking. In addition, the molecular mechanisms by which ethanol may interfere with inflammation (or with the production of inflammation mediators) were not fully investigated; in particular, dose–effect relations were rarely examined. This is especially important, given the epidemiological evidence that the effects of moderate and heavy drinking are completely different as regards cardiovascular diseases.

In that context of different (beneficial versus deleterious) effects of ethanol, depending at least partly on dosage, some investigators have studied the effects of non-ethanolic components in certain alcoholic beverages such as red wine. The recent discovery that resveratrol, a natural stilbene derivative found in fruits, vegetables, and in high concentration in many red wines, is a natural antagonist of the aryl hydrocarbon receptor may be of interest because several

Abbreviations: CHD, coronary heart disease; CRP, C reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein

ligands of that receptor are known to increase pro-inflammatory cytokine expression.[16] Although further studies are needed in that context, the idea that resveratrol might be both anti-inflammatory and cardioprotective (in particular in animal models of myocardial ischemia and infarction) has been put forward.[16 17] In that view, it seems that red wine, but not vodka, is able to inhibit NF-κβ activation in human peripheral monocytes, whereas ethanol itself could potentiate the activation of the same transcription factor in CD4+ lymphocytes.[14] As summarised by Stewart, these studies, taken as a whole, suggest that cell type and the presence of additional inflammation mediators may modify the specific effect of alcohol itself.[14] This emphasises the importance of studies conducted in humans and based on the consumption of alcoholic beverages in everyday life.

HUMAN STUDIES

The in vivo effect of ethanol on cytokine production in humans has been assessed in a few studies.[14] For instance, Mendall and colleagues[18] reported that tumour necrosis factor α (TNFα) concentrations are lower in drinkers than in abstainers. In a randomised, diet controlled intervention study, Sierksma and colleagues[19] studied the effect of four glasses (three glasses for women) of beer or alcohol-free beer (control) with dinner during two successive 3 week periods. The total diet was supplied to subjects who were apparently healthy. Plasma CRP and fibrinogen concentrations decreased by 35% and 12%, respectively (both $p < 0.05$) after the consumption of beer, as compared to alcohol-free beer consumption. The effect on CRP was significant in women, but non-significant in men, while sample size was small. The authors concluded that an anti-inflammatory action of alcohol may explain the link between moderate alcohol consumption and a lower risk of cardiovascular disease. It is noteworthy, however, that Mezzano and colleagues[20] did not detect any effect of moderate red wine drinking on CRP in healthy male students, thus confirming Skiersma's negative data in men.[19] The studies by Mezzano and Sierksma differed, however, in many aspects, including the amount and type of ethanol consumed during the intervention periods, the age of the subjects (all women included in Sierksma's study were postmenopausal), and the baseline concentrations of CRP which were quite high in Sierksma's study. This suggests that only those with high baseline CRP values would benefit from the anti-inflammatory (anti-CRP) effect of moderate ethanol drinking. Further studies with larger sample sizes and more homogeneous populations are therefore needed to confirm this point. Nonetheless, the results of the study by Zairis and colleagues[12] in this issue of *Heart* actually are in line with that theory.

POPULATION BASED STUDIES

On the other hand, data are scarce about the influence of alcohol on inflammation in population based samples. Imhof and colleagues[21] studied the association between alcohol consumption (assessed using a 7 day food record) and the concentrations of various positive or negative markers of systemic inflammation in a large population based sample of adults in Germany. This is an important study because, for the first time, a dose–effect investigation allowed examination of whether there is any difference in inflammation markers between heavy and moderate drinkers. In addition, the population sample in that study was probably very representative of the general adult population in Europe, since 6% (men) and 13% (women) declared to be total abstainers (about 7% on average in France). Among men, alcohol consumption showed a U shaped association with mean CRP and α1 globulin concentrations after adjustment for several potential confounders. Also, there was an inverted U shaped association between the negative acute phase reactant albumin and alcohol intake. The same relations were found in women, but they were non-significant.[21] Thus, non-drinkers and heavy drinkers had higher CRP and lower albumin concentrations than moderate drinkers. It is noteworthy that albumin actually is a strong predictor of CHD complications, whose effects on risk have been explained, at least partly, by its inhibitory action on platelet function and the risk of thrombosis.[22] Imhof and colleagues[21] concluded that in view of the robust associations between (positive or negative) markers of inflammation and the risk of CHD, an anti-inflammatory action of alcohol may contribute to the link between moderate drinking and a lower risk of CHD. Finally, the authors proposed that interleukin-6, one of the main regulators of the genes encoding acute phase reactants and the suppressor of albumin production by the liver, could be the underlying link between ethanol and inflammation, since a moderate consumption of ethanol seems to inhibit the production of interleukin-6 (by the liver as well as by the adipose tissue) whereas high concentrations of that cytokine have been reported in heavy drinkers.[21] Along the same lines, it is likely that ethanol may also act on toll-like receptor 4, the newly discovered lipopolysaccharide (LPS) receptor in macrophages, in the liver, although further studies with dose–effect relations are required.[23]

