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Chronic Binge Alcohol Consumption During Pregnancy Alters Rat Maternal Uterine Artery Pressure Response

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Abstract

We aimed to investigate pressure-dependent maternal uterine artery responses and vessel remodeling following gestational binge alcohol exposure. Two groups of pregnant rats were used: the alcohol group (28.5% wt/v, 6.0 g/kg, once-daily orogastric gavage in a binge paradigm between gestational day (GD) 5–19) and pair-fed controls (isocalorically matched). On GD20, excised, pressurized primary uterine arteries were studied following equilibration (60 mm Hg) using dual chamber arteriograph. The uterine artery diameter stabilized at 20 mm Hg, showed passive distension at 40 mm Hg, and redeveloped tone at 60 mm Hg. An alcohol effect (P=0.0025) was observed on the percent constriction of vessel diameter with greater pressure-dependent myogenic constriction. Similar alcohol effect was noted with lumen diameter response (P=0.0020). The percent change in media:lumen ratio was higher in the alcohol group (P<0.0001). Thus, gestational alcohol affects pressure-induced uterine artery reactivity, inward-hypotrophic remodeling, and adaptations critical for nutrient delivery to the fetus.

Keywords

FASD; pregnancy; uterine; alcohol

Introduction

Fetal Alcohol Spectrum Disorders (FASD) refers to the range of physical, mental, functional, and/or behavioral abnormalities following developmental alcohol exposure (Flak et al., 2014; Ramadoss, Lunde, Chen, West, & Cudd, 2007; Riley & McGee, 2005; Sokol, Delaney-Black, & Nordstrom, 2003). The United States Surgeon General and the American Academy of Pediatrics have issued recommendations to abstain from any alcohol use during

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pregnancy (General, 1981; U.S. Surgeon General & Vice Admiral Richard H. Carmona, 2005; Williams, Smith, & Committee On Substance, 2015). Despite these repeated advisories, the CDC recently estimated alcohol use in 10.1% of pregnant women aged 18–44 and binge drinking in 3.1% of pregnant women within the years 2011–2013 (Tan, Denny, Cheal, Sniezek, & Kanny, 2015). Among school-age children in the United States and some Western European countries the prevalence of FASD is estimated to be 2–5% (May et al., 2009).

In the past four decades, marked progress has been made to understand the effects of maternal alcohol consumption during pregnancy. Thus far, an extensive number of studies have focused on understanding alcohol's teratogenic role in brain & neurodevelopment (Flak et al., 2014; Riley & McGee, 2005; Riley, McGee, & Sowell, 2004), while little is known about its effects on the mother, specifically the maternal uterine artery which delivers all the nutrients and oxygen to the developing fetus and its supporting tissues. We herein focus on the effects of binge alcohol exposure on remodeling of the maternal uterine artery. During normal pregnancy, the maternal uterine artery undergoes outward hypertrophic remodeling, characterized by an increased vessel cross sectional area and a decreased ratio of medial thickness to lumen diameter or media:lumen ratio. Systemic vascular adaptations to pregnancy include increases in vascular compliance and a decrease in mean arterial blood pressure (Barron, Mandala, & Osol, 2010; M. Cipolla & Osol, 1994; Osol & Mandala, 2009). These changes to the maternal vasculature are essential for a healthy pregnancy outcome..

We and others have reported that alcohol consumption during pregnancy results in altered uterine endothelial adaptations (Ramadoss, Jobe, & Magness, 2011; Ramadoss & Magness, 2011, 2012a, 2012c), agonist-dependent vessel relaxation (Subramanian et al., 2014), spiral artery remodeling (Gundogan et al., 2008), and blood flow (Falconer, 1990). However, there exists no study on alcohol-related myogenic response, a critical gestational uterine vascular adaptation. In response to changes in the transmural pressure, the uterine artery will react by dilating or constricting to alter the resistance in order to maintain the perfusion rate, an intrinsic adaptation called myogenic reactivity (Barron et al., 2010; Bevan & Laher, 1991; Johansson, 1989; Telezhkin et al., 2008).The aim of this study was to investigate pressure-dependent maternal uterine artery responses and vessel remodeling parameters following chronic binge alcohol exposure during pregnancy.

