

Binge drinking causes endothelial dysfunction, which is not prevented by wine polyphenols: a small trial in healthy volunteers

M.L. Hijmering², D.W. de Lange^{1*}, A. Lorscheid², R.J. Kraaijenhagen³, A. van de Wiel²

¹Thrombosis and Haemostasis Laboratory, University Utrecht, Utrecht, the Netherlands,

²Department of Internal Medicine, Meander Medical Centre, Amersfoort, the Netherlands,

³Department of Clinical Chemistry, Meander Medical Centre, Amersfoort, the Netherlands,

*Corresponding author: tel.: +31 (0)30-250 30 37, e-mail: D.W.deLange@umcutrecht.nl

ABSTRACT

Background: Binge drinking (the consumption of large quantities (>5 units) of alcohol in a short period) is associated with increased cardiovascular mortality. Wine polyphenols are considered to be protective against cardiovascular diseases. We conducted an experimental study to evaluate the acute effects of alcohol consumption on flow-mediated vasodilation and general cardiovascular parameters, using beverages with high polyphenolic content (HPC) and low polyphenolic content (LPC).

Methods: Two groups of ten volunteers were asked to drink two different kinds of beverages. In 45 minutes, three units of red wine or an alcoholic beverage with a low polyphenolic count were consumed. Then 45 minutes were allowed for complete uptake of the alcohol or polyphenolic compounds. Next, all volunteers underwent blood pressure readings, ECG and flow-mediated vasodilation. Blood samples were taken at the same time for routine chemistry, inflammation parameters and lipids. Then the entire cycle was repeated once (in total six units of alcohol in 180 minutes).

Results: No differences were found between the two drinks. Alcohol itself dose-dependently increased forearm blood flow by vasodilation of both arterioles and distribution arteries. However, flow-mediated vasodilation (FMD) for the LPC group (n=10) decreased from 7.31 ± 4.78 (% \pm SD) to 2.82 ± 2.9 after three drinks and 1.21 ± 3.25 after six drinks. The FMD values for the HPC group (n=10) decreased from 8.61 ± 1.78 to 1.78 ± 3.71 and 1.19 ± 2.6 . There were no significant changes between the LPC and the HPC group at the three time points.

Conclusion: Although ethanol produces vasodilation at the level of the distribution artery as well as at an arteriolar

level, it causes a decrease in flow-mediated vasodilation. This endothelial dysfunction is not corrected by the polyphenols present in wine.

KEY WORDS

Alcohol, flow-mediated vasodilation, ethanol, polyphenols, cardiovascular disease

INTRODUCTION

The relationship between alcohol consumption and the incidence of atherosclerotic diseases has raised many debates. According to the results of large epidemiological studies, chronic moderate alcohol consumption, on average one unit a day, appears to have a protective effect on cardiovascular disease.¹ The mechanisms involved are not completely clear and various explanations have been given. In contrast to this cardioprotection, overconsumption of alcohol in a short period of time (binge drinking) results in increased cardiovascular mortality, especially sudden death, and acute coronary artery syndromes. This is of importance as the so-called moderate drinking pattern is not at all common. A study indicated that most light drinkers do not drink daily and most daily drinkers are not light drinkers.² Although the focus of most scientific articles has been on the cardioprotective effects of alcohol, the drinking pattern of our youths might actually put them at risk for cardiovascular events.

The cardioprotective effects of alcohol have been attributed to the increase in high-density lipoprotein cholesterol (HDL-c), decrease in plasma fibrinogen concentrations, or reduced platelet activity.¹ Additionally, cardioprotection may also be exerted by stimulation of endothelial nitric oxide synthase and decreased oxidative stress,³ which may lead to an increase in nitric oxide (NO) production. NO has a central role in counteracting most processes that eventually lead to atherosclerosis. Furthermore, ethanol consumption influences the fibrinolytic system as well as the composition of serum lipids.¹ Several authors have suggested that not ethanol per se, but other constituents of alcoholic beverages are responsible for the antiatherogenic action. Especially flavonoids, a group of phenols present in red wine, are attributed antiatherogenic abilities. They are capable of scavenging reactive oxygen species. Reactive oxygen species are highly reactive chemicals that, within the scope of atherosclerosis, produce cell damage and promote the vicious circle that results in atherosclerosis. Additionally, flavonoids stimulate the production of nitric oxide. Furthermore, red wine polyphenols can limit the effects of endothelin-1 (ET-1).⁴ ET-1 is one of the most powerful vasoconstrictors, produced locally by the endothelium. Levels of endothelin-1 are increased in heart failure, hypertension and other disease states that are associated with the development of atherosclerosis. Interestingly, alcohol is capable of stimulating ET-1 release by the endothelium directly.⁵

