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Binge Drinking Impairs Vascular Function in Young Adults

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Objectives The aim of this study was to assess whether young binge drinkers (BD) have impaired macrovascular and microvascular function and cardiovascular disease risk factors compared with age-matched alcohol abstainers (A).

Background Binge drinking rates are highest on college campuses and among those age 18 to 25 years; however, macrovascular and microvascular endothelial function in young adults with histories of repeated binge drinking (≥5 standard drinks in 2 h in men, ≥4 standard drinks in 2 h in women) has not been investigated.

Methods Cardiovascular profiles, brachial artery endothelial-dependent flow-mediated dilation (FMD), and flow-independent nitroglycerin (NTG)–mediated dilation and vasoreactivity of resistance arteries (isolated from gluteal fat biopsies) were evaluated in A and BD.

Results Men and women (18 to 25 years of age; A, n = 17; BD, n = 19) were enrolled. In the BD group, past-month mean number of binge episodes was 6 ± 1, and the mean duration of binge drinking behavior was 4 ± 0.6 years. FMD and NTG-mediated dilation were significantly lower in the BD group (FMD: 8.4 ± 0.7%, p = 0.022; NTG-mediated dilation: 19.6 ± 2%, p = 0.009) than in the A group (FMD: 11 ± 0.7%; NTG-mediated dilation: 28.6 ± 2%). Acetylcholine-induced and sodium nitroprusside–induced dilation in resistance arteries was not significantly different between the A and BD groups. However, endothelin-1–induced constriction was significantly enhanced in the BD group compared with the A group (p = 0.032). No differences between groups were found in blood pressure, lipoproteins, and C-reactive protein.

Conclusions Alterations in the macrocirculation and microcirculation may represent early clinical manifestations of cardiovascular risk in otherwise healthy young BD. This study has important clinical implications for screening young adults for a repeated history of binge drinking. (J Am Coll Cardiol 2013;62:201–7) © 2013 by the American College of Cardiology Foundation

Regular heavy episodic alcohol use (or "binge drinking") is one of the most serious public health problems confronting American colleges (1). More than half of college student drinkers engage in regular binge drinking, which is broadly defined as consuming more than 4 or 5 standard drinks (13 g alcohol/drink) in a 2-h period (2–4). Results from retrospective studies enrolling adults ranging in age from 40 to 60 years have found that binge drinking is associated with a heightened risk for cardiovascular (CV) events, such as stroke, sudden death, myocardial infarction, and increased mortality after myocardial infarction (5–8). Others have reported that an alcohol binge drinking pattern is associated with progression of carotid atherosclerosis (9). Several mechanisms may underlie the increased risk for adverse CV events; however, a central mechanism may be changes in vascular biology, such as endothelial dysfunction.

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The endothelium is a key regulator of vascular function. Endothelial dysfunction is an early indicator of blood vessel damage and atherosclerosis and a strong prognostic factor

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Abbreviations and Acronyms

A = alcohol abstainers
ACh = acetylcholine
BD = binge drinkers
BP = blood pressure
CRP = C-reactive protein
CV = cardiovascular
EC_{50} = half maximal effective concentration
ET = endothelin
FMD = flow-mediated dilation
L-NAME = N-nitro-L-arginine methyl ester
NO = nitric oxide
NTG = nitroglycerin
SNP = sodium nitroprusside

for future CV events (10,11). Impaired endothelium-independent dilation, reflective of smooth muscle dysfunction, is also linked to the development of atherosclerosis. Flow-mediated dilation (FMD) and nitroglycerin (NTG)–mediated dilation of the brachial artery are commonly used to evaluate endothelial-dependent and endothelial-independent function, respectively. To our knowledge, endothelial function in young adults with repeated histories of binge drinking has not been investigated, nor have studies simultaneously evaluated macrovascular and microvascular endothelial function. Endothelial cells can differ in structure and physiologic function, depending on the vasculature bed, making it clinically important to study vascular function at multiple vascular sites. This study was designed to test the hypothesis that young binge drinkers (BD) have impaired macrovascular and microvascular function compared with age-matched alcohol abstainers (A).

