Red Wine Acutely Induces Favorable Effects on Wave Reflections and Central Pressures in Coronary Artery Disease Patients

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Background: To investigate red wine's acute effects on aortic pressures and arterial stiffness in patients with coronary artery disease (CAD).

Methods: Fifteen patients with CAD were recruited in a double-blind, cross-over study, which was comprised of 2 study days. Each volunteer consumed either 250 mL of regular or 250 mL of dealcoholized red wine. Wave reflections, expressed as augmentation index (AIx), as well as central and peripheral blood pressures (BP) were assessed at fast and 30, 60, and 90 min postprandially.

Results: Both regular and dealcoholized red wine caused a significant decrease in AIx by 10.5% ± 1.4% (P = .001) and 6.1% ± 1.4% (P = .011), respectively, whereas no significant change was induced in mean BP and timing of wave reflections expressing pulse wave velocity. Peripheral systolic BPs remained unaltered in both beverages, whereas a significant decrease in peripheral and central diastolic BPs was observed after the dealcoholized red wine consumption (P = .03 and P = .035, respectively). Central systolic BP was decreased after the consumption of regular (−7.4 ± 2.4 mm Hg, P = .05) and dealcoholized red wine (−5.4 ± 2.7 mm Hg, P = .019).

Conclusions: Both types of red wine provoked favorable acute effects on wave reflections and central systolic pressures, whereas no such effect was evident at the brachial artery. Therefore, these findings could be attributed mainly to red wine antioxidant substances, rendering it a possible means of at least acute attenuation of increased wave reflections, arterial stiffness, and central pressures in patients with coronary artery disease. Am J Hypertens 2005;18:1161–1167 © 2005 American Journal of Hypertension, Ltd.

Key Words: Red wine, arterial stiffness, coronary artery disease, central pressures, wave reflections.

There is considerable evidence that moderate alcohol consumption, especially in the form of red wine, has a pronounced cardioprotective effect. It seems that alcohol, as well as the antioxidant substances in red wine increase HDL cholesterol, decrease platelet aggregation, amplify fibrinolysis and vasodilation.[1]

Although there is accumulating evidence suggesting that red wine and its constituents improve endothelial performance, both acutely[2,3] and after a long-term use,[4] there is little knowledge regarding the possible effect of this beverage on large artery properties. At the moment a link between endothelial dysfunction, related to nitric oxide (NO) production, and arterial stiffness has been proposed.[5] Moreover, long-term alcohol consumption in men is associated with pulse wave velocity with a J-shaped curve, indicating that moderate daily consumption of alcohol (two to three drinks per day) is associated with lower pulse wave velocity compared with higher daily intake or with complete abstinence from alcohol.[6] On the contrary, alcohol decreases arterial stiffness in healthy individuals in the acute postprandial state.[7] These findings suggest that there might be a difference between the acute and the long-term effect of alcohol on arterial stiffness. In addition, the controversial findings regarding the acute and

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Table 1. Characteristics of study participants (n = 15)

Characteristics	
Age (y)	52.4 ± 9.7
BMI (kg/m^2)	28.3 ± 1.8
Hypertension	7 (46.7%)
Hyperlipidaemia	8 (53.3%)
Family history	5 (33.3%)
Myocardial infarction	12 (80%)
Unstable angina	13 (86.7%)

Age and BMI in mean (SD); other characteristics are number (percentage).

long-term effects of alcohol on central and peripheral blood pressures (BPs) have been reported.[8] Data concerning the impact of red wine's antioxidants on arterial stiffness and hemodynamics are lacking. Moreover the response of the aforementioned factors to red wine consumption (with and without alcohol) in patients with coronary artery disease (CAD) remains unexplored. Therefore, the purpose of the present study was to assess the acute postprandial effect of red wine (with or without alcohol) on wave reflections, arterial stiffness, and central BPs.

