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Consumption of alcohol leads to platelet inhibition in men

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ABSTRACT

Introduction: Alcohol consumption has been shown to alter coagulation. However, thromboelastography with platelet mapping (TEG PM) to evaluate platelet function has not been studied.
Methods: A prospective, non-randomized study of healthy volunteers was conducted. Baseline TEG PM were collected. Subjects consumed alcoholic or non-alcoholic beverages for 2 h. Repeat TEG PM was collected.
Results: Fifty-four volunteers entered either the experimental group (EG, 17 women and 16 men) or control group (CG, 11 women and 10 men). After 2 h of alcohol or non-alcoholic drink consumption the median breath alcohol level was 0.08 [IQR 0.05, 0.12] in the EG and 0.00 in the CG. After consumption of alcohol, male EG subjects demonstrated higher median Adenosine Diphosphate (ADP) inhibition of platelet function (15.7% [3.9, 39.3] vs 8.2% [0, 30.1), $p = 0.035$), but female subjects did not. There was no evidence of increased arachidonic acid (AA) platelet inhibition in the EG compared to CG. Clot strength (TEG maximum amplitude) was not different between groups.
Conclusion: After consumption of alcohol, healthy male volunteers demonstrate ADP platelet inhibition by TEG PM.

Introduction

Estimates show that approximately 33% of trauma patients have a positive blood alcohol level at the time of admission.[1] Studies have shown mixed results regarding the effect of alcohol consumption on outcomes for trauma patients.[2,3] Multiple studies have shown that alcohol consumption alters coagulation and with hemorrhage being a leading cause of death in trauma, alcohol consumption could compound the effects of the acute coagulopathy of trauma.[4–7]

Coagulation in trauma has also been shown to differ between genders. Gee et al. showed that higher estrogen to progesterone ratios resulted in faster onset of clot formation and fibrin cross-linking.[8] Another study using thrombelastography (TEG) showed a hypocoagulable state in acutely intoxicated males but not female volunteers.[9] In the clinical setting, Cook et al. found that acute intoxication at the time of admission led to a relative hypocoagulable state on TEG that was not detected by conventional assays and was associated with a decreased incidence of deep venous thrombosis.[10]

Although there is evidence that alcohol affects coagulation and that it may affect different genders differently, it is unclear what the effect of alcohol is on platelet function. We hypothesized that acute alcohol intoxication would result in an alteration in platelet function and these alterations would differ by gender. To evaluate this hypothesis, we conducted a separate study from previous work published by our laboratory group to specifically investigate different platelet receptor function after consumption of alcohol.

Methods

We conducted a prospective, non-randomized observational study including 54 healthy volunteers. All protocols were approved by the Oregon Health & Science University Institutional Review Board (IRB) and consent was obtained from each participant prior to starting the experiment. Due to IRB restrictions at our institution, there is a mandate that volunteer participants involved in studies in which alcohol is consumed cannot be randomized into a consumption versus non-consumption group, regardless of the informed consent process. Each participant had a baseline blood alcohol level (BAL) measured with the Alcohawk Pro breath analyzer (Q3 Innovations LLC, Independence, IA) and a baseline

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peripheral venous blood sample which was analyzed using Thrombelastography with Platelet Mapping (TEG 5000) (Haemonetics Inc, Niles, IL). Fresh whole blood was drawn into citrated tubes, assayed at 37 °C into four different TEG-PM analyzers. The first assay was activated with Kaolin for maximal platelet activation. The second assay was performed with full platelet inhibition by blocking all thrombin and only allowing clot to form based on fibrin. The last two assays were activated with either an adenosine diphosphate (ADP) receptor agonist or arachidonic acid (AA) receptor agonist. Volunteers then chose to either enter the experimental group (EG), which consumed alcoholic beverages of their choice, or the control group (CG), which drank non-alcoholic beverages. The volunteers interacted in a social setting with the same food options for both the EG and CG. For those volunteers entering the EG, there was no minimal required amount of alcohol consumed but there was a maximal amount based on body weight (2g ethanol/kg) which corresponds to a maximum BAL of 200 mg/dL. After 2 h, a repeat BAL was measured and a second peripheral blood sample was obtained for repeat TEG-PM.

Inclusion criteria included age >21 years, completion of an alcoholism screening questionnaire, and the guarantee of a designated driver after the study for all volunteers. Exclusion criteria included positive initial BAL, suspected pregnancy, known clotting disorder, or current use of anticoagulants or antiplatelet agents such as aspirin, clopidogrel, warfarin, or any other novel anticoagulant.

Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL) using Mann-Whitney U and Wilcoxon signed ranked tests. Data were reported using medians and interquartile ranges. Significance was denoted as $p < 0.05$.

Results

Fifty-five volunteers participated in the study with 1 volunteer being excluded due to a positive BAL at baseline. There were 33 volunteers who chose to enter the EG (17 women, 16 men) and 21 volunteers who chose to enter the CG (11 women, 10 men). Baseline BAL was 0.00 mg/dl in both the EG and CG. After 2 h, the median BAL in the EG was 0.08 mg/dl (IQR 0.05, 0.12) and 0.00 mg/dl in the CG. Median age in the EG was 33 years (IQR 30, 39) and 32 in the CG (29, 35), which was not significantly different (Table 1). Baseline and post-consumption standard TEG values were also collected and were not significantly different between the CG and EG in either gender (Table 2).

For females in the CG, baseline median ADP inhibition was 4.0% (IQR 0.7, 12.8) and median AA inhibition was 0.0% (IQR 0.0, 16.1) which was not significantly different than post-consumption median ADP inhibition of 1.4% (IQR 0.0, 7.5) or median AA inhibition of 4.2% (IQR 0.0, 6.4) (Fig. 1).

For females in the EG, baseline median ADP inhibition was 9.4% (IQR 2.1, 24.5) and median AA inhibition was 3.1% (IQR 0.0, 6.9) which was not significantly different than post-consumption median ADP inhibition of 6.3% (IQR 4.4, 19.2) or median AA inhibition of 0.0% (IQR 0.0, 5.8) (Fig. 2).

For males in the CG, baseline median ADP inhibition was 6.9% (IQR 0.0, 10.8) and median AA inhibition was 0.0% (IQR 0.0, 17.3) which was not significantly different than post-consumption median ADP inhibition of 4.5% (IQR 0.0, 13.5) or median AA inhibition of 3.1% (IQR 0.0, 6.7) (Fig. 3).

For males in the EG, baseline median ADP inhibition was 8.3% (IQR 0.0, 30.1) which was statistically significantly different than post-consumption median ADP inhibition of 15.7% (IQR 3.9, 39.3), $p = 0.035$. For males in the EG, baseline median AA inhibition was 6.1% (IQR 0.3, 38.8) which was not significantly different than post-consumption median AA inhibition of 9.7% (IQR 0.0, 27.1) (Fig. 4).

Discussion

Alcohol consumption is common among trauma patients and alterations to normal physiology that alcohol may have are important to elucidate, as this has the potential to impact a large number of trauma patients. The prevalence of alcohol consumption also has a large socioeconomic burden on trauma systems throughout the world. With hemorrhagic shock being a leading cause of death in the trauma population and the high incidence of alcohol intoxication in trauma patients, it is important to investigate the connections between acute alcohol intoxication and the coagulation cascade.

Previous studies have shown slower clot formation and decreased clot strength after acute alcohol consumption and that these parameters may differ between males and females. Our study showed that acute alcohol consumption is associated with ADP-

Table 1
Demographics of volunteer participants.

	Control Group (CG)	Experimental Group (EG)
	n = 21	n = 33
Age (years), median (IQR)	32 (29,35)	33 (30,39)
Male	10	16
Female	11	17
Initial BAL (mg/dL)	0.00	0.00
Average Post-consumption BAL (mg/dL)	0.00	0.08

Table 2
Pre and Post-consumption TEG values. Median (IQR).

		R-time (min)	K-time (min)	α-angle (degrees)	Max Amplitude (mm)	LY-30 min (%)
Pre-consumption	Female CG	6.2 (5.9,8.1)	1.5 (1.5, 1.7)	68.3 (66.3,68.7)	62.9 (58.6,66.5)	2.1 (0.6,4.2)
	Female EG	6.8 (6.5,7.7)	1.7 (1.5,1.9)	65.6 (62.8,68.4)	61.7 (55.8,66.3)	1.5 (1.1,4.8)
Post-consumption	Female CG	7.6 (7.2,8.1)	1.7 (1.5,1.8)	66.3 (64.4,67.8)	63.9 (51.3,67.5)	1.2 (0.2,4.1)
	Female EG	7.1 (6.8, 7.5)	1.8 (1.7,1.8)	65.2 (63.7,66.2)	63.3 (56.1,65.0)	2.8 (0.6,6.6)
Pre-consumption	Male CG	7.4 (7.0,8.2)	1.9 (1.6,2.2)	62.5 (59.1,68.6)	60.1 (55.8,63.6)	9.9 (2.9,13.9)
	Male EG	7.2 (6.6,7.8)	1.9 (1.8,2.1)	63.2 (61.3,66.2)	60.6 (55.4,63.4)	3.9 (0.6,11.7)
Post-consumption	Male CG	7.3 (6.9,8.2)	1.9 (1.8,2.0)	63.6 (62.3,64.7)	60.9 (51.9,62.5)	8.6 (1.1,13.2)
	Male EG	7.0 (6.4,7.7)	1.9 (1.7,2.0)	64.4 (62.8,68.0)	62.0 (59.4,64.5)	2.4 (0.7,10.4)

