Impact of red wine on antioxidant status in vivo

Agewall and colleagues[1] demonstrated that endothelial-dependent increases in blood flow and brachial diameter 30–60 min after ingestion of 250 ml of de-alcoholized red wine were significantly greater than baseline pre-drinking responses. However, alcohol-containing red wine caused non-significant trends in the opposite direction. These findings imply that the inclusion of ethanol in wine offsets some of the beneficial effects of the other components of red wine, possibly polyphenolic antioxidant compounds. The authors argue that acute ethanol exposure may directly inhibit endothelium-dependent responses which have been demonstrated previously in animal vessels[2], although this has not been a universal finding. We wish to offer an alternative explanation.

Our study (quoted by the authors) demonstrated that ingestion of red wine, a beverage with powerful antioxidant properties, produces an increase in the antioxidant activity of human serum[3]. Ten healthy subjects ingested red wine (5·7 ml French Bordeaux/kg) over 30 min. At 60 min post-ingestion there was a significant increase in serum antioxidant activity of 66 μmol. 1⁻¹ (+14%) compared to baseline. However, when we subsequently examined the changes in major physiological antioxidants that might have contributed to this change we found that serum urate had increased over the same time period by 39 μmol. 1⁻¹ (+12%). Since urate shares a 1:1 stoichiometric equivalence with the trolox antioxidant standard, this suggested that over half of the red wine-induced increase could be attributed to changes in serum urate.

Uric acid concentration is strongly correlated with the development of vascular disease[4] although the mechanism is unclear. We suggest that the acute increase in urate caused by normal alcohol-containing red wine was the most likely factor offsetting the positive impact of the other red wine constituents. Indeed, uric acid concentration has previously been shown to have an inverse correlation with maximal lower limb blood flow[5]. The possibility that uric acid had direct effects on vascular function should be the subject of further investigation.

Our study suggested that only a small proportion of the antioxidant changes after the acute ingestion of wine can be attributed directly to wine constituents. In the light of this finding we would question the suggestion of the authors that it is the antioxidant content that produced the beneficial effects of the de-alcoholized red wine. In our opinion, there remains a need to establish whether red wine antioxidants are absorbed in sufficient quantity to have a significant acute effect on free radical-scavenging in the vascular wall.

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References


A reply

We observed increased flow-mediated dilatation of the brachial artery following ingestion of 250 ml of de-alcoholized red wine[3]. We do not, as suggested in the letter by Dr Maxwell and Dr Thorpe, argue that ethanol inhibited endothelium-dependent responses. Ingestion of alcohol-containing red wine was associated with an increase in blood flow and brachial artery diameter even before the induced hyperaemia. It is uncertain whether this dilatation associated with the ethanol was endothelium-dependent or not.

From our study it is not possible to explain the underlying mechanism behind the increased flow-mediated dilatation after de-alcoholized red wine ingestion. Recently, another study showed that purple grape juice ingestion was associated with an increase in flow-mediated dilatation of the brachial artery and reduced LDL susceptibility to oxidation in subjects with coronary heart disease[2]. The authors suggested that the action of flavonoids in grape juice was the underlying mechanism behind this observation. Several studies have demonstrated increased antioxidant activity following red wine ingestion[3–8]. White wine, which contains less flavonoids, has failed to show an antioxidant effect[4,5] suggesting that the antioxidant effect originates from the grape skin which is usually removed during white wine production. Furthermore, ethanol ingestion does not increase antioxidant activity[9].

Dr Maxwell and Thorpe suggest that more than 50% of the antioxidant increase following ingestion of red wine could be attributed to changes in serum urate. They highlight the need for a study to demonstrate that red wine antioxidants absorbed in sufficient quantity can have an acute effect on free radical-scavenging in the vascular wall. We agree that such a study is warranted although one could argue that the purple grape juice study by Stein et al.[9] is such a study. Furthermore, in the study of Serafini et al.[9] a significant rise in total plasma antioxidant capacity was paralleled by a concomitant increase in plasma concentrations of phenolic compounds after drinking de-alcoholized red wine. Thus, that observation suggests that absorption of red wine antioxidants...
contributes significantly to the increased plasma antioxidant activity.

