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Original Paper

A Daily Glass of Red Wine and Lifestyle Changes Do Not Affect Arterial Blood Pressure and Heart Rate in Patients with Carotid Arteriosclerosis after 4 and 20 Weeks

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Key Words
Alcohol · Carotid arteries · Diet · Blood pressure · Nutrition

Abstract
Background: Regular consumption of small amounts of red wine improves blood lipids. However, there is concern whether this beneficial effect might be counterbalanced by an increase in blood pressure (BP) and heart rate (HR), which are risk factors for cerebro-cardiovascular disease. In particular, we studied whether regular consumption of red wine with and without lifestyle changes (LC; healthy diet and physical activity advice) results in an increase in BP and HR. ***Methods:*** A prospective, unblinded randomized trial was performed in 108 patients (67% men) with carotid atherosclerosis documented by ultrasound, a mean BP of 122/79 mm Hg and a mean HR of 71 bpm at inclusion in the study. Sixty-eight percent were known and treated hypertensives. The mean 24-hour BP at baseline was 122/79 mm Hg. Half of the study participants, the control group, was seen by a nurse at baseline, after 4 and after 20 weeks, and was instructed not to change their eating and physical activity habits. In the other half, a dietician performed five sessions of 30 min each (at baseline, after 1 week and after 2, 3 and 4 weeks) giving advice on healthy eating based on a Mediterranean diet and physical exercise. The recommendations given were the following: 5 portions of fruit/vegetables per day, a diet low in absolute fat, a preference of vegetable oil (olive or rapeseed oil), whole-grain products, poultry, low-fat dairy products, 1 fat and 1 lean fish meal per week, reduced consumption of red meat, and avoidance of pork, ready-made meals, sugar and excessive salt intake. In addition, regular consumption of 1 bar of dark chocolate (25 g, >70% of cacao), 1–2 tomatoes, and

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3–5 walnuts as well as at least 30 min of moderate daily physical activity were recommended. Within these two groups, half of the patients were randomized either to avoid alcohol completely or to drink 100 ml (women) or 200 ml of red wine (men) daily. ***Results:*** Neither LC nor red wine had an effect on the mean systolic and diastolic 24-hour BP and HR after 4 and 20 weeks, as analyzed by general linear modeling. No difference was found for diurnal and nocturnal values. ***Conclusions:*** The possible beneficial effect of regular consumption of small amounts of red wine is not counterbalanced in the long term by an increase in the mean BP or HR in mainly normotensive and well-treated hypertensive patients with carotid atherosclerosis, neither in the patients given healthy lifestyle advice nor in those with a standard lifestyle. Yet, we remain cautious about actively advice patients to drink alcohol regularly given the well-known risks.

Introduction

Lifestyle changes (LC) including physical exercise and a Mediterranean diet improve the lipid profile. Physical exercise mainly increases HDL and reduces triglycerides; LDL is hardly affected [1, 2]. In their recent meta-analysis, Kastorini et al. [3] found an increase in HDL and a decrease in triglycerides when comparing a Mediterranean diet with a conventional diet. Some of the studies included red wine and others did not. Three food items in particular have been shown to improve the lipid profile: dark chocolate, tomatoes and walnuts, the latter two being frequently part of a Mediterranean diet [4–9]. Mediterranean diets [3, 10–12] as well as physical activity are known to lower blood pressure (BP) [10, 12–14]. Alcohol consumption and especially binge drinking are risk factors for high BP and cerebro-cardiovascular disease [15, 16]. Light to moderate alcohol consumption, and possibly in particular red wine consumption, is associated with a smaller risk for cerebro- and cardiovascular disease and an improved lipid profile [16–21]. Little is known on the effect of regular consumption of small quantities of alcohol on BP and heart rate (HR).

In this prospective, unblinded, randomized controlled trial, we assessed the effect of a small amount of red wine and LC, including the consumption of dark chocolate, tomatoes and walnuts associated with physical activity, on BP and HR in patients with arteriosclerosis documented by carotid ultrasound. In particular, we studied whether consumption of red wine on top of LC results in an increase in BP, thus counterbalancing the beneficial effect on blood lipids. The present work is part of the ALVINA project (an acronym of 'alimentation, vin, et activité physique' meaning 'nutrition, wine, and physical activity' in French), in which also other parameters were studied. The study outline, patients' baseline characteristics, results on lipids and the efficacy of lifestyle counseling are reported or submitted for publication elsewhere [22].

