LECTURE
ΔΙΑΛΕΞΗ

The relationship between wine consumption and vascular risk
From epidemiological evidence to biological plausibility

Epidemiological studies have suggested that vascular disease morbidity and mortality can be decreased by moderate alcohol consumption. A meta-analysis has been recently performed on 19 of these studies, selected on the basis of the availability of specific information on the relative risk associated with wine consumption. The results strongly favour the protective role of moderate (up to 300 mL per day) wine consumption against the risk of vascular events. Although some cardioprotective effects of most alcoholic beverages are probably due to ethanol-induced elevation of HDL-cholesterol, lowering of fibrinogen plasma levels and, perhaps, of platelet aggregation, it is reasonable to speculate that the vascular protective effects of wine, observed in French and in other populations, may be attributed in part also to the antioxidant, vasorelaxant, and antithrombotic properties of its polyphenolic components.

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Η σχέση μεταξύ κατανάλωσης οίνου και αγγειακού κινδύνου.
Από τις επιδημιολογικές ενδείξεις στη βιολογική αλήθοφάνεια

Περίληψη στο τέλος του άρθρου

Key words

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1. INTRODUCTION

An inverse association between moderate (1–3 drinks per day) alcohol consumption and cardiovascular disease (CVD) morbidity and mortality has been consistently shown in many epidemiological studies, independently from age, sex and smoking status.[1,3] The beneficial effect of alcohol also applies to total mortality.[4,5] On the other hand, alcohol consumption increases in a dose-dependent manner the risk of mortality for CVD (hypertension, arrhythmia) and cerebrovascular disease (hemorrhagic or ischemic stroke), as well as for other causes–cirrhosis, pancreatitis, neurodegenerative disorders, cancer, violent death.[6,7] After Renaud and de Lorgeril[8] suggested wine intake as one possible explanation for the lower than expected coronary heart disease (CHD) mortality rates in France, despite the prevalence of risk factors (the French Paradox), many ecological and observational studies have dealt with the question whether different alcoholic beverages are equivalent in their ability to protect against vascular disease, or a specific beverage, wine in particular, might offer a greater protection.[2,3]

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2. EPIDEMIOLOGICAL EVIDENCE

The different studies do not draw homogeneous conclusions and healthier lifestyle factors have been invoked to explain the lower rates of CVD found in wine drinkers in several studies: among northern Californians for istance, wine drinkers usually smoke less, exercise more and suffer less from obesity.[9]

2.1. Wine consumption and cardiovascular disease

Even when adjusting for other factors however, three large prospective studies have shown that there is added protection against vascular and all-cause mortality for consumers of wine than for consumers of beer or spirits.

The Copenhagen City Heart Study[5] showed that the risk of dying from CVD (but also from cerebrovascular disease and other causes) in a population of 13,285 subjects, followed for 10–12 years, steadily decreased with an increasing intake of wine, reaching a 49% of reduction for consumers of 3–5 drinks/day as compared to subjects who never drunk wine. Intake of either beer or spirits was not associated with any reduced risk. More recently, Renaud et al[10] reported wine and beer drinking to be associated to a lower relative risk of CVD in a population of 36,250 middle-aged healthy men in the area of Nancy, in France, followed for 12 years or more. The reduction in risk was however more significant for wine and, furthermore, only wine drinking was significantly associated with a 33% lower relative risk of all-cause mortality.

In both studies mentioned above, the effect of wine was independent of common risk factors such as age, sex, smoking, and body mass index, as well as of life-style-related factors such as education and income.

Adjustments for common, as well as other risk factors such as prevalence of diabetes and cholesterol levels, or health markers such as regular medical attendance, only attenuated, but did not eliminate, the greater protection against CHD and all-causes mortality by wine consumption as compared to other drinks observed in the British Regional Heart Study[11] that followed up 6,680 men for an average of 16.8 years. Wine drinkers might also have a better nutrition. Recently, a report[12] from a large Danish population showed that wine drinking was strongly associated with a healthy diet, defined as major intake of fruits, vegetables, fish, salads, and olive oil, a finding relevant for the interpretation of the relation between type of alcohol and CHD mortality in Denmark.[4] In that country wine is a selective type of beverages and a potential indicator of a healthy diet. In Italy, however, where wine is by far the most common type of alcoholic beverage, wine drinking is not a correlate for a healthy diet[13] but still results in protection against non fatal myocardial infarction, independently of recognised risk factors (serum cholesterol, diabetes, hypertension, family history of AMI), as shown by the case-control study designed in the framework of the GISSI-2 trial.[14]

2.2. Wine consumption and cerebrovascular disease

While the benefit of moderate alcohol consumption on overall coronary and other cardiac diseases is well established, the relationship with cerebrovascular disease, mainly stroke, is more controversial.[15] The overall evidence suggests a reduced risk of ischemic stroke, but little or no protection against hemorrhagic stroke. All cerebrovascular events substantially increase in heavy alcohol consumers. Some authors have discussed whether the effect of alcohol on the risk of stroke depends on the type of alcohol consumed.