Methods

Study Population

Study population was selected among male patients with angiographically detected CAD, who attended the Department of Clinical Therapeutics, "Alexandra" University Hospital, Athens, Greece for routine check-up. Augmentation index (AIx) was considered as the principal variable examined in the present study and the sample size was initially estimated based on the expected change in AIx after regular or dealcoholized red wine consumption. Given the variability of repeated AIx measurements,[9] the minimal statistically significant change in AIx with intervention that can be detected should be greater than 5%. Thus, a sample size of 15 subjects was estimated as efficient (80% power) to demonstrate a change by 6% in AIx (α = 0.05 and β = 0.20; two-tailed test).

Fifteen (15) men were enrolled (mean age, 52.4 ± 9.7 years; body mass index [BMI] 28.3 ± 1.8 kg/m^2) (Table 1). The coronary angiography was performed within the past 6 months and no revascularization procedure was carried out the past 3 months. Presence of diabetes mellitus, obesity, any liver, kidney, or endocrine diseases, and administration of antioxidant vitamin supplementation were designated as exclusion criteria. All patients were receiving nitrates, β-blockers, antiplatelets. Nine of them (60%) were taking angiotensin-converting enzyme inhibitors and 2 (13.3%), calcium channel blockers. Furthermore, all participants were ex-smokers and their alcohol use was in accordance with the recommendations (20 to 30 g alcohol/d). All patients gave their informed consent before entering the study; the protocol and the process for obtaining informed consent were approved by the local Scientific Committee.

Experimental Protocol

Subjects were randomly allocated to drink either a glass of 250 mL of red wine or 250 mL of dealcoholized red wine. The study was comprised of 2 study days in a randomized, double-blinded, cross-over design. On each study day, patients were instructed to attend the Vascular Laboratory of Alexandra Hospital, after a 12-h fast and absence from smoking, and all vasoactive medications were withheld for 24 h before each study day. All patients were studied in the morning hours and after a 15-min rest period in a temperature controlled (22° to 25°C), quiet room. Blood pressure and arterial stiffness measurements were performed at fast and 30, 60, and 90 min after wine consumption. All subjects completed the study without any dissatisfaction or alcohol-related problems.

Wine Preparation

Dealcoholized red wine (<1% ethanol) was prepared with lyophilization of a regular red wine (12% ethanol, Grand Reserve 1996, Boutaris, Greece) at −50°C and at 1 mb pressure for 6 h, using Cryodos 45 (Telstar, Spain). The concentrated red wine (±50%) was then diluted with tap water until it reached the initial volume. The Folin–Ciocalteau procedure[10] was used to assess total antioxidants concentration in wines used in the protocol. A UVIKON, spectrophotometer 931, Kontron Instruments (Milan, Italy) was used and results were expressed as micrograms of caffeic acid per 100 mL. A Hewlett-Packard model 1050 UV-DAD/FLD with Autosampler (Palo Alto, CA) and a Hewlett-Packard model 6890 with MS detector and Autosampler was used for high pressure liquid chromatography (HPLC)[11] and gas chromatography (GC/MSD), respectively, for the quality determination of antioxidants in red wine with and without alcohol. Finally, duo–trio tests* and a hedonic scale were used to test whether dealcoholized red wine could be well accepted by the subjects who would consume it, and whether it could be recognized compared with regular red wine.

Arterial Stiffness, Wave Reflections, and Central Pressures

Arterial stiffness and wave reflections were evaluated noninvasively by using radial artery applanation tonometry and pulse wave analysis.[12,13] The main principle of the method is based on: 1) the derivation of the central aortic

*Duo-trio test is a well-established method in order to assess if one can distinguish two different types of wine. Its participant is given three glasses of red wine, two of which contain the same wine. The participant then tastes all three wines in a random order and indicates which two are the same.

pressure waveform from the peripheral pressure waveform, by using generalized transfer functions and 2) the determination of central aortic pressure augmentation (AP) due to the reflected pressure waves. Tonometry of the radial artery was obtained by using a high-fidelity strain gauge transducer placed on the tip of a pencil-type tonometer (Millar Instruments, Inc, Houston, TX). Analysis of the derived aortic pressure waveforms was realized by the Sphygmocor System (ATCOR Medical, Sydney, Australia). Calibration of peripheral pressure recordings was obtained by measuring brachial systolic and diastolic BPs with a mercury sphygmanometer. Three measurements were performed in each case and the mean value of systolic and diastolic BP were calculated.