Methods

Study subjects and protocol. Thirty-eight nonsmoking healthy subjects were recruited from an urban university setting into this study: A (10 men, 9 women) and BD (11 men, 6 women). BD were defined as those who consumed ≥5 standard drinks (12 oz beer, 5 oz table wine, 1.5 oz 80-proof spirits, or 8 to 9 oz malt liquor) in a 2-h period in the past 2 weeks if male and ≥4 standard drinks in a 2-h period in the past 2 weeks if female (2). A were defined as those who consumed no more than 1 to 5 standard drinks in the past year. Exclusion criteria were history of diabetes, hypertension, pregnancy, CV disease or events, thyroid disease, pituitary tumor, a genetic disease causing disability, gout, illicit drug use, and body mass index ≥30 kg/m^2. The study was approved by the Office of Protection of Research Subjects and Institutional Review Board, and written consent was obtained from all subjects.

In all subjects, the following tests were performed: fasting lipid panel (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), insulin and glucose, complete blood count differential, C-reactive protein (CRP), and blood alcohol levels (Alverno Clinical Laboratories, Hammond, Indiana). Venous samples were drawn into a serum tube and an ethylenediaminetetraacetic acid–containing tube. Also measured were resting blood pressure (BP), heart rate, oxygen saturation, and temperature. Gluteal fat pad biopsies were performed, and resistance arteries were isolated for isolated perfused microvessel experiments.

All subjects completed questionnaires about medical history, diet, and alcohol beverage consumption. The Block Brief 2000 Food Frequency Questionnaire (NutritionQuest, Berkeley, California) was used to obtain information about diet. Alcohol consumption (pattern and frequency) was estimated using a modified version of the 6-item set of questions on binge drinking (12). Three additional questions were included on binge drinking that addressed the type of alcohol consumed, history of familial alcohol abuse, and duration of binge drinking. For BD, the rate of alcohol consumption (grams per hour) was calculated on the basis of their most recent binge drinking episode (rate = total grams of alcohol consumed/time spent consuming alcohol).

Measurement of FMD. All imaging studies were performed in the morning after an overnight fast. Similar to previously reported protocols and methods, ultrasound imaging was conducted using the MicroMaxx ultrasound machine (SonoSite, Seattle, Washington) (13). Imaging of the brachial artery was performed in a longitudinal plane, at approximately 5 cm proximal to the antecubital fossa of the right arm, abducted approximately 80° from the body, with the forearm supinated. The ultrasound probe (11 MHz) was positioned at a 60° insonation angle to visualize the anterior and posterior lumen-intima interfaces, to measure diameter or central flow velocity (pulsed Doppler). After baseline ultrasound imaging, Doppler readings of peak flow and mean flow were performed for at least 5 s. A BP cuff was placed on the forearm, distal to the antecubital fossa of the imaged arm, and inflated to 60 mm Hg above baseline systolic BP for 5 min. Once the cuff was released, BP and heart rate measurements in the opposite arm were taken, along with Doppler readings of the first 10 s after cuff release. The brachial artery was then imaged continuously to capture 30 s, 1 min, 2 min, and 3 min after BP cuff release. The response to NTG was used for the determination of endothelium-independent vasodilation. After obtaining a baseline (resting) brachial artery image, a sublingual NTG tablet (0.4 mg) was administered, and brachial artery images and measurements were repeated and obtained as detailed earlier.

Images were digitally recorded using Brachial Imagery (Medical Imaging, Iowa City, Iowa) and analyzed as previously described (13). Four hundred fifty frames were captured, digitized, and analyzed from the M-line (the border between the intima and media of the brachial artery) of the same location of blood vessel using visible landmarks with edge detection software. Approximately 75 frames (7.5 frames/s for 10 s) were analyzed for each baseline and time point measurement through a mean of brachial artery diameters over the entire RR interval. FMD and the response to NTG were calculated using the averaged minimal mean brachial artery diameter at baseline compared with the largest mean values obtained after release of the forearm occlusion or administration of NTG.