The acute effects of alcohol consumption have been investigated in previous studies. Results of these studies are conflicting because of the differences in study design and the population that is under investigation. In healthy, young volunteers the main vascular consequence of an acute dose of alcohol is vasodilatation.⁶⁻⁹ However, there is no consensus on its action on FMD. Hashimoto *et al.* observed a decrease in FMD after acute alcohol use, but FMD increased after consumption of de-alcoholised red wine.⁷ This suggests that the nonalcoholic constituents of red wine counteract the decrease in FMD caused by alcohol. However, others did not observe any change in endothelial function by red wine^{6,10} or even an increased FMD after the acute consumption of alcohol.¹¹ Unfortunately, most of the studies of alcohol effects on endothelial function could be affected by confounding factors. Arterial diameter and endothelial function measurements are extremely vulnerable to variables such as diseases, medication use, atherothrombotic risk factors, gender, age, menstrual cycle, postprandial period, and temperature.¹²

In short, moderate and prolonged alcohol and red wine consumption is associated with cardioprotection and possibly improved endothelial function in patients, but still little is known about the acute effects of a binge in healthy volunteers. We hypothesised that a binge might have opposite,

more deleterious effects that might explain the increased morbidity associated with this kind of drinking pattern.¹³⁻¹⁵ We therefore designed a binge drinking trial in volunteers without cardiovascular risks to assess the acute effects of ethanol on endothelial reactivity and cardiovascular parameters, using drinks with and without a high polyphenolic content.

MATERIALS AND METHODS

All studies were conducted in a single teaching hospital under standardised conditions, which included room temperature of 20 °C, no caffeine consumption in the week prior to the study, no eating or drinking for at least four hours before entering this study, no consumption of alcohol and no smoking one week prior to the study. To be eligible for inclusion, volunteers needed to be healthy in general terms, and were not on any medication that may have had an effect on the cardiovascular parameters measured. Other exclusion criteria included smoking within the last six months, body mass index >30 kg/m², cardiovascular diseases (assessed by clinical history taking, physical examination or ECG), diabetes mellitus, blood pressure >149/90 mmHg or treatment with antihypertensive agents, use of lipid-lowering medication or nonsteroidal anti-inflammatory drugs. None of the females who participated in this trial was using oral contraceptives, but we have no information on the phase of their menstrual cycle. Before agreeing to participate in this trial the volunteers consumed one alcoholic beverage a day on average. The local ethics committee approved the study protocol and all volunteers signed an informed consent form. This study was carried out in accordance with the Declaration of Helsinki (1998) of the World Medical Association. All studies were performed on a single day, starting at 6 pm. A typical study day started with a further explanation of the study protocol. Next, an 18-gauge cannula was inserted in a large cubital vein of the dominant arm for blood sampling. An ECG was recorded according to standard methods followed by automated noninvasive blood pressure measurements (SureSign by Phillips Medical) and flow-mediated vasodilation examination.

Drinks

The 20 volunteers were randomised to either the red wine group or the low-polyphenolic group. In total ten volunteers drank red wine and ten drank the low-polyphenolic Barcardi Breezer. The volunteers were asked to drink three glasses of an alcohol-containing beverage, either Barcardi Breezer (275 ml with 5.0 vol% of alcohol, adding up to 11 gram alcohol per drink) or red wine (Rioja, 110 ml with 13.0 vol% of alcohol, adding up to 11.4 gram of alcohol per glass). These drinks were chosen because red wine has a high polyphenolic count (HPC) and the Barcardi Breezer has a low polyphenolic

count (LPC) and is a popular binge drinking consumption in youths. These three drinks were consumed within a 45-minute period. After the third drink, 45 minutes were allowed for alcohol uptake into the circulation.¹⁶ After these 90 minutes, examination of flow-mediated vasodilation was performed and blood was collected for haematological and biochemical parameters. Then this cycle was repeated and after 180 minutes flow-mediated dilatation was examined and blood was collected for a second analysis. The polyphenols in the Rioja were measured by HPLC and the highest concentrations were catechin 11 mg/l, epicatechin 5 mg/l, quercetin 1 mg/l and gallic acid 45 mg/l.

