Influence of acute alcohol ingestion on sympathetic neural responses to orthostatic stress in humans

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Acute alcohol consumption is reported to decrease mean arterial pressure (MAP) during orthostatic challenge, a response that may contribute to alcohol-mediated syncope. Muscle sympathetic nerve activity (MSNA) increases during orthostatic stress to help maintain MAP, yet the effects of alcohol on MSNA responses during orthostatic stress have not been determined. We hypothesized that alcohol ingestion would blunt arterial blood pressure and MSNA responses to lower body negative pressure (LBNP). MAP, MSNA, and heart rate (HR) were recorded during progressive LBNP (−5, −10, −15, −20, −30, and −40 mmHg; 3 min/stage) in 30 subjects (age 24 ± 1 yr). After an initial progressive LBNP (pretreatment), subjects consumed either alcohol (0.8 g ethanol/kg body mass; n = 15) or placebo (n = 15), and progressive LBNP was repeated (posttreatment). Alcohol increased resting HR (59 ± 2 to 65 ± 2 beats/min, P < 0.05), MSNA (13 ± 3 to 19 ± 4 bursts/min, P < 0.05), and MSNA burst latency (1,313 ± 16 to 1,350 ± 17 ms, P < 0.05) compared with placebo (group × treatment interactions, P < 0.05). During progressive LBNP, a pronounced decrease in MAP was observed after alcohol but not placebo (group × time × treatment, P < 0.05). In contrast, MSNA and HR increased during all LBNP protocols, but there were no differences between trials or groups. However, alcohol altered MSNA burst latency response to progressive LBNP. In conclusion, the lack of MSNA adjustment to a larger drop in arterial blood pressure during progressive LBNP, coupled with altered sympathetic burst latency responses, suggests that alcohol blunts MSNA responses to orthostatic stress.

Additionally, bursts of MSNA are time locked to the cardiac cycle with an average burst latency of 1,300 ms (6, 7). Iwase et al. (11) demonstrated an association between altered sympathetic burst latencies and syncopal episodes. Specifically, syncope was associated with reductions in burst latencies and pulse synchronicity, suggesting that disturbances in MSNA burst latency could be relevant to neurally mediated syncope. Although studies have investigated the effects of alcohol on MSNA (10, 12, 22, 24, 31), no studies have examined the effect of alcohol on burst latencies. Therefore, the purpose of this study was to determine the influence of alcohol on MSNA responses to orthostatic challenge. We hypothesized that acute alcohol consumption would induce a greater drop in arterial blood pressure during progressive LBNP and that this attenuated blood pressure response would be associated with a reduced sympathoexcitatory response with regard to MSNA. Additionally, we hypothesized that acute alcohol ingestion would alter MSNA burst latency patterns.

METHODS

Subjects. Thirty volunteers were randomly assigned to alcohol (12 males, 3 females: age 23 ± 1 yr, height 180 ± 3 cm, weight 86 ± 3 kg, body mass index 27 ± 1 kg/m²) or placebo (11 males, 4 females: age 25 ± 1 yr, height 175 ± 2 cm, weight 76 ± 3 kg, body mass index 25 ± 1 kg/m²) groups. All subjects were healthy, nonsmoking adults and had no history of substance abuse, autonomic dysfunction, or cardiovascular disease. All females were tested 2–5 days after the start of their menstrual cycle (i.e., early follicular phase), because menstrual phase has been shown to influence MSNA responses to orthostatic stress (1, 9). The study was approved by the Institutional Review Board of Michigan Technological University, and all subjects provided written informed consent prior to the study.

Experimental design. Subjects arrived at the laboratory at 7:30 AM after abstaining from caffeine and exercise for ≥12 h and refraining from alcohol consumption for ≥72 h. Participants were instructed to not eat breakfast and were provided two granola bars (Nature Valley, General Mills Sales) and water (ad libitum). Subjects’ height and weight were recorded, followed by three seated resting blood pressures after 5 min of rest. Subjects were then placed in the supine position, with the bottom portion of their body in a LBNP chamber. All subjects wore a neoprene skirt that formed an airtight seal between the subject and LBNP chamber. The application of LBNP (below the 

A recent study reports that alcohol has an “overall drug harm” greater than that of heroine or crack cocaine, highlighting the serious negative consequences of alcohol abuse on both individuals and society (20). One important recognized “harm” associated with alcohol is increased cardiovascular risk. Specifically, alcohol can lead to increased incidence of both hypertension (22) and orthostatic hypotension (19), especially when one exceeds moderate intake (14, 36). Whereas alcohol-induced hypertension has been partially linked to sympathoexcitation (10, 12, 22), the role of sympathetic neural activity in the development of alcohol-induced hypotension remains unclear.