Methods

The study complies with the Declaration of Helsinki and was performed in Luxemburg after protocol approval by the National Research Ethics Committee (200801/06) and notification to the National Commission for Data Protection. The trial was registered at http://www.clinicaltrials.gov (NCT01146132). The first patient was included on June 4, 2009, and the last follow-up visit took place on October 10, 2011.

Hundred and twenty-two patients were followed up to 20 weeks. The enrolled participants were outpatients of the Department of Neurology and had undergone carotid and intra-

cranial bitemporal color-coded duplex sonography carried out with the Antares system (Siemens Healthcare, Erlangen, Germany). Inclusion criteria were age >30 years and the presence of plaques or stenosis without hemodynamic compromise (i.e. <70%) in at least one common carotid artery, the carotid bifurcation or the internal carotid artery. Exclusion criteria were a history of ocular or cerebral ischemia within the last 3 months, atrial fibrillation, a repeatedly measured systolic BP (SBP) >160 mm Hg or the incapacity to give informed consent. The experimental design of the study was a 2 × 2 factorial design. The patients were allocated to groups of different lifestyles in result of a randomization stratified for gender. Lots were drawn to generate the random allocation sequence, and block size was 4. The intervention allocation was concealed in a nontransparent envelope. The random allocation sequence was generated by an independent staff member; patients were enrolled by the principal investigator and were assigned to interventions by the study nurse. A first group received no lifestyle counseling and the second one received lifestyle counseling at baseline and after 1, 2, 3 and 4 weeks. Within each lifestyle group, the patients were either randomly advised to drink a glass of red wine a day (0.2 liter for males and 0.1 liter for females) or they were advised to avoid alcohol completely for the time of the study.

In the LC group, a dietician performed five sessions of 30 min each (at baseline, after 1 week and after 2, 3 and 4 weeks) giving advice on healthy eating based on a Mediterranean diet and physical exercise. In particular, 5 portions of fruit/vegetables per day, a diet low in absolute fat, a preference of vegetable oil (olive or rapeseed oil), whole-grain products, poultry, low-fat dairy products, 1 fat and 1 lean fish meal per week, reduced consumption of red meat and avoidance of pork, ready-made meals, sugar and excessive salt intake were recommended [23, 24]. A water intake of 1.5–2 liters a day was recommended as well. In addition, regular consumption of 1 bar of dark chocolate (25 g, >70% of cacao), 1–2 tomatoes, 3–5 walnuts as well as at least 30 min of moderate daily physical activity was recommended [6, 9, 25, 26]. The control group (no LC) was seen at baseline, after 4 and after 20 weeks by a nurse who instructed the patients not to change their eating and physical activity habits. The patients allocated to the wine group (within the LC and the no LC groups) underwent three short sessions of counseling by the nurse concerning the intake of red wine of their choice (200 ml for males and 100 ml for females) [20, 27, 28].

For the 24-hour BP and HR monitoring, we used the Cardioline Walk200b system (CARDIOLINE S.p.A., Cavareno, Italy). Measurements were carried out every 20 min during daytime (7:00 a.m.–09:59 p.m.) and every 30 min during nighttime using the same upper arm in each individual for follow-up measurements.

The predefined primary endpoint of the study was a change in the mean 24-hour SBP assessed at baseline and at 20 weeks. Secondary endpoints were changes in the mean 24-hour DBP, the mean 24-hour HR, the mean diurnal and nocturnal SBP, the mean diurnal and nocturnal DBP and the mean diurnal and nocturnal HR assessed at baseline and at 20 weeks as well as at baseline and at 4 weeks. As there are gender differences in alcohol distribution and metabolism, general linear model analyses were also stratified by gender.

