The effect of a high-fat meal on sympathetic vasoconstrictor responsiveness in healthy young males and females

by

Justin J. Duong

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Faculty of Kinesiology, Sport, and Recreation
University of Alberta

Abstract

Consumption of a high-fat (HF) meal has been linked to diminished vascular function, evidenced by decreased postprandial flow mediated dilation (FMD). This is thought to occur through a decrease in nitric oxide bioavailability. A postprandial decline in nitric oxide bioavailability may also increase sympathetic vasoconstrictor responsiveness; however, this has not been studied. There is also evidence that premenopausal females show a cardio-protective effect against the effects of HF meal ingestion. Therefore, the purpose of the present study was to investigate the hypotheses that 1) a HF meal would heighten sympathetic vasoconstrictor responsiveness and impair flow mediated vasodilation (FMD) in healthy young adults and 2) females would have reduced sympathetic vasoconstrictor responsiveness and maintained FMD after a HF meal compared to males. In a randomized cross-over design, young males (n=15) and females (n=15) consumed either a HF or an iso-caloric low-fat (LF) meal on separate days. Two hours postprandial, subjects underwent brachial artery FMD and cold-pressor (CPT) tests to measure endothelial function and sympathetic vasoconstrictor responsiveness, respectively. Beat-by-beat blood pressure was measured by finger photoplethysmography and mean arterial pressure (MAP) was calculated. Forearm blood flow (FBF) was measured by Doppler ultrasound at the brachial artery and forearm vascular conductance (FVC) was calculated as FBF/MAP. FMD was calculated as the percentage increase in brachial artery diameter from baseline and normalized for cumulative shear rate. Sympathetic vasoconstrictor responsiveness was calculated as the percentage decrease in FVC (%ΔFVC) in response to the CPT compared to resting baseline values. FMD was found to be lower ($p<0.05$) following the HF meal compared

to the LF meal (LF: 7.1 ± 2.1%; HF: 6.1 ± 1.8%). Shear rate area under the curve (AUC) was also significantly different ($p<0.05$) between meals (HF: 4.5 ± 1.2.1 s^{-1}·s x 10^4; LF: 4.1 ± 0.9 s^{-1}·s x 10^4). However, FMD normalized to shear AUC was not different ($p>0.05$) between meal conditions (LF: 1.6 ± 0.5 s^{-1}·s x10^{-4}, AUC; HF: 1.6 ± 0.6 s^{-1}·s x10^{-4}, AUC). Similarly, a HF meal did not alter ($p>0.05$) sympathetic vasoconstrictor responsiveness (LF: -27.9 ± 18.4 %ΔFVC; HF: -27.3 ± 15.8 %ΔFVC) The increase in blood pressure in response to the CPT was also not different ($p>0.05$) between meal condition (LF: 32.0±17.1 mmHg; HF: 35.4±17.9 mmHg). Absolute ($p>0.05$) and relative VO_{2max} ($p>0.05$) were not correlated to FMD, normalized FMD, or sympathetic vasoconstrictor responsiveness in males or females for either meal condition. Brachial artery diameter was positively correlated ($p<0.05$) with absolute VO_{2max} in males. Relative VO_{2max} was positively correlated ($p<0.05$) with baseline diameter in the LF condition but not the HF condition in males ($p>0.05$). Baseline brachial diameter was not significantly correlated to absolute ($p>0.05$) or relative VO_{2max} ($p>0.05$) in females. FMD was greater ($p<0.05$) in females (LF: 8.1± 2.1%; HF: 7.4± 1.4%) compared to males (LF: 6.3± 1.5%; HF: 5.1± 1.2%). Shear rate was also found to be significantly higher ($p<0.05$) in females (LF: 5.0± 1.2 s^{-1}·s x 10^4; HF: 4.4 ± 1.1 s^{-1}·s x 10^4) compared to males (LF: 4.1 ± 0.9 s^{-1}·s x 10^4; HF: 3.7 ± 0.6 s^{-1}·s x 10^4). However, when FMD was normalized to shear rate AUC, there was no significant difference between males (LF: 1.6 ± 0.4; HF: 1.4 ± 0.4 s^{-1}·s x10^{-4}, AUC) and females (LF: 1.7 ± 0.5; HF: 1.8 ± 0.6 s^{-1}·s x10^{-4}, AUC) ($p>0.05$). Blood pressure response to CPT in males (LF: 25.1 ± 13.9; HF: 26.7 ± 11.1 mmHg) and females (LF: 22.7 ± 13.9; HF: 25.4 ± 15.2 mmHg) was similar ($p>0.05$). Δ%FVC was also not significantly different in males (LF: -28.3 ± -22.6; HF: -26.3 ± 16.6%) or females

(LF: -27.1 ± 13.8; HF: -30.4 ± 15.2%) ($p>0.05$). These data suggest that a HF meal may reduce endothelial function in both males and females as measured by FMD. However, when normalized to shear rate, this difference appears to be abolished. Furthermore, our data indicate a HF meal does not heighten sympathetic vasoconstrictor responsiveness in healthy young males and females.

Preface

This thesis is an original work by Justin Duong. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, “High fat meal and sympathetic vasoconstriction”, Pro00086720, January 9, 2019

Acknowledgements

I would like to thank my supervisor Dr. Darren DeLorey for his guidance throughout my time here. It was a pleasure to work with him and I cannot express enough gratitude for being so welcomed in a foreign environment from my very first visit to Edmonton. I am very grateful for his continued mentorship throughout the process of completing this study and writing this thesis. Being able to dive deeper into this field and seeing research from a new perspective has been a great experience and I will certainly be taking Dr. DeLorey's advice with me to my future pursuits.

I would like to extend my deepest thanks to Breanne Collison, Steven Canduro, Majed Karim, Brendan Kelly, Shawn Lywood, Annick Meckes, and Shawn Taggart and for their many hours in the lab helping me to hone my ability to collect ultrasound images, collect data, and giving me feedback during the various stages of my degree. This project would not be complete if not for their input and assistance in helping me fine-tune my ultrasound skills along with my writing. I would like to thank my committee member Dr. Michael Kennedy for providing feedback and direction throughout the completion of this project. Finally, I would like to thank all of the participants that gave their time to volunteer for this study and make this project possible.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

BH_4 – tetrahydrobiopterin

BP – blood pressure (mmHg)

cGMP – cyclic guanosine monophosphate

CPT – cold pressor test

CVD – cardiovascular disease

eNOS – endothelial nitric oxide synthase

ET-1 – endothelin 1

FBF – forearm blood flow (L/min)

FMD - flow-mediated dilation

FVC – forearm vascular conductance (L/min/mmHg)

HR – heart rate (bpm)

MAP – mean arterial pressure (mmHg)

MBV – mean blood velocity (cm/s)

MSNA – muscle sympathetic nerve activity

NO - nitric oxide

NOS – nitric oxide synthase

O_2 – oxygen

O_2^- - superoxide anion

PPL – postprandial lipemia

ROS - reactive oxygen species

SNS – sympathetic nervous system

TPR – total peripheral resistance (mmHg/min/mL)

TRG - triglyceride

TRL – triglyceride-rich lipoproteins

VO_{2max} – incremental test to volitional exhaustion

VO_2 – oxygen consumption (L/min)

Chapter 1: Introduction

Introduction

The typical "North American" diet is characterized by a relatively high fat content, and has been associated with vascular dysfunction and increased risk for the development of cardiovascular disease (CVD) (Teeman et al., 2016). High-fat content has been extensively studied for its role in atherosclerotic plaque development due to increased prevalence of this diet in the developed world. Several studies have reported that consumption of even a single high fat meal can impair cardiovascular function, indicated by acute endothelial dysfunction and an increased inflammatory response 2-4 hours post meal ingestion (Bae et al., 2001; Ballard, Miller, Robinson, & Olive, 2008; Faulk & Bartholomew, 2012; Jakulj et al., 2007; Johnson, Padilla, Harris, & Wallace, 2011; Rudolph et al., 2007; Tsai, Li, Lin, Chao, & Chen, 2004; Vogel, Corretti, & Plotnick, 1997). Ingestion of a high-fat meal induces a state of hypertriglyceridemia disrupting normal endothelial function and facilitating the pathogenesis of atherosclerosis (Bae et al., 2001; Tsai et al., 2004; Tushuizen et al., 2006). Given that the average person consumes 3 or 4 meals per day, the significant amount of time spent in this postprandial phase may play a significant role in the development of atherosclerosis and CVD (Burns, Miyashita, & Stensel, 2015; Emerson et al., 2017; Teeman et al., 2016; Thijssen et al., 2011; Thom, Early, Hunt, Harris, & Herring, 2016).

The endothelium is an extremely important vascular structure that regulates vascular resistance and tissue blood flow through the release of vasodilator and vasoconstrictor substances, including nitric oxide (NO) (Rajendran et al., 2013;

Vanhoutte, Shimokawa, Feletou, & Tang, 2017). NO has been identified as an important factor for arterial vasodilation (Harris, Nishiyama, Wray, & Richardson, 2010; Lopes Krüger et al., 2016; Sandoo, van Zanten, Metsios, Carroll, & Kitas, 2010) and protection against platelet aggregation, inflammation and atherogenesis (Khaddaj Mallat, Mathew John, Kendrick, & Braun, 2017; Lopes Krüger et al., 2016; Vanhoutte et al., 2017). NO is also important in the inhibition of peripheral sympathetic vasoconstriction (Casey et al., 2010; Chavoshan et al., 2002; Huang et al., 1995; Jendzjowsky, N. G. & DeLorey, 2013a; Jendzjowsky, N. G. & Delorey, 2013b; Lamping & Faraci, 2003; Wray et al., 2011). HF meal consumption is thought to cause endothelial dysfunction through significant reductions in NO bioavailability and its protective effects, leading to pro-thrombotic and inflammatory signaling (Rajendran et al., 2013). A single HF meal causes prolonged exposure to elevated triglyceride (TRG) and triglyceride-rich lipoprotein (TRL) levels known as postprandial lipemia (PPL) (Lopes Krüger et al., 2016; Teeman et al., 2016). These higher concentrations of blood lipids increase mitochondrial β-oxidation and result in an accumulation of electrons at the termination of the electron transport chain and the reduction of oxygen (O_2) into superoxide anions (O_2^-), a type of reactive oxygen species (ROS) (Lopes Krüger et al., 2016). O_2^- scavenges NO and creating peroxynitrate ($ONOO^-$), decreasing NO bioavailability (Barton, Baretella, & Meyer, 2012; Bauer & Sotníková, 2010; Bruno et al., 2012; Lopes Krüger et al., 2016; Vanhoutte et al., 2017). O_2^- and $ONOO^-$, both powerful oxidizing agents, further reduces NO bioavailability by oxidizing tetrahydrobioptern (BH_4), an essential cofactor for the production of endothelium-derived NO (Shah et al., 2017). Inactivation of BH_4 leads to endothelial nitric oxide synthase (eNOS) uncoupling, decreasing NO synthesis (Lopes Krüger et al., 2016; Moncada &

Higgs, 2006; Vanhoutte et al., 2017). Uncoupled eNOS can also produce O_2^- resulting in further oxidative stress (Moncada & Higgs, 2006; Vanhoutte et al., 2017).

PPL also initiates a pro-inflammatory signaling response that is a precursor to the formation of fatty streaks and atherosclerotic plaques. It has been proposed that elevated postprandial TRL levels in the postprandial state leads to greater transfer of triglycerides to lipoproteins, decreasing the level of high-density lipoproteins (HDL) levels while increasing production of small low-density lipoproteins (LDL) that remain in circulation for longer periods of time (Lopes Krüger et al., 2016; Teeman et al., 2016). Small LDL molecules are able to penetrate the vascular endothelium, where they are oxidized by ROS before adhering to the endothelial wall. Monocytes are recruited to the subendothelial space following the adherence of LDL, where they are converted to macrophages to scavenge the oxidized lipoproteins (Lopes Krüger et al., 2016). These macrophages release cytokines, leading to the release of pro-inflammatory molecules, such as interleukin-6 and tumor necrotic factor-α, which are important in the regulation of atherosclerotic plaques (Emerson et al., 2017; Teeman et al., 2016). Once fully saturated, macrophages are converted to foam cells initiating the formation of fatty streaks and atherosclerosis (Teeman et al., 2016). Additionally, the ingestion of a HF meal may lead to a postprandial decrease in shear stress (Poitras et al., 2014). Shear stress plays an important role in the development of atherosclerosis and CVD (Lehoux & Jones, 2016; Li, Yang, Wang, & Wei, 2014; Morbiducci et al., 2016). The development of atherosclerotic plaques most commonly occur in areas characterized by low turbulent blood flow and decreased shear stress such as arterial branch points, curvatures, and bifurcations (Lehoux & Jones, 2016; Morbiducci et al., 2016). Reduced shear stress may

contribute to atherosclerotic development with HF meal ingestion, as shear stress has been shown to be an important mediator of eNOS activity and the release of NO (Lopes Krüger et al., 2016; Moncada & Higgs, 2006; Sandoo et al., 2010; Vanhoutte et al., 2017).

Flow-mediated dilation (FMD) has been established as an independent predictor of future cardiovascular events (Harris et al., 2012; Thijssen et al., 2011; Thom et al., 2016) and may be an important tool to non-invasively assess postprandial vascular response to HF meal ingestion (Bae et al., 2001; Ballard et al., 2008; Das et al., 2018; Faulk & Bartholomew, 2012; Harris, Tedjasaputra, Zhao, & Richardson, 2012; Jakulj et al., 2007; Johnson et al., 2011; Rudolph et al., 2007; Schillaci et al., 2001; Shah et al., 2017; Vogel et al., 1997). The technique of FMD exposes a peripheral limb to a brief period of ischemia induced by a pressure cuff. Subsequent release of the cuff increases arterial blood flow and shear stress on the endothelial wall. This has been termed reactive hyperemia and is linked to higher eNOS activation and dilation in the conduit vessels, suggesting this dilation is an endothelial dependent and NO mediated mechanism (Corretti et al., 2002; Green, Daniel J., Dawson, Groenewoud, Jones, & Thijssen, 2014; Harris et al., 2010; Thijssen et al., 2011). An acute increase in shear stress opens mechanosensitive channels on the surface of the endothelium inducing an influx of calcium into the cell, which binds to calmodulin (Sandoo et al., 2010; Thijssen et al., 2011). This calcium-calmodulin complex binds to and activates eNOS to produce NO (Sandoo et al., 2010). NO diffuses into the vascular smooth muscle and binds soluble guanylyl cyclase, increasing the production of cyclic guanosine monophosphate (cGMP) (Harris et al., 2010; Lopes Krüger et al., 2016; Moncada & Higgs, 2006; Sandoo et al.,

2010; Vanhoutte et al., 2017). Higher cGMP decreases smooth muscle tension by stimulating sarcoplasmic reticulum calcium reuptake as well as reducing sarcoplasmic reticulum calcium release, causing vasodilation (Lopes Krüger et al., 2016; Sandoo et al., 2010; Vanhoutte et al., 2017). After several minutes, prolonged shear stress can directly activate protein kinase B to phosphorylate and activate eNOS to sustain vasodilation even with low intracellular endothelial calcium concentrations (Corretti et al., 2002; Sandoo et al., 2010).

Several studies have reported a decrease in FMD response after a HF meal compared to a LF meal (Bae et al., 2001; Harris et al., 2012; Jakulj et al., 2007; Padilla, Harris, Fly, Rink, & Wallace, 2006; Vogel et al., 1997). Among those, several have found that the effects of HF meal ingestion are mediated by increased oxidative stress. Bae and colleagues (2001) found that HF meal ingestion caused reduced FMD response by oxidative stress impairment of endothelium-dependent vasodilation in healthy young males. Direct measurement of blood lipid profiles and O_2^- concentrations showed significantly higher levels of LDL and O_2^- production rate 2-hours after HF meal ingestion compared to baseline (Bae et al., 2001). Higher circulating TRG levels were negatively correlated to FMD response and positively correlated to O_2^- formation. Taken together, the authors concluded that an increased circulating TRG level promotes ROS production and LDL oxidation, while also blunting the production of endothelium-derived NO, collectively leading to endothelial dysfunction (Bae et al., 2001). A study conducted by Tsai and colleagues (2004) saw similar reductions in FMD accompanying an increase in circulating TFG after a HF meal. Additionally, they reported that this was correlated with a decrease in the endogenous antioxidant enzyme, glutathione peroxidase,

as well as urinary excretion of 8-epi-Prostaglandin F2α, a marker of oxidative stress (Tsai et al., 2004). Finally, Tushuizen and colleagues (2006) measured the effects of two consecutive HF meals to simulate real-life situations. In addition to FMD reduction and higher TRG, the ratio of oxidized LDL to total LDL was significantly increased after both meals and was significantly correlated to elevated TRG (Tushuizen et al., 2006). Additionally, malondialdehyde, a product of lipid oxidation, was found to be significantly higher after the meals and was negatively correlated to FMD response further suggesting oxidative stress is heavily involved in PPL induced endothelial dysfunction (Tushuizen et al., 2006). Overall, oxidative stress appears to be a highly important regulator of PPL endothelial dysfunction.