Chemistry

Routine chemistry consisted of blood cell count, creatinine, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase (γ GT), alkaline phosphatase, carboxyl deficient transferrin (CDT) and lipids. CDT and γ GT levels were used to screen for chronic alcohol (ab)use, although the average alcohol consumption was one drink daily. Blood cell counts were performed on Sysmex SE-9000, Sysmex TOA, Kobe, Japan. Chemistry and ethanol levels were performed on an LX20 from BeckmanCoulter, Brea (LA), California, USA.

Flow-mediated vasodilation

The technique of flow-mediated vasodilation (FMD) is an elegant noninvasive technique, which tests the capability of a forearm artery to dilate in response to a flow stimulus. Inhibition of FMD is generally considered to reflect endothelium dysfunction. Numerous studies have shown that loss of vasodilation is associated with the extent of atherosclerosis in a patient. Moreover, the endothelial function measured in the forearm arteries correlates nicely with the endothelial function of the coronary artery. In our study, we used B-mode ultrasonography on an ATL HDI 5000 operating at 7.5 to 12.5 MHz with focus points on the 'near' and 'far' walls. All measurements were performed in the nondominant arm by the same investigator. These recordings were subsequently analysed off-line by an interpreter unaware of the alcohol level. This technique has been described extensively and found to be reproducible.¹⁷

ECG

All ECGs were recorded on a Siemens ambulant electrocardiography machine. All ECGs were manually interpreted, and the reader was unaware of the alcohol level of the individual.

Statistical analysis

All measurements took place at predefined time points (before, after three drinks and after the full dose). We used the actual serum alcohol level rather than the fixed time point in analysis. Both groups, high polyphenolic content

(HPC) and low polyphenolic content (LPC), were tested for normality and differences were detected by performing repeated-measures ANOVA. In case of a non-normal distribution a Wilcoxon signed-rank test or Mann-Whitney rank-sum test was used. A level of $p < 0.05$ was considered significant.

A regression analysis was performed on the effect of the delta (observed value – baseline value) FMD values in relation to the delta serum ethanol level (LPC) and delta alcohol levels in the red wine group (HPC) and curves were constructed.

RESULTS

In total 20 volunteers completed the study. Baseline characteristics of the study population are summarised in *table 1*. None of the baseline characteristics were significantly different between the two groups.

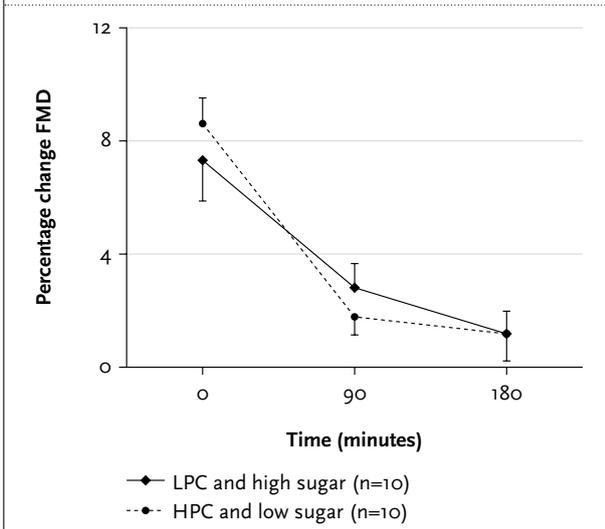
Endothelium and nonendothelium dependent changes in local haemodynamics

Table 1. Baseline characteristics. All values are means with standard deviation in brackets

	LPC	HPC	P value
Gender (male/female)	7/3	6/4	NS
Age (years)	34.7 (10.6)	36.4 (9.0)	NS
Height (cm)	179 (11.4)	180.1 (6.9)	NS
Bodyweight (kg)	77.5 (11.1)	79.8 (14.0)	NS
Mean arterial blood pressure (mmHg)	114.8 (12)	111.6 (13)	NS
Carboxyl deficient transferrin (%)	2.20 (0.49)	2.58 (1.18)	NS

Flow mediated vasodilation (FMD) for the LPC group (n=10) decreased from 7.31 ± 4.78 (% \pm SD) to 2.82 ± 2.9 after three drinks and 1.21 ± 3.25 after six drinks. The FMD values for the HPC group (n=10) decreased from 8.61 ± 1.78 to 1.78 ± 3.71 and 1.19 ± 2.6 . There were no significant changes between the LPC and the HPC group at the three time points. These changes in FMD have been visualised in *figure 1*. The flow through the brachial artery as measured by B-mode ultrasonography of the LPC group rose significantly from 54 ± 40 to 87 ± 41 and 143 ± 75 ml/min at the different times of measuring and increasing serum levels of ethanol (mean \pm SD, $p = 0.007$). The forearm blood flow of the HPC group rose nonsignificantly from 85 ± 55 to 110 ± 71 and finally 116 ± 56 ml/min (mean \pm SD, $p = 0.2$). These values are summarised in *table 2*. Although the increase in forearm flow was significant for both groups there was no significant change between the LPC and HPC group. Baseline diameter of the brachial artery diameter increased progressively but