Materials and Methods

Treatment groups and alcohol dosing paradigm

All experimental procedures were in accordance with National Institutes of Health guidelines (NIH Publication No. 85–23, revised 1996) with approval by the Animal Care and Use Committee at the Texas A&M University. Rats were housed in a temperature-controlled room (23°C) with a 12:12-hour light–dark cycle. Timed pregnant Sprague–Dawley rats were purchased from Charles River (Wilmington, MA). Two groups were utilized including a nutritional pair-fed control and a binge alcohol group. The number of animals in the pair-fed control and alcohol groups were n=11 and n=12 respectively. Uterine arteries that were either mechanically damaged during tissue preparation for pressure

myography or did not show any functional response by constricting at 60 mm Hg were not studied, and the number of these vessels was not different between treatment groups (Novak, Ramirez, Gandley, Sherwood, & Conrad, 2002; Veerareddy, Campbell, Williams, Baker, & Davidge, 2004). Maternal uterine arteries from a total of n=8 rats in each group exhibited pressure-dependent vascular response by constricting at 60 mm Hg and were all analyzed. Dams in the alcohol group received a binge-like- dose of 6 g/kg body-weight/day of 28.5% w/v, ethanol via oral gavage from GD 5–19 (Thomas, Idrus, Monk, & Dominguez, 2010; Thomas, Sather, & Whinery, 2008). The regimen of exposure utilized in this study is based on reported alcohol consumption patterns in pregnant women and FASD animal models (Caetano, Ramisetty-Mikler, Floyd, & McGrath, 2006; Church & Gerkin, 1988; Cudd, Chen, & West, 2002; May et al., 2013; Thomas et al., 2010; Thomas et al., 2008). Daily feed intake of the alcohol rat was measured. The pair-fed control dams were matched with alcohol-fed dams of similar weight, and food intake was measured daily and yoked (Thomas, Abou, & Dominguez, 2009). Pair-fed control animals were also gavaged daily with isocaloric maltose-dextrin to control for the calories derived from alcohol. There was no significant maternal weight difference between the groups on GD 20 (Pair-fed controls, 310 ± 8 g; Alcohol, 305 ± 7 g). Animals were sacrificed on GD 20, one day after the last alcohol exposure.

Tissue preparation

Following sacrifice, the whole uterus was transferred to a large 200 mm petri dish filled with solidified Sylgard containing cold HEPES – Bicarbonate Solution pH 7.4 (NaCl 130 mM; KCl 4 mM; $MgSO_4.7H_2O$ 2.5 mM; $NaHCO_3$ 4.05 mM; $CaCl_2$, 2.4 mM; HEPES 10 mM; KH_2PO_4 1.18 mM; Glucose 6 mM; EDTA 0.024 mM), where it was pinned to facilitate the cutting of the uterine artery. Primary uterine artery of approximately 3–5 mm was cut between bifurcations and washed in HEPES-Bicarbonate Solution, to remove excess fat and connective tissues. A dual-chamber arteriograph was used for our experiments, which permits vessels from a control and an alcohol-fed dam to be studied consecutively under identical experimental conditions

2.3 Pressure myography

A dual-chamber pressure myograph system (Living Systems Instruments, VT) was used for the experiments. The chamber consisted of an inflow and an outflow port to maintain the bath level such that the vessel remained submerged under the superfusate of warmed HEPES buffer. There were two glass cannulas on opposite sides of the chamber. The vessel was mounted on these cannulas positioned above a cover glass from where it was visualized utilizing an inverted microscope (Accu-Scope) mounted with a CCIR camera (IonOptix Corporations, MA). One of the cannula was connected to a pressure transducer, which converted fluid pressure into an electrical signal and sent this data to the pressure servo controller. Based on the output value, the pressure servo controller in-turn sent signal to the pressure pump to maintain the set pressure. The pressure was observed with the pressure monitor and was recorded with IonWizard software (IonOptix Corporations, MA). Simultaneously, the camera sent the image to the video dimension analyzer software (IonWizard, IonOptix Corporation, MA) which calculated various parameters such as vessel diameter, lumen diameter, media:lumen ratio, etc.

The chambers, cannulas, tubing, and stopcocks were primed with HEPES buffer prior to mounting the vessel, to ensure no air passed into the vessel. Each vessel was transferred to one of the two chambers of the dual-chamber pressure myograph system. Using a dissection microscope, the endothelium-intact vessel was then mounted on the glass cannulas that were connected to the pressure transducer and tied using two nylon ligatures. Excess blood was removed from inside the vessel by slowly injecting buffer through the stop valve using a syringe attached to a 45μm syringe filter. The opposite end was tied off using a nylon ligature, which was in-turn ligated to the opposite glass cannula. The chamber was placed on the inverted microscope to complete the setup described above (Figure 1). The pressure transducer tubing was filled with warm 37°C HEPES buffer, and were connected via stopcocks to the cannulas, creating a closed-pressure system.