The coefficient of variation (intraobserver) was 1.5% for brachial artery diameter, 6.3% for FMD, and 3.2% for NTG-induced dilation. The peak flow velocity was observed from 5 seconds of baseline diameter Doppler readings, and 10 s of post–cuff release Doppler readings were recorded for shear rate calculations. Shear rate was calculated as blood velocity (cm/s) divided by vessel diameter (cm) (14).

Gluteal adipose biopsy and resistance artery function. Microvessels in subcutaneous fat are easily accessible and have been used to investigate microvascular function in humans (15). Approximately 2 ml of fat tissue was removed and transferred to (4°C) HEPES solution. Resistance arteries (approximately 150 μm) were isolated and cannulated in an organ chamber with glass micropipettes filled with KREBS solution (pH = 7.40) (16). Both ends of the vessel were secured, and the vessel was maintained at an intraluminal pressure of 20 mm Hg for 30 min, after which intraluminal pressure was gradually increased to 60 mm Hg for an additional 30 min. Preparations were visualized with video cameras and monitors (model VIA-100, Boeckeler, Tucson, Arizona). After the 30-min equilibration period, vessels were constricted (30% to 50% of baseline diameter) with endothelin (ET)-1 (100 to 200 pmol/l final concentration), and dose-response curves were measured using acetylcholine (ACh) (10^{-9} to 10^{-4} mol/l; A, n = 10; BD, n = 12) and the nitric oxide (NO) donor sodium nitroprusside (SNP) (10^{-9} to 10^{-4} mol/l; A, n = 8; BD, n = 8). Resistance arteries were monitored continuously, and internal diameters were measured at the maximal diameter after each dilator dose. Dose responses to ACh were measured in the absence and presence of the NO synthase inhibitor N-nitro-L-arginine methyl ester (L-NAME) (10^{-4} mol/l; A, n = 9; BD, n = 11). Maximal responses to papaverine (10^{-4} mol/l) were measured at the end of each dose response of ACh. In separate experiments, also determined were constrictor responses to ET-1 (10^{-11} to 10^{-7} mol/l; A, n = 9, BD, n = 10).

Materials. The pharmacological compounds L-NAME, ACh, SNP, and ET-1 were obtained from Sigma-Aldrich Corporation (St. Louis, Missouri). Chemical reagents for buffer solutions were purchased from Sigma-Aldrich Corporation and Fisher Scientific (San Jose, California).

Statistical analysis. Analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina) and SigmaPlot version 12.0 (SigmaPlot, San Jose, California). All data are reported as mean ± SE, with $p < 0.05$ considered significant unless otherwise noted. Nutritional questionnaires were sent to NutritionQuest for calorie and other nutrient analysis. Normality was tested using the Shapiro-Wilk test. The A and BD group differences were determined using independent *t* tests. Mann-Whitney *U* tests were used for continuous variables (e.g., demographics, CRP, lipids, FMD, and NTG-mediated dilation) and chi-square tests for categorical variables. For dose-response experiments, data are expressed as percentages, with 100% representing the change from constricted diameter to the maximal diameter at 60 cm H_2O intraluminal pressure. Dose responses to ACh (with or without L-NAME), SNP, and ET-1 were compared using a 2-factor, repeated-measures analysis of variance with a Bonferroni adjustment. ET-1 half maximal effective concentration (EC_{50}) values were computed using SigmaPlot with the Dynamic Fit Wizard and with an equation ($Y = \min + \max - \min / 1 + 10^{(\log EC50 - X)}$ Hillslope) for *XY* pair data.

Analyses of covariance were performed on endothelium-dependent and endothelium-independent vasodilation, to examine the relationship of binge drinking, controlling for covariates (age, sex, and ethnicity) using a general linear model. Covariates were tested with binge drinking status individually because of the small sample size. Effect sizes and 95% confidence intervals (CIs) were computed without covariates (17).