Figure 1. Change in FMD as function of time. This shows the FMD (\pm SEM) at baseline ($t=0$ minutes), after the first three drinks ($t=90$ minutes) and after six drinks ($t=180$ minutes). The results are shown for the low polyphenol drink (LPC) and for the high polyphenol containing group (wine, HPC). No statistical difference exists between the two types of beverage at the three different time points ($p=0.48$ at $t=0$, $p=0.51$ at $t=90$ and $p=0.98$ at $t=180$ minutes). The decrease in FMD within each group and for the two groups combined (both) is highly significant ($p<0.001$).



not significantly from 4.1 ± 0.7 to 4.5 ± 0.6 and 4.5 ± 0.7 mm (mean \pm SD, $p=0.4$) in the LPC group and from 4.1 ± 0.7 to 4.4 ± 0.8 and 4.4 ± 0.6 mm (mean \pm SD, $p=0.23$) in the HPC group at the three time points.

The net stimulus on the endothelium, expressed as the maximum blood flow evoked by brief forearm occlusion, increased slightly but nonsignificantly (from 288 ± 114 to 350 ± 126 and finally 350 ± 126 ml/min in the HPC group, $p=0.26$ and from 243 ± 142 to 282 ± 142 and finally 282 ± 54 ml/min in the LPC group, $p=0.23$). To show the net effect of alcohol on FMD a regression plot was constructed for delta (begin – endpoint) FMD vs delta alcohol. A significant correlation was found ($r=0.46$, $p=0.04$) for both the HPC and LPC group (figure 2A).

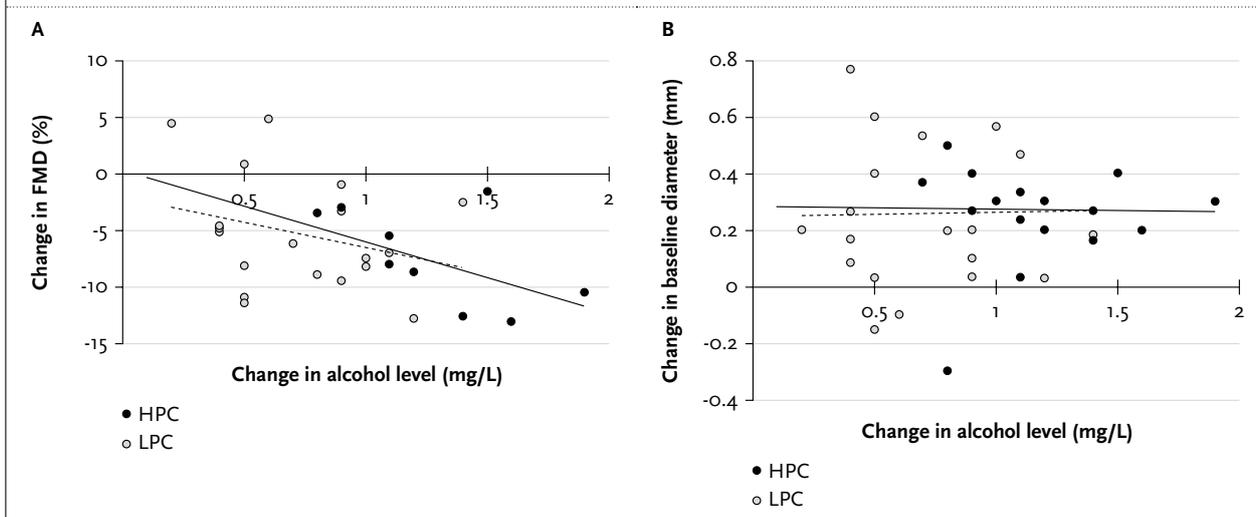
The formula for FMD depends on the baseline diameter, as the artery's capacity to dilate reciprocally diminishes with its diameter. The decrease in the observed FMD could therefore be caused by an increase in baseline diameter. A graph was constructed for delta baseline diameter vs the delta alcohol (figure 2B). The baseline diameter in both the HPC and LPC group increased somewhat but this did not seem to correlate with the change in alcohol level ($r=0.05$, $p=NS$). The observed decrease in FMD appears to be, at least partially, explained by an increase in baseline diameter.