The intent-to-treat (ITT) and per-protocol (PP) populations were defined in order to show the effect of the intervention given the environment of the patients for the former, and to show the true effect of the intervention of all other parameters being controlled. The ITT population included only patients who had attended the first and at least the 4-week visit. The PP included the ITT patients and excluded those who admitted not to have followed the instructions or who did not present themselves at the 20-week visit. The ITT population was the primary population. The groups (defined by LC and red wine intake) were compared at their baseline values. For continuous variables, normality was verified using the Shapiro-Wilk test. Where the values were normally distributed, a two-sample t test was used. Otherwise, the Wilcoxon-Mann-Whitney test was applied. Dichotomous data was compared

using Pearson's χ^2 test. In case the expected cell frequencies were lower than 5, Fisher's exact test was applied. A general linear model with Tukey-Kramer adjustment for multiple comparisons was used to assess the primary endpoints. The absolute change value represented the dependent value. In case the normality assumption of the model residuals was violated, ANOVA on ranks was used. A p value below 0.05 was considered significant. All tests were two-tailed, and all analyses were performed by using the SAS System v9.2 (SAS Institute, Cary, N.C., USA).

Results

The ITT population included 108 subjects. Out of the 122 selected patients, 14 were closed out because they dropped out of the study before the 4- or 20-week visit. The PP population excluded 3 patients of the wine group who never drank wine during the study, 3 patients who drank considerable amounts of alcohol in the abstinent group, and 2 patients who did not attend the 20-week visit but had attended the 4-week visit. Therefore, the PP population included 100 patients.

The groups were well balanced (table 1). The mean daily alcohol intake at baseline was 14.6 g with a maximum of 57 g. No difference was found between the groups. There was homogeneity between the groups in all baseline parameters. No serious adverse events related to the study were recorded. Table 2 gives the distribution of the baseline BP values in relation to the classification of the European Society of Hypertension [29, 30]. Most subjects were normotensives (or treated hypertensives).

Table 3 gives the results for the primary endpoint and the secondary endpoints in the ITT population. There was no effect of the interventions on the 24-hour, diurnal and nocturnal SBP, DBP and the mean HR difference between the baseline and 4- and 20-week values, as analyzed by general linear modeling. In the PP analysis, however, despite the fact that the global explanation was not significant with p = 0.2142, there was a significant effect of wine on the nocturnal HR (p = 0.0178, rank model) after 4 weeks. This effect was only significant in the LC group, indicating a higher nocturnal HR in the wine drinkers compared to the no wine drinkers with a mean difference of 4.2 bpm.

Discussion

Our study failed to find evidence of an effect of regular, small amounts of red wine on the mean 24-hour BP and HR in patients with carotid arteriosclerosis, neither after 4 weeks nor after 20 weeks. Therefore, the beneficial effect a daily glass of red wine on blood lipids is not counterbalanced by a raise in BP or HR [16–21]. We did not find any effect of LC including Mediterranean diet and physical exercise on BP and HR. Only the PP analysis in the LC group showed a higher nocturnal HR (mean difference 4.2 bpm) in the wine drinkers compared to the no wine drinkers.

Mediterranean diets are known to lower BP [3, 10–12]. The effect is pronounced if weight loss is associated with the diet [31]; however, without weight loss, the situation is less clear and 2 large studies reported that there is only a beneficial effect on blood lipids but not on BP [11, 32]. This is in line with our study, where no effects on weight and BP were found. Moreover, the DASH trial had already found that the effect of diet on BP is more pronounced in hypertensive patients [33]. The participants in our study were mainly normotensive (either primarily or treated).