Progressive lower body negative pressure (LBNP) is a common experimental approach that displaces central blood volume toward the lower extremities and is often used to evoke an orthostatic challenge. Progressive LBNP typically results in an increase in muscle sympathetic nerve activity (MSNA), which induces peripheral vasoconstriction to help maintain arterial blood pressure and prevent orthostatic hypotension (8, 15, 26). Narkiewicz et al. (19) reported a reduction of arterial blood pressure during LBNP after alcohol but not placebo. It is possible that the attenuated arterial blood pressure response was due to decreases in MSNA, but this has not been determined. Several studies have reported that alcohol alters resting MSNA (10, 12, 22, 24, 31), suggesting that alcohol may influence MSNA responses to orthostatic stress.
in both groups.

Fig. 1. Changes in systolic (SAP), diastolic (DAP), and mean (MAP) arterial pressures and heart rate (HR) during progressive lower body negative pressure (LBNP) protocol of 3 min each at different negative pressures: 1100, 2600, and 3100 mmHg (pretreatment). Following this LBNP protocol, each subject’s head was slightly elevated to allow ingestion of either the alcohol or placebo through a straw over a 15-min consumption period. The content of the alcohol or placebo is detailed below. After consumption of the alcohol or placebo, subjects rested supine for 30 min to allow for drink absorption. The 5-min baseline and progressive LBNP protocol were then repeated (posttreatment).

Treatement. The alcohol group consumed 2.5 ml/kg body mass of vodka (40% alcohol by volume) diluted in a 1:4 mixture of Crystal Light, whereas the placebo group consumed 12.5 ml/kg body mass of Crystal Light. Thus, each treatment contained the same total fluid volume and alcohol content. *P < 0.05 pre- vs. posttreatment baseline data in respective groups; †P < 0.05 posttreatment relative to pretreatment.

Venous occlusion plethysmography (ECD; D. E. Hokanson, Bellevue, WA) was used to measure changes in forearm blood flow (FBF) during each baseline and progressive LBNP stage. Mercury-in-silastic strain gauges were placed around the subject’s left forearm at the point of greatest circumference. Cuffs were placed around the subject’s left wrist and upper arm. The wrist cuff was inflated to 220 mmHg to occlude blood flow to the hand. The upper arm cuff was inflated to 60 mmHg for 8 s, followed immediately by deflation for 7 s. Thus, each complete venous occlusion plethysmography cycle lasted 15 s. FBF was measured in milliliters per 100 milliliters per minute. Forearm vascular conductance (FVC) was calculated as MAP divided by FBF, whereas forearm vascular conductance (FVC) was calculated as FBF divided by MAP.

Blood alcohol content was measured with a portable breath analyzer (Alco-Sensor III, Intoximeters) to 1) verify that subjects did not have alcohol in their system before the experiment was started, 2) determine blood alcohol content prior to the posttreatment protocol, and 3) indicate that the subject’s blood alcohol content was returned to a sufficient level to leave the laboratory. The portable breath analyzer was provided by Michigan Tech Public Safety, and study investigators were given a demonstration on its proper use by a trained public safety officer.

Data analysis. Data were imported and analyzed in the WinCPRS software program (Absolute Aliens, Turku, Finland). Muscle sympathetic bursts were automatically detected on the basis of amplitude using a signal-to-noise ratio of 3:1 within a 0.5-s search window.