Table 2. Changes in alcohol, routine haematology, chemistry, and markers of inflammation in plasma and FMD.

	LPC			HPC			P value
	t=0	t=90	t=180	t=0	t=90	t=180	
Alcohol concentration (‰)	0.0	0.5 (0.2)	0.96 (0.2)	0.0	0.58 (0.2)	1.25 (0.3)	NS
Haematology							
Haemoglobin (mmol/l)	8.5 (1.1)	8.4 (1.0)	8.4 (1.1)	8.4 (0.9)	8.5 (1.0)	8.4 (1.2)	NS
Haematocrit(l/l)	0.39 (0.04)	0.39 (0.04)	0.39 (0.05)	0.39(0.04)	0.39 (0.04)	0.39 (0.06)	NS
Chemistry							
Creatinine (μ mol/l)	79.4 (12.1)	78.6 (15.1)	76.0 (13.4)	75.9 (11.6)	72.6 (10.3)	68.2 (12.6)	NS
Glucose (mmol/l)	5.8 (0.9)	7.2 (1.7)	7.6 (2.0)	5.5 (0.8)	4.8 (0.5)	4.8 (0.3)	$p<0.004^{\dagger}$
ALAT (U/l)	25.5 (8.5)	24.8 (7.8)	22.5 (9.2)	21.5 (9.1)	22.8 (9.8)	22.2 (10.1)	NS
ASAT (U/l)	16.0 (4.3)	15.9 (2.8)	15.2 (3.4)	16.8 (4.8)	17.8 (8.5)	17.3 (6.3)	N
γ GT (U/l)	14.9 (5.3)	14.3 (5.0)	12.7 (4.7)	20.0 (17.0)	19.9 (17.5)	20.7 (18.4)	$p<0.05^*$
Lipids							
Cholesterol (mmol/l)	4.82 (0.8)	4.74 (0.8)	4.54 (0.8)	4.68 (1.1)	4.75 (1.2)	4.77 (1.0)	NS
Apolipoprotein A1 (g/l)	1.42 (0.29)	1.44 (0.24)	1.40 (0.21)	1.31(0.28)	1.06 (0.17)	1.09 (0.17)	$p<0.05^{**}$
Apolipoprotein B (g/l)	0.79 (0.14)	0.76 (0.17)	0.75 (0.14)	0.80(0.21)	0.83 (0.32)	0.87 (0.32)	NS
HDL cholesterol (mmol/l)	1.42 (0.38)	1.39 (0.36)	1.32 (0.33)	1.21(0.33)	1.22 (0.36)	1.25 (0.31)	NS
LDL cholesterol (mmol/l)	2.87 (0.53)	2.72 (0.54)	2.64 (0.57)	2.79(0.74)	2.80 (0.73)	2.84 (0.65)	NS
Triglycerides (mmol/l)	1.22 (0.66)	1.39 (0.66)	1.30 (0.64)	1.53(0.84)	1.61 (0.90)	1.49 (0.82)	NS
Miscellaneous							
C-reactive protein (mg/l)	5.9 (1.7)	6.0 (1.9)	5.2 (0.7)	6.4 (2.3)	7.1 (3.2)	6.2 (2.0)	NS
Mannose binding lectin (mg/l)	1.49 (1.17)	1.43 (1.12)	1.49 (1.31)	1.31(0.76)	1.10(0.79)	1.22 (0.90)	NS
Measurements							
FMD (% change)	7.3 (4.8)	2.8 (2.9)	1.2 (3.3)	8.6 (1.8)	1.8 (3.7)	1.2 (2.6)	NS
Baseline diameter (mm)	4.1 (0.7)	4.5 (0.6)	4.5 (0.7)	4.1 (0.7)	4.4 (0.8)	4.4 (0.6)	NS
Flow (ml/min)	54 (40)	87 (41)	143 (75)	85 (55)	110 (71)	116 (56)	$p<0.05^{\#}$
Heart rate (bpm)	71 (8)	73 (8)	77 (14)	61 (7)	59 (8)	63 (7)	NS
Mean arterial pressure (mmHg)	117 (10)	111 (9)	109 (12)	111 (12)	112 (17)	115 (11)	NS

Values are means with SD in brackets. NS = not significantly different; † = a significant increase in glucose levels was observed in the LPC groups after three drinks because of the high glucose contents of the drinks. * The γ GT levels in the HPC count were significantly higher than in the low polyphenolic group, this was due to one volunteer. ** For unknown reasons apolipoprotein A1 decreased significantly in the HPC group. $^{\#}$ Flow increased significantly in the LPC group after 6 drinks ($t=180$ minutes).