Experimental protocol and data analysis

Transmural vessel pressure was gradually increased and set to 60 mm Hg using the pressure servo controller. The vessels were allowed to equilibrate in the 37°C superfusate buffer for 60 min, or until the vessels started showing myogenic tone (Withers, Taggart, Baker, & Austin, 2009). The pressure was then lowered to 20 mm Hg where constriction was inhibited (Barron et al., 2010) and baseline measurements of vessel diameter, lumen diameter, and media:lumen ratio were recorded. The diameter was considered stable when the constrictions stabilized or there were no detectable changes in measured variables (3min – 5min). Subsequently, the pressure was increased by 20 mm Hg, starting 40 mm Hg until the pressure reached 120 mm Hg. After the measurements were complete, the data were transferred to a computer for analysis. The maximal contracted diameters at the stabilized state were determined for each pressure. The percent change from the baseline was analyzed by a two-way ANOVA with the treatment group as the between factor and the pressure as the within factor. Further pairwise comparisons were performed when appropriate using Fisher's protected LSD. Level of significance was established *a priori* at $P < 0.05$.

Results

The dual-chamber arteriograph system described above is graphically represented (Figure 1). To illustrate the pressure-dependent response of a uterine artery, an experimental tracing from a control and an alcohol-fed pregnant dam is depicted in Figure 2. The maternal uterine artery diameter stabilized at 20 mm Hg, showed passive distension with increase in pressure to 40 mm Hg, and redeveloped tone at 60 mm Hg and was maintained until 120 mm Hg.

In both control and alcohol treatment groups, maternal uterine artery exhibited pressure-dependent myogenic constriction as pressure was increased from 40 mm Hg (Figure 3). The percent change in the uterine artery vessel diameter from baseline showed a significant main effect of pressure in both the control and alcohol groups (pressure effect, $P < 0.000l$). There was also a main effect of alcohol on the percent constriction of the uterine artery vessel diameter (alcohol effect, $P = 0.0025$); the alcohol group exhibited significantly greater pressure-dependent constriction compared to the controls.

The uterine artery lumen diameter displayed a significant main effect of pressure in both control and alcohol groups (pressure effect, $P < 0.0001$; Figure 4). Similar to the uterine

artery vessel diameter, percent change in uterine artery lumen diameter was significantly greater in the alcohol group; the alcohol group exhibited greater pressure-dependent constriction of lumen diameter compared to the control group (alcohol effect, $P = 0.0020$).

The percent change in the media:lumen ratio, an indicator of vessel remodeling, was significantly higher in the alcohol group compared to the controls (alcohol effect, $P < 0.0001$; Figure 5). Both the control and the alcohol groups displayed a significant main effect of pressure (pressure effect, $P < 0.0001$).

Discussion

The purpose of this study was to investigate the functional response of the maternal uterine artery to changes in intra-luminal pressure following chronic binge alcohol exposure during pregnancy. Three salient findings can be gleaned from the current study: First, gestational alcohol exposure results in greater pressure-dependent uterine artery constriction. Second, uterine artery vessel/lumen diameters and the medial:lumen ratio together indicate gestational alcohol-induced inward hypotrophic remodeling. Third, our overall findings suggest that *in vivo* binge-alcohol exposure leads to altered gestational uterine arterial adaptations.

In this study, both the excised uterine arties of control and alcohol-fed rats exhibited decreases in the uterine artery diameter as the intraluminal pressure was increased from 40 mm Hg. However, compared to the controls, gestational alcohol exposure resulted in greater pressure-dependent uterine artery constriction, and the effect was most pronounced at physiologic pressures of 80 mm Hg – 120 mm Hg. Interestingly, we observed that the uterine arteries of the control group maintained their diameter throughout this range of pressures, whereas the alcohol group exhibited lower vessel diameter at the same pressures. We can deduce using Poiseuille's equation that resistance is inversely proportional to the radius to the fourth power, and thus changes in diameter observed in our study can lead to large significant decreases in uterine blood flow. These data are consistent with previous reports demonstrating ~40% decrease in uterine blood flow (UBF) following chronic binge alcohol exposure in sheep (Sawant, Ramadoss, Hankins, Wu, & Washburn, 2014). Chronic alcohol-induced UBF decrease of about ~40% would lead to a reduction in the uterine artery radius to normalize the shear, as noted in our study. Previous studies demonstrate that uterine artery myogenic constriction is decreased in pregnancy compared to non-pregnant mice and sheep (Veerareddy, Cooke, Baker, & Davidge, 2002; Xiao, Buchholz, & Zhang, 2006), whereas others have shown increased myogenic reactivity in myoendometrial arteries of rabbits and radial uterine arteries of rats (M. J. Cipolla, Binder, & Osol, 1997; Osol & Cipolla, 1993). Although the current manuscript is the first to report alcohol-induced myogenic constriction, other rat model studies investigating developmental insults have demonstrated that maternal undernutrition during pregnancy resulted in significantly increased myogenic tone in radial uterine arteries on GD 20 when compared with controls (Veerareddy et al., 2004). It is well established that myogenic adaptations are important during pregnancy to regulate blood flow to the feto-placental compartment. Collectively, our data suggest that alcohol-induced uterine artery adaptations may contribute to altered

hemodynamics in the utero-placental circulation which are critical for delivery of gas and nutrients (Veerareddy et al., 2002; Washburn, Sawant, Lunde, Wu, & Cudd, 2013).