Augmentation index was used to characterize wave reflections and calculated as the ratio of the AP to the aortic pulse pressure (PP). The magnitude and timing of the arterial wave reflection are dependent on the elastic properties of the arterial walls.[14] Applanation tonometry and pulse wave analysis have been described in detail and validated previously.[15] The stiffer the arterial system, the greater the augmentation of the central aortic pressure (increased AIx) is due to the earlier return of the reflected waves at systole.

Because AIx is influenced by heart rate,[16] which is likely different in each patient and might be altered after red wine consumption, an index normalized for heart rate of 75 beats/min (AI 75) was used in accordance with Wilkinson et al.[16]

Pulse wave velocity, which characterizes arterial stiffness, was assessed indirectly by the arrival time (Δt, msec) of reflected waves at the aorta. The Δt represents the time needed for pressure waves to travel from the central to the peripheral arterial sites and return back to the aorta due to wave reflections. This time is easily calculated by detecting the inflection point (due to wave reflections) at the systolic part of aortic pressure waveform. Time derivatives are used for the determination of the inflection point by the Sphygmocor software. Timing of wave reflections is often used as an indirect estimator of pulse wave velocity, whereas it has been proposed as a more direct estimator of arterial stiffness than Aix.[16]

The Δt is dependent on body height and thus it cannot be strictly compared across individual subjects. As a result a between-subjects analysis of Δt should always control for height differences. In the present study, adjustment for height was not necessary, as no comparisons were made between different groups or subjects. The analysis was based on repeated measurements on the same subject to assess the effect of red wine on Δt. In such a design, the observed Δt changes are attributed to factors other than height.

Mean arterial BP was calculated by integration of the continuous radial pressure waveforms instead of the "1/3" formula:

$$MAP = \frac{\sum_{i=to}^{td} P_i}{n}$$

where *to* the time at the onset of systole, *td* the time at the end of diastole pressure, and *n* the total pressure values recorded by tonometry.

Statistics

All continuous variables were assessed for homogeneity of variance and normal distribution. The following analyses were performed aiming to assess 1) the total (overall) effects during the 90-min period and 2) maximal effects induced by the two types of red wines. Variables measured at baseline, 30, 60, and 90 min after drinking of each type of wine were evaluated by analysis of variance for repeated measures and Bonferroni corrected Student *t* test for multiple comparisons. A further ANOVA design with the two beverages for four time periods (fast, 30, 60, and 90 min after consumption) was applied to assess the comparative effects of the two beverages on the measured variables. It should be highlighted that in a repeated measurement design the curve joining the means (and ANOVA) may not be a good descriptor of a typical curve (response) for each individual in a repeated measurement study. As previously described, effects evaluated by ANOVA may be underestimated and thus separated analysis per individual may reveal more information.[17] Maximal change of every variable, induced after each beverage consumption, was estimated per individual as the maximal or minimal value observed minus the baseline value. Comparisons of maximal response of hemodynamic parameters were made by using the nonparametric Wilcoxon test. Data are expressed as mean $\pm$ standard deviation (SD) unless otherwise stated; a P value $< .05$ was considered statistically significant.

Results

Analysis of both regular and dealcoholized red wine showed that the two beverages had similar quality and concentration of antioxidant substances (658 μg/100 mL of caffeic acid for regular red wine *v* 650 μg/100 mL of caffeic acid of dealcoholized red wine) and that in general the only differentiation between them was their alcohol content (12% and <1% of ethanol, respectively). In addition, results from the duo–trio tests and the hedonic scale analysis showed that the subjects could n°t distinguish the two wines, as they could n°t correctly recognize the presence or absence of alcohol.