Table 1. Pre- and posttreatment baseline values for alcohol and placebo groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
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</thead>
<tbody>
<tr>
<td>SAP, mmHg</td>
<td>120 ± 3</td>
<td>124 ± 4*</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>64 ± 2</td>
<td>69 ± 2*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>83 ± 2</td>
<td>87 ± 2*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>59 ± 2</td>
<td>65 ± 2*†</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>13 ± 3</td>
<td>19 ± 4*</td>
</tr>
<tr>
<td>MSNA, bursts/100 heart beats</td>
<td>23 ± 5</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>MSNA burst latency, ms</td>
<td>1,313 ± 16</td>
<td>1,350 ± 17*†</td>
</tr>
<tr>
<td>FBF, ml·100 ml−1·min−1</td>
<td>2.1 ± 0.2</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>FVR, mmHg·ml−1·100 ml·1·min−1</td>
<td>45 ± 4</td>
<td>47 ± 4</td>
</tr>
<tr>
<td>FVC, ml·100 ml−1·min−1·mmHg−1</td>
<td>2.5 ± 0.2</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>BAC, %</td>
<td>0.00 ± 0.00</td>
<td>0.08 ± 0.01*†</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 15 for alcohol and n = 15 for placebo unless otherwise noted). SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity (n = 13 for alcohol and n = 12 for placebo); FBF, forearm blood flow; FVR, forearm vascular resistance; FVC, forearm vascular conductance (n = 15 for alcohol and n = 13 for placebo, all forearm variables); BAC, blood alcohol content. *P < 0.05 pre- vs. posttreatment baseline values in respective groups; †P < 0.05 posttreatment relative to pretreatment values.
centered on a 1.3-s expected burst peak latency from the previous R-wave. Potential bursts were displayed and edited by one trained investigator blinded to the intervention. The average burst area occurring during baseline was normalized to a mean value of 100. MSNA was expressed as bursts per minute, bursts per 100 heart beats, and total MSNA (i.e., the sum of the normalized burst areas per minute). MSNA burst latency was measured from the peak of a burst on the mean voltage neurogram to the R-wave preceding the burst by one complete cardiac cycle.

Statistical analysis. Subject characteristics for alcohol and placebo groups were compared using independent *t*-tests. We used repeated-measures ANOVA with time (progressive LBNP stages) and treatment (pre- vs. posttreatment) as the within-factor variable and group (alcohol vs. placebo) as the between-factor variable to analyze values at rest (group × treatment interaction) and throughout the LBNP protocol (group × time × treatment interaction). When significant group × time × treatment interactions were detected, each group was analyzed separately as time × treatment, and a priori post hoc analyses of treatment were performed when a respective time × treatment interaction was significant. Means were considered significantly different when *P* < 0.05. Results are expressed as means ± SE.

RESULTS

Pre- and posttreatment baseline values for the alcohol and placebo groups are shown in Table 1. HR, MSNA burst
frequency, and blood alcohol content were significantly elevated during alcohol but not placebo (group \times treatment, P < 0.05). In contrast, alcohol and placebo elicited similar increases in MAP (treatment, P < 0.05; group \times treatment interaction, P > 0.05). Both alcohol and placebo increased MSNA burst latency, but increases were significantly augmented in the alcohol group (group \times treatment interaction, P < 0.02), as shown in Table 1.

Figure 1 demonstrates that SAP, DAP, and MAP responses to progressive LBNP were significantly blunted after alcohol but not placebo (group \times time \times treatment, P < 0.05). In contrast, HR responses were similar during progressive LBNP before and after both treatments. Figure 2 demonstrates that there were no differences in MSNA responses between the pre- and posttreatment for the alcohol or placebo groups. However, Fig. 3 demonstrates that alcohol altered MSNA burst latency responses to progressive LBNP compared with placebo (group \times time \times treatment, P < 0.01).

Figure 4 represents the FBF responses to progressive LBNP for the alcohol and placebo groups. Increases in FVR were significantly blunted (group \times time \times treatment, P < 0.05) during progressive LBNP following the consumption of alcohol, whereas FVR responses were not altered by placebo. However, changes in FBF and FVC were not different between groups (group \times time \times treatment, P > 0.05) during progressive LBNP.

DISCUSSION

The present study examined sympathetic neural and cardiovascular responses to progressive LBNP before and after consumption of alcohol or placebo. Our findings reveal that alcohol consumption compromises the maintenance of arterial blood pressure and increases in FVR during orthostatic challenge, consistent with a previous study (19). However, the blunted arterial blood pressure and FVR responses to LBNP after alcohol consumption were not accompanied by an attenuated MSNA response. In contrast, alcohol altered MSNA burst latency at rest and in response to progressive LBNP, a finding of interest when one considers that altered MSNA burst latencies may be associated with increased incidence of syncope (11). The lack of MSNA adjustment to the larger drop in arterial blood pressure during progressive LBNP, coupled with altered sympathetic burst latency responses, suggests that alcohol blunts MSNA responses to orthostatic stress.