The Copenhagen City Heart Study[16] prospectively examined a cohort of 13.329 subjects for 16 years and found weekly wine consumption being significantly associated to a reduced risk of stroke. The association for daily wine consumption was statistically borderline ($P=0.06$). Intake of either beer or spirits was not associated with reduced risk of stroke. Subjects who drunk >42 units per week had a 1.5 fold significant increase in risk.

The Northern Manhattan Stroke Study,[17] found drinking up to 2 drinks per day of any type of alcoholic beverage to be significantly associated to lower first ischemic stroke risk in a elderly mult-ethnic population. However, those who were predominantly wine drinkers consumed, on average, less alcohol than those who drank beer or spirits or were combination drinkers. Intake of 7 of more drinks of alcohol per day was significantly associated to an almost 3 fold increased risk.

Finally, from an Australian case-control study among 331 pairs,[18] both wine or spirit consumption lowered intracerebral haemorrhage risk in men, but only wine did it significantly; for women, wine only was protective, although not significantly. Drinking more than 6 units per day of alcohol was significantly associated to a 3.4 fold increased risk. The effects described in the above studies were independent of history of diabetes, cardiac disease, hypertension, and of several common confounding factors.

2.3. Wine consumption and vascular risk

At present, a rigorous overall estimation of the relative vascular risk associated with any specific alcoholic beverage is lacking. We have recently performed an overview of the literature[19] aiming at evaluating the relationship between wine consumption and vascular risk, and at giving a quantitative estimate of this relationship. More than 50 studies were screened, from which only 19 could be selected that gave quantitative estimation on the relative risk associated to wine consumption. The main outcome measure was wine consumption versus the relative risk of morbidity and mortality from vascular disease. The results obtained support the protective role of moderate wine consumption against the risk of vascular events. In fact, pooling data from 13 prospective and case-control studies reporting only relative risk

10 days supplementation of drinking water with red wine, white wine or alcohol. Red wine supplementation induced significant prolongation of template bleeding time, decrease in platelet adhesion to fibrillar collagen, and reduction in thrombus weight. Alcohol-free red wine was almost as effective as the original beverage, while white wine was almost ineffective. The NO synthase inhibitor L-NAME prevented the effects of red wine, suggesting the role of alcohol-independent factors interfering with the NO pathway. The difference in polyphenolic contents between red wine and white wine and the increased radical trapping antioxidant activity found in the plasma of rats given red wine strongly favour the role of polyphenols rather than of alcohol in the observed effects. At William Harvey Research Institute in London, M. Carrier and co-workers, our partners in the ongoing FAIR European project "Wine and Cardiovascular Disease", are studying the response to acethylcholine-induced vasodilatation as a marker of endothelial dysfunction consequent to oxidative stress. In cholesterol fed rabbits, acetylcholine-induced vasodilatation was markedly impaired but, after 8 weeks administration of red wine extracts together with the cholesterol-rich diet, a significant ($P<0.05$) improvement in endothelial function was apparent (fig. 2).

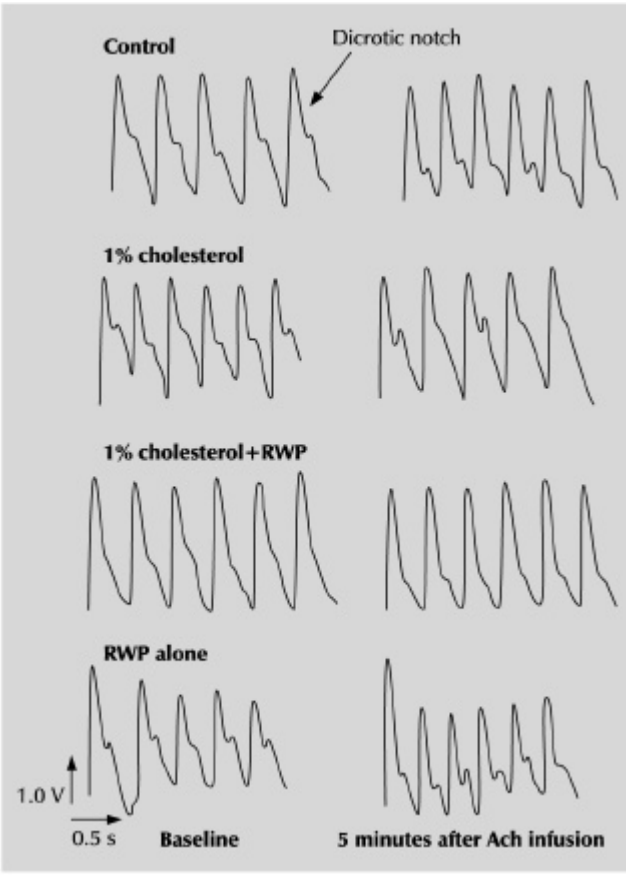

Figure 2. Comparison of photoplethysmography (PPG) trace recording at baseline and after 5 minutes of acetylcholine (Ach) infusion in rabbit fed for 8 weeks with a standard diet (control), 1% cholesterol diet, 1% cholesterol plus red wine polyphenolic extracts (RWP, 20 mg/100 mL). Endothelial vasodilation is assessed by analysing the inflexion point (dicrotic notch) on the descending limb of arterial pulse waves. A PPG sensor is applied on the dorsal side of the rabbit ear and acetylcholine is infused in the marginal contralateral ear vein. (M. Carrier et al, unpublished results).