We herein demonstrate that the uterine arteries of the alcohol-administered rats undergo inward hypotrophic remodeling, as measured by a decrease in lumen diameter and an increased media:lumen ratio (M. J. Mulvany, 1999). This is in contrast to normal pregnancy uteroplacental vascular adaptations, which is associated with outward-hypertrophic remodeling, i.e. an increased lumen diameter and a decreased media:lumen ratio, resulting in decreased resistance and increased blood flow (R. Magness, 1998; Osol & Mandala, 2009; Rosenfeld, 1977). An increase in media:lumen ratio corresponds to increased resistance to blood flow (Folkow, Hallback, Lundgren, & Weiss, 1970; M. Mulvany, Hansen, & Aalkjaer, 1978). Future studies on elastin, collagen, and smooth muscle remodeling are warranted to further characterize alcohol-induced uterine artery programing.

Our overall findings suggest that *in vivo* binge-alcohol exposure leads to altered gestational uterine arterial adaptations. During a healthy pregnancy, gestation-induced 30–50 fold increase in uterine blood flow is critical to meet the developmental requirements of the growing fetus (Rosenfeld, 1977). In women, uterine vascular resistance and resistance index decrease from 1.93 ± 0.22 mm $Hg \cdot ml^{-1} \cdot min$ and 0.89 in the non-pregnant state to 0.14 ± 0.01 mm $Hg \cdot ml^{-1} \cdot min$ and 0.52 by 34 weeks of gestation, respectively (Browne et al., 2011; Zamudio et al., 1995). Furthermore, animal models employing microspheres have validated that cardiac output to the uterus increases from 0.5% in non-pregnant state to 7.7% and 15.7% by the 2^{nd} and 3^{rd} trimester-equivalents of pregnancy, respectively (R. R. Magness, 1998; Rosenfeld, 1977). The aforementioned uterine vascular adaptations are essential for guaranteeing the nutrient requirements of the fetus be met throughout pregnancy and thus for normal fetal growth and development (R. R. Magness, 1998; Myers, Sparks, Makowski, Meschia, & Battaglia, 1982; Stock, 1994). Our current findings of alcohol-induced altered uterine artery adaptations are supported by earlier work on the impact of alcohol on uterine vasculature, specifically uterine artery endothelial mRNA (Ramadoss & Magness, 2012b) and protein profile (Ramadoss & Magness, 2012a), endothelial derived vasodilatory pathways (Magness, Sullivan, Li, Phernetton, & Bird, 2001), endothelial cell proliferation (Jobe et al., 2010), and spiral artery remodeling (Gundogan et al., 2008).

From the current study and others, it is evident that chronic binge alcohol exposure disrupts maternal uterine artery adaptations during pregnancy. The underlying mechanisms of alcohol-mediated pressure-dependent vascular response of the maternal uterine artery remain to be determined. Alcohol consumption during pregnancy is linked with intrauterine growth restriction and low birthweight (Kuehn et al., 2012), hallmark features of Fetal Alcohol Syndrome, and we hypothesize that maladaptive changes to uterine circulation may play a causal role in these abnormalities. Thus, we aim to continue to explore the consequences of alcohol exposure on the maternal vascular compartment so that we may better understand how these changes impact the fetus.

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Highlights

- Gestational alcohol exposure increases pressure-dependent uterine artery constriction
- Gestational alcohol induces inward hypotrophic remodeling of the uterine artery
- Binge-alcohol exposure during pregnancy leads to altered uterine arterial adaptations