In a very recent study, Albert and colleagues[24] examined the association between alcohol consumption and CRP among participants in the PRINCE (pravastatin inflammation/CRP evaluation) study.[24] One the main points of interest in that study is that the average consumption of ethanol was quite low (as compared to most European populations), which gave the opportunity of studying the alcohol–CRP relation within ranges of ethanol intake different from those reported by Zairis and colleagues[12] and Imhof and colleagues.[21] In that study, those considered ''heavy drinkers'' (more than two drinks per day) had a lower body mass index and triglyceride values than abstainers, which is quite paradoxical. In fact, these ''heavy drinkers'' would have been ''moderate drinkers'' in a study involving European consumers.[10 12 21] In contrast (and as expected), total and HDL cholesterol concentrations were higher with heavier alcohol use. Among the inflammation markers, only CRP was measured. On the whole, there was a progressive decline in CRP concentrations with increased alcohol intake. The lowest CRP values were measured among participants drinking 5–7 drinks per week, and there was no significant difference between that group and the ''heavy drinkers'' and no U shaped association. This observation was still present after adjustment for several potential confounders including smoking, blood pressure, diabetes, HDL cholesterol, aspirin use, and hormone replacement therapy in women.[24] Thus, this cross sectional survey is in line with the studies by Imhof and colleagues[21] and Zairis and colleagues[12] and again supports the hypothesis that the cardioprotective effect of alcohol is (at least partly) mediated through an anti-inflammatory effect.

CONCLUSIONS

The main limitation of the theory (proposed by Zairis and colleagues[12]) that moderate ethanol drinking is cardioprotective through anti-CRP effects is that a risk marker (such as CRP) is not necessarily a causal factor, as discussed above in regard to CRP, statins, and post-angioplasty restenosis. In addition, inflammation, in particular vascular inflammation, is a very complex phenomenon involving a number of local and systemic mediators as well as several circulating (platelets, leucocytes) and arterial cells (smooth muscle cells,

endothelial cells, monocytes–macrophages); at present, there is no evidence that CRP is a causal (or even a major) factor in that context. Further studies are obviously required to explore that intriguing (and appealing) theory.

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IMAGES IN CARDIOLOGY

Isolated commissural detachment of the aortic valve after minor trauma

A 38 year old male patient with a history of hypertension was sent to the emergency room for shortness of breath for two days. His history revealed only minor chest trauma two weeks previously. The diagnostic workup suggested severe aortic regurgitation caused by infective endocarditis.

Intraoperative transoesophageal echocardiography showed that the commissure between the right coronary and non-coronary cusp of the aortic valve was detached from the aortic wall, with resultant right coronary cusp prolapse and severe aortic regurgitation. Successful repair of the detached commissure of the aortic valve was done under hypothermic cardiopulmonary bypass. The patient was discharged uneventfully seven days after the operation.

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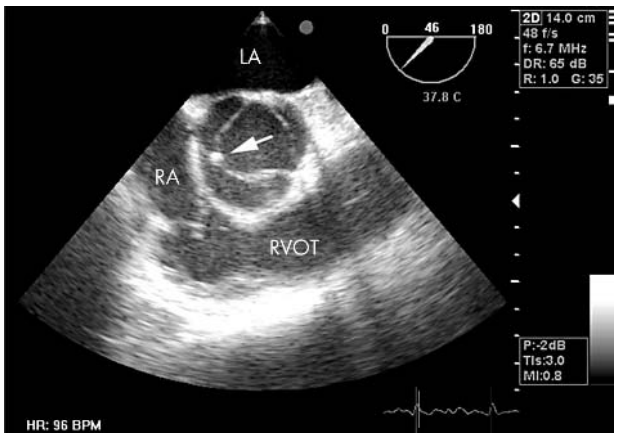
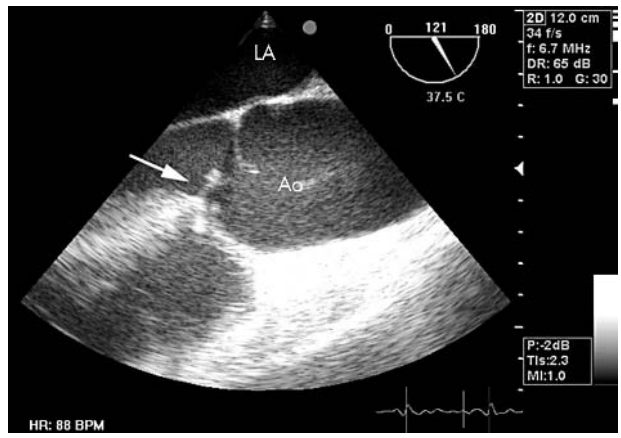


Multiplane transoesophageal echocardiography of the aortic valve, short axis. The commissure (arrow) between the right and non-coronary cusp was detached from the aortic wall. LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract.



Multiplane transoesophageal echocardiography of the aortic valve, long axis. The right coronary cusp of the aortic valve was prolapsed into the left ventricular outflow tract (arrow), which led to severe regurgitation. The aortic root was intact without dissection. LA, left atrium; Ao, Aorta.