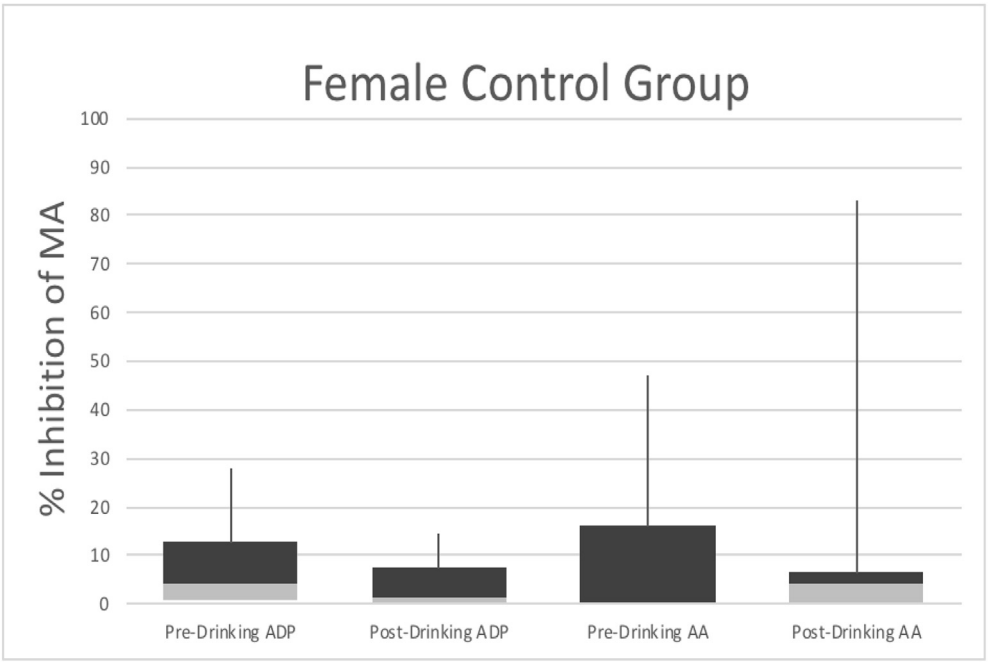

Fig. 1. Female CG pre and post-consumption ADP and AA inhibition.

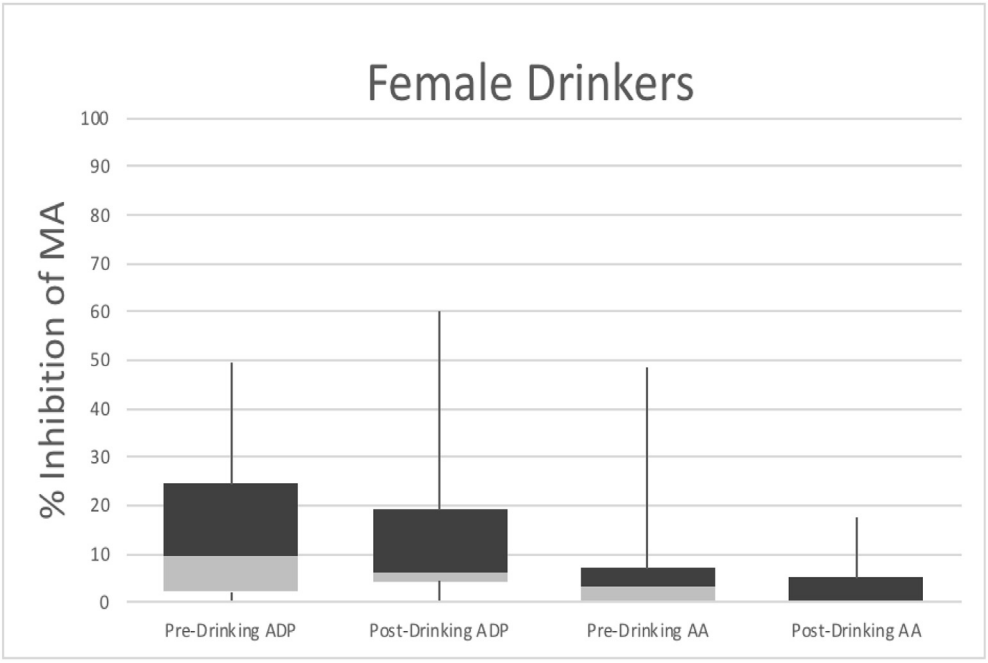

Fig. 2. Female EG pre and post-consumption ADP and AA inhibition.