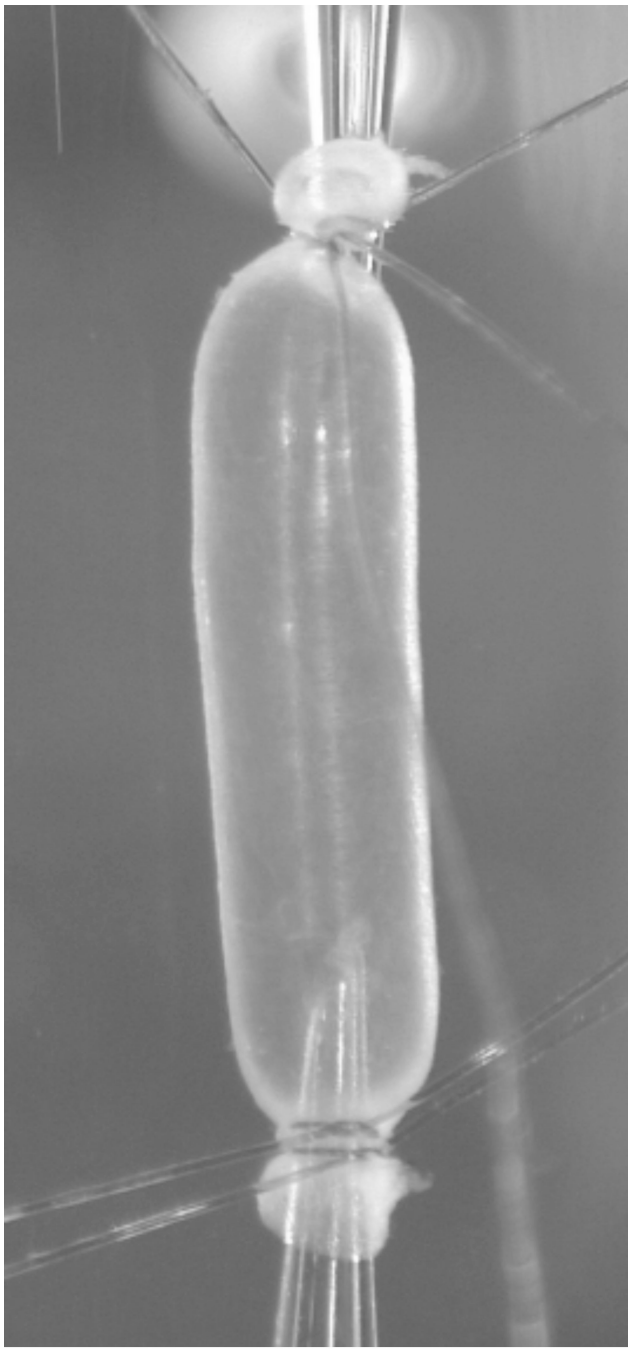

Figure 1. Cannulated and pressurized uterine artery

Representative picture of the maternal uterine artery (gestational day 20) mounted in a pressure arteriograph.