Table 1. Baseline demographic values, past medical history, BP treatment and mean BP and HR

	No LC	LC	p value	Red wine	No red wine	p value	Total
Number	55	53		56	52		108
Mean age, years	63.4 (10.6)	63.7 (8.1)	n.s.	64.1 (9.1)	63.0 (9.9)	n.s.	63.6 (9.5)
Men, %	69	64	n.s.	68	65	n.s.	67
Daily alcohol intake, g	14.7 (14.7)	14.5 (14.2)	n.s.*	15.4 (14.3)	13.7 (14.6)	n.s.*	14.6 (14.4)
Daily alcohol intake of men, g	16.2 (14.5)	15.2 (11.9)	n.s.*	16.5 (13.4)	14.8 (13.2)	n.s.*	15.7 (13.3)
Daily alcohol intake of women, g	11.4 (14.9)	13.4 (18.0)	n.s.*	13.0 (16.0)	11.8 (17.2)	n.s.*	12.4 (16.4)
Mean weight, kg	81.6 (16.2)	77.2 (16.3)	n. s.	79.5 (14.3)	79.4 (18.4)	n.s.	79.4 (16.3)
Mean BMI	27.8 (4.2)	27.3 (4.5)	n.s.	27.4 (3.9)	27.7 (4.8)	n.s.*	27.6 (4.4)
Smokers, %	11	4	n.s.	5	10	n.s.	7
Hypertension, %	69	66	n.s.	71	63	n.s.	68
Hyper-/dyslipidemia, %	76	72	n.s.	71	77	n.s.	74
Diabetes mellitus, %	13	11	n.s.	14	10	n.s.	12
Previous stroke, %	20	21	n.s.	25	15	n.s.	20
Previous TIA, %	15	9	n.s.	11	13	n.s.	12
Previous MI, %	11	8	n.s.	7	12	n.s.	9
Angina pectoris, %	7	4	n.s.	5	6	n.s.	6
Intermittent claudication, %	0	2	n.s.	0	2	n.s.	1
On ACE inhibitor, %	4	11	not tested	4	12	not tested	7
On angiotensin II antagonist, %	56	32	not tested	55	33	not tested	44
On calcium antagonist, %	29	25	not tested	27	27	not tested	27
On beta blocker, %	29	38	not tested	41	25	not tested	33
On diuretic, %	22	23	not tested	27	17	not tested	22
On renin inhibitor, %	2	2	not tested	2	2	not tested	2
On alpha blocker, %	5	6	not tested	5	6	not tested	6
Mean 24-hour systolic BP, mm Hg	121.6 (10.9)	122.8 (11.6)	n.s.*	122.7 (12.4)	121.6 (9.8)	n.s.*	122.2 (11.2)
Mean 24-hour diastolic BP, mm Hg	79.4 (8.1)	78.0 (7.9)	n.s.*	79.3 (8.6)	78.1 (7.3)	n.s.*	78.7 (8.0)
Mean 24-hour HR, bpm	71.4 (7.3)	70.5 (7.7)	n.s.*	70.8 (7.1.)	71.1 (8.0)	n.s.	70.9 (7.5)
Mean diurnal SBP, mm Hg	124.2 (10.5)	126.1 (12.0)	n.s.*	126.1 (12.5)	124.1 (9.7)	n.s.*	125.1 (11.2)
Mean diurnal DBP, mm Hg	83.4 (8.9)	82.3 (8.6)	n.s.	83.8 (9.4)	81.8 (7.8)	n.s.	82.9 (8.7)
Mean diurnal HR, bpm	74.8 (7.8)	73.5 (8.2)	n.s.	73.9 (7.5)	74.5 (8.5)	n.s.	74.2 (8.0)
Mean nocturnal SBP, mm Hg	115.9 (14.3)	114.9 (14.2)	n.s.*	115.1 (15.6)	115.7 (12.6)	n.s.*	115.4 (14.2)
Mean nocturnal DBP, mm Hg	70.4 (8.6)	68.2 (9.0)	n.s.*	69.4 (9.3)	69.2 (8.4)	n.s.*	69.3 (8.8)
Mean nocturnal HR, bpm	63.7 (8.2)	63.2 (7.7)	n.s.*	63.6 (8.0)	63.3 (8.0)	n.s.*	63.5 (7.9)

Values in parentheses are SD. No differences were found between the LC and the no LC group and between the red wine and the no red wine group in the Student t tests and Wilcoxon-Mann-Whitney tests (indicated by *), respectively. Categorical values were tested with the χ^2 test or Fisher's exact test, respectively. TIA = Transient ischemic attack; MI = myocardial infarction; ACE = angiotensin-converting enzyme.