While the effect of a HF meal on vasodilator function has been studied extensively, sympathetic vasoconstrictor responsiveness has received little attention. Several studies have implicated NO in the inhibition of sympathetic vasoconstriction in resting vascular beds (Häbler, Wasner, & Jänig, 1997; Jendzjowsky, N. G. & DeLorey, 2013a; Jendzjowsky, N. G. & Delorey, 2013b; Moncada & Higgs, 2006; Nase & Boegehold, 1996; Sandoo et al., 2010; Tesfamariam, Weisbrod, & Cohen, 1987; Vanhoutte et al., 2017). In a study conducted by Tesfamariam, Weisbrod, and Cohen (1987), electrical stimulation of adrenergic nerves caused increased arterial sympathetic vasoconstriction in isolated rabbit carotid arteries. After physical or chemical removal of the endothelium, vasoconstriction was augmented, suggesting that the endothelium and the release of NO are important modulators of adrenergic vasoconstriction (Tesfamariam et al., 1987). Nase and Boegehold (1996) found similar results with perivascular nerve stimulation in the small intestine of rats. Blockade of nitric oxide synthase (NOS)

significantly increased sympathetic vasoconstriction that was reversed with an infusion of L-arginine, a precursor of NO (Nase & Boegehold, 1996). The authors conclude endogenous NO attenuates neurogenic vasoconstriction in intestinal vasculature (Nase & Boegehold, 1996). A separate study in resting rat skeletal muscle yielded similar results with electrical stimulation of the lumbar sympathetic trunk (Häbler et al., 1997). Low frequency stimulation of the sympathetic trunk induced a more pronounced vasoconstrictor response in hindlimb vascular beds after blockade of NOS providing further evidence of NO-mediated inhibition of sympathetic vasoconstriction at rest (Häbler et al., 1997). Our own lab has provided evidence of NO mediated inhibition of sympathetic vasoconstriction in resting skeletal muscle. In the presence of both selective neuronal nitric oxide synthase and non-selective NOS blockade, vasoconstriction was augmented in resting skeletal muscle of healthy rats (Jendzjowsky, N. G. & DeLorey, 2013a). While the contribution of NO to the inhibition of sympathetic vasoconstriction in vascular beds at rest has been well defined in animal models, it has not been as clearly elucidated in human models. Durand and colleagues (2005) reported that NO is capable of inhibiting sympathetic vasoconstriction in cutaneous vasculature (Durand, Davis, Cui, & Crandall, 2005). Studies examining contracting skeletal muscle and functional sympatholysis in humans have established that NO is an important mediator of sympathetic vasoconstriction in contracting skeletal muscle (Casey et al., 2010; Chavoshan et al., 2002; Wray et al., 2011). However, there is evidence that NO does not influence resting skeletal muscle vascular response at rest. Dinenno and Joyner (2004), reported that vasoconstrictor response was unaltered by NOS blockade in the forearm at rest in human skeletal muscle (Dinenno & Joyner, 2004). While there is some

controversy in the literature as to the effect of NO at rest, the collective evidence points towards NO as an important mediator of sympathetic vasoconstriction in skeletal muscle (Casey et al., 2010; Chavoshan et al., 2002; Häbler et al., 1997; Jendzjowsky, N. G. & DeLorey, 2013a; Jendzjowsky, N. G. & Delorey, 2013b; Lerman, Sandok, Hildebrand, & Burnett, 1992; Nase & Boegehold, 1996; Tesfamariam et al., 1987; Thomas & Victor, 1998; Wray et al., 2011). Therefore, a HF meal may augment sympathetic vasoconstriction via a reduction in NO bioavailability, which is important in the inhibition of sympathetic vasoconstriction at rest.

Several studies have also shown the ingestion of a meal increases sympathetic nervous system (SNS) activity (Berne, Fagius, & Niklasson, 1989; Fagius & Berne, 1994; Scott et al., 2013; Vaz et al., 1995). This effect seems to be modulated in part by meal composition (Berne et al., 1989; Fagius & Berne, 1994). Pure carbohydrate elicits significantly higher muscle sympathetic nerve activity (MSNA) than either pure fat or pure protein meals due to the modulating effect of insulin (Fagius & Berne, 1994). However, the mere entrance of a meal to the gastrointestinal tract seems to account for a part of the rise in MSNA (Fagius, 2003).This increase in MSNA may elicit vasoconstriction, higher vascular resistance, and elevated blood pressure in the postprandial state. While no studies have directly measured sympathetic vasoconstriction after a HF meal, Jakulj and colleagues (2007) administered a series of stressors to a group of healthy young men and women after a HF meal (Jakulj et al., 2007). Physiological stress was induced by arm ischemia, isometric handgrip exercise, and cold pressor test (CPT). They found that systolic blood pressure, diastolic blood pressure, and total peripheral resistance (TPR) were significantly higher in the HF meal compared to a LF

meal in response to stress. The authors concluded that the HF meal induced systemic vasoconstriction as indicated by increased TPR reactivity (Jakulj et al., 2007). Direct measurement of skeletal muscle sympathetic vasoconstriction may further our understanding of the acute effect of a HF meal on postprandial vascular function and the control of blood pressure.

Aerobic fitness may affect the vascular response to ingestion of a HF meal. Increased aerobic capacity and endurance exercise training have been shown to enhance vascular function (Clarkson et al., 1999; Green, D. J., Spence, Halliwill, Cable, & Thijssen, 2011; Green, D. J. & Smith, 2018; Kasikcioglu et al., 2005). With 10 weeks of aerobic exercise training, healthy young males showed increased aerobic fitness that was accompanied by enhanced endothelial-dependent vasodilation as measured by brachial artery FMD (Clarkson et al., 1999). A later study found that aerobic fitness was positively associated with FMD. Health young endurance athletes were found to have significantly higher VO_{2max} values compared to sedentary controls. This enhanced aerobic capacity corresponded to higher FMD in the endurance athletes (Kasikcioglu et al., 2005). Collectively, exercise training and aerobic fitness seem to enhance endothelial function (Green, D. J. et al., 2011). Chronic training has been shown to increase NOS expression and NO bioavailability, which may be the mechanism responsible for this enhanced endothelial function (Ballard et al., 2008; Fukai et al., 2000; Jendzjowsky, N. G., Just, & DeLorey, 2014). There is also evidence that exercise training influences vasoconstrictor function (Green, D. J. et al., 2011). In response to sympathetic stimulation, blood pressure and heart rate response to several stressors were significantly attenuated in aerobically trained individuals compared to their sedentary counterparts

(O'Sullivan & Bell, 2001). A similar blunting was observed in the sedentary group after being aerobically trained for 5 weeks in addition to significant improvement to their VO_{2max}, suggesting that exercise training can blunt sympathetic arousal to various stimuli (O'Sullivan & Bell, 2001). Enhanced aerobic fitness and the associated increase in vascular function may therefore protect against the vascular dysfunction driven by the ingestion of a HF meal.

Sex may modulate the vascular response to a HF meal (Bloomer, Richard J., Ferebee, Fisher-Wellman, Quindry, & Schilling, 2009; Bloomer, Richard J. & Lee, 2013; Harris et al., 2012; Schillaci et al., 2001). It has been proposed that females have an inherent protection against decreases in FMD following a HF meal compared to their males (Harris et al., 2012; Schillaci et al., 2001). High levels of circulating ovarian hormones in premenopausal women have been linked to reduced oxidative stress, compared to males, following a high-fat meal (Bloomer, Richard J. et al., 2009; Bloomer, Richard J. & Lee, 2013; D'Urzo, King, Williams, Silvester, & Pyke, 2018; Harris et al., 2012; Hashimoto et al., 1995). Estrogen may upregulate endogenous antioxidant production which may lead to an enhanced ability to clear circulating TRG, decreasing oxidative stress (Bloomer, Richard J. et al., 2009; Bloomer, Richard J. & Lee, 2013). However, the mechanism behind this lowered oxidative stress has not been fully determined (Bell et al., 2001; Bloomer, R. J. & Fisher-Wellman, 2010; Bloomer, Richard J. et al., 2009; Bloomer, Richard J. & Lee, 2013). Estrogen also plays a part in the regulation of endothelial-dependent vasodilation at rest. In a study conducted by Hashimoto and colleagues (1994), the follicular and luteal stages of the menstrual cycle, which are associated with the increase of serum ovarian hormones compared to the

menses phase, saw higher FMD than menses. During the menses phase, hormone levels were comparable to those of male subjects, as was FMD, suggesting that endothelium-dependent vasodilation is positively modulated by the level of circulating hormones (Hashimoto et al., 1995). Harris and colleagues (2012) saw a similar phasic difference in FMD response in premenopausal females with HF meal ingestion at different points during the menstrual cycle. Females showed increases in FMD during the follicular and luteal compared to the menses phase (Harris et al., 2012).The menses phase yielded similar FMD response between men and women. However, pre- and post-meal FMD was not different during any individual phase. In contrast, male subjects showed a significant decrease in post-meal FMD again suggesting premenopausal females exhibit an inherent protection to postprandial changes in endothelial function after a HF meal (Harris et al., 2012). This result mirrors an earlier study which also concluded that ingestion of a high-fat meal does not decrease FMD in premenopausal females compared to males. However, this was only done during the follicular phase in females (Schillaci et al., 2001).

Sex also seems to be an important mediator of sympathetic regulation of vascular resistance and blood pressure (Hart, E. C. J. & Charkoudian, 2014; Hogarth, Mackintosh, & Mary, David A. S. G., 2007; Just & DeLorey, 2017; Kneale, Chowienczyk, Brett, Coltart, & Ritter, 2000). Premenopausal women generally exhibit lower blood pressure and MSNA than their male counterparts at rest (Hart, E. C. J. & Charkoudian, 2014). Additionally, young females do not exhibit the positive relationship between TPR and MSNA that is shown in young males (Charkoudian, Hart, Barnes, & Joyner, 2017; Hart, E. C., Joyner, Wallin, & Charkoudian, 2012; Hart, E. C. J. & Charkoudian, 2014) suggesting women display altered neurovascular transduction or a blunted

vasoconstrictor responsiveness (Hogarth et al., 2007; Just & DeLorey, 2017). Young females have also shown a blunted sympathetic vasoconstrictor response to a variety of different stimuli in comparison to young males (Hart, E. C. J. & Charkoudian, 2014; Hogarth et al., 2007). This seems to be due to the protective effect of estradiol as both sympathetic nerve activity and blood pressure increase after menopause (Charkoudian et al., 2017). In response to both isometric handgrip exercise and CPT, young females showed an attenuated vascular response despite similar increases in efferent sympathetic activity compared to male subjects (Hogarth et al., 2007). Similarly, when injected with noradrenaline to elicit sympathetic response, young women displayed blunted vasoconstriction (Kneale et al., 2000). However, this difference was abolished with the addition of a β-adrenergic antagonist, suggesting that β-adrenergic vasodilation counteracts α-adrenergic vasoconstriction in females (Kneale et al., 2000). Furthermore, administration of the systemic, non-selective β-adrenergic inhibitor propranalol resulted in a significant and positive relationship of MSNA and TPR (Hart, E. C. et al., 2011). Taken together, this suggests that β receptors systemically offset the relationship between peripheral vasoconstriction and MSNA in healthy, young women (Hart, E. C. J. & Charkoudian, 2014). In contrast to these results, leg vascular response to IHG showed no difference between young male and female subjects and was not altered by propranolol injection (Pellinger & Halliwill, 2007). Furthermore, in response to isoproterenol, a β-adrenergic agonist, men and women reported similar forearm blood flows suggesting that there may not be a difference in β-adrenergic receptor responsiveness or function between sexes (Limberg et al., 2016). These conflicting findings could indicate that sex-

specific differences in sympathetic vasoconstrictor response operate through other mechanisms and warrant further investigation.

To summarize, there is evidence that a single HF meal may cause acute postprandial endothelial dysfunction quantified primarily in the literature by impaired postprandial FMD. A HF meal may also augment sympathetic vasoconstriction, evidenced by increased postprandial TPR and MSNA. Mechanistically, this decline in endothelial function may be the result of decreased availability of NO, which is known to mediate arterial dilation and inhibit sympathetic vasoconstriction. However, the effect of a HF meal on sympathetic vasoconstrictor responsiveness is currently not known. Furthermore, females are understudied compared to males when looking at the acute effect of a HF meal on vascular function. Specifically, females may experience lower oxidative stress after a HF meal compared to males, resulting in preserved vascular function.

Purpose and Hypotheses

The objective of this study was to investigate the effect of a HF meal compared to a LF meal on sympathetic vasoconstrictor responsiveness during a CPT in healthy young males and females. We also aimed to determine whether sex influences vascular responsiveness to a HF meal. It was hypothesized that a HF meal would 1) augment sympathetic vasoconstrictor responsiveness and impair FMD in healthy young adults; 2) premenopausal females would exhibit protection in both sympathetic vasoconstrictor responsiveness and FMD after a HF meal compared to males.

Significance

The "Western" diet is characterized by high amounts of fat and is correlated to significantly higher incidence of CVD development and obesity (Fung et al., 2001). Even a single HF meal has been shown to acutely reduce vascular function, evidenced by reduced endothelial function, suggesting a reduction in NO bioavailability (Bae et al., 2001; Tsai et al., 2004; Tushuizen et al., 2006). This postprandial decline in NO bioavailability may impair NO mediated inhibition of sympathetic vasoconstriction and significantly elevate sympathetic vasoconstrictor responsiveness.

Females remain significantly understudied compared to males. Study of females is important as females exhibit physiological differences in vascular function. Specifically, premenopausal women are shown to have lower resting blood pressure, and lower resting MSNA than males due to the protective influence of circulating ovarian hormone (Hart, E. C. J. & Charkoudian, 2014). Females display a blunted postprandial decline in endothelial function, evidenced by preserved FMD (Harris et al., 2012; Schillaci et al., 2001) and lower oxidative stress (Bloomer, Richard J. et al., 2009; Bloomer, Richard J. & Lee, 2013) after a HF meal. However, to my knowledge, no other study has examined whether this protective effect is extended to the effect of a HF meal on sympathetic vasoconstriction. The findings from this study will advance our comprehensive knowledge of the acute vascular effects of a HF meal in healthy young males and females. It also further expands the role of sex in vascular function during the postprandial phase.

References

Bae, J. H., Bassenge, E., Kim, K. B., Kim, Y. N., Kim, K. S., Lee, H. J., . . . Schwemmer, M. (2001). Postprandial hypertriglyceridemia impairs endothelial function by enhanced oxidant stress. *Atherosclerosis, 155*(2), 517-523.

Ballard, K. D., Miller, J. J., Robinson, J. H., & Olive, J. L. (2008). Aerobic capacity and postprandial flow mediated dilation. *International Journal of Exercise Science, 1*(4), 163-176.

Barton, M., Baretella, O., & Meyer, M. R. (2012). Obesity and risk of vascular disease: Importance of endothelium-dependent vasoconstriction. *British Journal of Pharmacology, 165*(3), 591-602. doi:10.1111/j.1476-5381.2011.01472.x

Bauer, V., & Sotníková, R. (2010). Nitric oxide--the endothelium-derived relaxing factor and its role in endothelial functions. *General Physiology and Biophysics, 29*(4), 319-340.

Bell, C., Paterson, D. H., Kowalchuk, J. M., Moy, A. P., Thorp, D. B., Noble, E. G., . . . Cunningham, D. A. (2001). Determinants of oxygen uptake kinetics in older humans following single-limb endurance exercise training. *Experimental Physiology, 86*(5), 659-665.

Berne, C., Fagius, J., & Niklasson, F. (1989). Sympathetic response to oral carbohydrate administration. evidence from microelectrode nerve recordings. *The Journal of Clinical Investigation, 84*(5), 1403-1409. doi:10.1172/JCI114313

Bloomer, R. J., & Fisher-Wellman, K. H. (2010). Lower postprandial oxidative stress in women compared with men. *Gender Medicine, 7*(4), 340-349. doi:10.1016/j.genm.2010.07.001 [doi]

Bloomer, R. J., Ferebee, D. E., Fisher-Wellman, K. H., Quindry, J. C., & Schilling, B. K. (2009). Postprandial oxidative stress: Influence of sex and exercise training status. *Medicine and Science in Sports and Exercise, 41*(12), 2111-2119. doi:10.1249/MSS.0b013e3181a9e832

Bloomer, R. J., & Lee, S. (2013). Women experience lower postprandial oxidative stress compared to men. *SpringerPlus, 2*, 553. doi:10.1186/2193-1801-2-553

Bruno, R. M., Ghiadoni, L., Seravalle, G., Dell'oro, R., Taddei, S., & Grassi, G. (2012). Sympathetic regulation of vascular function in health and disease. *Frontiers in Physiology, 3*, 284. doi:10.3389/fphys.2012.00284

Burns, S. F., Miyashita, M., & Stensel, D. J. (2015). High-intensity interval exercise and postprandial triacylglycerol. *Sports Medicine (Auckland, N.Z.), 45*(7), 957-968. doi:10.1007/s40279-015-0327-6

Casey, D. P., Madery, B. D., Curry, T. B., Eisenach, J. H., Wilkins, B. W., & Joyner, M. J. (2010). Nitric oxide contributes to the augmented vasodilatation during hypoxic exercise. *The Journal of Physiology, 588*(Pt 2), 373-385. doi:10.1113/jphysiol.2009.180489

Charkoudian, N., Hart, E. C. J., Barnes, J. N., & Joyner, M. J. (2017). Autonomic control of body temperature and blood pressure: Influences of female sex hormones. *Clinical Autonomic Research: Official Journal of the Clinical Autonomic Research Society, 27*(3), 149-155. doi:10.1007/s10286-017-0420-z

Chavoshan, B., Sander, M., Sybert, T. E., Hansen, J., Victor, R. G., & Thomas, G. D. (2002). Nitric oxide-dependent modulation of sympathetic neural control of oxygenation in exercising human skeletal muscle. *The Journal of Physiology, 540*(Pt 1), 377-386.

Clarkson, P., Montgomery, H. E., Mullen, M. J., Donald, A. E., Powe, A. J., Bull, T., . . . Deanfield, J. E. (1999). Exercise training enhances endothelial function in young men. *Journal of the American College of Cardiology, 33*(5), 1379-1385. doi:S0735-1097(99)00036-4 [pii]

Corretti, M. C., Anderson, T. J., Benjamin, E. J., Celermajer, D., Charbonneau, F., Creager, M. A., . . . Vogel, R. (2002). Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the international brachial artery reactivity task force. *Journal of the American College of Cardiology, 39*(2), 257-265.

Das, E. K., Lai, P. Y., Robinson, A. T., Pleuss, J., Ali, M. M., Haus, J. M., . . . Phillips, S. A. (2018). Regular aerobic, resistance, and cross-training exercise prevents reduced vascular function following a high sugar or high fat mixed meal in young healthy adults. *Frontiers in Physiology, 9*, 183. doi:10.3389/fphys.2018.00183

Dinenno, F. A., & Joyner, M. J. (2004). Combined NO and PG inhibition augments alpha-adrenergic vasoconstriction in contracting human skeletal muscle. *American Journal of Physiology.Heart and Circulatory Physiology, 287*(6), 2576. doi:10.1152/ajpheart.00621.2004 [doi]

Durand, S., Davis, S. L., Cui, J., & Crandall, C. G. (2005). Exogenous nitric oxide inhibits sympathetically mediated vasoconstriction in human skin. *The Journal of Physiology, 562*(Pt 2), 629-634. doi:jphysiol.2004.075747 [pii]

D'Urzo, K. A., King, T. J., Williams, J. S., Silvester, M. D., & Pyke, K. E. (2018). The impact of menstrual phase on brachial artery flow-mediated dilatation during handgrip exercise in healthy premenopausal women. *Experimental Physiology, 103*(2), 291-302. doi:10.1113/EP086311

Emerson, S. R., Kurti, S. P., Harms, C. A., Haub, M. D., Melgarejo, T., Logan, C., & Rosenkranz, S. K. (2017). Magnitude and timing of the postprandial inflammatory response to a high-fat meal in healthy adults: A systematic review. *Advances in Nutrition (Bethesda, Md.), 8*(2), 213-225. doi:10.3945/an.116.014431

Fagius, J. (2003). Sympathetic nerve activity in metabolic control--some basic concepts. *Acta Physiologica Scandinavica, 177*(3), 337-343. doi:10.1046/j.1365-201X.2003.01086.x

Fagius, J., & Berne, C. (1994). Increase in muscle nerve sympathetic activity in humans after food intake. *Clinical Science (London, England: 1979), 86*(2), 159-167.