Acute Red Wine Effects on Peripheral and Aortic Hemodynamics

Systolic BP Peripheral systolic BP was not affected by the type of wine (Fig. 1A, Table 2). In contrast, central systolic BP was significantly reduced by both regular and

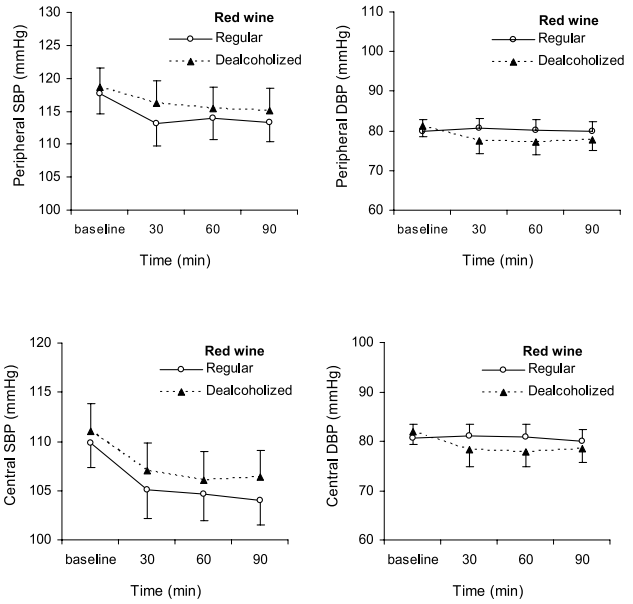

FIG. 1 Acute effect of regular and dealcoholized red wine on (**A**) peripheral and (**B**) central systolic (SBP) and diastolic blood pressure (DBP). (**A**) Peripheral pressures. An overall statistically significant decrease was observed in peripheral DBP after dealcoholized red wine consumption (ANOVA: $P = .03$, F = 3.99). (**B**) Central pressures. Overall effect of regular and dealcoholized red wine on central SBP (ANOVA: $P = .019$, F = 3.67 and $P = .05$, F = 3.47, respectively). An overall statistically significant decrease was observed in central DBP after dealcoholized red wine consumption (ANOVA: $P = .035$, F = 3.97). Bars represent standard error of mean values.

dealcoholized wines as compared with the baseline values (Fig. 1B). Maximal change of central systolic BP differed significantly between the two types of wine (Table 2).

Diastolic BP Regular wine had no significant effect on either central or peripheral diastolic BP, as shown in Fig. 1. However, dealcoholized red wine induced a significant reduction in both peripheral and central diastolic BPs. Maximal response of diastolic BP tended to be higher after consumption of dealcoholized compared to regular wine, although it did not reach statistically significant levels (Table 2).

Pulse Pressure Peripheral PP was not altered significantly after either dealcoholized or regular red wine consumption. On the other hand, regular red wine led to a reduction in central PP. The maximal change of peripheral and central PP per individual was significantly greater when regular wine was consumed compared to dealcoholized wine (Table 2) (Fig. 2).

Mean BP Neither regular nor dealcoholized red wine affected significantly mean BP during the 90-min period after consumption.

Acute Red Wine Effects on Wave Reflections and Arterial Stiffness

Regular red wine consumption resulted in a maximal decrease in AIx (heart rate corrected, AI 75) up to 7%, which remained significant 30, 60, and 90 min after drinking (Fig. 3). Dealcoholized red wine also induced a significant reduction in AI 75 by almost 5%, 30 and 60 min after drinking and returned to baseline values at 90 min (Fig. 3). The sample's mean AIx maximal change (per individual) was significantly greater after regular compared to dealcoholized red wine only when corrected for heart rate changes (Table 2). A significant increase in heart rate was observed after consumption of both types of wine by 2.5 – 5 beats/min, necessitating the correction of AIx and the use of AI 75 instead. The arrival time of reflected waves at the central aorta (Δt) remained statistically unaffected by the consumption of both beverages, implying no change in pulse wave velocity.

Discussion

In the present study, the effect of acute consumption of either regular or dealcoholized red wine on arterial hemodynamics was investigated for the first time in patients with CAD. A significant decrease in wave reflections and arterial stiffness as well as a reduction in central systolic BP was detected, after administration of both beverages. On the other hand, no effect was observed on peripheral systolic BP. These findings offer additional information regarding the acute effects of red wine on hemodynamics and stiffness, which to our knowledge are limited only to healthy subjects.[7] Findings arising from short-term consumption of alcohol, especially red wine, in patients with CAD are particularly valuable, because in most cases these patients are advised to consume an average daily amount.