Figure 2. The change in FMD as function of change in alcohol level during the entire experiment ($t=90$ and $t=180$ minutes) is shown in figure 2A. This is a significant decrease as can be observed from the trend lines ($r=0.46$, $p=0.04$). The dark line represents the HPC group and the dotted line the LPC group. The difference of the baseline diameter in relation to the increase in alcohol level is shown in figure 2B. Though there is an increase in the average baseline diameter, this relation is not significant. Nor is there a significant correlation between alcohol concentration and increase in baseline diameter ($r=0.06$, $p=NS$).



Heart rate and conduction times during the experiment

Heart rate (HR) for the two groups combined ($n=20$) did not increase significantly from 66.6 ± 9.2 to 66.3 ± 10.6 and 70.7 ± 13 beats/min (mean \pm SD, $p=0.07$) and plotting the changes in HR vs the changes in ethanol levels did not show a relation ($r=0.05$, $p=NS$). Delta alcohol vs delta PQ time showed a trend to significance ($r=0.43$, $p=0.06$, results not shown in table 2).

Blood pressure during the experiment

Blood pressure of both groups combined remained virtually constant during the experiment, showing no significant change after the first three drinks (MAP 114.8 ± 12 vs 111.6 ± 13 vs 112 ± 12 mmHg (mean \pm SD; table 2).

Alcohol-induced changes in serum levels of risk factors for CVD

For unknown reasons apolipoprotein A1 levels dropped significantly after three glasses of red wine. No other significant changes were seen in any of the monitored lipid fractions (HDL, LDL, and total triglycerides), or in the inflammation parameters evaluated (CRP and mannose binding lectin) that are more associated with cardiovascular disease than normal CRP (table 2); we did not measure high sensitive CRP levels.

Glucose concentrations during the experiment

Glucose levels rose significantly from 5.8 to 7.6 mmol/l in the LPC group ($p<0.001$), whereas no significant change was observed in the HPC group (from 5.5 to 4.8 mmol/l). Table 2 summarises the values obtained.

DISCUSSION

Our experiment shows that binge drinking, even at socially accepted levels, produces profound changes in haemodynamics irrespective of polyphenolic content of the beverage. Binge drinking increased baseline forearm flow but heart rate and blood pressure remained stable. More importantly, rapid consumption of alcohol decreased flow-mediated vasodilation in our experiment. This contradicts previous reports of beneficial effects of moderate and prolonged alcohol consumption on FMD in patients with coronary artery disease¹⁸⁻²⁰ and improvement of FMD after consumption of red wine.⁶⁻⁹

Some differences in design and selection of subjects might have contributed to these differences. Of note, most trials with alcohol and FMD have been performed in patients with established coronary artery disease.¹⁸⁻²⁰ It is known that patients with coronary artery disease have endothelial dysfunction, which is related to cardiovascular outcome within five years of follow-up. We, on the other hand, used healthy volunteers, which might explain some differences in FMD measurements.¹⁷ More important is that most trials were performed with a longer follow-up. This allows the metabolic effects of alcohol or polyphenol-induced modulations in gene expression to take place.¹ However, binge drinking presumes cessation of alcohol consumption after the binge. Therefore, long-term beneficial effects of metabolism or gene expression will not take place after a binge. Furthermore, previous studies performed on healthy volunteers corroborate our results and showed that a four-week exposure to alcohol did not change FMD,²¹ but increased blood pressure.²²

Few studies have actually looked at FMD after acute ingestion of alcohol. We found that alcohol actually decreased FMD. This is in agreement with a previous study that observed a small decrease in FMD after consumption of Japanese vodka.⁷ In contrast to this previous study we did observe a decrease in FMD after consumption of red wine, while they described improvement. However, our volunteers drank more red wine (on average 3.15 mg alcohol/kg). It might be that the alcohol intake opposes the beneficial effects of the red wine polyphenols, while at a lower alcohol count such effects might still be discernable. This theory is corroborated by the fact that the FMD is improved when de-alcoholised wine is consumed, but is unaltered when red wine containing alcohol is consumed.⁶