Faulk, K. E., & Bartholomew, J. B. (2012). The moderating effect of physical activity on cardiovascular reactivity following single fat feedings. *Psychophysiology, 49*(1), 145-149. doi:10.1111/j.1469-8986.2011.01283.x

Fukai, T., Siegfried, M. R., Ushio-Fukai, M., Cheng, Y., Kojda, G., & Harrison, D. G. (2000). Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. *The Journal of Clinical Investigation, 105*(11), 1631-1639. doi:10.1172/JCI9551 [doi]

Fung, T. T., Rimm, E. B., Spiegelman, D., Rifai, N., Tofler, G. H., Willett, W. C., & Hu, F. B. (2001). Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. *The American Journal of Clinical Nutrition, 73*(1), 61-67. doi:10.1093/ajcn/73.1.61 [doi]

Green, D. J., & Smith, K. J. (2018). Effects of exercise on vascular function, structure, and health in humans. *Cold Spring Harbor Perspectives in Medicine, 8*(4), 10.1101/cshperspect.a029819. doi:a029819 [pii]

Green, D. J., Spence, A., Halliwill, J. R., Cable, N. T., & Thijssen, D. H. (2011). Exercise and vascular adaptation in asymptomatic humans. *Experimental Physiology, 96*(2), 57-70. doi:10.1113/expphysiol.2009.048694 [doi]

Green, D. J., Dawson, E. A., Groenewoud, H. M. M., Jones, H., & Thijssen, D. H. J. (2014). Is flow-mediated dilation nitric oxide mediated?: A meta-analysis. *Hypertension (Dallas, Tex.: 1979), 63*(2), 376-382. doi:10.1161/HYPERTENSIONAHA.113.02044

Häbler, H. J., Wasner, G., & Jänig, W. (1997). Attenuation of neurogenic vasoconstriction by nitric oxide in hindlimb microvascular beds of the rat in vivo. *Hypertension (Dallas, Tex.: 1979), 30*(4), 957-961. doi:10.1161/01.hyp.30.4.957

Harris, R. A., Nishiyama, S. K., Wray, D. W., & Richardson, R. S. (2010). Ultrasound assessment of flow-mediated dilation. *Hypertension (Dallas, Tex.: 1979), 55*(5), 1075-1085. doi:10.1161/HYPERTENSIONAHA.110.150821

Harris, R. A., Tedjasaputra, V., Zhao, J., & Richardson, R. S. (2012). Premenopausal women exhibit an inherent protection of endothelial function following a high-fat meal. *Reproductive Sciences (Thousand Oaks, Calif.), 19*(2), 221-228. doi:10.1177/1933719111418125

Hart, E. C., Charkoudian, N., Wallin, B. G., Curry, T. B., Eisenach, J., & Joyner, M. J. (2011). Sex and ageing differences in resting arterial pressure regulation: The role of the beta-adrenergic receptors. *The Journal of Physiology, 589*(Pt 21), 5285-5297. doi:10.1113/jphysiol.2011.212753 [doi]

Hart, E. C., Joyner, M. J., Wallin, B. G., & Charkoudian, N. (2012). Sex, ageing and resting blood pressure: Gaining insights from the integrated balance of neural and haemodynamic factors. *The Journal of Physiology, 590*(9), 2069-2079. doi:10.1113/jphysiol.2011.224642 [doi]

Hart, E. C. J., & Charkoudian, N. (2014). Sympathetic neural regulation of blood pressure: Influences of sex and aging. *Physiology (Bethesda, Md.), 29*(1), 8-15. doi:10.1152/physiol.00031.2013

Hashimoto, M., Akishita, M., Eto, M., Ishikawa, M., Kozaki, K., Toba, K., . . . Ouchi, Y. (1995). Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation, 92*(12), 3431-3435.

Hogarth, A. J., Mackintosh, A. F., & Mary, David A. S. G. (2007). Gender-related differences in the sympathetic vasoconstrictor drive of normal subjects. *Clinical Science (London, England: 1979), 112*(6), 353-361. doi:10.1042/CS20060288

Huang, P. L., Huang, Z., Mashimo, H., Bloch, K. D., Moskowitz, M. A., Bevan, J. A., & Fishman, M. C. (1995). Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature, 377*(6546), 239-242. doi:10.1038/377239a0

Jakulj, F., Zernicke, K., Bacon, S. L., van Wielingen, L. E., Key, B. L., West, S. G., & Campbell, T. S. (2007). A high-fat meal increases cardiovascular reactivity to psychological stress in healthy young adults. *The Journal of Nutrition, 137*(4), 935-939. doi:10.1093/jn/137.4.935

Jendzjowsky, N. G., Just, T. P., & DeLorey, D. S. (2014). Exercise training augments neuronal nitric oxide synthase-mediated inhibition of sympathetic vasoconstriction in contracting skeletal muscle of rats. *The Journal of Physiology, 592*(21), 4789-4802. doi:10.1113/jphysiol.2014.278846 [doi]

Jendzjowsky, N. G., & DeLorey, D. S. (2013). Role of neuronal nitric oxide in the inhibition of sympathetic vasoconstriction in resting and contracting skeletal muscle of healthy rats. *Journal of Applied Physiology (Bethesda, Md.: 1985), 115*(1), 97-106. doi:10.1152/japplphysiol.00250.2013

Jendzjowsky, N. G., & Delorey, D. S. (2013). Short-term exercise training enhances functional sympatholysis through a nitric oxide-dependent mechanism. *The Journal of Physiology, 591*(6), 1535-1549. doi:10.1113/jphysiol.2012.238998

Johnson, B. D., Padilla, J., Harris, R. A., & Wallace, J. P. (2011). Vascular consequences of a high-fat meal in physically active and inactive adults. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme, 36*(3), 368-375. doi:10.1139/H11-028

Just, T. P., & DeLorey, D. S. (2017). Sex differences in sympathetic vasoconstrictor responsiveness and sympatholysis. *Journal of Applied Physiology (Bethesda, Md.: 1985), 123*(1), 128-135. doi:10.1152/japplphysiol.00139.2017

Kasikcioglu, E., Oflaz, H., Kasikcioglu, H. A., Kayserilioglu, A., Umman, S., & Meric, M. (2005). Endothelial flow-mediated dilatation and exercise capacity in highly trained endurance athletes. *The Tohoku Journal of Experimental Medicine, 205*(1), 45-51. doi:JST.JSTAGE/tjem/205.45 [pii]

Khaddaj Mallat, R., Mathew John, C., Kendrick, D. J., & Braun, A. P. (2017). The vascular endothelium: A regulator of arterial tone and interface for the immune system. *Critical Reviews in Clinical Laboratory Sciences, 54*(7-8), 458-470. doi:10.1080/10408363.2017.1394267

Kneale, B. J., Chowienczyk, P. J., Brett, S. E., Coltart, D. J., & Ritter, J. M. (2000). Gender differences in sensitivity to adrenergic agonists of forearm resistance vasculature. *Journal of the American College of Cardiology, 36*(4), 1233-1238.

Lamping, K., & Faraci, F. (2003). Enhanced vasoconstrictor responses in eNOS deficient mice. *Nitric Oxide: Biology and Chemistry, 8*(4), 207-213.

Lehoux, S., & Jones, E. A. (2016). Shear stress, arterial identity and atherosclerosis. *Thrombosis and Haemostasis, 115*(3), 467-473. doi:10.1160/TH15-10-0791 [doi]

Lerman, A., Sandok, E. K., Hildebrand, F. L., & Burnett, J. C. (1992). Inhibition of endothelium-derived relaxing factor enhances endothelin-mediated vasoconstriction. *Circulation, 85*(5), 1894-1898.

Li, X., Yang, Q., Wang, Z., & Wei, D. (2014). Shear stress in atherosclerotic plaque determination. *DNA and Cell Biology, 33*(12), 830-838. doi:10.1089/dna.2014.2480 [doi]

Limberg, J. K., Johansson, R. E., Peltonen, G. L., Harrell, J. W., Kellawan, J. M., Eldridge, M. W., . . . Schrage, W. G. (2016). B-adrenergic-mediated vasodilation in young men and women: Cyclooxygenase restrains nitric oxide synthase. *American Journal of Physiology. Heart and Circulatory Physiology, 310*(6), 756. doi:10.1152/ajpheart.00886.2015

Lopes Krüger, R., Costa Teixeira, B., Boufleur Farinha, J., Cauduro Oliveira Macedo, R., Pinto Boeno, F., Rech, A., . . . Reischak-Oliveira, A. (2016). Effect of exercise intensity on postprandial lipemia, markers of oxidative stress, and endothelial function after a high-fat meal. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme, 41*(12), 1278-1284. doi:10.1139/apnm-2016-0262

Moncada, S., & Higgs, E. A. (2006). The discovery of nitric oxide and its role in vascular biology. *British Journal of Pharmacology, 147 Suppl 1*, 193. doi:10.1038/sj.bjp.0706458

Morbiducci, U., Kok, A. M., Kwak, B. R., Stone, P. H., Steinman, D. A., & Wentzel, J. J. (2016). Atherosclerosis at arterial bifurcations: Evidence for the role of haemodynamics and geometry. *Thrombosis and Haemostasis, 115*(3), 484-492. doi:10.1160/TH15-07-0597 [doi]

Nase, G. P., & Boegehold, M. A. (1996). Nitric oxide modulates arteriolar responses to increased sympathetic nerve activity. *The American Journal of Physiology, 271*(3 Pt 2), 860. doi:10.1152/ajpheart.1996.271.3.H860 [doi]

O'Sullivan, S. E., & Bell, C. (2001). Training reduces autonomic cardiovascular responses to both exercise-dependent and -independent stimuli in humans. *Autonomic Neuroscience : Basic & Clinical, 91*(1-2), 76-84. doi:S1566-0702(01)00288-0 [pii]

Padilla, J., Harris, R. A., Fly, A. D., Rink, L. D., & Wallace, J. P. (2006). The effect of acute exercise on endothelial function following a high-fat meal. *European Journal of Applied Physiology, 98*(3), 256-262. doi:10.1007/s00421-006-0272-z

Pellinger, T. K., & Halliwill, J. R. (2007). Effect of propranolol on sympathetically mediated leg vasoconstriction in humans. *The Journal of Physiology, 583*(Pt 2), 797-809. doi:10.1113/jphysiol.2007.137422

Poitras, V. J., Slattery, D. J., Levac, B. M., Fergus, S., Gurd, B. J., & Pyke, K. E. (2014). The combined influence of fat consumption and repeated mental stress on brachial artery flow-mediated dilatation: A preliminary study. *Experimental Physiology, 99*(4), 715-728. doi:10.1113/expphysiol.2013.077131

Rajendran, P., Rengarajan, T., Thangavel, J., Nishigaki, Y., Sakthisekaran, D., Sethi, G., & Nishigaki, I. (2013). The vascular endothelium and human diseases. *International Journal of Biological Sciences, 9*(10), 1057-1069. doi:10.7150/ijbs.7502

Rudolph, T. K., Ruempler, K., Schwedhelm, E., Tan-Andresen, J., Riederer, U., Böger, R. H., & Maas, R. (2007). Acute effects of various fast-food meals on vascular function and cardiovascular disease risk markers: The hamburg burger trial. *The American Journal of Clinical Nutrition, 86*(2), 334-340. doi:10.1093/ajcn/86.2.334

Sandoo, A., van Zanten, J. J., Metsios, G. S., Carroll, D., & Kitas, G. D. (2010). The endothelium and its role in regulating vascular tone. *The Open Cardiovascular Medicine Journal, 4*, 302-312. doi:10.2174/1874192401004010302 [doi]

Schillaci, G., Marchesi, S., Siepi, D., Lupattelli, G., Vaudo, G., Pasqualini, L., & Mannarino, E. (2001). Gender differences in postprandial endothelial function. *The American Journal of Cardiology, 87*(11), 1323-1325.

Scott, E. M., Greenwood, J. P., Pernicova, I., Law, G. R., Gilbey, S. G., Kearney, M. T., & Mary, David A S G. (2013). Sympathetic activation and vasoregulation in response to carbohydrate ingestion in patients with congestive heart failure. *The Canadian Journal of Cardiology, 29*(2), 236-242. doi:10.1016/j.cjca.2012.03.020

Shah, Y., Bass, L., Davison, G. W., Seigler, N., Pollock, J. S., Thomas, J., & Harris, R. A. (2017). BH4 improves postprandial endothelial function after a high-fat meal in men and postmenopausal women. *Menopause (New York, N.Y.), 24*(5), 555-562. doi:10.1097/GME.0000000000000785

Teeman, C. S., Kurti, S. P., Cull, B. J., Emerson, S. R., Haub, M. D., & Rosenkranz, S. K. (2016). Postprandial lipemic and inflammatory responses to high-fat meals: A review of the roles of acute and chronic exercise. *Nutrition & Metabolism, 13*, 80. doi:10.1186/s12986-016-0142-6

Tesfamariam, B., Weisbrod, R. M., & Cohen, R. A. (1987). Endothelium inhibits responses of rabbit carotid artery to adrenergic nerve stimulation. *The American Journal of Physiology, 253*(4 Pt 2), 792. doi:10.1152/ajpheart.1987.253.4.H792 [doi]

Thijssen, D. H. J., Black, M. A., Pyke, K. E., Padilla, J., Atkinson, G., Harris, R. A., . . . Green, D. J. (2011). Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *American Journal of Physiology. Heart and Circulatory Physiology, 300*(1), 2. doi:10.1152/ajpheart.00471.2010

Thom, N. J., Early, A. R., Hunt, B. E., Harris, R. A., & Herring, M. P. (2016). Eating and arterial endothelial function: A meta-analysis of the acute effects of meal consumption on flow-mediated dilation. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity, 17*(11), 1080-1090. doi:10.1111/obr.12454

Thomas, G. D., & Victor, R. G. (1998). Nitric oxide mediates contraction-induced attenuation of sympathetic vasoconstriction in rat skeletal muscle. *The Journal of Physiology, 506 (Pt 3)*, 817-826.

Tsai, W., Li, Y., Lin, C., Chao, T., & Chen, J. (2004). Effects of oxidative stress on endothelial function after a high-fat meal. *Clinical Science (London, England: 1979), 106*(3), 315-319. doi:10.1042/CS20030227

Tushuizen, M. E., Nieuwland, R., Scheffer, P. G., Sturk, A., Heine, R. J., & Diamant, M. (2006). Two consecutive high-fat meals affect endothelial-dependent vasodilation, oxidative stress and cellular microparticles in healthy men. *Journal of Thrombosis and Haemostasis: JTH, 4*(5), 1003-1010. doi:10.1111/j.1538-7836.2006.01914.x

Vanhoutte, P. M., Shimokawa, H., Feletou, M., & Tang, E. H. C. (2017). Endothelial dysfunction and vascular disease - a 30th anniversary update. *Acta Physiologica (Oxford, England), 219*(1), 22-96. doi:10.1111/apha.12646

Vaz, M., Turner, A., Kingwell, B., Chin, J., Koff, E., Cox, H., . . . Esler, M. (1995). Postprandial sympatho-adrenal activity: Its relation to metabolic and cardiovascular events and to changes in meal frequency. *Clinical Science (London, England: 1979), 89*(4), 349-357.

Vogel, R. A., Corretti, M. C., & Plotnick, G. D. (1997). Effect of a single high-fat meal on endothelial function in healthy subjects. *The American Journal of Cardiology, 79*(3), 350-354.

Wray, D. W., Witman, M. A. H., Ives, S. J., McDaniel, J., Fjeldstad, A. S., Trinity, J. D., . . . Richardson, R. S. (2011). Progressive handgrip exercise: Evidence of nitric oxide-dependent vasodilation and blood flow regulation in humans. *American Journal of Physiology. Heart and Circulatory Physiology, 300*(3), 1101. doi:10.1152/ajpheart.01115.2010

Chapter 2: The effect of a high-fat meal on vascular reactivity in healthy young males and females

Introduction

"Western" dietary patterns, often characterized by high amounts of fat content, have been identified as predictors of increased CVD biomarkers and obesity risk (Fung et al., 2001; Teeman et al., 2016). It has been reported that even acute HF meals can induce endothelial dysfunction for several hours following consumption through increased levels of circulating TRG and TRL (Bae et al., 2001; Ballard, Miller, Robinson, & Olive, 2008; Faulk & Bartholomew, 2012; Jakulj et al., 2007; Johnson, Padilla, Harris, & Wallace, 2011; Rudolph et al., 2007; Tsai, Li, Lin, Chao, & Chen, 2004; Tushuizen et al., 2006; Vogel, Corretti, & Plotnick, 1997). With the average person eating multiple meals a day, chronic hypertriglyceridemia in the postprandial phase may be significant in the development of atherosclerosis and CVD (Burns, Miyashita, & Stensel, 2015; Emerson et al., 2017; Fuller, Summers, & Valentine, 2017; Teeman et al., 2016; Thom, Early, Hunt, Harris, & Herring, 2016). PPL increases oxidative stress by producing ROS and lowering NO bioavailability at the endothelium (Bae et al., 2001; Tsai et al., 2004; Tushuizen et al., 2006). This phenomenon is linked to decreased postprandial FMD, which has been established as a measure of vascular health and an independent predictor of future cardiovascular events (Thijssen et al., 2011). In addition to influencing endothelial function as measured by FMD, a HF meal also seems to heighten total peripheral resistance and blood pressure (Jakulj et al., 2007) as well as MSNA (Fagius & Berne,

1994). Together, these may be indicative of increased sympathetic vasoconstrictor responsiveness in response to a HF meal.