Wave Reflections and Arterial Stiffness

Augmentation index diminished for 60 min after the consumption of both beverages. However, red wine containing alcohol, extended the AIx reduction up to 90 min postprandially. These findings are in accordance with previous results of Mahmud and Feely[7] in eight healthy normotensive subjects. On the other hand, our findings also indicate a significant decrease in AIx with dealcoholized red wine for 60 min postprandially, which implies that the constituents (mainly antioxidants) of red wine

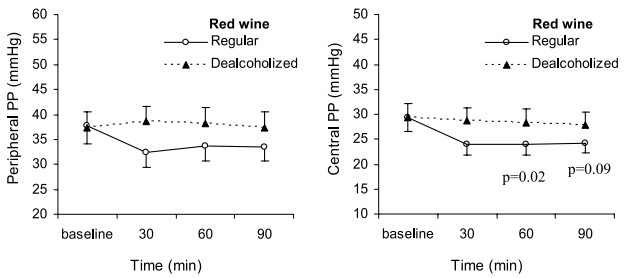

FIG. 2 Acute effect of regular and dealcoholized red wine on peripheral and central pulse pressure (PP). An overall statistically significant decrease was observed only in central pulse pressure after regular red wine consumption (ANOVA: $P = .006$, F = 6.16). Bars represent standard error of mean values.

Table 2. Baseline and maximal hemodynamic changes after consumption of regular and dealcoholized red wine (irrespective of time)

Variable	Regular wine	Dealcoholized wine	*P*
AIx (%)			
Baseline	26.5 ± 2.6	27.6 ± 2.3	.404
Maximal change	−11.8 ± 5.6	−8.3 ± 4.4	.066
AI 75 (%)			
Baseline	22.8 ± 1.8	23.0 ± 1.8	.866
Maximal change	−10.5 ± 1.4	−6.1 ± 1.4	.036
Mean blood pressure (mm Hg)			
Baseline	92.7 ± 2.3	94.0 ± 2.3	.508
Maximal change	−2.7 ± 2.3	−3.8 ± 2.1	.630
Peripheral SBP (mm Hg)			
Baseline	117.7 ± 3.2	118.6 ± 3.0	.716
Maximal change	−6.7 ± 2.7	−2.7 ± 2.4	.412
Peripheral DBP (mm Hg)			
Baseline	80.0 ± 2.8	81.3 ± 2.6	.547
Maximal change	−1.4 ± 1.6	−3.9 ± 2.2	.339
Peripheral PP (mm Hg)			
Baseline	37.8 ± 3.7	37.3 ± 3.3	.789
Maximal change	−6.9 ± 2.5	0.2 ± 1.8	.012
Central SBP (mm Hg)			
Baseline	109.8 ± 2.4	111.0 ± 2.7	.573
Maximal change	−7.4 ± 2.4	−5.4 ± 2.7	.589
Central DBP (mm Hg)			
Baseline	80.7 ± 2.8	81.9 ± 2.6	.557
Maximal change	−1.3 ± 1.5	−4.8 ± 1.9	.157
Central PP (mm Hg)			
Baseline	29.3 ± 2.9	29.3 ± 2.7	1.000
Maximal change	−7.1 ± 1.9	−2.3 ± 1.6	.023
Heart rate (beats/min)			
Baseline	67.1 ± 3.4	65.5 ± 3.0	.274
Maximal change	3.1 ± 1.5	4.1 ± 0.9	.102

other than alcohol might have an independent additional effect on AIx. This hypothesis is supported by another study, which found that another strong antioxidant, vitamin C, reduces arterial stiffness as measured by AIx, 6 h after its administration, indicating a possible favorable acute effect of antioxidants on arterial stiffness.[18]

These effects become even more prominent when taking into account that wave reflections assessed by the AIx are associated with an increased risk of CAD.[19] The AIx has been proposed as an independent risk marker for premature CAD.[20] The direct interaction between wave reflections and left ventricular function should also be stressed.[21]