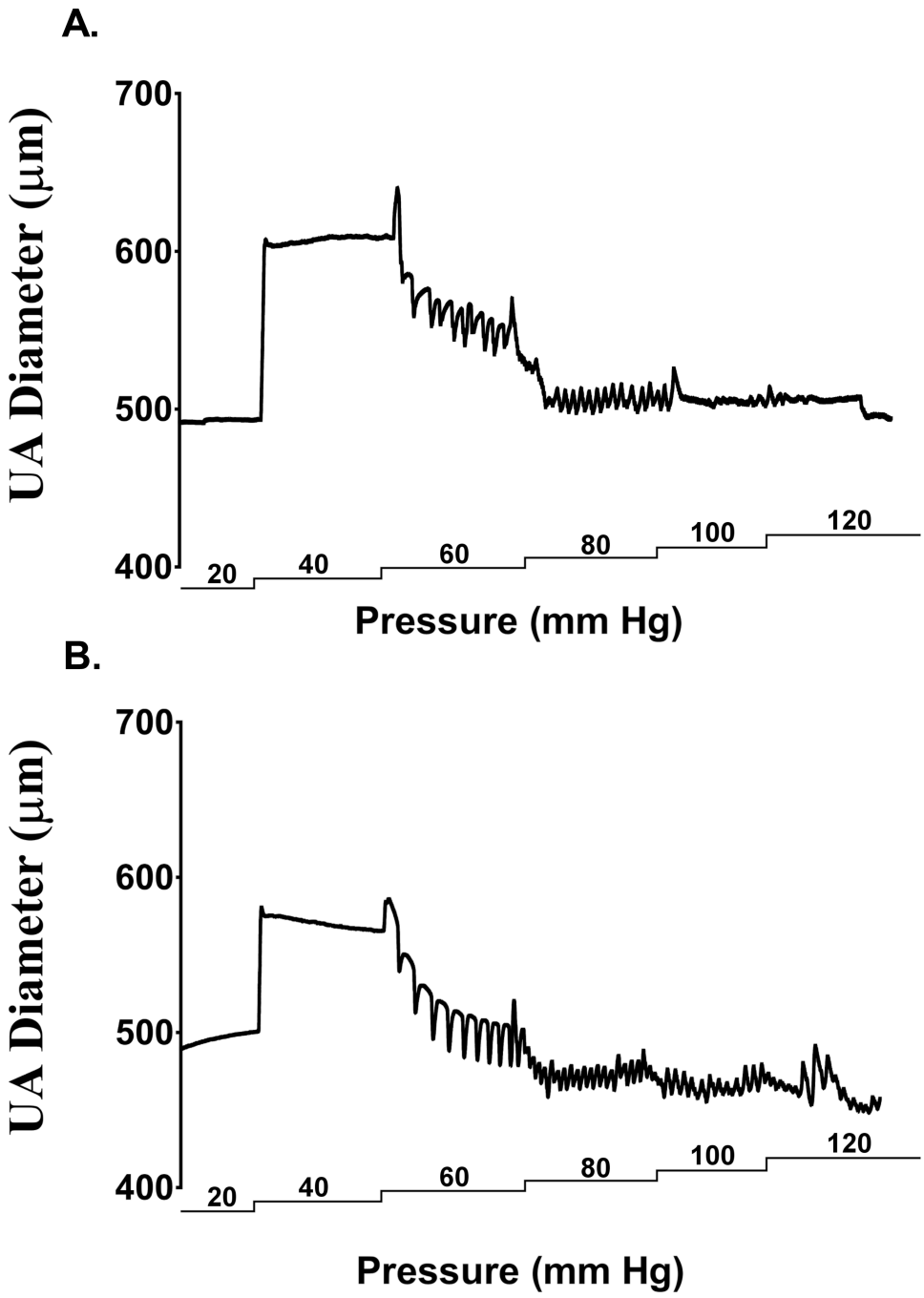

Figure 2. Uterine artery (UA) pressure arteriograph traces from (a) pair-fed control and (b) alcohol dams

The maternal uterine artery diameter stabilized at 20 mm Hg, showed passive distension with increase in pressure to 40 mm Hg, and maintained tone between 60 mm Hg and 120 mm Hg.