The presence of NO in the peripheral vasculature seems to be important in mediating local vasoconstriction (Casey et al., 2010; Chavoshan et al., 2002; Huang et al., 1995; Jendzjowsky, N. G. & DeLorey, 2013a; Jendzjowsky, N. G. & Delorey, 2013b; Lamping & Faraci, 2003; Thomas & Victor, 1998; Wray et al., 2011). Numerous studies in both animal (Jendzjowsky, N. G. & DeLorey, 2013a; Jendzjowsky, N. G. & Delorey, 2013b; Lerman, Sandok, Hildebrand, & Burnett, 1992; Thomas & Victor, 1998) and human models (Casey et al., 2010; Chavoshan et al., 2002; Wray et al., 2011) have reported that NO is important to the inhibition of sympathetic vasoconstriction (Moncada & Higgs, 2006; Sandoo, van Zanten, Metsios, Carroll, & Kitas, 2010; Toda & Okamura, 2003; Toda & Okamura, 2015). As such, lower levels of circulating NO result in blunted vasodilatory tone and a corresponding increase in vascular resistance and blood pressure associated with hypertension (Gamboa et al., 2007; Huang et al., 1995; Toda & Okamura, 2003). PPL-induced endothelial dysfunction after a HF meal is primarily thought to be caused by reduced NO bioavailability as a result of lipid metabolism driving increased production of ROS (Bae et al., 2001; Tsai et al., 2004; Tushuizen et al., 2006). This reduction in postprandial circulating NO may also augment sympathetic vasoconstrictor responsiveness. Additionally, the entrance of nutrients into the digestive track increase SNS activity in the periphery (Berne, Fagius, & Niklasson, 1989; Fagius & Berne, 1994; Scott et al., 2013; Vaz et al., 1995). While the strength of the response is mediated by the composition of the meal consumed, this increase in MSNA seems to occur regardless of macronutrient breakdown of the meal consumed (Fagius & Berne, 1994). This increase in

MSNA may also influence sympathetic vasoconstrictor responsiveness after a HF meal. There is evidence that a HF meal increases blood pressure and TPR in response to physiological and mental stress, which may be indicative of increased vasoconstriction (Jakulj et al., 2007). However, direct measurements of peripheral sympathetic vasoconstriction after a HF meal have not been investigated.

Sex may play an important role in mediating the vascular response to HF meal consumption. High levels of estrogen have been implicated in reduced oxidative stress in women after a HF meal as compared to males (Bloomer, Ferebee, Fisher-Wellman, Quindry, & Schilling, 2009; Bloomer & Lee, 2013; D'Urzo, King, Williams, Silvester, & Pyke, 2018). While the mechanism is not fully understood, high levels of estrogen may upregulate endogenous antioxidant production and reduce oxidative stress, providing premenopausal women an inherent protection in vascular function against the insult of a HF meal (Bloomer et al., 2009; Bloomer & Lee, 2013). Furthermore, females also exhibit differences in sympathetic regulation of blood pressure and vascular function at rest (Hart, E. C. J. & Charkoudian, 2014; Hogarth, Mackintosh, & Mary, David A. S. G., 2007; Just & DeLorey, 2017). In addition to having generally lower blood pressure and MSNA, studies have reported premenopausal females having a blunted sympathetic vasoconstriction response to various stimuli despite comparable increases in sympathetic activity compared to males (Hart, E. C. J. & Charkoudian, 2014; Hogarth et al., 2007). This reduced vasoconstriction has been linked to multiple factors, including estradiol levels (Charkoudian, Hart, Barnes, & Joyner, 2017; Hart, E. C. et al., 2011; Hart, E. C. J. & Charkoudian, 2014) and augmented β-adrenergic receptor activity (Hart, E. C. et al., 2011; Hart, E. C. J. & Charkoudian, 2014; Kneale, Chowienczyk, Brett, Coltart, & Ritter,

2000). Finally, studies have also provided evidence that the level of circulating ovarian hormones seems to modulate endothelium-mediated vasodilation (Harris, Tedjasaputra, Zhao, & Richardson, 2012; Schillaci et al., 2001). Studies have reported that young females do not exhibit a reduction in postprandial FMD after HF meal consumption compared to males, further suggesting a protective effect on the vasculature (Harris et al., 2012; Schillaci et al., 2001).

Thus, the main purpose of this study was to examine the effect of a HF meal on sympathetic vasoconstrictor responsiveness. We also sought to examine whether sex influences postprandial vasoconstrictor responsiveness. It was hypothesized that a HF meal would 1) augment sympathetic vasoconstrictor responsiveness and impair FMD in healthy young adults; 2) premenopausal females would exhibit protection in both sympathetic vasoconstrictor responsiveness and FMD after a HF meal compared to males.

Methods

Subjects

This study was approved by the University of Alberta Health Research Ethics Board. Thirty healthy, young males (n=15) and females (n=15) volunteered and provided written informed consent to participate in the study (Table. 1). All subjects were non-obese, non-smokers, and did not have any diseases or conditions which may affect the respiratory, cardiovascular, metabolic, neurological, or musculoskeletal disease. Subjects were not taking any medications known to alter the cardiovascular, respiratory, or metabolic response to exercise. Subjects were recreationally active, but were not engaged in an exercise training program during the project.

Experimental Protocol

Subjects reported to the Integrative Human Exercise Physiology Laboratory (4-246 Van Vliet Complex) in the Faculty Kinesiology, Sport, and Recreation at the University of Alberta on three separate occasions. Subjects were instructed to abstain from exercise, caffeine, alcohol, and ibuprofen for at least 24 hours prior to all testing. Subjects were also instructed to fast for 12 hours prior to testing on days 2 and 3. Laboratory temperature was maintained at 21°C.

Day 1: Subjects completed an incremental exercise test to volitional exhaustion (VO_{2max}) on a cycle ergometer (Ergoselect 200 K, Ergoline, Bitz, Germany) to determine maximal aerobic capacity. Testing began with 2 minutes of resting data collection, after which work rate was progressively incremented in a ramp-like manner at a rate of $30 W \cdot min^{-1}$ until volitional exhaustion. One minute of passive recovery was recorded after cessation of exercise. Criteria used to establish a maximal test included a plateau in VO_2 despite an increase in work rate, a respiratory exchange ratio >1.10, achievement of >90% of age-predicted maximal heart rate (HR) or volitional exhaustion.

Day 2 and 3: Testing on days 2 and 3 was separated from initial fitness testing by at least 24 hours. Participants reported to the lab on two separate occasions and were randomly assigned to low-fat or high-fat conditions. Meal composition was designed similarly to previous studies that have employed standardized HF meals to induce endothelial dysfunction (Bae et al., 2001; Ballard et al., 2008; Harris et al., 2012; Jakulj et al., 2007; Tsai et al., 2004; Tushuizen et al., 2006; Vogel et al., 1997). HF meals were obtained from a local McDonald's and consisted of the following standard breakfast items: Sausage McMuffin®, Egg McMuffin®, and two hash brown patties (McDonald's

Corporation) which contained 980kcal, 52g fat (17g saturated, 0.5 trans), 92g carbohydrate, 33g protein, 250mg cholesterol, and 2260mg sodium. The low-fat meal was modeled after control meals used in previous studies and consisted of 168g of Frosted Flakes® (Kellogg Company, Battle Creek, Michigan), 1.5 cups of 1% partly skimmed milk, and 2 cups orange juice (Jakulj et al., 2007; Padilla, Harris, Fly, Rink, & Wallace, 2006; Vogel et al., 1997). The low-fat meal contained 978.5 kcal, 3.7g fat (1.1g saturated), 222g CHO, 22.7g protein, 7.4 cholesterol, and 952.5mg sodium. Subjects reported to the laboratory at 8AM and were required to finish each meal within a 20-minute period. Approximately 1.5 hours after meal ingestion, subjects assumed a supine position and were instrumented with a 3-lead electrocardiogram(ECG) and Finometer to assess beat-to-beat blood pressure by finger photo-plethysmography (Finometer™, Finapres Medical Systems, Amsterdam, Netherlands). Blood pressure was also taken manually. 2-hours post meal ingestion, continuous measures of blood flow velocity and arterial diameter were taken at the brachial artery. Baseline video recording was taken for 1 minute prior to inflation of cuff occlusion at the forearm. The cuff was inflated on the forearm for a period of 5 minutes. Video recording was resumed during the last 30 seconds of cuff inflation and continued 3-minutes post occlusion. Video was captured using an ECG gated trigger system (Vascular Imager, Medical Imaging Applications LLC, Iowa) and commercially available USB frame grabber. The pressure cuff was placed on the forearm distal to the ultrasound probe. Following 30-minutes of recovery from the FMD protocol, subjects submerged their right foot in -4°C ice-water slurry for 3 minutes to elicit a sympathoexcitatory vascular response. By placing their extremity into ice-water, subjects underwent an involuntary increase in sympathetic nerve activity,

vasoconstriction, and blood pressure (Seals, 1991; Victor, Leimbach, Seals, Wallin, & Mark, 1987). Importantly, this increase in sympathetic outflow is mediated by afferent type III and IV fibers without the contribution of central command (Rowell, 1993). Video capture was recorded 30 seconds prior to submersion of the foot, throughout the 3 minute CPT, and 1 minute after the foot was removed. All ultrasound measurements were conducted on the right arm.

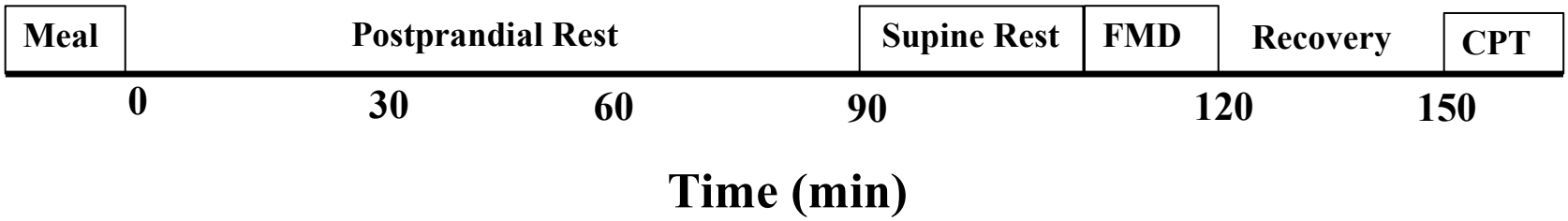

Figure 1. Timeline of testing on days 2 and 3. Following meal ingestion, subjects underwent ~1.5 hours postprandial rest period. Subsequently, 12 mins of resting data were collected prior to the assessment of flow-mediated dilation (FMD). FMD was followed by ~30 minutes of recovery. After recovery, subjects performed a 3-min cold pressor test (CPT), submerging their right foot in an ice-water slurry to determine sympathetic vasoconstriction as measured by the percent change from baseline to nadir forearm vascular conductance (FVC).

Figure 2. Representation of experimental setup and instrumentation

Measurements

VO_2, carbon dioxide production, respiratory exchange ratio, and ventilation were measured in 10-second averages using a mass flow sensor and metabolic cart (Vmax® 229d; Viasys™ Healthcare, Palm Springs, California). Oxygen consumption (VO_2), CO_2 production (VCO_2), RER, and minute expired ventilation (VE) were measured with a low-resistance mass-flow meter on a breath-by-breath basis via open-circuit indirect calorimetry (Vmax® 229d; Viasys™ Healthcare, Palm Springs, CA, USA). Subjects breathed through a mouthpiece, with their nose occluded, for the VO_2max test. Before each test, the flow-meter was calibrated with a 3-litre calibration syringe at a range of flow rates expected during the VO_2max test. The O_2 and CO_2 analyzers were calibrated with gases of known concentration.

The ECG was continuously recorded in a three-lead configuration (Vascular Imager, Medical Imaging Applications LLC, Iowa) and HR was derived from the ECG waveform.

Beat-by-beat arterial BP was measured by finger photo-plethysmography (Finometer™, Amsterdam, Netherlands). BP was also measured by sphygmomanometer at rest before FMD and CPT, and Finometer BP was corrected to manually measured pressures.

Vascular measures were assessed 2-hours post meal ingestion which is adequate time to report a significant difference in postprandial lipemia (PPL) (Bae et al., 2001; Faulk & Bartholomew, 2012; Jakulj et al., 2007; Tsai et al., 2004; Vogel et al., 1997). Mean blood velocity (MBV) and arterial diameter were measured using pulsed-Doppler ultrasonography (GE Vivid I, Waukesha WI, USA). Data were acquired using a 4.4 MHz probe with a 60° angle of insonation placed on the right brachial artery. Forearm blood flow (FBF) was calculated as FBF

($ml \cdot min^{-1}$) = MBV ($cm \cdot s^{-1}$)$\cdot \pi r^2 \cdot 60$, where r is the radius of the brachial artery. Forearm vascular conductance (FVC, $ml \cdot min^{-1} \cdot mmHg^{-1}$) was calculated as FBF/MAP.

FMD was calculated as the percentage change in arterial diameter (%FMD) from baseline to the peak diameter after cuff release (Corretti et al., 2002). FMD was expressed as a percentage of baseline diameter in order to control for differences in resting brachial artery diameter between subjects (Ballard et al., 2008).Shear rate was calculated as Shear Rate FMD (s^{-1}) = [8 x MBV(cm/s)] / [Diameter (cm)]. FMD normalized to cumulative shear rate which was defined as the area under the curve for the first 90 seconds after cuff release and calculated as the percentage FMD over the area under the curve of shear rate (%FMD/AUC shear rate).

Sympathetic vasoconstrictor responsiveness was defined as the percentage change in FVC (Δ%FVC) of the nadir response to the CPT and the preceding baseline measure. This percentage change in response to sympathoexcitatory stimulation accurately reflects the change in resistance vessel radius over different measures of baseline values of vascular conductance and is the accepted method of quantifying the magnitude of sympathetic vasoconstrictor responsiveness (Buckwalter & Clifford, 2001; Thomas & Segal, 2004). Peak FVC response was taken as the mean of the lowest 20 cardiac cycles that corresponded to the visually identified peak increase in blood pressure during the CPT.

Data and Statistical Analysis

Data were recorded using a PowerLab 16/30 system and Chart 7™ data acquisition software (AD Instruments, Colorado Springs, CO, USA) at a sampling frequency of 1000Hz during the 12 minutes of resting data and 100Hz during the assessments of FMD and CPT protocols.

All data were reported as mean ± standard deviation. Relationships between aerobic fitness, brachial artery diameter, and vascular function were assessed by Pearson-product correlations. The effect of meal condition on FMD, peak shear, shear rate AUC, normalized FMD, FVC, and blood pressure response, were analyzed by two-way repeated (Sex x Meal) measures ANOVA. When significant F-ratios were identified, Student-Newman-Keuls post hoc analyses were performed. A p-value < 0.05 was considered statistically significant. Statistics were performed using the analytical software SigmaPlot (SigmaPlot Version 13.0, Systat Software Inc., San Jose, CA, USA).

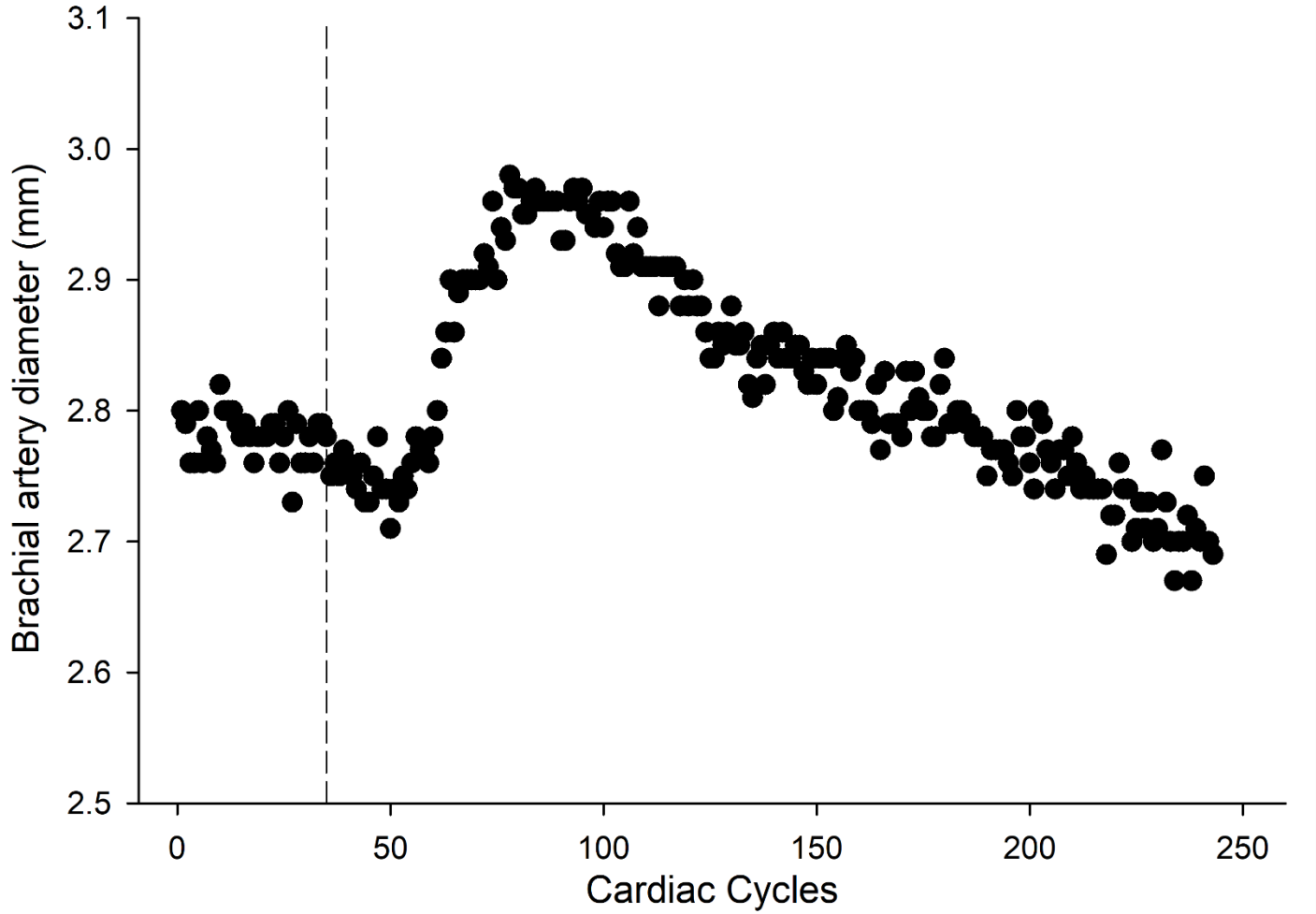

Figure 3. Typical response tracing of the brachial artery diameter in response to FMD.