Previous studies have determined that alcohol increases resting HR (10, 12, 19, 22, 24, 25, 31), MAP (10, 12, 22), and MSNA (10, 12, 22, 24, 25, 31). The present study confirms previously reported increases in resting HR and MSNA after alcohol ingestion, but similar increases of resting MAP in the alcohol and placebo groups preclude a conclusion that acute alcohol ingestion elicited an acute increase in arterial blood pressure. It is plausible that gastric distention may have contributed to both alcohol- and placebo-induced increases of resting MAP since such distention has been reported to increase arterial blood pressure (33). However, distention of splanchnic organs has also been associated with increases in MSNA (5, 23), yet our placebo group did not demonstrate increases in resting MSNA. We did not measure gastric distention, a noted limitation that must be considered when interpreting the resting blood pressure data of the present study. Grassi et al. (10) previously demonstrated concomitant increases in MSNA and arterial blood pressure after alcohol ingestion, suggesting that the alcohol induced pressor effect occurs, in part, through increased MSNA. The present findings allow for additional interpretation by demonstrating that alcohol does not always elicit parallel increases in arterial blood pressure and MSNA.

Prior investigations have noted that alcohol may compromise orthostatic tolerance to LBNP (4, 19). Eisenhofer et al. (4) found that moderate alcohol intake resulted in a decrease in systolic arterial blood pressure during four levels of progressive LBNP, possibly through an impaired vasoconstrictive response. Narkiewicz et al. (19) later determined that indeed alcohol impairs forearm vasoconstriction during LBNP, leading to orthostatic hypotension. However, the mechanism underlying the alcohol-mediated impairment of both arterial blood pressure and forearm vasoconstriction was not determined. Increases in MSNA during LBNP occur primarily through a baroreflex response (26), and peripheral vasoconstriction is often related to the extent of MSNA activation (8, 15). The present study once again demonstrated that alcohol elicited a blunted arterial blood pressure response and impaired forearm vasoconstriction during orthostatic stress, but these attenuated responses were not associated with concurrent re-
ductions of MSNA (Figs. 1 and 2). Thus, evidence is accumu-
lating to suggest that alcohol consistently reduces arterial blood
pressure responsiveness to orthostatic challenges, and our find-
ings provide new mechanistic insight by demonstrating that
this altered arterial blood pressure response does not appear to
be mediated by a reduced MSNA response. However, given
that MSNA typically increases in response to reductions in
arterial blood pressure (via sympathetic baroreflex pathways),
it is reasonable to suggest that the more dramatic drop of
arterial blood pressure during combined alcohol and progres-
sive LBNP should have augmented MSNA responses. This did
not occur, suggesting a potential impairment of sympathetic
baroreflex function with alcohol, a response that may have
contributed to the altered vasoconstriction during combined
alcohol and progressive LBNP. Nevertheless, the remarkably
similar increases of MSNA during progressive LBNP in both
groups and treatments suggest that other factors must play a
role in the more dramatic drop in arterial blood pressure during
orthostatic stress and alcohol ingestion.

Fig. 4. Changes in forearm blood flow (FBF), forearm vascular resistance (FVR), and forearm vascular conductance (FVC) during progressive LBNP. Increases in FVR were significantly blunted by alcohol (group × time × treatment, P < 0.05). Group × time × treatment interactions were P > 0.05 for both FBF and FVC, whereas the time effect was P < 0.01 for each treatment in both groups. *P < 0.05 vs. corresponding post-alcohol value.

If changes in MSNA responsiveness are not primarily re-
sponsible for the alcohol-mediated attenuation of arterial blood
pressure during orthostatic stress, what is? First, it is important
to note that the attenuated forearm vasoconstriction during alcohol and LBNP was modest, and although there was a significant group × time × treatment interaction for FVR, there was a lack of significance when expressed as FVC. Evidence suggests that changes in regional vascular conductance may better indicate changes in blood pressure and regional blood flow than regional vascular resistance (21). Furthermore, changes in vascular resistance may be less reliable when cardiac output is not in a steady state (21). Thus, changes in FVR during progressive LBNP should be interpreted with some caution. Additionally, the study by Narkiewicz et al. (19) did not report FVC during progressive LBNP following the consumption of alcohol. It is possible that the alcohol-mediated attenuation of MAP during orthostatic stress may be related to alterations in other vascular beds. For example, alcohol has been demonstrated to increase splanchnic blood flow (16), whereas progressive LBNP decreases splanchnic blood flow (28). It is possible that the alcohol-mediated vasodilation of the splanchnic bed at rest may influence LBNP-mediated vasoconstriction of this same bed. The present study only examined forearm vascular responses and did not assess blood flow to the splanchnic region or other vascular regions.

