Alcohol consumption and arterial stiffness in men

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Objective **Moderate alcohol consumption has been proposed to be anti-atherogenic and protect against coronary heart disease. Arterial stiffness provides a summary measure of atherosclerotic arterial damage and cardiovascular risk. A vascular protective effect of moderate alcohol consumption would be reflected in an inverse association between alcohol intake and aortic stiffness.**

Design **A cross-sectional study.**

Setting **The male population of Utrecht.**

Participants **Of 370 men, aged 40–80 years, alcohol intake was calculated from a standardized questionnaire and aortic stiffness was non-invasively assessed by pulse-wave velocity (PWV) measurement of the aorta.**

Results **There were no non-drinkers; therefore the group consuming 0–3 glasses of alcoholic beverage per week was chosen as the reference group in the analyses. Those drinking 4–10, 11–21 and 22–58 glasses of alcoholic beverage per week had a −0.77 m/s (95% confidence interval, −1.26 to −0.28), −0.57 m/s (95% confidence interval, −1.07 to −0.08) and −0.14 m/s (95% confidence interval, −0.65 to 0.36) difference in mean PWV compared with those drinking 0–3 glasses per week. Adjustment for factors that correlated with PWV or alcohol consumption did not change the strength of the association.**

Conclusion **Among men aged 40–80 years there is a J-shaped association between alcohol consumption and PWV. This further supports a decreased risk of cardiovascular disease with moderate alcohol consumption.** ***J Hypertens*** **22:357–362 © 2004 Lippincott Williams & Wilkins.**

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Introduction

The effects of alcohol on the cardiovascular system suggest a higher risk of cardiovascular disease (CVD) in non-drinkers and heavy alcohol consumers and a protective effect of moderate alcohol intake, leading to a U-shaped association [1]. Mechanisms proposed to explain a positive health effect of moderate alcohol consumption involve prevention of atherogenesis through beneficial effects on lipoprotein metabolism [2], hemostasis [3] and inflammatory processes [4]. In addition, epidemiological studies have shown that moderate alcohol consumption reduces the risk of diabetes mellitus type 2 [5] and increases insulin sensitivity [6].

Apart from studies on these factors, information on the relation of alcohol intake and vascular damage may point to pathophysiological pathways to explain the effects further. Indicators of vascular damage are stiffer arteries, specifically stiffness of the aorta [7]. The aortic pulse-wave velocity (PWV) is a non-invasive measurement of the distensibility of the aorta, which is reported to be a reliable index of aortic stiffness [8]. Prospective studies have shown that the aortic PWV is a strong independent predictor of cardiovascular death among the elderly [9] and subjects with hypertension [10,11].

A cardioprotective effect of moderate alcohol consumption would be reflected in an inverse association between alcohol intake and aortic stiffness. We have previously reported an inverse association between alcohol and PWV in postmenopausal women [12]. To further provide evidence for the hypothesis, we investigated the association between alcohol consumption and aortic PWV in a cross-sectional study in a well-defined group of men aged 40–80 years.

Methods

Subjects

Subjects were recruited by sending a letter to 770 randomly selected female participants of a study conducted by the Julius Center for Health Sciences and Primary Care [13]. In this letter the women were asked

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whether they knew possibly interested male volunteers aged 40–80 years. Via this recruitment 240 men volunteered for participation. Additionally, 1230 personal invitation letters were sent to male inhabitants of Utrecht (aged 40–80 years) by means of a random selection from the municipal register. Via this recruitment 390 men volunteered for participation. Of the total 630 (240 + 390) potential volunteers, 16 subjects were excluded because they were not living independently and were not physically or mentally able to visit the study center independently. No additional health-related eligibility criteria were used. Of the remaining 614 men eventually 400 men were randomly selected to participate in this study, with equal numbers in each age-decade across the range from 40 to 80 years. The study was approved by the Institutional Review Board of the University Medical Center Utrecht and written informed consent was obtained from all participants. Data collection took place between March 2001 and April 2002.