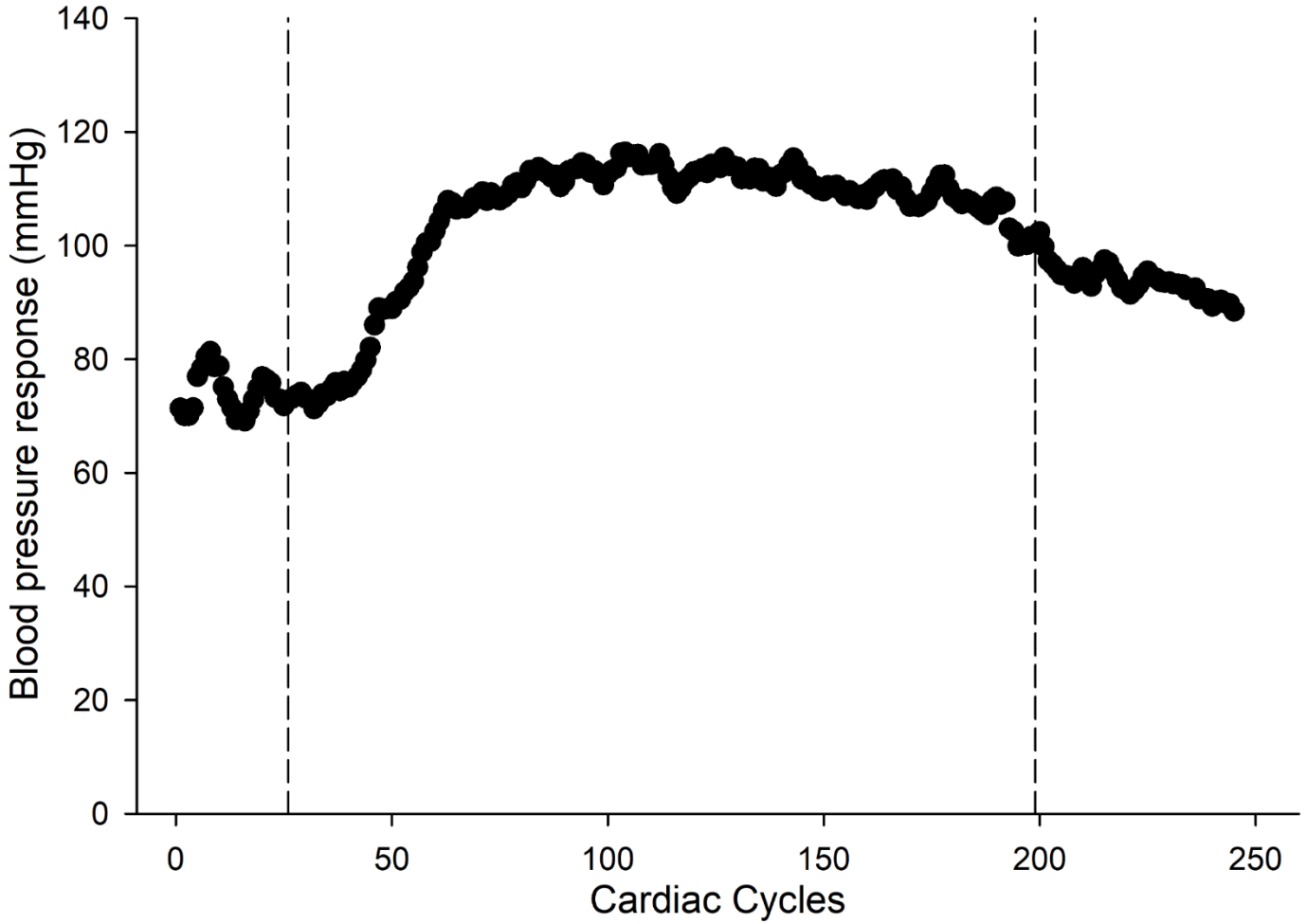

Figure 4. Typical response tracing of the mean arterial blood pressure response to CPT.

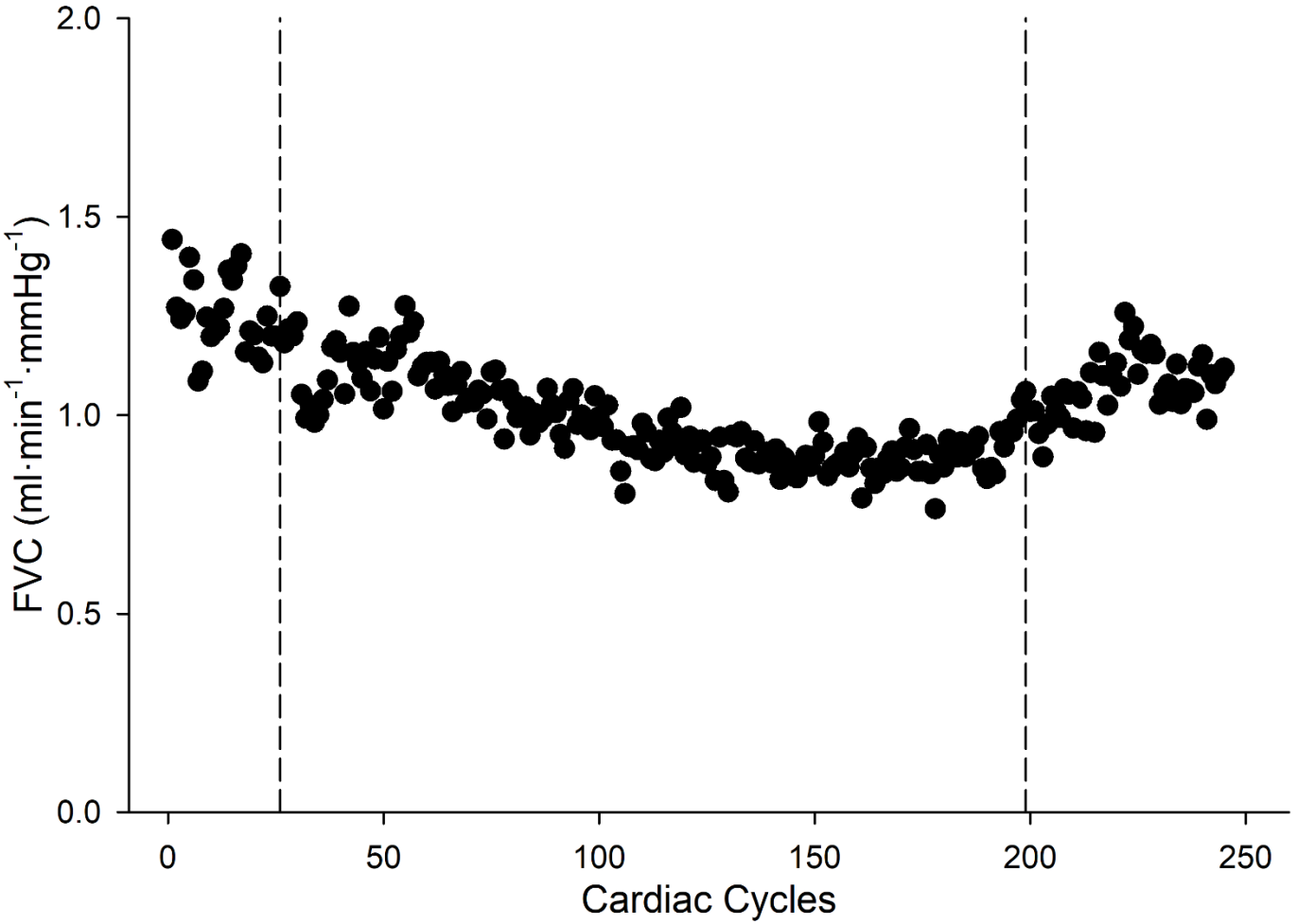

Figure 5. Typical response tracing of the FVC response to CPT.

Results

Subject Characteristics

Subject age, height, weight, absolute and relative VO_{2max}, and resting hemodynamic measures are reported in Table 1. 15 males (25±6yrs) and 15 females (23±4yrs) participated in the current study. Baseline hemodynamics before FMD (Table 2) and CPT (Table 3) are also reported.

Table 1. Participant characteristics.

	Male	Female
Age (yrs)	25.3 ± 5.9	23.1 ± 4.7
Height (cm)	177.6 ± 6.1	166.6 ± 6.8†
Weight (kg)	77.7 ± 8.8	62.0 ± 7.9†
Absolute VO_{2max} (L/min)	4.1 ± 0.7	2.4 ± 0.5†
Relative VO_{2max} (ml/kg/min)	52.6 ± 7.5	39.6 ± 5.8†

Values are mean ± SD. † Significant difference between sex ($p<0.05$).

Table 2. Resting hemodynamics prior to FMD

	Male		Female	
	LF	**HF**	**LF**	**HF**
Baseline Diameter (mm)	4.1 ± 0.3	4.1 ± 0.3	3.1 ± 0.3†	3.1 ± 0.3†
Heart Rate (bpm)	61.2 ± 10.8	58.7 ± 10.1*	70.1 ± 6.5†	65.9 ± 9.5*†
Mean Arterial Pressure (mmHg)	77.1 ± 4.9	77.7 ± 7.1	75.3 ± 5.5	72.6 ± 3.8
FVC ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	0.861 ± 0.368	0.854 ± 0.286	0.513 ± 0.134†	0.577 ± 0.213†

Forearm Vascular Conductance (FVC). Values are mean ± SD. * Significant effect of meal ($p<0.05$). † Significant difference between sex ($p<0.05$).

Table 3. Resting hemodynamics prior to CPT

	Male		Female	
	LF	**HF**	**LF**	**HF**
Baseline Diameter (mm)	4.1 ± 0.3	4.1 ± 0.3	3.1 ± 0.3†	3.0 ± 0.2†
Heart Rate (bpm)	65.6 ± 10.6	63.9 ± 11.5*	76.1 ± 10.9†	71.8 ± 10.5*†
Mean Arterial Pressure (mmHg)	75.6 ± 6.1	76.3 ± 6.8	74.3 ± 6.0	72.0 ± 4.5
FVC ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	0.948 ± 0.324	0.904 ± 0.339	0.563 ± 0.224†	0.550 ± 0.202†

Forearm Vascular Conductance (FVC). Values are mean ± SD. * Significant effect of meal ($p<0.05$). † Significant difference between sex ($p<0.05$).

Aerobic Fitness and Vascular Reactivity

Absolute VO_{2max} was positively correlated to baseline diameter in both meal conditions in males (LF: r=0.740, p=0.002; HF: r=0.745, p=001). Baseline diameter was positively correlated to relative VO_{2max} in the LF meal condition (r=0.539, p=0.040), however, it was not correlated in the HF condition in males (r=0.481, p=0.069). Baseline diameter was not correlated to either absolute (LF: r=-0.020, p=0.944; HF: r=0.040, p=0.888) or relative VO_{2max} in females (LF: r=-0.128, p=0.650; HF: r=-0.086, p=0.760). Absolute VO_{2max} was not significantly correlated to FMD after either meal in males (LF: r=0.086, p=0.762; HF: r=0.271, p=0.328) or females (LF: r=0.009, p=0.975; HF: r=-0.005, p=0.986). Relative VO_{2max} was not significantly correlated to FMD after either meal in males (LF: r<0.001, p=0.999; HF: r=0.136, p=0.629) or females (LF: r=0.125, p=0.657; HF: r=0.440, p=0.101). Absolute VO_{2max} was not significantly correlated to normalized FMD after either meal in males (LF: r=0.339, p=0.216; HF: r=0.221, p=0.429) or females (LF: r=0.073, p=0.797; HF: r=-0.228, p=0.413). Relative VO_{2max} was not significantly correlated to normalized FMD after either meal in males (LF: r=0.387, p=0.154; HF: r=0.066, p=0.814) or females (LF: r=0.045, p=0.872; HF: r=0.201, p=0.472). Absolute VO_{2max} were also not correlated to Δ%FVC in either meal conditions for males (LF: r=-0.319, p=0.247; HF: r=-0.375, p=0.168) or females (LF: r=-0.228, p=0.414; HF: r=-0.013, p=0.964). Relative VO_{2max} was not significantly correlated to Δ%FVC after either meal in males (LF: r=-0.315, p=0.253; HF: r=-0.283, p=0.307) or females (LF: r=-0.026, p=0.926; HF: r=0.025, p=0.930).

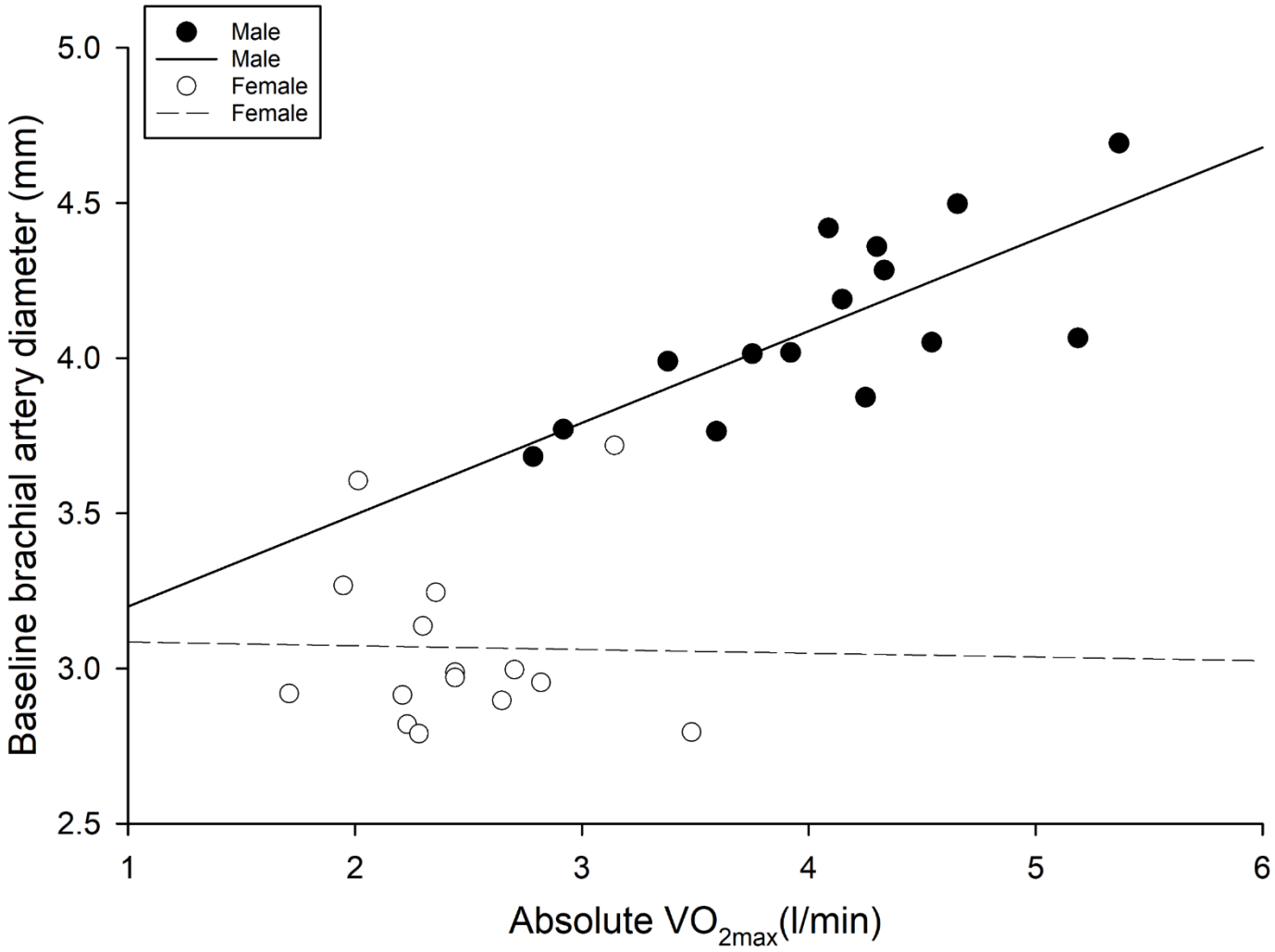

Figure 6. Relationship between absolute VO_{2max} and baseline brachial artery diameter after the ingestion of a LF meal.

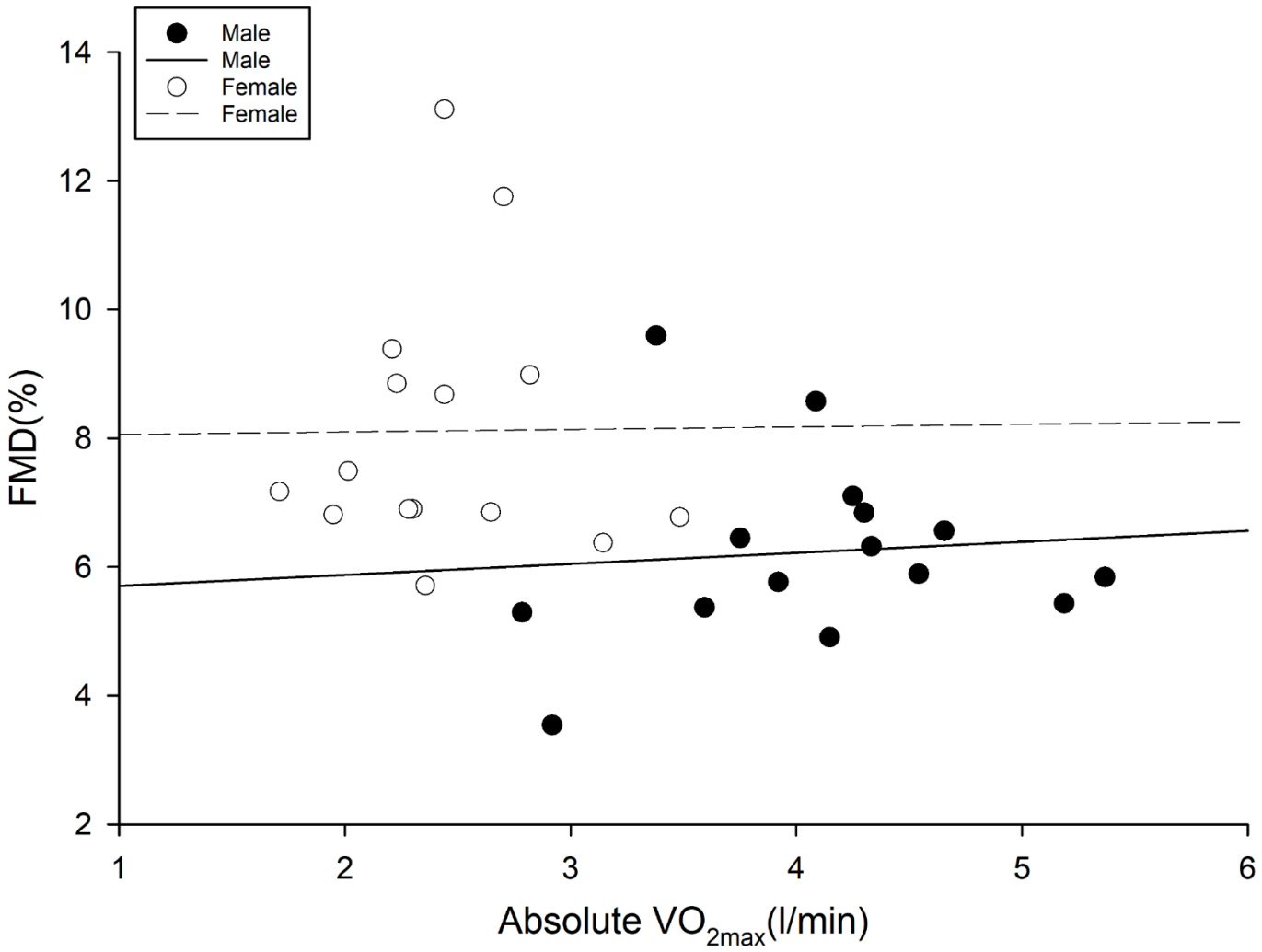

Figure 7. Relationship between absolute VO_{2max} and FMD after the ingestion of a LF meal.