receptor mediated platelet inhibition in men but not in women. Previous studies looking at the effect of alcohol consumption on the coagulation cascade were performed at higher levels of intoxication than in the current study. The difference found at lower levels of alcohol intoxication could possibly be even more pronounced with higher levels of intoxication. The combination of platelet dysfunction with impaired clot formation and fibrin cross-linking shown in other studies may lead to different resuscitation strategies in acutely intoxicated male trauma patients.

This study along with others has shown differences in coagulation between genders, but when it comes to platelet receptor function, debate remains whether the alterations are due to androgens or estrogens as platelets contain receptors for both of these hormones. The vast majority of research in this field comes from interventional cardiology looking at different antiplatelet medications after coronary stenting. Yu et al. looked at platelet reactivity in 8,448 patients taking clopidogrel after percutaneous coronary intervention and found that women were more likely to maintain high ADP receptor activity than men, indicating their platelet ADP receptors were less sensitive to clopidogrel.[11] In a

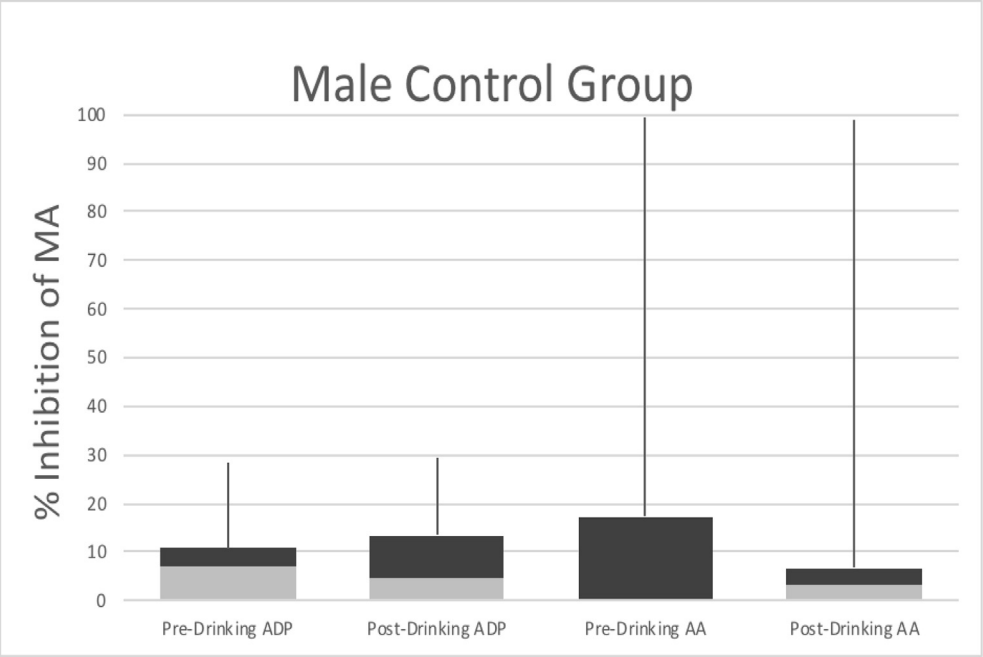

Fig. 3. Male CG pre and post-consumption ADP and AA inhibition.