3.2 Studies in humans

The potential *in vivo* properties of wine and its derived products have been evaluated in term of their ability to enhance plasma antioxidant status, considered as an index of the capacity of the organism to counteract oxidative insults in general, as well as to reduce specific oxidative processes, those related to atherogenic LDL modifications in particular.

Several reports have documented in volunteers an increase of plasma antioxidant capacity or protection of LDL from oxidation, paralleled by increased polyphenol concentration in plasma, after prolonged, but also after short-term consumption of red wine or alcohol-free red wine. Other studies have compared the capacity of different alcoholic beverages to reduce platelet aggregation or modulate fibrinolysis.[24]

From these observations, even though sometime controversial, it seems plausible that absorption of polyphenols from wine or from wine-derived products may change the composition and the chemical properties of plasma and its isolated components, resulting in antiatherogenic and antithrombotic effects.

As mentioned abore, severe endothelial dysfunction consequent to oxidative stress is observed in different pathological conditions such as hypercholesterolemia and diabetes, and it is considered to play a major role in the progression of atherosclerosis and subsequent clinical manifestation, such as myocardial ischemia.

The modulator effects of short-term ingestion of a relatively high dose of red wine on endothelial function have been shown by Shimada et al,[28] who measured changes of coronary blood flow velocity consequent to adenosine-induced vasodilation in 10 healthy volunteers before and after ingestion of red wine, white wine or vodka. Coronary flow velocity significantly increased only after red wine intake (fig. 3).

Interestingly, grape-derived products too may ameliorate endothelial function: in patients with coronary artery

The benefit coming from wine may overcome those of other types of alcohol, not only because of the way wine is drunk, preferably at mealtime and in moderate quantities, but also because the antioxidant polyphenols, which render wine unique, may confer further protection with mechanisms different and possibly additive to those of alcohol itself. Wine is the alcoholic beverage of choice of Mediterranean populations and together with olive oil, vegetables, cereals and fruit, may contribute to the lower rates of CVD observed among these populations.[32] A very recent study[33] indicates that in USA too, adherence of healthy women to lifestyle guidelines including exercise, abstinence from smoking, a diet high in cereal fiber, marine n-3 fatty acids, and folate, and at least half a drink of alcoholic beverage per day, is associated to a very low risk of CHD.

People should therefore be informed of what lifestyle changes might be beneficial to them. Perhaps there are not enough elements to encourage lifetime teetotallers to start drinking, and it may be better to insist on the control of other risk factors. They should however, in the absence of contraindications, be informed of the benefit deriving from a moderate consumption and of the hazards of their continued abstinence. People who are already moderate alcohol consumers should be encouraged to continue, especially if they are at high cardiovascular risk. The hazards of heavy drinking should be highlighted, and people should always be encouraged to cut their consumption to a moderate level.[34]

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ΠΕΡΙΛΗΨΗ

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Επιδημιολογικές μελέτες υπαινίσσονται ότι η νοσηρότητα και θνησιμότητα λόγω αγγειακών νόσων μπορεί να μειωθεί με τη μέτρια κατανάλωση αλκοολούχων ποτών. Μία μετα-ανάλυση έγινε πρόσφατα σε 19 από τις μελέτες αυτές, οι οποίες επιλέχθησαν με βάση τις ειδικές πληροφορίες για το σχετικό κίνδυνο με την κατανάλωση αλκοολούχων ποτών. Τα αποτελέσματα συνηγορούν έντονα υπέρ της ύπαρξης προστατευτικής δράσης της μέτριας, μέχρι 300 mL ημερησίως, κατανάλωσης οίνου εναντίον του κινδύνου αγγειακών επεισοδίων. Αν και κάποιες καρδιοπροστατευτικές δράσεις των περισσότερων αλκοολούχων ποτών πιθανώς οφείλονται στην προκαλούμενη από την αιθανόλη αύξηση της HDL χοληστερόλης, στην ελάττωση του ινωδογόνου του πλάσματος και ίσως στη συσσώρευση των αιμοπεταλίων είναι λογικό να υποθέσουμε ότι οι προστατευτικές δράσεις του οίνου επί των αγγείων, που παρατηρήθηκαν στη Γαλλία και σε άλλους πληθυσμούς, μπορούν να αποδοθούν εν μέρει και στις αντιοξειδωτικές, αγγειοδιασταλτικές και αντιθρομβωτικές ιδιότητες των πολυφαινολικών συστατικών του.

Λέξεις ευρετηρίου: Εγκεφαλοαγγειακά νοσήματα, Καρδιαγγειακά νοσήματα, Οίνος, Πολυφαινόλες

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