Table 2. Distribution of BP values at baseline for the whole cohort of 108 patients

	Low	Normal	Borderline	Mild	Moderate	Severe
Diurnal SBP	0 (0)	91 (84.26)	8 (7.41)	7 (6.48)	2 (1.85)	0 (0)
Diurnal DBP	0 (0)	72 (66.67)	16 (14.81)	16 (14.81)	4 (3.70)	0 (0)
Nocturnal SBP	1 (0.93)	74 (68.52)	12 (11.11)	11 (10.19)	8 (7.41)	2 (1.85)
Nocturnal DBP	1 (0.93)	64 (59.26)	17 (15.74)	21 (19.44)	4 (3.70)	1 (0.93)

Values are numbers of subjects with percentages in parentheses. The vast majority of the subjects was normotensive. To classify BP, we used the limits of the European Society of Hypertension. For orientation, normal diurnal SBP was 100–135 mm Hg, nocturnal SBP 91–120 mm Hg, diurnal DBP 65–85 mm Hg and nocturnal DBP 51–70 mm Hg [31, 33].

Table 3. Absolute change of BP and HR

	No LC (n = 55)	LC (n = 53)	p	Red wine (n = 56)	No red wine (n = 52)	p
Baseline – 4 weeks						
Mean 24-hour SBP, mm Hg	–0.9 (9.3)	–1.3 (8.6)	n.s.	–1.6 (9.6)	–0.5 (8.0)	n.s.
Mean 24-hour DBP, mm Hg	–0.0 (5.9)	–0.8 (5.6)	n.s.	–0.9 (6.0)	0.2 (5.4)	n.s.
Mean 24-hour HR, bpm	–0.6 (4.7)	–0.4 (6.1)	n.s.	0.1 (5.5)	–1.1 (5.3)	n.s.
Mean diurnal SBP, mm Hg	–0.5 (9.3)	–1.9 (9.3)	n.s.	–1.7 (10.0)	–0.6 (8.5)	n.s.
Mean diurnal DBP, mm Hg	0.3 (6.2)	–1.1 (6.5)	n.s.	–1.0 (6.4)	0.3 (6.3)	n.s.
Mean diurnal HR, bpm	–0.9 (5.3)	–0.1 (6.4)	n.s.*	0.1 (5.9)	–1.1 (5.9)	n.s.*
Mean nocturnal SBP, mm Hg	–2.1 (11.0)	0.6 (11.6)	n.s.	–1.4 (11.7)	–0.2 (11.0)	n.s.
Mean nocturnal DBP, mm Hg	–1.2 (7.5)	0.1 (7.8)	n.s.	–1.3 (7.8)	0.2 (7.4)	n.s.
Mean nocturnal HR, bpm	–0.4 (5.2)	–1.1 (6.7)	n.s.	0.0 (6.4)	–1.5 (5.3)	n.s.
Baseline – 20 weeks						
Mean 24-hour SBP, mm Hg	–0.3 (9.4)	–0.5 (10.5)	n.s.*	–0.5 (10.1)	–0.3 (9.7)	n.s.*
Mean 24-hour DBP, mm Hg	–0.1 (6.3)	–0.3 (6.8)	n.s.	–0.7 (6.5)	0.3 (6.6)	n.s.
Mean 24-hour HR, bpm	1.2 (5.6)	0.2 (5.0)	n.s.*	0.9 (5.6)	0.4 (5.0)	n.s.*
Mean diurnal SBP, mm Hg	–0.8 (9.3)	–1.4 (11.4)	n.s.*	–1.6 (10.6)	–0.5 (10.2)	n.s.*
Mean diurnal DBP, mm Hg	–0.3 (6.8)	–0.5 (8.4)	n.s.	–1.4 (7.6)	0.7 (7.5)	n.s.
Mean diurnal HR, bpm	0.9 (5.1)	0.1 (5.7)	n.s.	0.4 (5.3)	0.7 (5.5)	n.s.
Mean nocturnal SBP, mm Hg	0.3 (12.4)	1.5 (11.7)	n.s.*	1.7 (11.9)	–0.0 (12.2)	n.s.*
Mean nocturnal DBP, mm Hg	–0.0 (7.7)	–0.1 (7.4)	n.s.*	0.4 (7.2)	–0.6 (7.9)	n.s.*
Mean nocturnal HR, bpm	0.3 (6.4)	0.4 (6.2)	n.s.	0.8 (6.1)	–0.2 (6.5)	n.s.