Results

Clinical characteristics. Demographic characteristics were not significantly different between the A and BD groups (Table 1); however, BD were more likely to be white (p = 0.004). Nutritional histories (macronutrient and micronutrient intake) and white and red blood cell values

Table 1 Demographic and Metabolic Characteristics

Characteristic	Abstainers (n = 19)	Binge Drinkers (n = 17)	p Value
Median age (yrs)	24.5	23	0.526
25th percentile	21	21.5	
75th percentile	29	25	
Men	53%	65%	0.463
White	21%	76%	0.004
Body mass index (kg/m^2)	23.7 ± 0.9	25.0 ± 1	0.370
Systolic blood pressure (mm Hg)	114 ± 3	120 ± 2	0.092
Diastolic blood pressure (mm Hg)	67 ± 1	70 ± 2	0.163
Heart rate (beats/min)	64 ± 1	65 ± 2	0.800
Total cholesterol (mg/dl)	162.16 ± 8.88	166.12 ± 6.18	0.689
Median LDL cholesterol (mg/dl)	82	86	0.975
25th percentile	67	67	
75th percentile	118	107	
HDL cholesterol (mg/dl)	54.83 ± 3.09	61.78 ± 5.02	0.21
Median triglycerides (mg/dl)	61.0	78.5	0.159
25th percentile	44.0	62.2	
75th percentile	104	98.7	
Glucose (mg/dl)	85.05 ± 1.98	89.01 ± 1.98	0.167
Insulin (μIU/l)	6.48 ± 1.09	4.69 ± 0.71	0.167
CRP (mg/dl)	1.29 ± 0.59	1.60 ± 0.70	0.421
Blood alcohol (%)	ND	0.01 ± 0.002	0.762
AST (IU/l)	19 ± 1	23 ± 2	0.058
ALT (IU/l)	9 ± 1	11 ± 1	0.249

Values are mean ± SEM or % except as indicated.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2 Brachial Artery Characteristics

Variable	Abstainers (n = 19)	Binge Drinkers (n = 17)	p Value
Baseline brachial FMD diameter (mm)	3.5 ± 0.1	3.9 ± 0.2	0.049
Maximal brachial FMD diameter (mm)	3.9 ± 0.1	4.3 ± 0.2	0.053
Δ flow (cm/s)	98 ± 12	80 ± 10	0.176
Peak flow (cm/s)	142 ± 7	128 ± 9	0.142
Δ shear rate (s)	98 ± 12	95 ± 15	0.433
Peak shear rate (s)	412 ± 18	328 ± 20	<0.005
Baseline brachial NTG-mediated dilation diameter (mm)	3.5 ± 0.1	4.00 ± 0.2	0.017
Maximal brachial NTG-mediated dilation diameter (mm)	4.5 ± 0.1	4.8 ± 0.2	0.153

Values are mean ± SEM.
FMD = flow-mediated dilation; NTG = nitroglycerin.

were not significantly different between groups (data not shown). All lipid values and CRP were similar between groups (Table 1). The mean time since the last binge episode in the BD group was 65 ± 11 h. Subjects in the BD group drank alcohol at a rate of 34 ± 7 g. During the month before the study, the mean number of binge episodes in the BD group was 6 ± 1. The mean duration of binge drinking behavior was 4 ± 0.6 years.

Brachial artery endothelium-dependent and endothelium-independent dilation. Except for baseline brachial FMD diameter and change in shear rate, blood vessel characteristics were not different between the A and BD groups (Table 2). Unadjusted FMD and NTG-induced dilation were significantly lower in the BD group compared with the A group ($p = 0.022$ and $p = 0.009$, respectively) (Fig. 1). When baseline brachial artery diameter was tested as a predictor, there remained a significant difference between groups, though the effect was slightly attenuated. The effect size (eta squared) was 0.25 (95% CI: 0.023 to 0.47) for FMD and 0.61 (95% CI: 0.32 to 0.74) for NTG-mediated dilation. Also, because the BD group had a higher proportion of white subjects, this variable was tested individually as a covariate in a multivariate model, as well as age and sex. No covariates were statistically significant.

Microvascular resistance artery endothelium-dependent and endothelium-independent dilation. ACh-induced dilation in resistance arteries was not significantly different between the A and BD groups ($p = 0.365$) (Fig. 2). The presence of L-NAME significantly blocked ACh-induced dilation in the A group ($p = 0.002$) but not in the BD group ($p = 0.155$). SNP-induced dilation in resistant arteries was not significantly different between groups ($p = 0.948$) (Fig. 3). Because ET-1 was used to pre-constrict vessels before ACh dose-response experiments, we compared the dose used for pre-constriction, and there was no significant difference between groups (A, 1.6×10^{-8}; BD, 1.4×10^{-8}; $p = 0.442$).