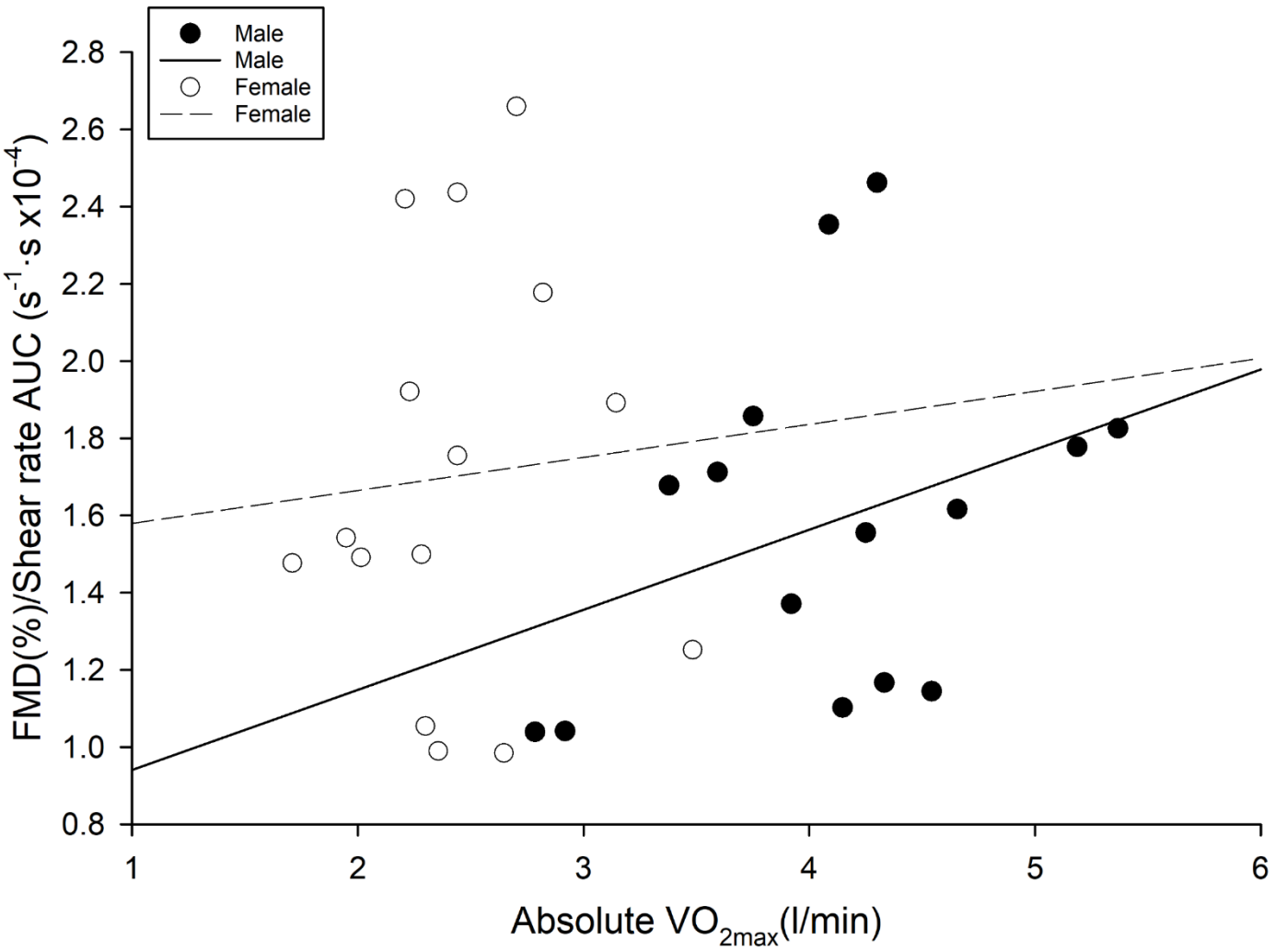

Figure 8. Relationship between absolute VO_{2max} and normalized FMD after the ingestion of a LF meal.

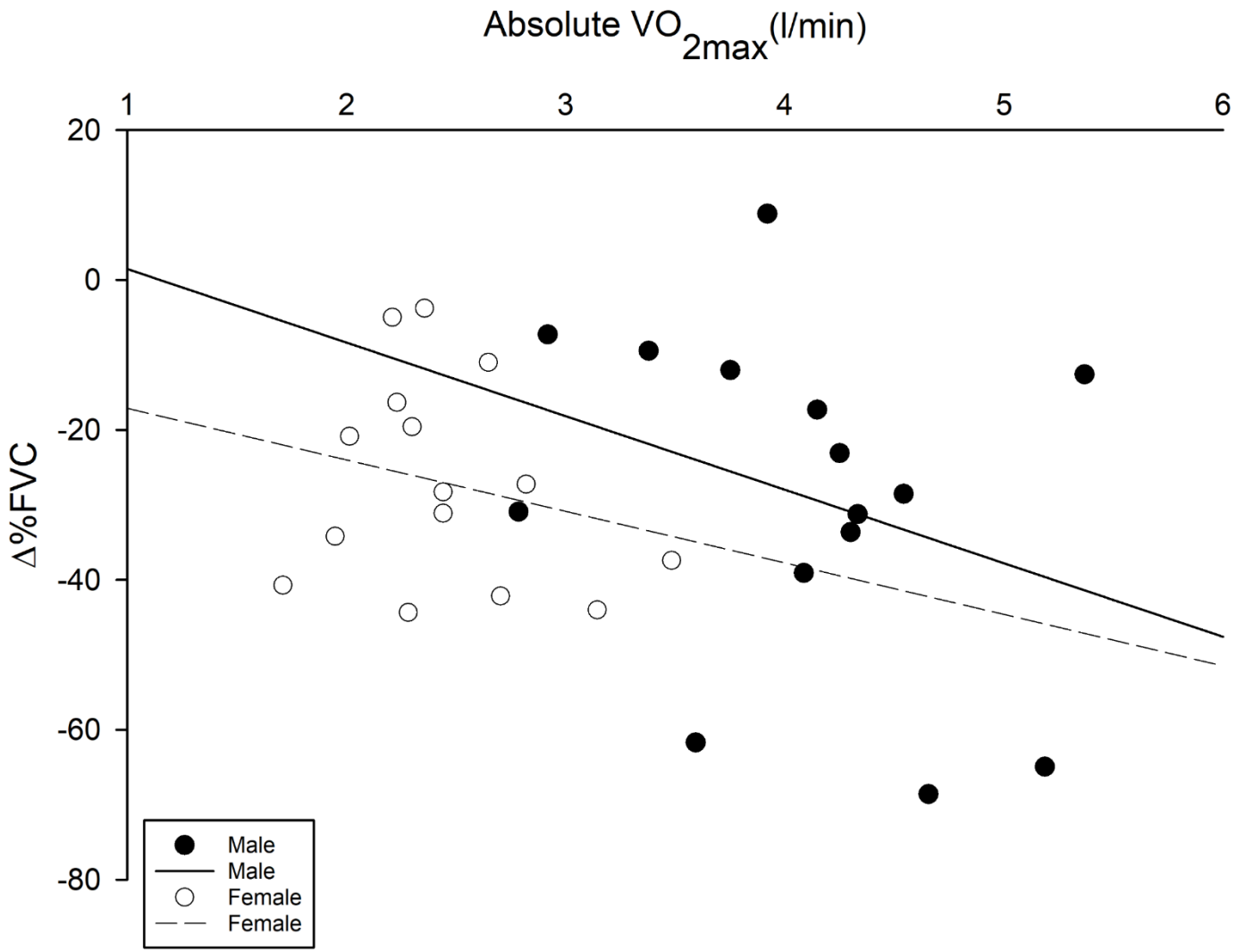

Figure 9. Relationship between absolute VO_{2max} and sympathetic vasoconstrictor responsiveness (Δ%FVC) after the ingestion of a LF meal.

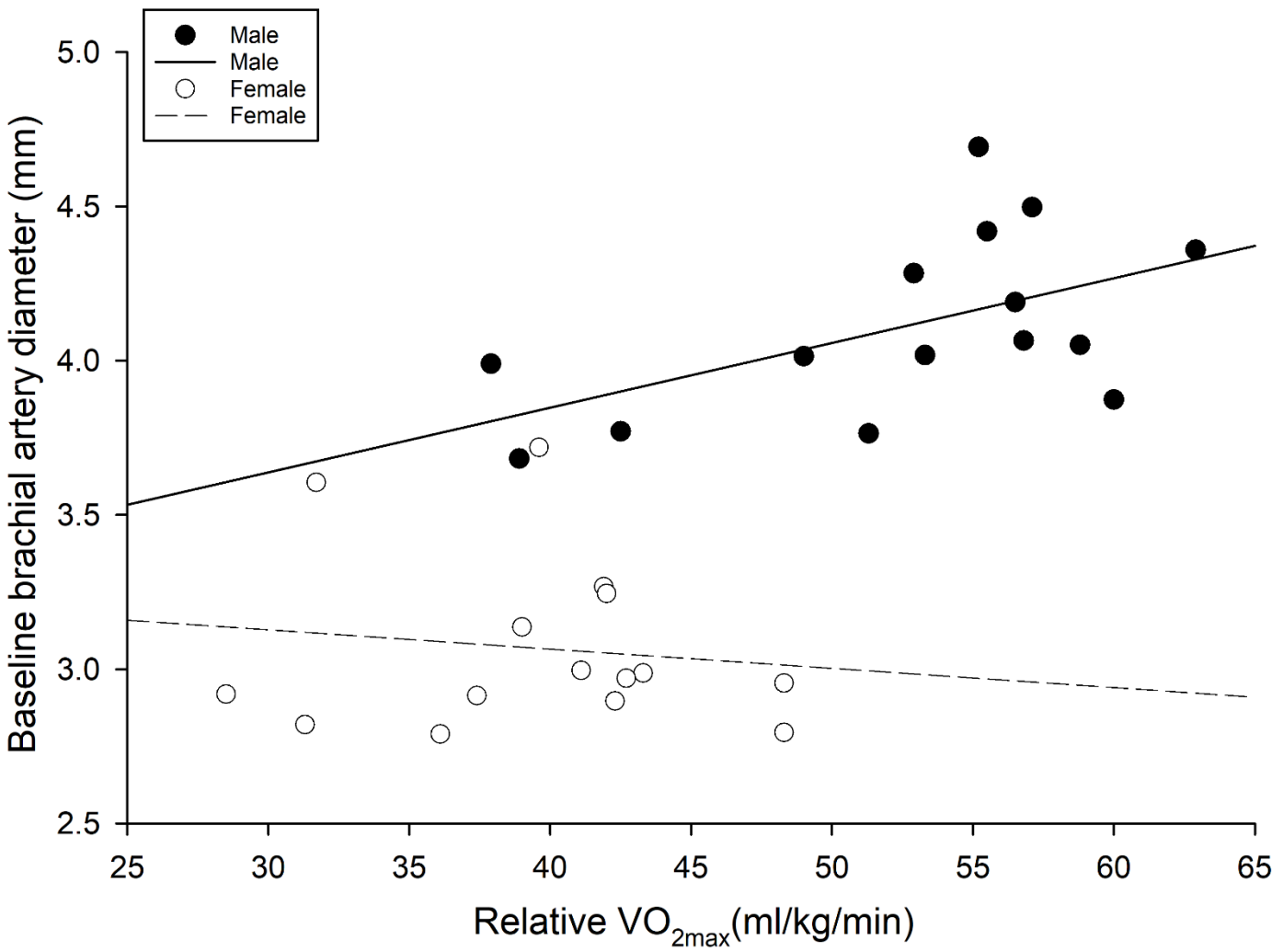

Figure 10. Relationship between relative VO_{2max} and baseline brachial artery diameter after the ingestion of a LF meal.

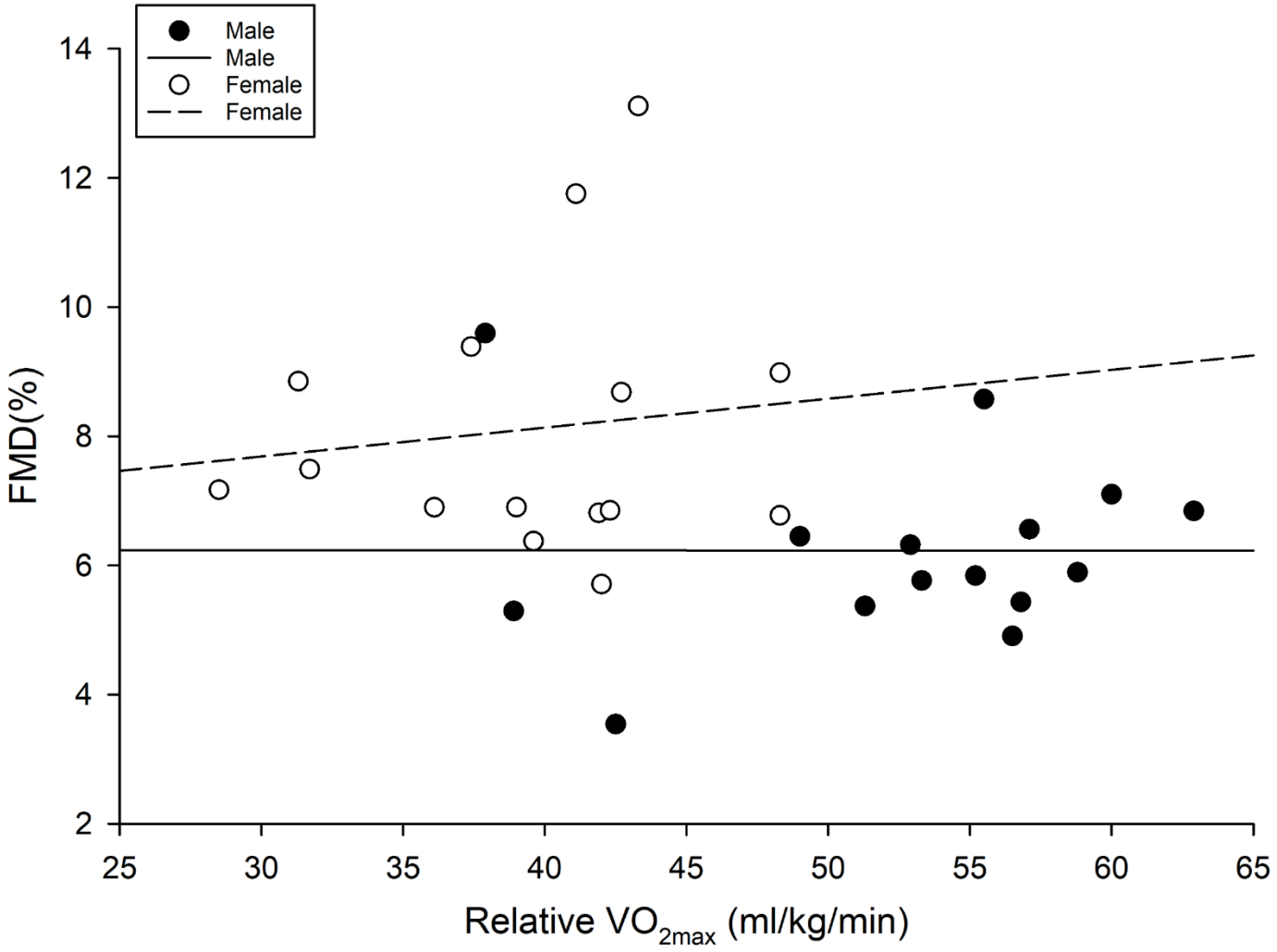

Figure 11. Relationship between relative VO_{2max} and FMD after the ingestion of a LF meal.

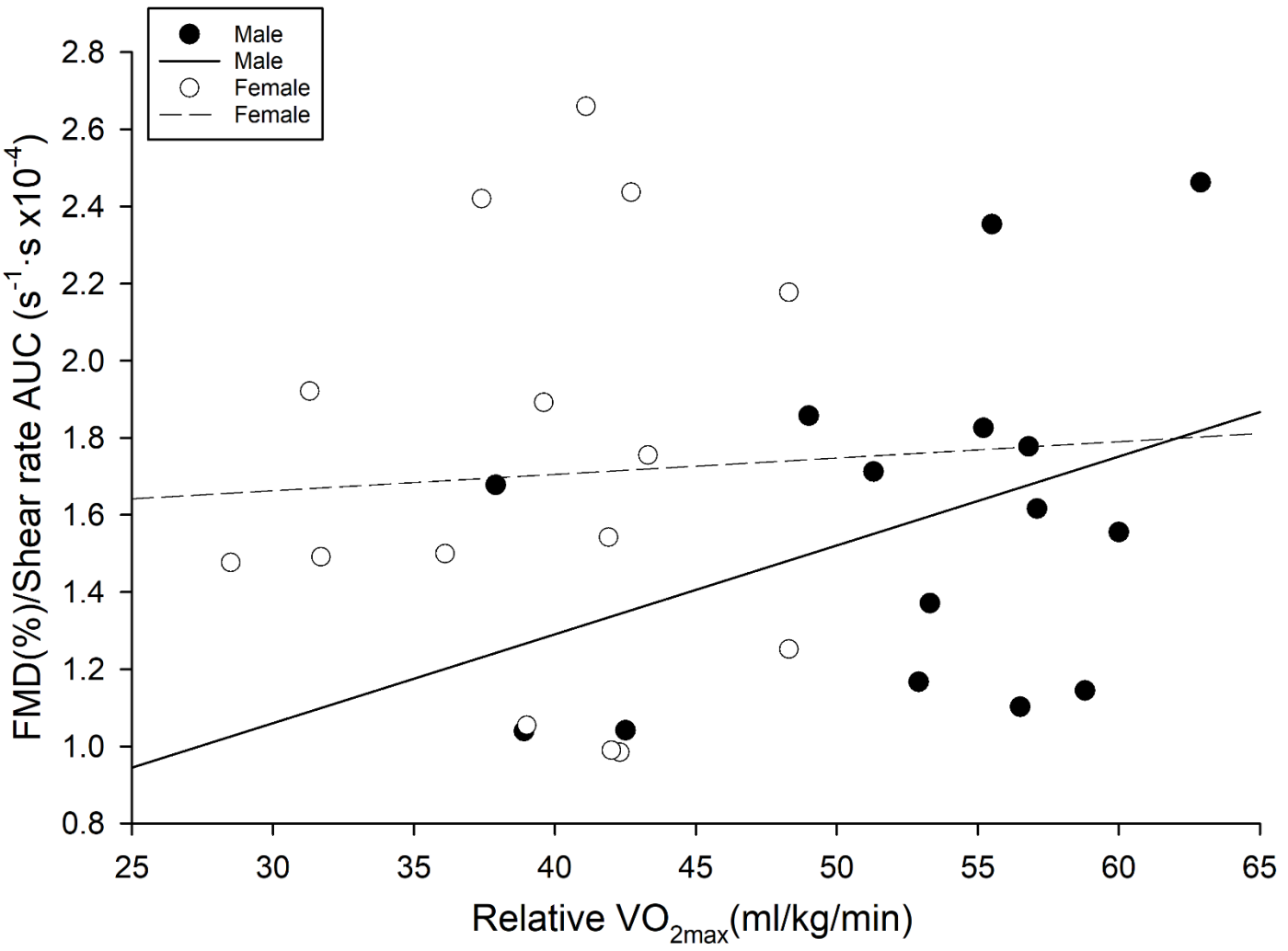

Figure 12. Relationship between relative VO_{2max} and normalized FMD after the ingestion of a LF meal.