Measurements

Demographic and behavioral variables

Height, weight, waist and hip circumference were measured with the participant in standing position wearing indoor clothes and no shoes. Physical activity was assessed using a questionnaire that was validated in an elderly population [14]. Low scores represent low physical activity. Smoking was estimated from self-report and categorized in current, former, and never smokers. Alcohol intake was estimated using a validated food frequency questionnaire [15,16]. The socio-economic status was recorded by life-long occupation in four levels: scientific (level 1), high-grade (level 2), middle-grade (level 3) and low-grade profession (level 4).

Prevalence of disease

A medical doctor obtained information on the prevalence of disease and the use of medication from a specified medical history. Diseases were classified by using the ICD-10 classification. Hypertension was defined as systolic blood pressure $\geqslant 160$ mmHg and/or diastolic blood pressure $\geqslant 100$ mmHg and/or use of anti-hypertensive medication. Diabetes mellitus was defined as treatment with insulin or oral hypoglycemic agents and/or fasting plasma venous glucose > 6.9 mmol/l. Hyperlipidemia was defined as serum total cholesterol > 6.5 mmol/l and/or treatment with lipid-lowering medication. Presence of CVD was defined as coronary heart disease, peripheral artery disease or stroke.

Laboratory measurements

Venipuncture was performed to collect fasting blood samples. Platelet-free serum was obtained by centrifugation and was immediately stored at -20°C until analysis. Fasting total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides were measured using an automatic enzymatic procedure (Synchron LX Systems; Beckman Coulter, USA). The low-density lipoprotein-cholesterol concentration was estimated using the Friedewald formula [17]. High sensitivity C-reactive protein (CRP) was measured using a Behring Nefelometer II (Dade Behring, Liederbach, Germany). The lower limit of detection was 0.175 mg/l and the inter-assay variation was 2.4%. Insulin was measured using an IMMULITE 2000 Analyzer (DPC, Los Angeles, California, USA). The lower limit of detection was 2 mU/l, and the inter-assay variation was 8.6, 4.8, 4.4, 5.1 and 5.4% at 14, 27, 86, 175 and 354 mU/l, respectively. The fasting blood glucose was determined using a reagent-strip glucose oxidase method. Glucose levels were assessed using a GlucoTouch reflectometer (LifeScan, Inc., Benelux, Beerse, Belgium). Venous whole blood was immediately applied to the test strip. The Homeostasis Model Assessment (HOMA) index, a measure of insulin resistance, was calculated as fasting glucose (mmol/l) $\times$ [fasting insulin (mU/l) / 22.5] [18].

Cardiovascular assessments

Blood pressure was measured in the morning after 10 min rest, twice in the right brachial artery (lying position) with a semi-automated device (Dinamap 8100; Critikon Inc., Tampa, Finland). The average of the two measurements of systolic and diastolic blood pressure was used for analysis. The mean arterial blood pressure (MAP) was calculated as diastolic blood pressure + [1 / 3 $\times$ (systolic blood pressure – diastolic blood pressure)]. Pulse pressure was defined as systolic blood pressure minus diastolic blood pressure.

For the PWV measurement, participants were asked to lie down for 10 min before starting and to refrain from talking during the procedure. The PWV was determined with the use of a SphygmoCor device (PWV Medical, Sydney, Australia), which allowed an online pulse wave recording and automatic calculation of PWV with two transducers (Millar SPT 301 pressure transducer; Millar Instruments, Sydney, Australia), one positioned at the base or the neck for the common carotid artery and the other over the femoral artery, as previously described [19,20]. The average of 10 successive waveforms was used in the analyses to cover a complete respiratory cycle. The whole procedure was repeated three times per subject and the average PWV value was used for the analysis.

In order to evaluate the reproducibility of the technique in our laboratory, a subset of 20 participants had their PWV re-measured several weeks after their first visit. The mean difference in PWV of the repeated measurements between visits was 0.091 m/s (standard

deviation, 1.5). The intra-class correlation coefficient was 85%, indicating that 85% of the variance in the PWV measurements was due to patient differences, whereas 15% could be attributed to differences between visits (measurement error and intra-individual variability).