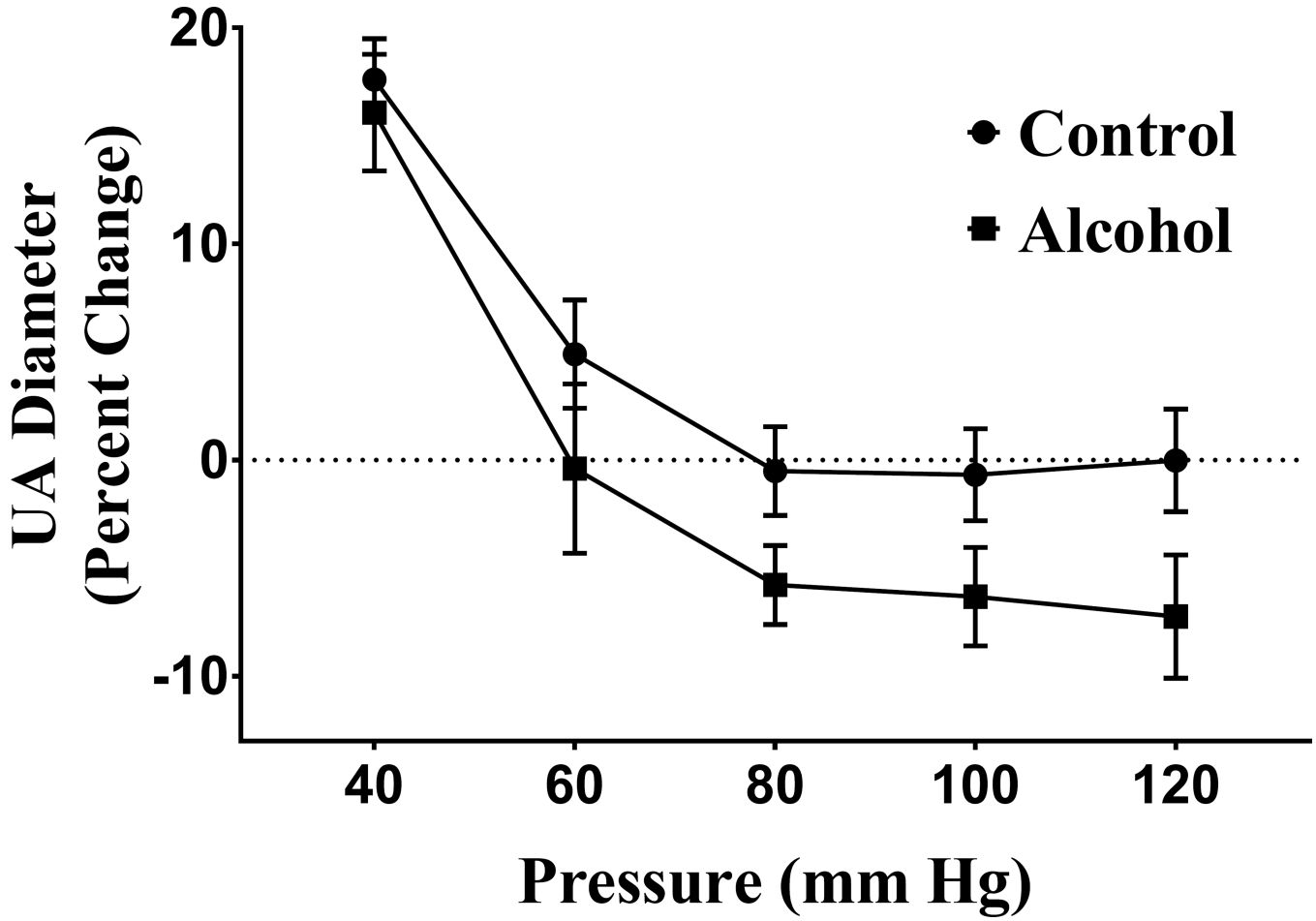

Figure 3. Effect of alcohol on percent change of uterine artery (UA) diameter with pressure

Percent change (from baseline) in uterine artery vessel diameter was significantly greater in the alcohol group compared to the control group and the alcohol group exhibited greater pressure-dependent constriction (pressure effect, $P < 0.0001$; alcohol effect, $P = 0.0025$).

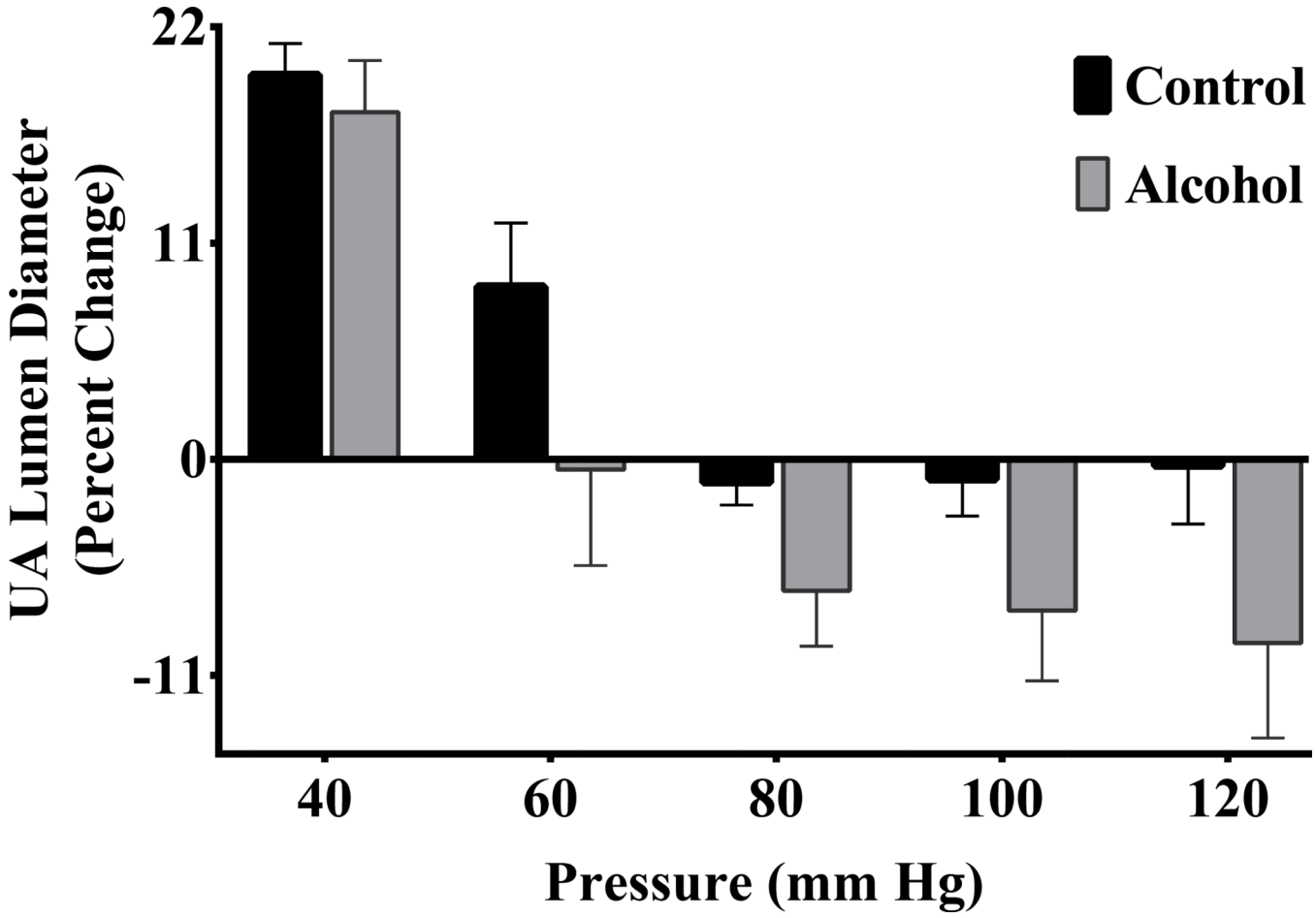

Figure 4. Effect of alcohol on percent change of uterine artery (UA) lumen diameter with pressure

Percent change (from baseline) in uterine artery lumen diameter was significantly greater in the alcohol group; alcohol group exhibited greater pressure-dependent constriction of lumen diameter compared to the control group (pressure effect, $P < 0.0001$; alcohol effect, $P = 0.0020$).