Alcohol is reported to induce peripheral vasodilation (13), which is thought to be mediated by neurohormonal substances (35). Plasma vasopressin has been reported to increase significantly during progressive LBNP (32), whereas acute alcohol ingestion appears to suppress resting plasma vasopressin levels during the first hour of ingestion (3). It is possible that plasma vasopressin decreased after alcohol and impaired vasoconstriction during LBNP in the present study, but we did not measure vasopressin levels. Additionally, ethanol has been shown to elevate other hormones during orthostatic stress, such as noradrenaline (4) and epinephrine (27). Takahashi et al. (27) found that individuals who experience syncope during orthostatic challenge after consuming alcohol have augmented plasma epinephrine levels. It was proposed that the increased epinephrine could have induced vasodilation by binding to β2 receptors (27). These hormones, along with other mechanisms such as nitric oxide and prostaglandins (35), may contribute to the vasodilatory and hypotensive effects of alcohol.

Previous studies have demonstrated changes in MSNA burst latency using a variety of interventions to specifically elicit MSNA responses (6, 34). For example, Valsalva’s maneuver, simulated diving, deep breathing (6), and arousal from sleep (37) all decrease MSNA burst latencies. Fagius et al. (6) proposed that shorter than normal MSNA burst latency might be an advantage for blood pressure regulation in emergency situations. On the other hand, Iwase et al. (11) reported that MSNA burst latencies decrease, whereas the standard deviations of latencies increase as individuals approach presyncope. Our findings demonstrate that alcohol increases MSNA burst latency at rest and alters burst latency responses to progressive LBNP. Specifically, MSNA burst latencies increased slightly throughout our moderate progressive LBNP protocol during both alcohol and placebo pretreatments as well as the placebo posttreatment, a finding that is consistent with Cooke et al. (2). Interestingly, burst latencies decreased during combined alcohol and progressive LBNP. This finding lends further support that alcohol alters MSNA responses to orthostatic challenge and, when taken in conjunction with the findings of Iwase et al. (11), may lend insight into alcohol-mediated syncope.

It is important to note that our progressive LBNP protocol was not designed to specifically bring participants to presyncope, and we acknowledge this as a limitation. Only one participant experienced presyncopal symptoms during LBNP at −40 mmHg, and this individual was in the placebo group. We cannot be certain how alcohol affects MSNA during actual presyncope, but we believe it is reasonable to speculate that the alcohol-mediated attenuation of arterial blood pressure observed during progressive LBNP would translate and contribute to reduced orthostatic tolerance. Future investigations examining the influence of alcohol on arterial blood pressure responses to orthostatic stress might focus on protocols specifically designed to induce presyncope. One common form of syncope is a neurally mediated, or vasovagal, syncope in which a withdrawal of MSNA induces a rapid hypotensive episode (17, 18). Alcohol is thought to predispose individuals to neurally mediated syncope (29), but it is not clear whether a withdrawal of MSNA actually occurs during syncopal or presyncopal episodes related to alcohol. Moreover, this issue is complicated by a recent article by Cooke et al. (2) that reports that MSNA was maintained or increased in seven of 17 healthy subjects experiencing presyncope during intense LBNP. Also relevant to the present study, Cooke et al. (2) reported a decrease in MSNA burst latency during intense LBNP, consistent with the findings of Iwase et al. (11), suggesting that this may be a primary factor in presyncope and syncope.

In conclusion, alcohol elicits a more dramatic drop of arterial blood pressure during progressive LBNP that is not associated with attenuated MSNA responsiveness. However, alcohol increases MSNA burst latency at rest and alters MSNA burst latency responses to progressive LBNP. This potential disturbance of MSNA burst latency, coupled with a lack of MSNA adjustment to the reductions in arterial blood pressure during orthostatic stress, suggests that alcohol impairs MSNA and arterial blood pressure relations in humans.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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