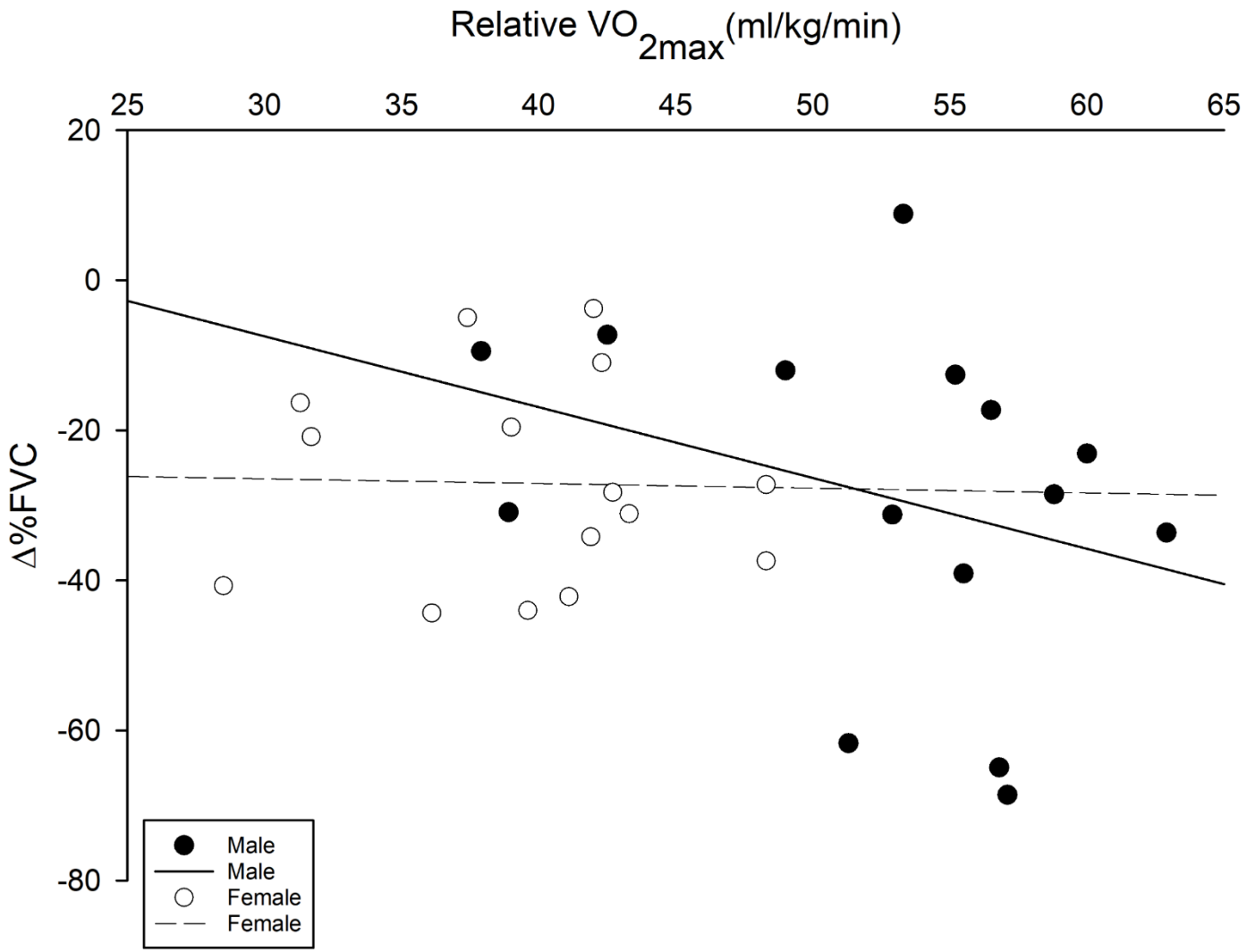

Figure 13. Relationship between relative VO_{2max} and sympathetic vasoconstrictor responsiveness (Δ%FVC) after the ingestion of a LF meal.

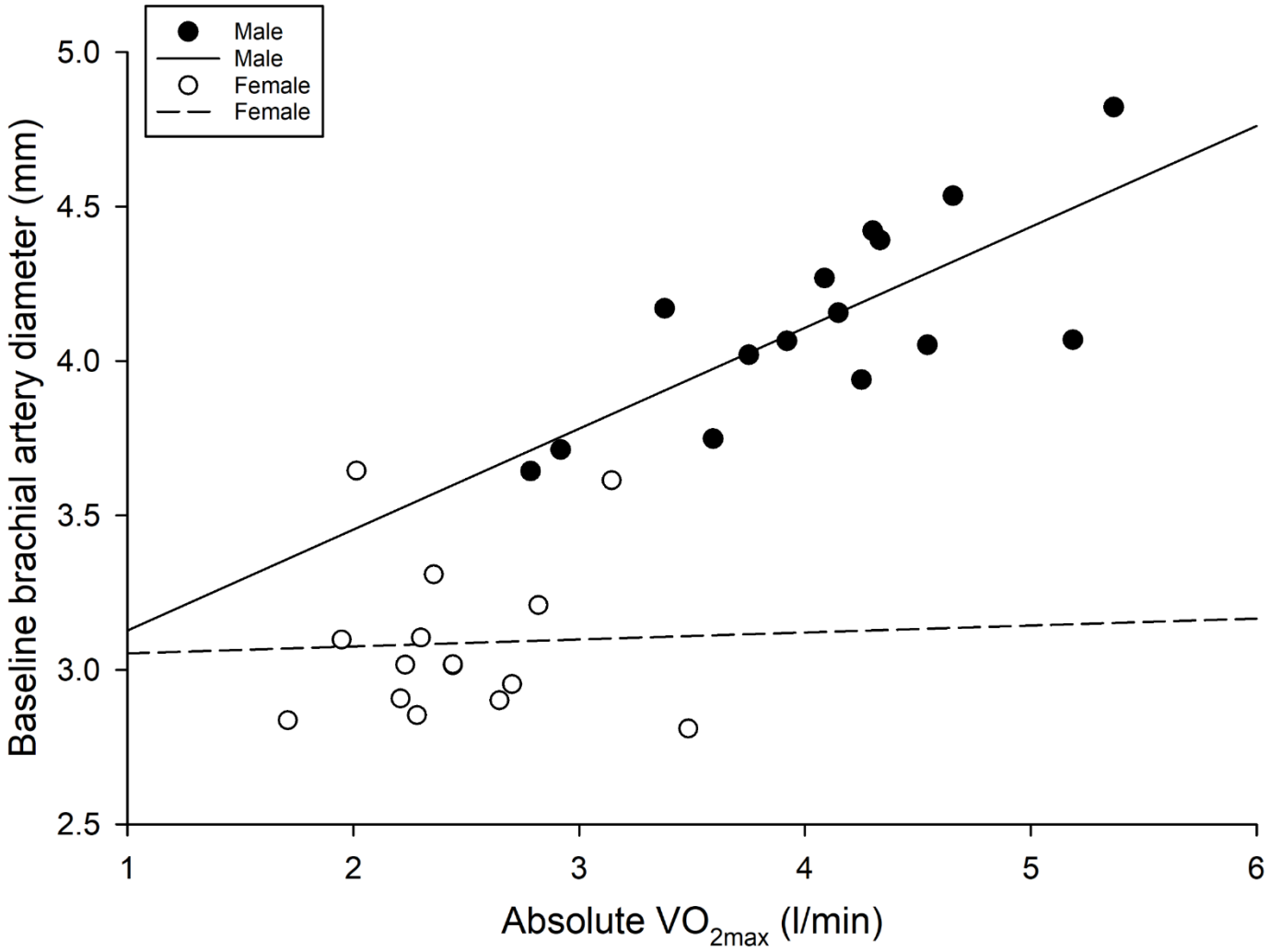

Figure 14. Relationship between absolute VO_{2max} and baseline brachial artery diameter after the ingestion of a HF meal.

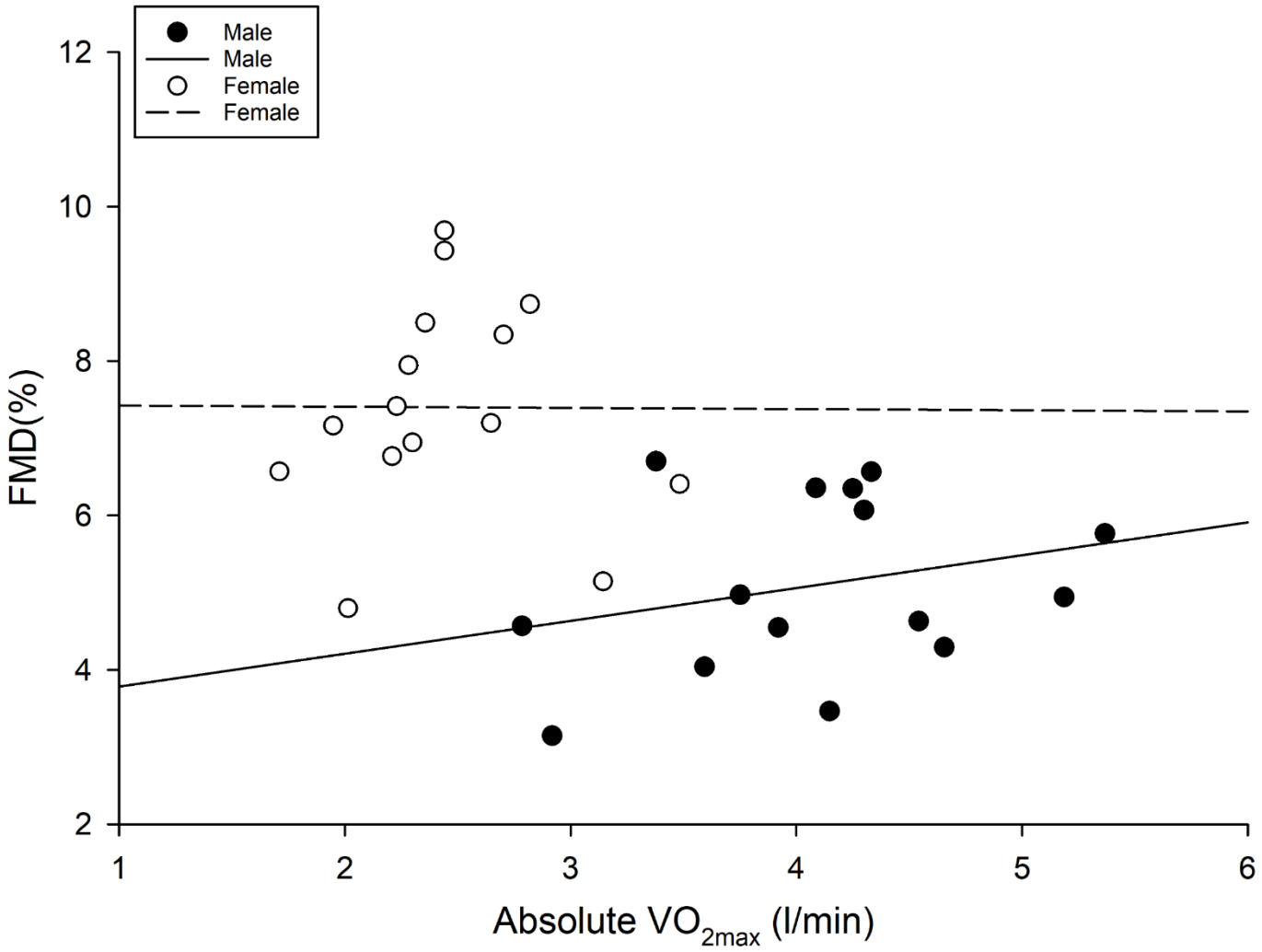

Figure 15. Relationship between absolute VO_{2max} and FMD after the ingestion of a HF meal.

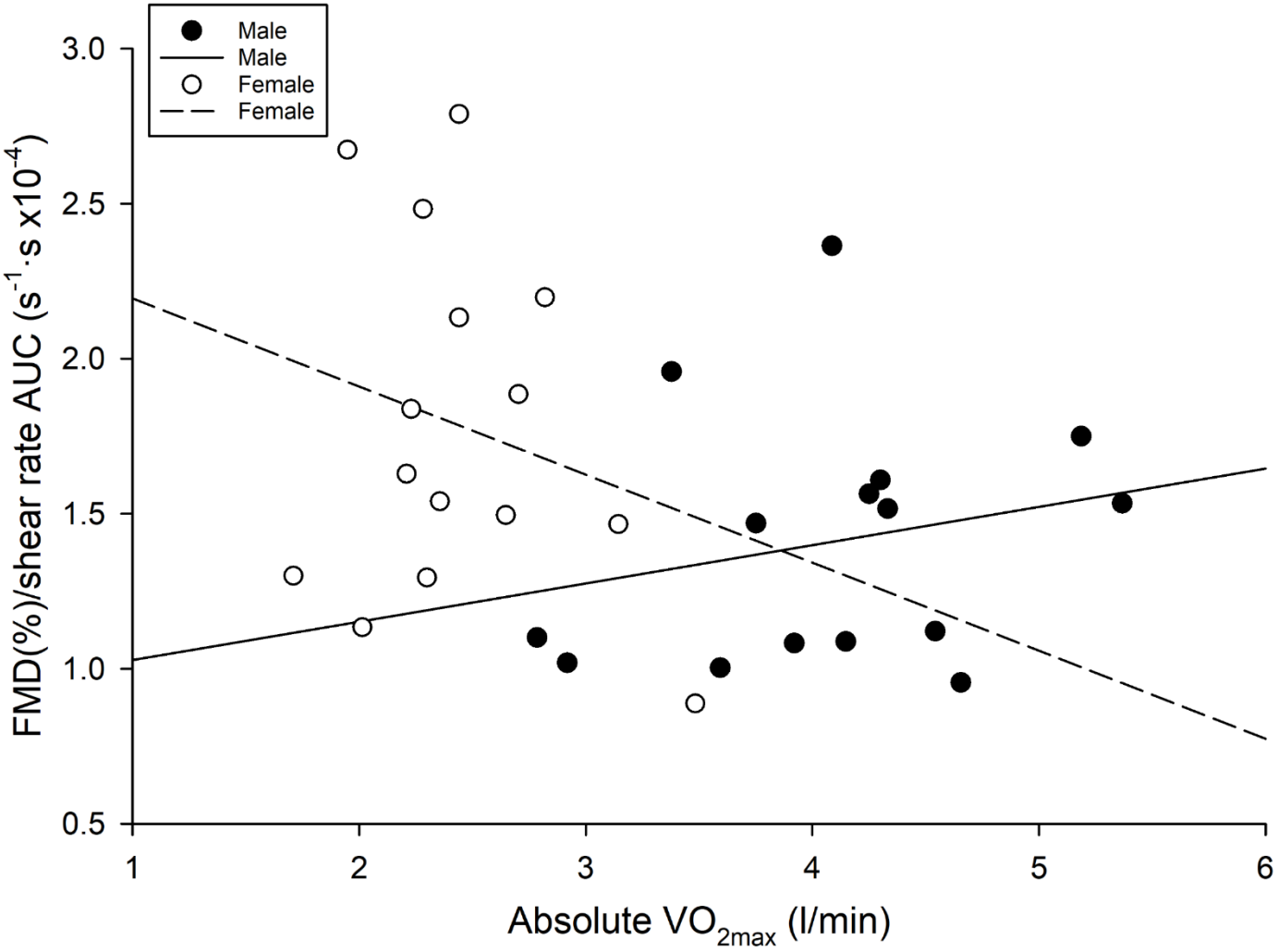

Figure 16. Relationship between absolute VO_{2max} and normalized FMD after the ingestion of a HF meal.