We showed that increasing levels of alcohol decreased the FMD. However, this decrease cannot be explained by an increase in basal diameter alone. Firstly, a direct relation was observed between the change in FMD and the change in ethanol concentration, whereas no such relation was found for basal diameter. Secondly, the baseline flow was slightly increased, which should have resulted in a higher FMD. It is difficult to translate our results to other publications. For example, the net FMD values observed in our experiment were less than the average values of our historical controls that received sublingual nitroglycerin as an exogenous NO donor. However, the FMD values were somewhat higher than in a previous reported trial of alcohol consumption and FMD.²¹ Again, this might be partially explained by the selection of subjects and study methods. Plasma concentrations of polyphenols are known to peak at approximately 30 minutes after oral administration.¹⁶ In our experiment we could not show a higher FMD in the group that consumed a high polyphenolic drink, although we measured FMD at the moment when the plasma level of polyphenols should have been high. Despite variable absorption of red wine polyphenols from the gut,¹⁶ previous studies have shown a positive effect of wine consumption on FMD.⁶ However, in a cross-over study of 16 healthy volunteers high or low intake of alcohol lasting four weeks did not influence FMD.²¹

Our results question the potential of polyphenols in wine to counteract endothelial dysfunction. It appears that the decrease in FMD caused by this amount of alcohol is not compensated by polyphenols. Knowing that the absorption of polyphenols is poor, it might be that the peak concentrations after a binge are insufficient to compensate the decrease of FMD.¹⁶ However, in some trials acute consumption of red wine or de-alcoholised red wine showed improvement of the FMD.^{6-9,18,23}

The strength of this study is that the volunteers in our experiment consumed a large amount of alcohol and wine in a short period: a binge. This closely resembles the drinking patterns of the modern youth² and is possibly more related to cardiovascular events than a moderate

consumption of alcohol and red wine.²² Furthermore, the subjects were young, healthy adults and not patients with proven coronary artery disease, who might benefit more from cardioprotection. It appears that especially young males have drinking patterns, like binge drinking, that put them at risk for cardiovascular disease while not having any other cardiovascular risk factors.

Some comments have to be made on the methodology of this study. This study used a healthy, young volunteers in a non-cross-over design. Yet, the number of volunteers is comparable to previous studies on this subject.⁶⁻⁹ Additionally, we did not include a control group, consuming no alcohol but only water. We therefore have no control for the time element or the possible influence of consuming a drink. However, in our experience, the influence of time, taking an interval between FMD measurements of one hour, is negligible, while in our pilot study no effect of drinking water on FMD could be demonstrated. This is corroborated by another study on FMD that showed no influence of water consumption on FMD up to 120 minutes.²⁴

A second consideration is that the volunteers in the low LPC group had increased levels of glucose during the experiment. This is caused by the higher glucose content of the LPC drinks. The effects of a high glucose count on FMD are somewhat conflicting. Acute high glucose levels are known to influence FMD, though high carbohydrate diets have been shown not to influence FMD.²⁵ If anything, this increased glucose level should actually augment the difference in FMD with the HPC group, an observation we could not confirm in our experiment.

A third consideration is that although we tried to standardise the FMD test as much as possible, we can not exclude influence of some 'external' factors, such as sympathetic activation. Various reports in literature show that activation of the sympathetic nervous system might decrease FMD, although some claim that it has different effects on the baseline brachial artery diameter and that a blunted FMD is not a general response.²⁶

Our study shows that alcohol consumption produces vasodilation at both the arteriolar level, indicated by the rise in unstimulated forearm flow, and at the level of a distribution artery. As the mean arterial pressure and heart rate did not change significantly, this change in cardiac afterload is possibly compensated by an increase in stroke volume. The consumption of alcohol at these levels might therefore increase cardiac work, which together with the induction of endothelial dysfunction may play a role in the observed increase in cardiovascular mortality.^{14,27} Binge drinking refers to heavy drinking on a single drinking occasion or drinking heavily and continuously over a number of days or weeks, abstaining and then repeating the cycle. These modern drinking patterns in young healthy adults might just expose them to all the cardiovascular risks without any of its benefits.