At several concentrations tested, ET-1–induced constriction was significantly enhanced in the BD group compared with the A group ($p = 0.002$) (Fig. 4). EC_{50} for ET-1 was significantly more potent in the BD group (9.4 ± 0.1 nmol/l) than the A group (8.7 ± 0.3 nmol/l) ($p = 0.032$).

Discussion

We demonstrate that young adults with normal serum lipoprotein, triglyceride, CRP, glucose, and insulin levels and histories of binge drinking (mean 4 years) had reduced FMD and NTG-induced dilation. This study addressed the importance of binge drinking on macrovascular and

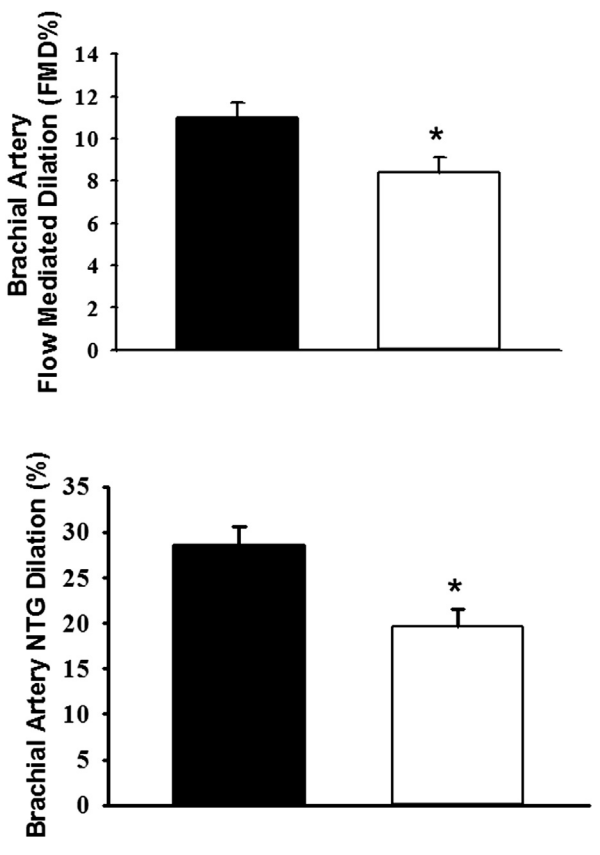

Figure 1 Brachial FMD and NTG-Induced Dilation in the A and BD Groups

Brachial flow-mediated dilation (FMD) **(top)** and nitroglycerin (NTG)–induced dilation **(bottom)** were significantly lower in binge drinkers (BD) compared with alcohol abstainers (A) ($p = 0.022$ and $p = 0.009$, respectively). Values are mean ± SEM.

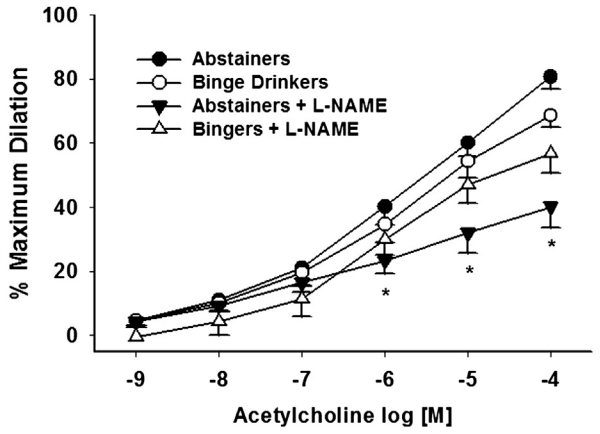

Figure 2 ACh-Induced Dilation in the A and BD Groups

Acetylcholine (ACh)–induced dilation in resistance arteries was similar between alcohol abstainers (A) (n = 11) and binge drinkers (BD) (n = 10) (p = .365). N-nitro-L-arginine methyl ester (L-NAME) significantly blocked ACh-induced dilation in the A group (p = 0.007) but not in the BD group (p = 0.155). Values are mean ± SEM. *Significant difference (p ≤ 0.008) between ACh-induced dilation and ACh + L-NAME–induced dilation in the A group.