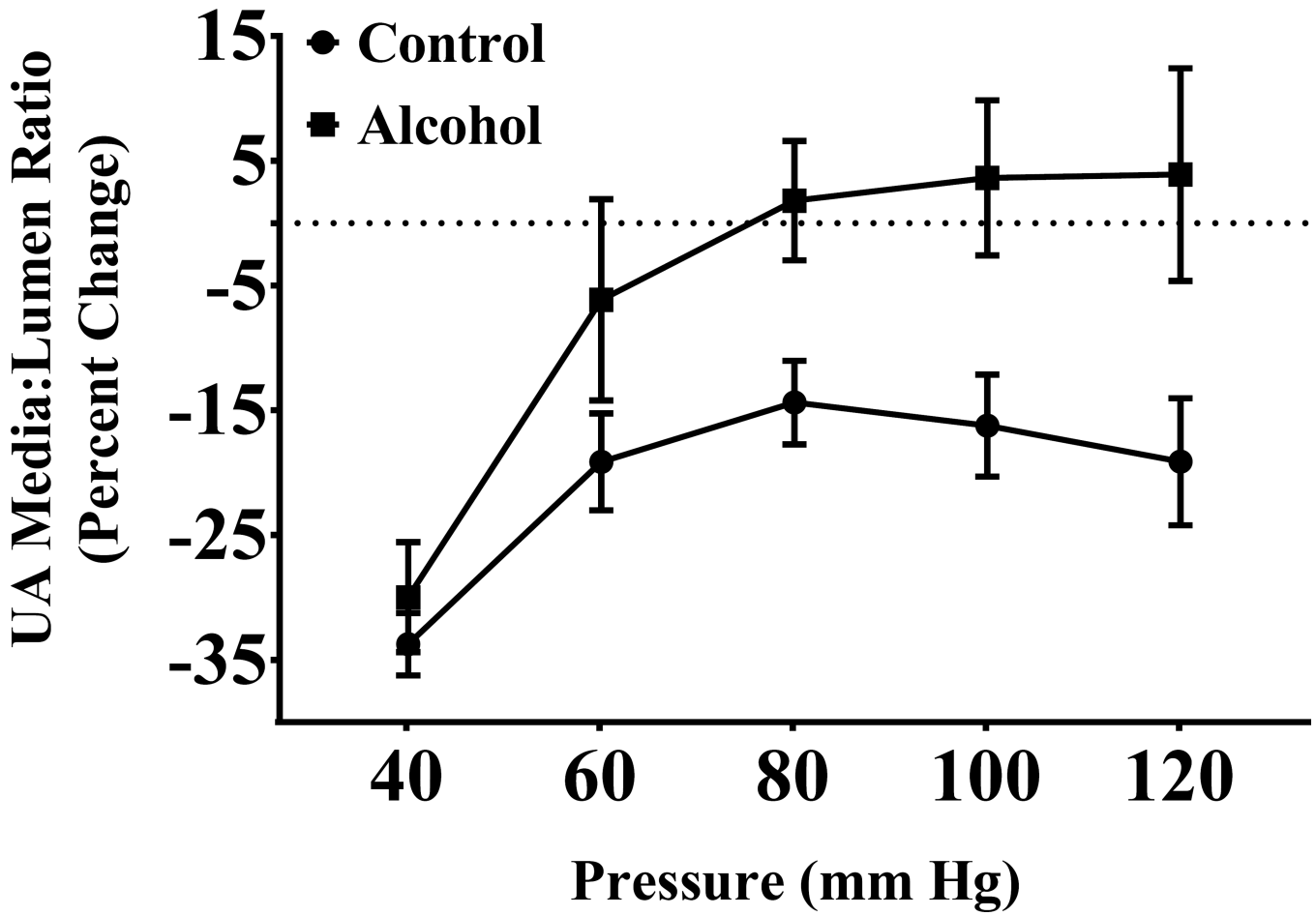

Figure 5. Effect of alcohol on percent change of uterine artery (UA) media:lumen ratio

Percent change in uterine artery media:lumen ratio was significantly higher in the alcohol group compared to the control group (pressure effect, $P < 0.0001$; alcohol effect, $P < 0.0001$).