Data analysis

PWV and alcohol consumption data were not available for 22 and three men, respectively. In addition, extreme values of two PWV measurements (2.75 and 30.5 m/s) and three alcohol intake levels (86, 107 and 119 drinks/week) were not included, leaving 370 men for analysis. Visual inspection of the PWV values and alcohol consumption data suggested the presence of a J-shaped relation, therefore alcohol intake was divided into four levels (0–3, 4–10, 11–21 and 22–58 glasses of alcoholic beverage per week), so that approximately 25% of the participants were in each level of alcohol intake. There were no non-drinkers in this population sample of males; therefore the group consuming 0–3 glasses alcoholic beverage per week was chosen as the reference group in the analyses. The alcohol intake levels were put into the model as dummy variables. The association between alcohol consumption and PWV was examined, using multiple linear regression analysis, adjusted for age, MAP and heart rate (model A). The latter adjustments are based on literature indicating that these variables are major determinants of PWV [21,22]. There were no true confounders (variables related both to PWV and alcohol intake), but for the sake of completeness model A was extended with factors that correlated significantly ($P < 0.05$) with PWV or alcohol intake; namely, waist-to-hip ratio, current smoking, HDL-cholesterol, cholesterol, HOMA and socio-economic status (model B).

To evaluate whether the association between alcohol intake and PWV differed across prevalence of CVD, prevalence of diabetes mellitus, prevalence of hypertension or prevalence of hyperlipidemia, multiplicative interaction terms were constructed and estimated with a linear regression model. Interaction terms were (borderline) significant for hypertension and diabetes mellitus ($P = 0.005$ and $P = 0.07$, respectively). Therefore, we checked the effect of alcohol consumption on PWV among subjects with diabetes mellitus or hypertension.

Data were analyzed using the SAS statistical software package (SAS/STAT Version 8.02; SAS Institute, Cary, North Carolina, USA). The associations are presented with the linear regression coefficient (β) and its 95% confidence interval (95% CI).

Results

The general characteristics of the study population are presented in Table 1. The characteristics of the two recruited groups did not differ after adjustment for age (data not shown). In Table 2 the mean alcohol intake, PWV value and HDL-cholesterol concentration by level of alcohol intake are presented. The HDL-cholesterol concentration increased with increasing alcohol intake.

Table 1 General characteristics of the study population

Characteristic	
n	370
Age (years)	59.9 (11.3)
Body mass index (kg/m^2)	26.1 (3.5)
Waist-to-hip ratio	0.97 (0.06)
Alcohol (glasses/week)	13.5 (12.8)
Physical activity score	18.1 (7.4)
Socio-economic status	2.6 (1.0)
Current smokers (%)	24.3
Former smokers (%)	53.0
Diabetes mellitus (%)	10.5
Cardiovascular disease (%)	15.9
Hypertension (%)	25.1
Hyperlipidemia (%)	34.3
Total cholesterol (mmol/l)	5.8 (1.0)
HDL-cholesterol (mmol/l)	1.31 (0.34)
LDL-cholesterol (mmol/l)	3.9 (0.9)
Triglycerides (mmol/l)	1.58 (1.39)
Glucose (mmol/l)	5.9 (1.5)
Insulin (mU/l)	8.5 (5.5)
Homeostasis Model Assessment	2.4 (2.1)
C-reactive protein (mg/l)[a]	1.4 (1.2–1.7)
Systolic blood pressure (mmHg)	138 (19.4)
Diastolic blood pressure (mmHg)	77 (8.8)
Mean arterial pressure (mmHg)	128.4 (15.8)
Pulse pressure (mmHg)	60.5 (16.7)
Heart rate (bpm)	64.0 (10.1)
Pulse wave velocity (m/s)	9.37 (2.45)

Data are shown as mean (standard deviation) in the case of continuous variables, and as percentages in the case of categorgorical variables. HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]C-reactive protein data are shown as median (95% confidence interval).

There was a J-shaped association between alcohol consumption and PWV (Table 3, model A). The lowest PWV values were observed with an alcoholic beverage intake of 4–10 and 11–21 glasses per week (8 and 6% reduction in PWV, respectively). Additional adjustment for factors that correlated with PWV or alcohol consumption (model B) did not change the strength of the association.