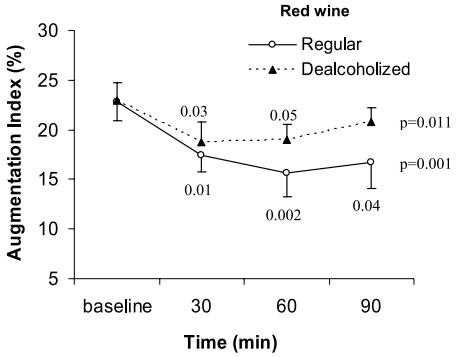

FIG. 3 Acute effect of regular and dealcoholized red wine on augmentation index (normalized for 75 beats/min). Overall effects of regular (ANOVA: $P = .001$, $F = 6.17$) and dealcoholized red wine (ANOVA: $P = .011$, $F = 4.2$) on augmentation index. Bars represent standard error of mean values.

Another interesting observation is the fact that there was no significant alteration in peripheral systolic BP by either type of wine. This finding implies that the observed changes in AIx by both wines are independent from their possible effects on BP. It is suggested that the reduction in AIx could be attributed to improvement of arterial stiffness, or vasodilatation, or both. In vitro studies have supported that alcohol and red wine's antioxidants may enhance NO production,[22] inhibit endothelin-1 synthesis[23] inducing vasodilation, which explains in part our finding. In addition, there are in vivo studies showing that there is a significant vasodilation and increased production of NO after regular or dealcoholized red wine consumption.[1,2,24,25] Furthermore, NO as well as endothelin-1 have been directly related not only to vasodilation but also to wave reflections, pulse wave velocity, and arterial stiffness,[26] rendering NO and endothelin-1 synthesis as major mechanisms involved in AIx changes as reported in this study.

Nevertheless, more research is needed to obtain elements capable to clarify the exact mechanisms underlying the present observations, such as direct measurement of total antioxidant capacity or isoprostanes in the postprandial state. Furthermore, because data regarding an acute effect of red wine on ventricular ejection are lacking, we cannot exclude a possible contribution of such an effect on central hemodynamics.

Central and Peripheral BPs

Although there was no effect of the two wines on peripheral BP, a significant effect on central BP was evident. Both types of wine markedly diminished central systolic BP. The fact that both beverages had similar effect on central systolic BP indicate that this effect could be attributed to the antioxidants of red wine regardless alcohol content. Moreover, central but not brachial PP was significantly reduced by regular red wine consumption, whereas no effect was observed by the dealcoholized red wine. The fact that central systolic BP was decreased in both cases, whereas the diastolic BP was reduced only after the consumption of dealcoholized red wine possibly explains the reduction in central PP by regular red wine. The vasoactive properties of alcohol should not be overlooked.

Discrepancies between central and peripheral BP response to vasoactive substances have also been documented in various reports.[27,28] This makes us skeptical about a possible underestimation of red wine's impact on BPs, when measuring only peripheral and not central BP, as it seems that central pressures are more sensitive and in some cases offer more information than peripheral BP. The fact that the secretion of NO by endothelial cells is diminished in a CAD population[29] may partly explain why in our study no effect was detected in peripheral pressures and only to central ones, whereas Mahmud and Feely[7] also noticed a reduction in peripheral BP in a rather small (n = 8) number of healthy individuals. The induced greater reduction of central compared to peripheral pressures by consumption of red wine should be highlighted especially in patients with CAD, as it has been shown that central (carotid) pressure is a better predictor than brachial pressure of the severity of coronary artery disease.[30]

In conclusion, arterial stiffness, wave reflections, and central BP of patients with CAD seem to be improved in the postprandial phase by the consumption of red wine. These effects are possibly related not only to alcohol but also to the red wine's antioxidants. Red wine pressor effects were more pronounce at the aorta than in the brachial artery, necessitating simultaneous estimation of central pressures. Arterial stiffness and endothelial function could possibly underlie the results of the present study and merits more extensive investigation by a more direct approach. Whether long-term use of red wine with or without alcohol leads to an improvement in arterial stiffness, wave reflections, and central pressure, and also to a decrease in cardiovascular risk in patients with CAD, remain unexplored.

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