In summary, both purple grape juice and de-alcoholized red wine ingestion are followed by an increase in flow-mediated dilatation of the brachial artery. The underlying mechanism behind this observation is not clear; however, reduced LDL susceptibility to oxidation was also observed after purple grape juice ingestion. It is reasonable to suggest that components of the grape skin possess biological vasoactive qualities. Exactly which component(s) these are is uncertain, although there is a large body of data supporting the involvement of phenolic compounds from grape skins.

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References


A reply

We are thankful to Drs Wilde and Priori for their letter addressing very important issues directly related to the Brugada syndrome, but also indirectly to any type of inheritable disease.

Wilde and Priori question the validity of pharmacological testing for the Brugada syndrome. In disagreement with the preliminary results reported by Priori, we have observed a 100% sensitivity with a pharmacological challenge with a class I drug. In our genotyped families, no negative results have been found so far. Differences in electrocardiographic responses to class I drugs in Italian and Flemish families may relate to different mutations and to their electrophysiological effects.

Wilde and Priori correctly point out that a 50% prevalence is expected for a disease inherited as an autosomal dominant trait. We have analysed the mode of inheritance of Brugada syndrome in 35 Flemish families.

Using phenotype data, we found that the Brugada syndrome was familial in about 50% of cases and sporadic in the other half. In the familial cases a clearly recognisable autosomal dominant mode of inheritance was present in about half of the families, but was unclear in the other half. The expected prevalence of the disease was, thus, one-fourth the total number of familial cases, or 12.5% for the total population and not 50%.

Our observed prevalence of 15% fits very well with these predictions. We cannot accept, therefore, the recalculations by Drs Wilde and Priori of the differences in sudden death rates between affected and non-affected

References


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Brugada syndrome and sudden death

In their recent analysis of the causes of sudden death in 25 families with the Brugada syndrome, a strongly significant difference was observed in the cause of death between the 50 electrocardiographically identified affected family members and 284 non-affected members. In identifying affected patients, the authors assumed a 100% sensitivity and specificity of the class I drug challenge, as shown before in a genotyped population. However, these data have been challenged by Priori et al. who observed only 20% sensitivity. A critical appreciation of this discrepancy is warranted because of the potential impact of the diagnosis in asymptomatic individuals.

In light of the autosomal dominant inheritance of the syndrome, a surprisingly low prevalence of 15% (50/334) was observed in the Flemish families. Statistically a 50% prevalence is anticipated. This suggests a serious underestimation of the disease because the 50% mortality was observed in electrocardiographically affected carriers. It may, however, mean that clinically silent carriers are at no increased risk. Such a conclusion seems highly relevant in terms of choosing treatment modalities for genetically affected asymptomatic individuals.

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members. Our conclusion, that sudden death in families with inheritable causes for sudden death is not always related to the hereditary disease, can be sustained.

We all agree that genetics will provide a definitive diagnosis, but technology has not yet evolved to provide this test in a time frame that is acceptable to clinicians. Meanwhile we have to rely on clinical parameters to risk stratify those individuals affected by a lethal disease.

These parameters are neither sufficiently sensitive nor specific. Our only recommendation, based on the findings, was to be careful when interpreting a presumed familial sudden death because the wrong assessment of the lethality of a disease in a family could mislead the therapeutic approach in the remaining members of the family.

We are sure that Drs Wilde and Priori read the editorial accompanying our article[1]. We fully agree with Dr Farré on the many questions that remain open, not only as regards the Brugada syndrome, but for any hereditary disease causing cardiac arrhythmias.

Wilde and Priori discuss the existing difficulties of providing appropriate guidelines for diagnosis, assessment of prognosis and treatment of patients with inheritable diseases. These difficulties mainly arise from the unavailability of genetic data to make the appropriate genotype to phenotype correlation. Genetic data are usually not available because they are obtained mainly through funded research. Genetic analysis is costly and faces many ethical, moral and even political concerns. We would be happy to join forces with Wilde and Priori to convince the appropriate authorities of the need to provide the necessary funds in the shortest possible time. For many of us genetic testing has become as indispensable as the 12-lead electrocardiogram.