REFERENCES

1. de Lange DW, van de Wiel A. Drink to prevent: review on the cardioprotective mechanisms of alcohol and red wine polyphenols. *Semin Vasc Med* 2004;4:173-86.
2. Knupfer G. Drinking for health: the daily light drinker fiction. *Br J Addict* 1987;82:547-55.
3. Soardo G, Donnini D, Varutti R, et al. Alcohol-induced endothelial changes are associated with oxidative stress and are rapidly reversed after withdrawal. *Alcohol Clin Exp Res* 2005;29:1889-98.
4. Corder R, Douthwaite JA, Lees DM, et al. Endothelin-1 synthesis reduced by red wine. *Nature* 2001;414:863-4.
5. Foitzik T, Hotz HG, Hot B, Kirchengast M, Buhr HJ. Endothelin-1 mediates the alcohol-induced reduction of pancreatic capillary blood flow. *J Gastrointest Surg* 1998;2:379-84.
6. Agewall S, Wright S, Doughty RN, Whalley GA, Duxbury M, Sharpe N. Does a glass of red wine improve endothelial function? *Eur Heart J* 2000;21:74-8.
7. Hashimoto M, Kim S, Eto M, et al. Effect of acute intake of red wine on flow-mediated vasodilatation of the brachial artery. *Am J Cardiol* 2001;88:1457-60, A9.
8. Tawakol A, Omland T, Creager MA. Direct effect of ethanol on human vascular function. *Am J Physiol Heart Circ Physiol* 2004;286: H2468-H2473.
9. Vlachopoulos C, Tsekoura D, Tsiamis E, Panagiotakos D, Stefanadis C. Effect of alcohol on endothelial function in healthy subjects. *Vasc Med* 2003;8:263-5.
10. Djousse L, Ellison RC, McLennan CE, et al. Acute effects of a high-fat meal with and without red wine on endothelial function in healthy subjects. *Am J Cardiol* 1999;84:660-4.
11. Bau PF, Bau CH, Naujorks AA, Rosito GA. Early and late effects of alcohol ingestion on blood pressure and endothelial function. *Alcohol* 2005;37:53-8.
12. Vapaatalo H, Mervaala E. Clinically important factors influencing endothelial function. *Med Sci Monit* 2001;7:1075-85.
13. Fuchs FD, Chambless LE, Whelton PK, Nieto FJ, Heiss G. Alcohol consumption and the incidence of hypertension: The Atherosclerosis Risk in Communities Study. *Hypertension* 2001;37:1242-50.
14. Kauhanen J, Kaplan GA, Goldberg DD, Cohen RD, Lakka TA, Salonen JT. Frequent hangovers and cardiovascular mortality in middle-aged men. *Epidemiology* 1997;8:310-4.
15. Kauhanen J, Kaplan GA, Goldberg DE, Salonen R, Salonen JT. Pattern of alcohol drinking and progression of atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999;19:3001-6.
16. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr* 2005;81:230S-242S.
17. Bots ML, Westerink J, Rabelink TJ, de Koning EJ. Assessment of flow-mediated vasodilatation (FMD) of the brachial artery: effects of technical aspects of the FMD measurement on the FMD response. *Eur Heart J* 2005;26:363-8.
18. Whelan AP, Sutherland WH, McCormick MP, et al. Effects of white and red wine on endothelial function in subjects with coronary artery disease. *Intern Med J.* 2004;34:224-8.
19. Teragawa H, Fukuda Y, Matsuda K, et al. Effect of alcohol consumption on endothelial function in men with coronary artery disease. *Atherosclerosis* 2002;165:145-52.
20. Stein JH, Keevil JG, Wiebe DA, Aeschlimann S, Folts JD. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. *Circulation* 1999;100:1050-5.
21. Zilkens RR, Rich L, Burke V, Beilin LJ, Watts GF, Puddey IB. Effects of alcohol intake on endothelial function in men: a randomized controlled trial. *J Hypertens* 2003;21:97-103.
22. Zilkens RR, Burke V, Hodgson JM, Barden A, Beilin LJ, Puddey IB. Red wine and beer elevate blood pressure in normotensive men. *Hypertension* 2005;45:874-9.
23. Karatzi K, Papamichael C, Aznaouridis K, et al. Constituents of red wine other than alcohol improve endothelial function in patients with coronary artery disease. *Coron Artery Dis* 2004;15:485-90.
24. Lekakis J, Rallidis LS, Andreadou I, et al. Kremastinos DT. Polyphenolic compounds from red grapes acutely improve endothelial function in patients with coronary heart disease. *Eur J Cardiovasc Prev Rehabil* 2005;12:596-600.
25. Keogh JB, Grieger JA, Noakes M, Clifton PM. Flow-mediated dilatation is impaired by a high-saturated fat diet but not by a high-carbohydrate diet. *Arterioscler Thromb Vasc Biol* 2005;25:1274-9.
26. Dyson KS, Shoemaker JK, Hughson RL. Effect of acute sympathetic nervous system activation on flow-mediated dilation of brachial artery. *Am J Physiol Heart Circ Physiol* 2006;290:H1446-H1453.
27. Pletcher MJ, Varosy P, Kiefe CI, Lewis CE, Sidney S, Hulley SB. Alcohol consumption, binge drinking, and early coronary calcification: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Epidemiol* 2005;161:423-33.