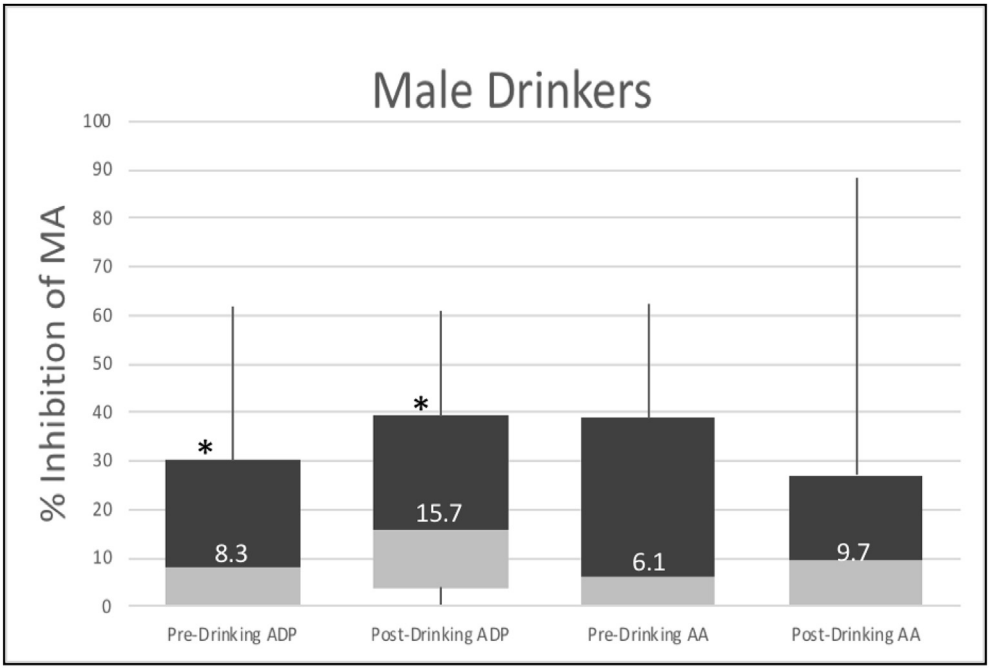

Fig. 4. Male EG pre and post-consumption ADP and AA inhibition (*p = 0.035).

separate study looking at 160 patients with stable coronary artery disease, women had a significantly inferior response to ADP antagonist therapy but a similar response to AA antagonist therapy when compared to men.[12] Jaremo et al. studied 73 patients' platelet ADP receptor function after acute cerebrovascular infarction and found that female's ADP receptors were less reactive than males.[13] These studies show that the platelet ADP receptor in females responds differently to agonist and antagonists than males suggesting that there is either some inherent difference in this receptors configuration between genders or it is being modulated by some other mechanism. This could explain the differences seen in the current study in that the female participant's platelet ADP receptors appear to be more resistant to alterations than males by acute alcohol intoxication.

While estrogen and progesterone levels, oral contraceptive use, or menstrual cycle status was not assessed, this study provides a basis for future studies investigating the interactions between sex hormones, alcohol, and coagulation. The lack of these values was a limitation of our study and these should be included in future studies of coagulation and platelet function.

Many institutions, including ours, are using TEG PM with increasing frequency for patient management decisions. Currently, TEG PM is generally used for patients on anti-platelet medications such as aspirin or clopidogrel to assess inhibition of the ADP or AA receptor as desired for patients after cardiac or vascular interventions. TEG PM can also be used to assess for the need for platelet transfusion in patients reportedly taking anti-platelet medications who present with hemorrhage after trauma or other causes. Daley et al. reviewed 90 patients with traumatic brain injury and found that regardless of the use of antiplatelet medications, the patients with platelet ADP receptor inhibition on TEG PM had a four-fold higher in-hospital mortality.[14] With the association of ADP platelet receptor inhibition and alcohol intoxication in the current study, this provides basis for further larger studies on intoxicated patients. TEG PM could play a role in aiding decisions on therapeutic interventions for those patients with active hemorrhage who are acutely intoxicated.

Our study did have limitations which should be taken into account. First, due to limitations by our IRB, we were unable to perform a randomized study so volunteers were able to choose whether or not they would imbibe. Those who chose to enter the EG may differ from those in the CG in that they tend to drink alcohol more often and these differences were not controlled for. There was also a limitation on the amount of alcohol a volunteer could consume, leading to lower blood alcohol levels than our previous studies and lower than what is often seen in the clinical setting. Therefore, there may have been other differences at higher levels of intoxication that were not observed. Also, the type of alcohol consumed was beer, wine, or liquor and was up to the volunteer's discretion. Men and women in the EG may have chosen different types of alcohol which could have contributed to the gender differences we observed. Also, the status of the female participant's menstrual cycle and use of oral contraceptives was not assessed. Since different levels of estrogen and progesterone have been shown to alter coagulation, this may have confounded our results. Lastly, we did not obtain platelet counts of the participants, but although this is a commonly collected lab value it only tells the total number of platelets and not the function of those platelets as the TEG PM does.

In summary, we found that acute alcohol consumption is associated with ADP mediated inhibition of platelets in men but not in women. When combined with previous studies, alcohol consumption in men leads to a relative hypocoagulable state in all aspects of TEG and TEG-PM but not in women. Although further investigation and larger studies are needed, but these differences in coagulation may contribute to differences in outcomes for intoxicated male trauma patients compared to other trauma patients.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.02.020.

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