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References


Clinical implications of increased plasma angiotensin II concentrations despite ACE inhibitor therapy in patients with congestive heart failure: the issue of non-compliance with therapy
Roig et al.[1] measured plasma angiotensin II concentrations in 70 outpatients with congestive heart failure who were either receiving chronic enalapril or captopril therapy. They found plasma angiotensin II concentrations to be elevated in 35 (50%) of patients (median 33 pg . ml⁻¹ (range 17–84), normal range 5–15). Multi-variate regression analyses identified plasma renin activity (P<0.0004), norepinephrine (P=0.02) and interleukin-6 (P=0.003) as independent predictors of increased plasma angiotensin II. After follow-up (35 ± 29 months) those patients with elevated plasma angiotensin II concentrations at baseline had experienced more adverse events (death, cardiac transplantation or deterioration in heart failure), compared with those patients with normal plasma angiotensin II concentrations at baseline (41% vs 14%, P=0.01).

Clearly, elevated plasma angiotensin II concentrations are bad for you. Neurohormonal activation in heart failure contributes to disease progression[2], and is an adverse prognostic sign[3]. One plausible explanation for the ‘breakthrough’ of plasma angiotensin II concentrations, despite ACE inhibitor therapy, is the synthesis of angiotensin II by non-ACE pathways which are known to be present in human blood vessels[4,5]. Furthermore, the potential beneficial effects of combination therapy with an AT1 receptor antagonist in those patients with ‘breakthrough’ of plasma angiotensin II concentrations provide a plausible basis for the use of these drugs in heart failure[6].

I have a number of criticisms of this paper. Firstly, the authors do not report which method they used to measure plasma angiotensin II concentrations. It is extremely difficult to measure plasma angiotensin II accurately, as high concentrations of angiotensin I, as may occur with ACE inhibitor therapy, tend to cross-react with angiotensin II antiserum in the assay thereby generating ‘false positive’ results[7].

The authors also fail to consider the possible contribution of poor compliance with ACE inhibitor therapy, as an alternative explanation for their findings. The population in their study consisted of outpatients, and as such, neither pill-counts nor any biochemical measurement of compliance, were documented. Inappropriately elevated concentrations of either serum ACE or plasma AcSDKP (N-acetyl-lysyl- aspartyl-lysyl-proline, an endogenous peptide metabolised by ACE) may be useful indicators of poor compliance in patients who should be taking chronic ACE inhibitor therapy. Struthers et al. have recently demonstrated that biochemical measures of compliance are sensitive and specific tools for detecting non-adherence with ACE inhibitor therapy, with perhaps the exception of captopril[8].

‘Breakthrough’ of plasma angiotensin II concentrations can be a real clinical problem. There are, however, several plausible explanations for this phenomenon. Given that poly-pharmacy and non-compliance with therapy are increasing problems in the management of heart failure patients[9,10], biochemical screening for poor compliance with ACE inhibitor therapy may become a useful clinical tool.

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References
Measurement of angiotensin II (AII) was performed previous to ethanol extraction of plasma samples. The extracted plasma AII was determined by a sensitive and specific radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, Ca, U.S.A.). Although the existence of a false-positive result cannot be completely excluded, this possibility is unlikely for several reasons. The antibody used to measure AII is highly specific since it displays a cross-reactivity of angiotensin I (AI) lower than 0.1%. On the other hand, we actually measure AI concentration in all patients when PRA is determined. The difference between basal AI concentrations and those spontaneously generated after 3 h incubation at 37 °C is the standard method to assess this parameter, and patients under ACE inhibitor therapy did not show important augmentations of basal plasma AI levels.

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A reply
We agree that non-adherence with ACE inhibitor therapy cannot be totally ruled out in our study. However, all 70 studied patients are included in the heart failure outpatient clinic of our institution and have been followed-up by the same doctor since 1994. Unfortunately, although plasma AcSDKP may be a useful indicator of poor compliance, we did not, as a rule, measure plasma AcSDKP in our patients. The lack of ACE activity measurement was pointed out in the paper as a limitation of the study.