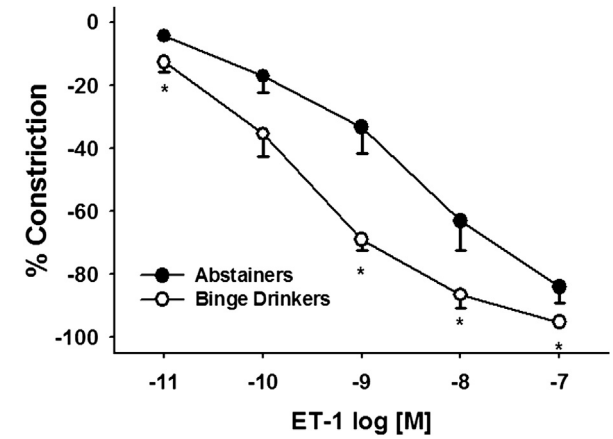

Figure 4 ET-1–Induced Constriction in the A and BD Groups

Endothelin (ET)-1–induced constriction was significantly greater in binge drinkers (BD) (n = 10) compared with alcohol abstainers (A) (n = 10) (p = 0.002). Values are mean ± SEM. *Significant difference (p ≤ 0.01).

microvascular function and found important changes in both vascular beds.

Binge drinking and macrovascular function. Our findings of impairment in brachial artery endothelial-dependent and endothelial-independent vasodilation are similar to those of others who have examined the one-time effect of a single binge episode on endothelial function (18–20). Bau et al. (19) found that FMD and NTG-induced dilation were impaired 4 h after alcohol intoxication, returning to baseline levels 13 h after alcohol intoxication. There are also reports that FMD is impaired in abstinent subjects with long-term histories of alcohol abuse or alcoholism (21–23). Our findings suggest that young BD have developed FMD impairments that are equivalent to those found in subjects with lifetime histories of daily heavy alcohol consumption (>6 drinks/day for >8 years). Because our subjects were tested 24 to 96 h after their most recent binge drinking episodes, the time course for restoration of FMD that might occur with the cessation of binge drinking is unknown. It is important to note that NTG-mediated dilation was also reduced in BD, suggesting that there could be reduced smooth muscle cell responses to NO and altered post-receptor signal transduction events, such as alterations in the cyclic guanosine monophosphate pathway.

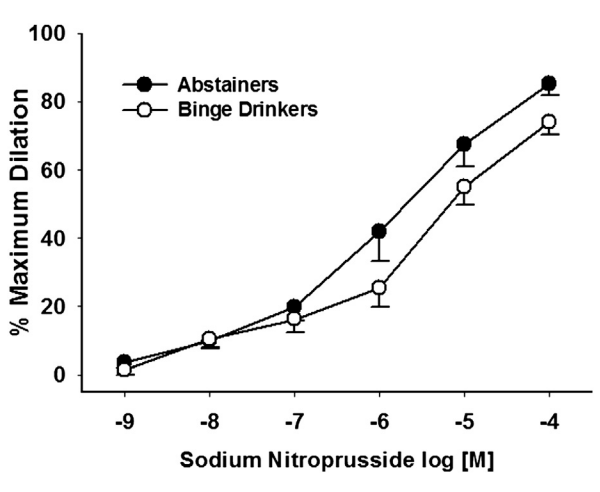

Figure 3 SNP-Induced Dilation in the A and BD Groups

Sodium nitroprusside (SNP)–induced dilation was similar between alcohol abstainers (A) (n = 5) and binge drinkers (BD) (n = 6) (p = 0.948). Values are mean ± SEM.