Table 2 Alcohol intake, pulse wave velocity and high-density lipoprotein (HDL)-cholesterol by level of alcohol intake, adjusted for age, mean arterial pressure and heart rate

Alcohol intake level (glasses/week)	*n*	Alcohol intake (glasses/week)	Pulse wave velocity (m/s)	HDL-cholesterol (mmol/l)
0–3	87	0.7 (0.5)	9.76 (0.18)	1.21 (0.04)
4–10	98	6.3 (0.5)***	8.99 (0.17)**	1.30 (0.03)
11–21	98	15.1 (0.5)***	9.18 (0.17)*	1.34 (0.03)**
22–58	87	32.5 (0.5)***	9.62 (0.18)	1.41 (0.04)***

Data are shown as mean (standard error of the mean). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; difference from the reference group (alcohol intake level 0–3 glasses/week).

Table 3 Regression coefficients (95% confidence interval) describing the change in pulse wave velocity (m/s) per level of alcohol intake compared with the reference group

Alcohol intake level (glasses/week)	*n*	Model A	Model B
4–10	98	−0.77 (−1.26 to −0.28)**	−0.74 (−1.25 to −0.23)**
11–21	98	−0.57 (−1.07 to −0.08)*	−0.58 (−1.10 to −0.06)*
22–58	87	−0.14 (−0.65 to 0.36)	−0.05 (−0.59 to 0.50)

Model A, adjusted for age, mean arterial pressure and heart rate. Model B, as model A with additional adjustment for waist-to-hip ratio, current smoking, high-density lipoprotein-cholesterol, cholesterol, Homeostasis Model Assessment and socio-economic status. *$P < 0.05$, **$P < 0.01$; difference from the reference group (alcohol intake level 0–3 glasses/week).

A trend to a J-shaped association was also observed among subjects with diabetes mellitus or hypertension (Table 4). A significant decrease in PWV was present for an alcohol intake of 4–10 glasses per week in subjects with hypertension (19% reduction in PWV). In subjects with diabetes mellitus PWV the lowest PWV was observed with an alcohol intake of 4–10 glasses per week, but probably due to the small numbers this decrease was not statistically significant.

Discussion

This cross-sectional study among men aged 40–80 years provides evidence for a J-shaped relation between alcohol consumption and aortic stiffness as measured by PWV, with the lowest PWV values for an alcoholic beverage intake of 4–10 and 11–21 glasses/week.

Some aspects of the study need to be addressed. The use of self-reported information on alcohol intake may have introduced misclassification in exposure, specifically for those in the heavier drinking groups [23]. However, selective misclassification of heavy drinkers as non-drinkers seems unlikely because we observed a positive graded association between alcohol consumption and HDL-cholesterol, a finding that supports the rank-order validity of self-reported alcohol intake. In general, self-report of true alcohol consumption tends to be underestimated. Combined with the absence of a non-drinking reference group in our population this might have influenced the shape of the curve.

Table 4 Pulse wave velocity by level of alcohol intake, adjusted for age, mean arterial pressure and heart rate, within subjects with diabetes mellitus or hypertension

	Alcohol intake level (glasses/week)	*n*	Pulse wave velocity (m/s)
Diabetes mellitus	0–3	16	11.03 (0.48)
	4–10	5	10.30 (0.90)
	11–21	11	10.54 (0.61)
	22–58	7	11.18 (0.81)
Hypertension	0–3	16	12.33 (0.54)
	4–10	22	10.04 (0.45)**
	11–21	25	11.34 (0.43)
	22–58	30	11.48 (0.39)

Data are shown as mean (standard error of the mean). **$P < 0.01$; difference from the reference group (alcohol intake level 0–3 glasses/week).

No information was available on drinking pattern and changes in drinking behaviour. However, the focus here is on the long-term vascular effect estimated by arterial stiffness, and as drinking patterns among middle-aged and older subjects tend to be stable over time [24] we do not expect a major impact on the validity of the data.

Aortic PWV is an indirect marker of increased aortic stiffness or decreased aortic compliance and is affected by various hemodynamic factors such as blood pressure apart from the presence of atherosclerosis. Although high alcohol consumption is associated with an increased blood pressure [25], this is unlikely to have influenced the results as we adjusted for MAP.