Values in parentheses are SD. p values are from a general linear model. When the values were not normally distributed, ANOVA on ranks was used (indicated by *).

Physical activity has also been described to lower BP [10, 12–14]. However, this effect seems to be restricted to younger patients. After 6 months, there was no effect of exercise on SBP and only a mild effect on DBP (–2.2 mm Hg) in 55- to 75-year-old patients with mild hypertension compared to a control group [34]. A reason could be aortic stiffness in this age group, similar to the age group in our study.

Alcohol has a biphasic effect on BP and HR. An initial vasodilatation with a drop in BP is followed by vasoconstriction and a rise in BP [35–37]. The drop in BP is accompanied by a rise in HR and vice versa [35]. On the first day of alcohol intake, the mean 24-hour BP dropped and HR increased compared to baseline. However, after 7 days of regular alcohol intake at dinner, no changes in the mean 24-hour BP and HR were noted in 14 male habitual drinkers with essential hypertension in the study by Abe et al. [35]. However, after 7 days, BP was lower and HR higher between 6 p.m. and midnight. Between midnight and 8 a.m., BP was higher as compared to baseline [35]. We did not find any effect of regular alcohol intake on the 24-hour BP and HR values. Reasons for this finding were that (a) the time of alcohol intake was at the subject's discretion; (b) BP and HR were measured after 4 and 20 weeks, respectively, and (c) there was an attenuation of the BP and HR reaction to alcohol with time, which has already been described in the study by Abe [35].

Heavy alcohol consumption and binge drinking are risk factors for high BP and cerebrocardiovascular disease [15, 16]. Cessation of heavy alcohol intake (100–380 g daily) in men reduced SBP and DBP by 7 mm Hg and HR by 8 bpm after 1 month [38]. In our study, the mean daily alcohol intake at baseline was 14.6 g with a maximum of 57 g daily, and the amount studied was about 12 and 24 g, respectively. These values were far lower and the effects of withdrawal and exposition were less pronounced, which explains our different results. During

our study, a continuous, small amount of daily alcohol intake was administered, and binge drinking was discouraged in both the wine drinkers and the no wine drinkers.

Zilkens et al. [39] compared 4 weeks of control abstinence with similar periods of daily consumption of red wine (375 ml), dealcoholized red wine (375 ml) or beer (1,125 ml) in 28 normotensive men in random order. The ambulatory SBP, DBP and HR were not different between control abstinence and dealcoholized red wine. However, compared with control abstinence, both red wine and beer increased awake SBP (2.9 and 1.9 mm Hg, respectively; $p < 0.05$) and asleep HR (5.0 and 4.4 bpm; $p < 0.05$). The amount of alcohol used in this study (375 ml of wine and 1,125 ml of beer, respectively) was higher than the one we used (100 and 200 ml of red wine, respectively). This may explain why HR and BP did not change in the long term in our study. In the PP population of our study, there was only a transient increase in the nocturnal HR of the LC group that was drinking wine for 4 weeks as compared with the LC group that did not drink wine at all.

Alcohol shows interactions with BP medication. Drinkers show lower levels of telmisartan as compared to non-drinkers when taking the same dose of telmisartan [40]. A majority of the subjects in our study was on angiotensin II receptor antagonists. Nevertheless, there was no increase in BP in the wine-drinking group.

Our study demonstrates that in mainly normotensive and well-treated hypertensive patients with cerebrovascular disease, the possible effect of the regular intake of small amounts of red wine is not counterbalanced by an increase in the mean SBP or DBP or by an increase in HR in the long term. Limitations of our study are the relatively small number of participants subdivided into four groups and the fact that we studied the effect of counseling and not the actual change in behavior.

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Disclosure Statement

None of the authors had a personal or financial conflict of interest.

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