Binge drinking and microvascular function. A unique aspect of our study was the use of subcutaneous gluteal fat pad biopsy to study isolated resistance arteries under ex vivo conditions. In contrast to decreased FMD in the brachial arteries of the BD group, there were no differences between groups in response to all doses of the endothelium-dependent vasodilator ACh and the NO donor SNP. Our results suggest that the effects of binge drinking on FMD and ACh-induced and SNP-induced dilation are divergent. In addition, L-NAME had no inhibitory effect on ACh-induced dilations, which implies the possibility that other endothelial or non-endothelium-dependent pathways may be involved in vasodilation in resistance arteries. These differences may relate to the experimental preparation and the absence of circulating vasoconstrictor mediators in the ex vivo preparation, such as norepinephrine or flow stimuli (shear stress vs. ACh). Also, others have reported that dilations to flow and ACh can be divergent in the context of pathological conditions (i.e., high cholesterol) (24).

In certain CV disease states, NO bioavailability is reduced, and other endothelium-derived dilator substances or non-endothelium-derived factors, such as hydrogen peroxide, may compensate for the lack of NO (16,25). Both acute and long-term ethanol exposure is associated with the excessive generation of reactive oxygen species and oxidative stress and is believed to play a central role in alcohol toxicity (26). Yogi et al. (27) found that ethanol (100 mmol) increased superoxide and hydrogen peroxide generation in cultured aorta vascular smooth muscle cells. Others have found that impairments in NO-dependent vasorelaxation occurred with increased reactive oxygen species production and overproduction of ET-1 (28). Although in our study, circulating ET-1 levels were not measured, we found enhanced ET-1–induced constrictions and a lower EC_{50} in the BD compared with the A group, indicating increased vasoconstrictor responsiveness to ET-1 (Fig. 3). ET-1 may reduce NO production and increase NO degradation (29), and increased plasma levels of ET-1 have been found in heavy alcohol consumers (23,30), making it important to elucidate the effects of binge drinking on ET-1 and ET-1 receptors in the setting of binge drinking.

Binge drinking and accelerated atherosclerosis. In other populations, such as healthy postmenopausal women, endothelial dysfunction was found to be significantly associated with the future development of hypertension (31). In the CARDIA (Coronary Artery Risk Development in Young Adults) study, Pletcher et al. (32) found that binge drinking in adults (mean age 25.2 years) was significantly associated with greater coronary calcification, suggesting the presence of coronary artery atherosclerosis. Recently, Liu et al. (33) reported that binge drinking rather than daily moderate drinking was associated with accelerated plaque development in a mouse model of accelerated atherosclerosis. Also, in a prospective evaluation of adults admitted for first-ever brain infarction, Hillbom et al. (34) found that acute intake of more than 40 g of ethanol during the 24 h preceding the brain infarction on weekends and holidays was significantly associated with cerebral infarction in young (16 to 40 years) and middle-age (41 to 60 years) subjects. One mechanism suggested for the binge-associated increased stroke risk is hypertension; however, at least in younger subjects, hypertension prevalence is low. These data from both epidemiologic and animal models suggest the need to evaluate the pattern of alcohol consumption in relationship to CV risk and adverse events.

Study limitations. This study had important limitations related to both clinical sample and study design. We had a small sample size, and the study was cross-sectional, warranting future longitudinal assessment. We also used self-report to measure alcohol consumption. Others, though, have shown that self-report methods offer a reliable and valid approach to measuring alcohol consumption (35). Another limitation may relate to the greater baseline brachial artery diameter and lower peak shear rates found in the BD group. The latter may contribute to the lower FMD in the BD group because larger baseline diameters are associated with reduced FMD (36). Our results, though, show that there is a significant effect of binge drinking on FMD and NTG-induced dilation, even after correcting for baseline diameter as a covariate.

Conclusions

Young adults without histories of CV disease who engaged in frequent and heavy episodic binge drinking had reduced FMD and NTG-induced dilation. The microvascular vasodilator responses to ACh and SNP were not different between groups; however, microvessels isolated from the BD group had enhanced vasoconstrictor responses to the potent vasoconstrictor ET-1. Our data show alterations in macrovascular and microvascular function associated with binge drinking that are similar to those seen in association with recognized CV risk factors. This study adds to a growing chain of evidence suggesting that, in contrast to regular and moderate alcohol consumption, binge drinking may be a risk factor for future clinical CV disease.

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