To our knowledge there are only four previous reports presenting the effect of alcohol consumption on aortic PWV. A cross-sectional study in Japanese-American men and women reported that the risk for high aortic PWV was lower among current drinkers and ex-drinkers than among non-drinkers [26]. In a follow-up study in middle-aged Japanese men the incidence of aortic stiffness was not related to alcohol intake [27], whereas another longitudinal study in Japanese men from the same group of investigators suggested that alcohol is an important risk factor for development of aortic stiffness at an intake of more than 16 glasses of alcoholic beverage per week [28]. We recently showed an inverse association between alcohol consumption and aortic PWV in a cross-sectional study among postmenopausal women. In addition, we found some evidence for the presence of a J-shaped relation [13]. A similar trend to increased PWV was seen in the current study in the subjects consuming 22–58 glasses/week.

The decrease in PWV observed in the present study is comparable with that observed in postmenopausal women [12]. Drinking between 4 and 21 glasses of alcoholic beverage per week decreased PWV by approximately 0.7 m/s. Based on a study in postmenopausal women this would translate to a risk reduction of stroke and coronary heart disease of 0.6 and 1% [19].

The mechanism by which moderate alcohol intake may reduce aortic stiffness is unknown, but there are several possibilities. Alcohol consumption increases HDL-cholesterol [2], with associated increases in paraoxonase activity [2] and cholesterol efflux [29]. This may decrease the amount of cholesterol within peripheral cells, and thus increase the flexibility of the vascular wall.

However, the relation between alcohol intake and PWV could not be explained by HDL-cholesterol in the present study. With increasing age the arteries become stiffer due to a decrease in elastin and an increase in collagen and connective tissues in the arterial wall [30]. Alcohol intake might delay or change this process, possibly by an effect on gene expression. Damage to the vascular wall due to inflammation might also raise arterial stiffness. The observed decrease in plasma CRP [4] with moderate alcohol intake could reduce the risk or the extent of lesions of the vascular wall and explain an improved vascular elasticity. In the current study there was a trend to decreased CRP with an alcohol intake of 4–10 and 11–21 glasses per week compared with an intake of 0–3 glasses of alcoholic beverage per week ($\beta = -1.4$, 95% CI, −3.9 to 1.0 and $\beta = -0.9$, 95% CI, −3.3 to 1.6, respectively). CRP did not significantly correlate with PWV or alcohol intake, therefore additional adjustment for CRP was not performed. Finally, epidemiological studies have shown that moderate alcohol consumption reduces the risk of diabetes mellitus type 2 [5] and increases insulin sensitivity [6]. This effect of alcohol might decrease the formation and cross-linking of glycated collagen in the vascular wall, which is accelerated in a hyperglycemic milieu. In the current study an increase in HOMA was associated with higher PWV ($\beta = 0.09$, $P = 0.03$). HOMA decreased with increasing alcohol intake, but only significantly with an alcohol intake of 22–58 glasses per week ($\beta = -0.68$, 95% CI, −1.32 to −0.05). Additional adjustment for HOMA did not change the strength of the association between alcohol consumption and PWV, suggesting that the association may be explained by some unknown or unmeasured factor(s).

It is generally accepted that physical activity is associated with decreased cardiovascular morbidity and mortality. However, in the literature there is no sound evidence that physical activity affects aortic stiffness/arterial distensibility. In two cross-sectional studies [31,32] a positive effect of physical activity on the arterial wall structure was observed, whereas in the ARIC study habitual physical activity did not have a strong, consistent positive effect on arterial distensibility [33]. This suggests that the reduced risk of cardiovascular disease in physically active subjects can probably not be fully explained by a reduction in PWV. In our study physical activity did not correlate with PWV nor alcohol intake, indicating that physical activity could not have confounded the association between PWV and alcohol intake.

In conclusion, the results of the present study support a direct positive effect of moderate alcohol intake on vascular elasticity in men aged 40–80 years. This may explain part of the reduced CVD risk associated with moderate alcohol use.

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