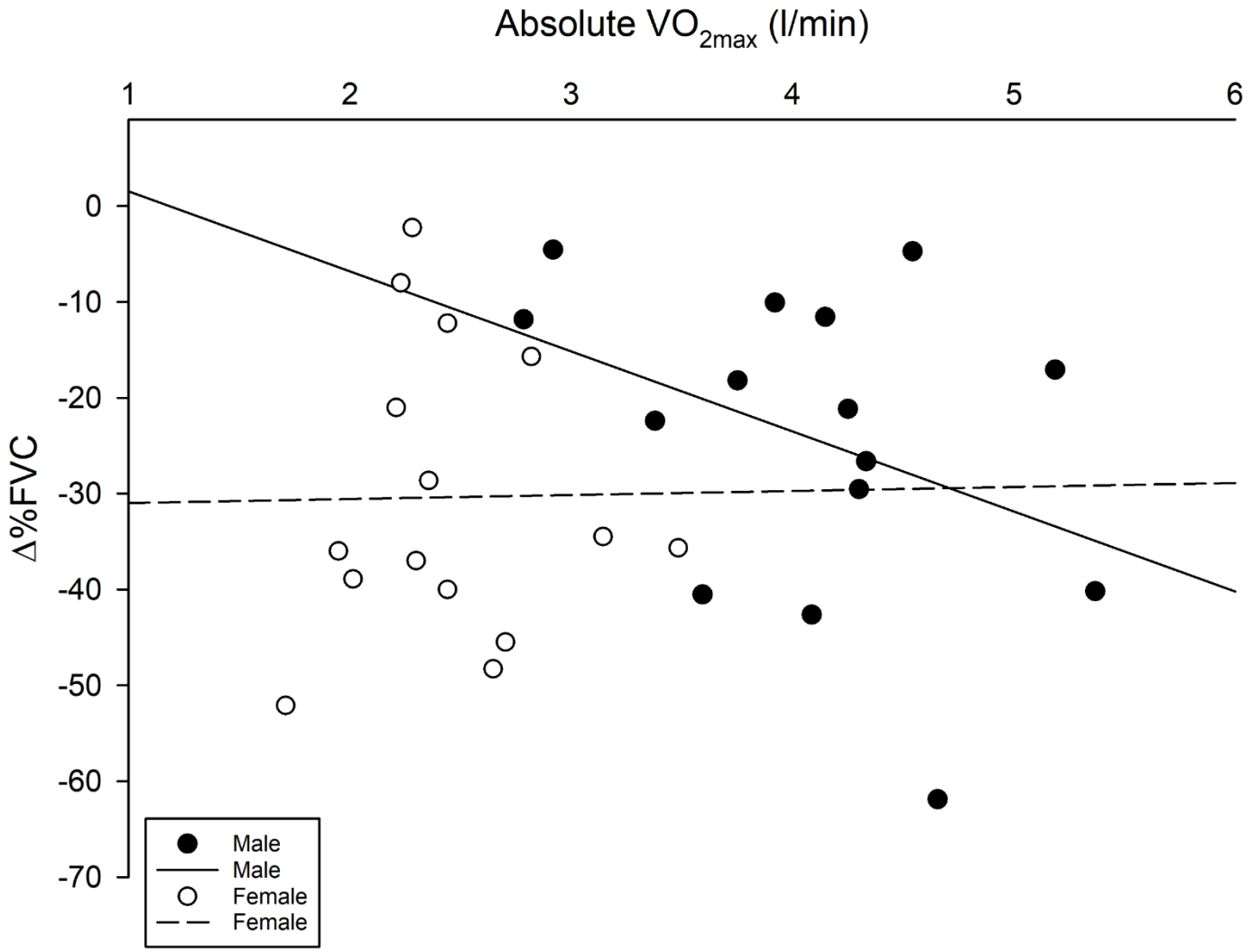

Figure 17. Relationship between absolute VO_{2max} and sympathetic vasoconstrictor responsiveness (Δ%FVC) after the ingestion of a HF meal.

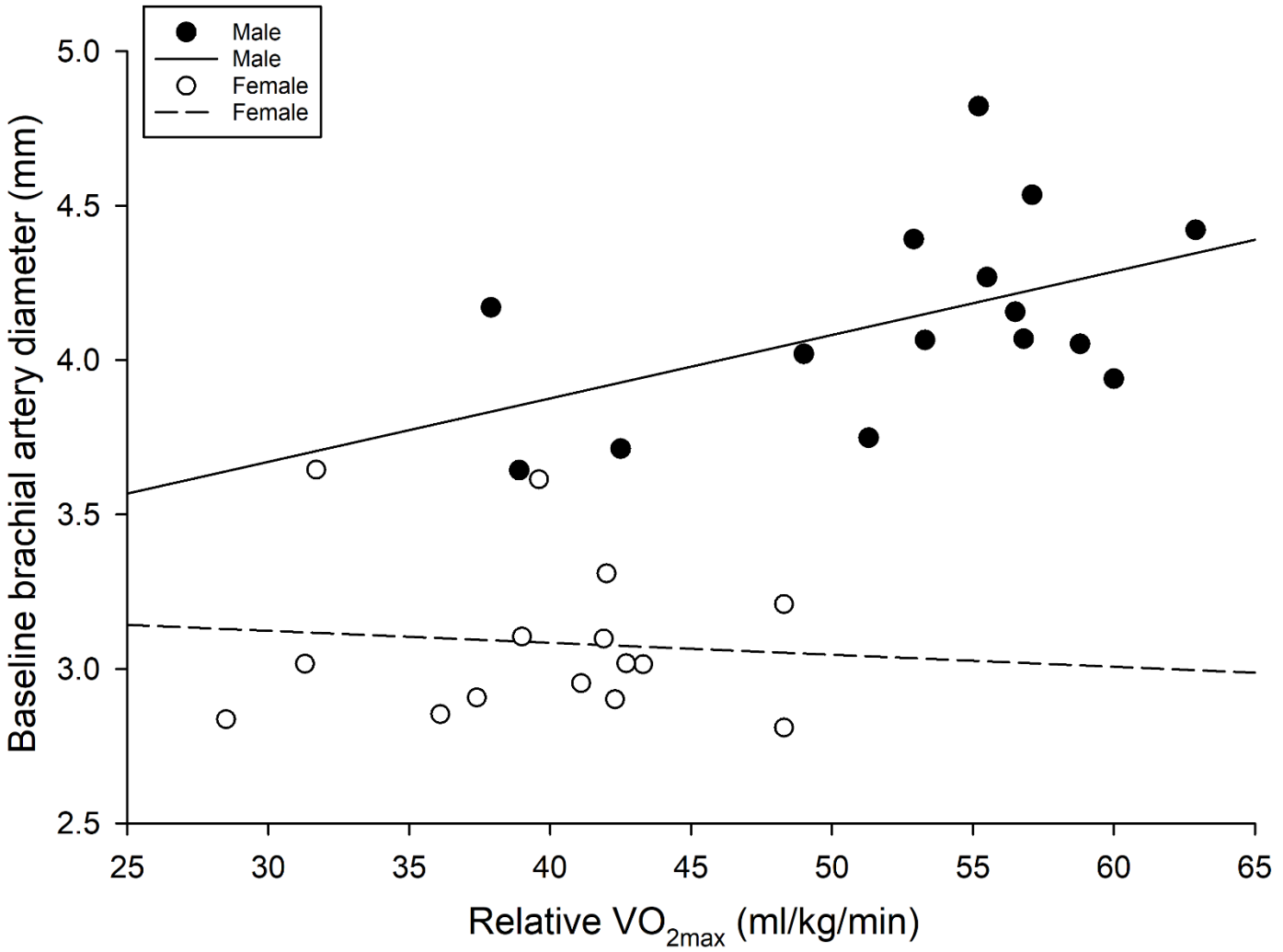

Figure 18. Relationship between relative VO_{2max} and baseline brachial artery diameter after the ingestion of a HF meal.

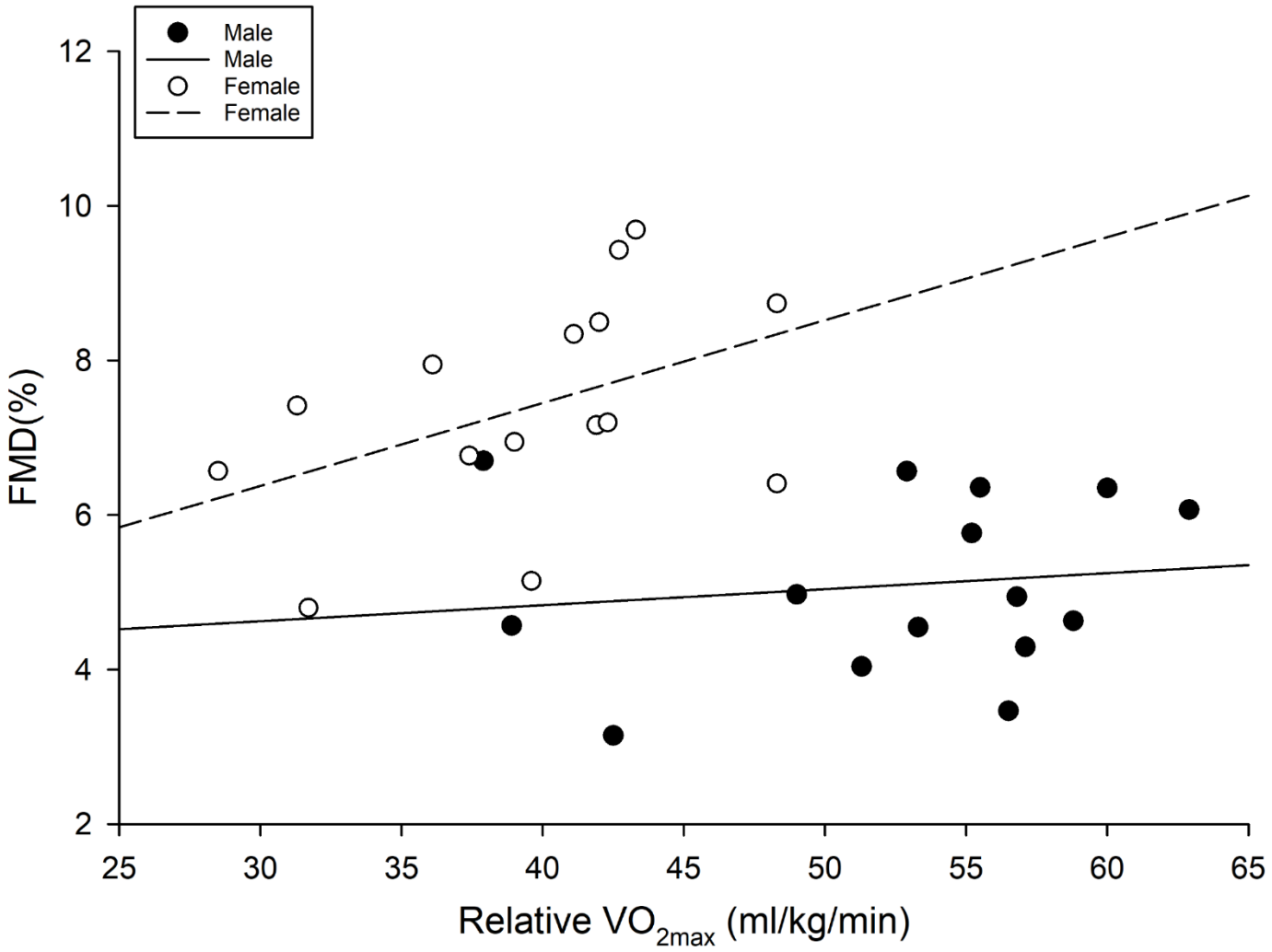

Figure 19. Relationship between relative VO_{2max} and FMD after the ingestion of a HF meal.

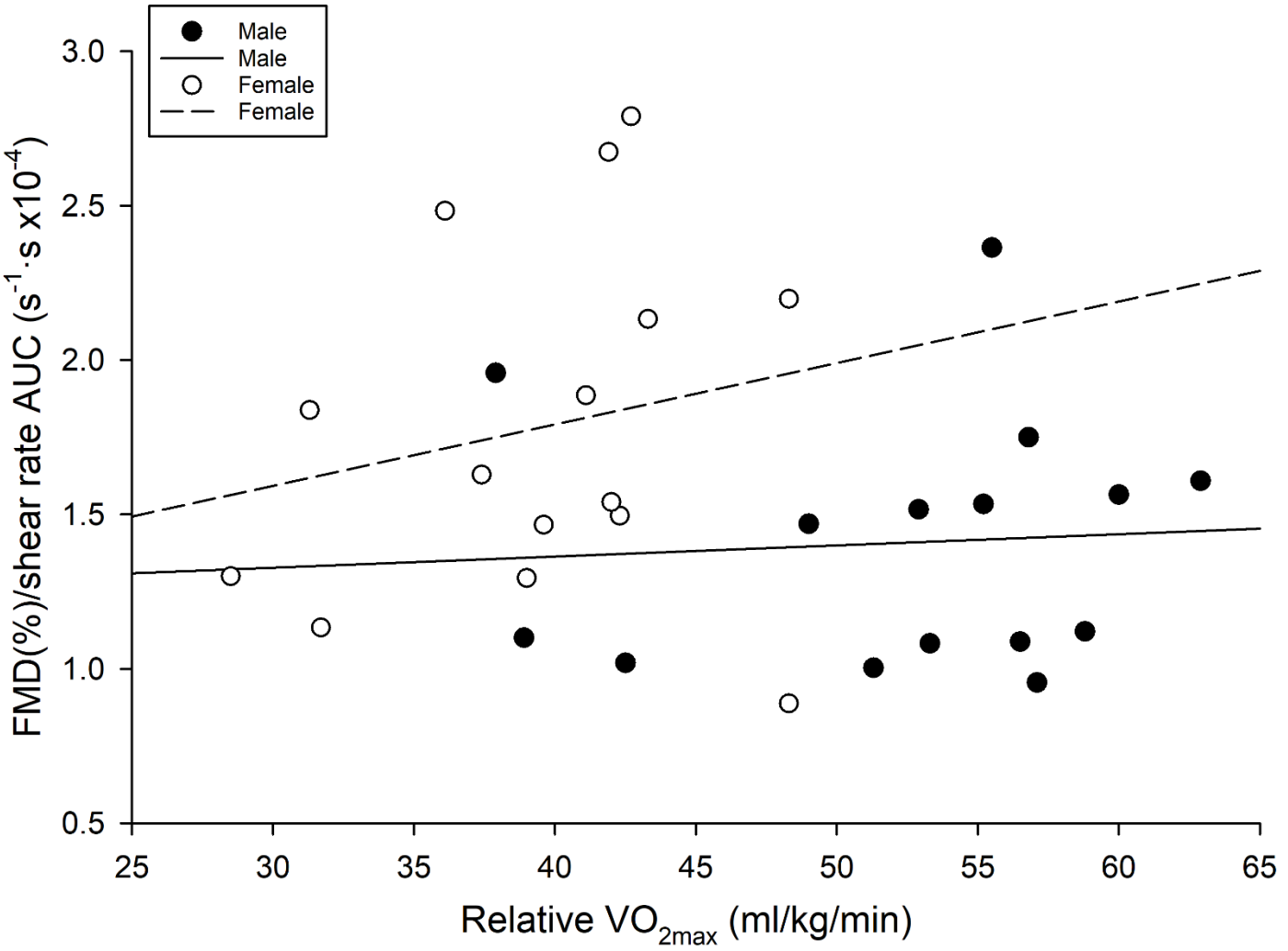

Figure 20. Relationship between relative VO_{2max} and normalized FMD after the ingestion of a HF meal.

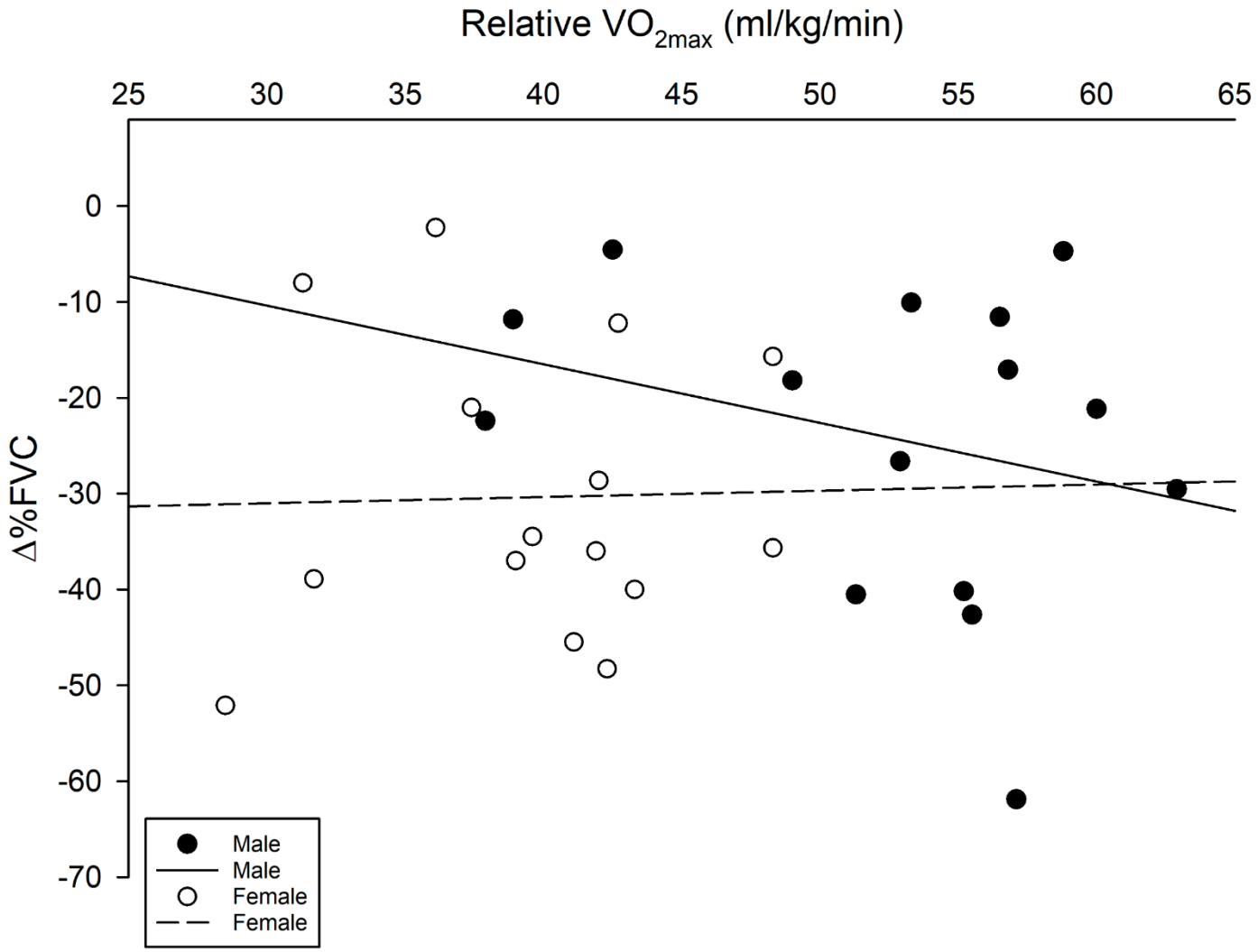

Figure 21. Relationship between relative VO_{2max} and sympathetic vasoconstrictor responsiveness (Δ%FVC) after the ingestion of a HF meal.

FMD and Shear Rate

Baseline diameters were not found to be significantly different ($p>0.05$) between meal conditions in either males or females. Postprandial FMD was significantly lower ($p<0.05$) in the HF meal compared to the LF meal. Peak shear was significantly higher ($p<0.05$) after LF meal compared to HF meal. Shear rate AUC in response to the meals was significantly higher ($p<0.05$) in the LF condition compared to the HF meal, in both males and females. When normalized to shear rate AUC, this difference was abolished ($p>0.05$).

Effect of the HF meal on Sympathetic Vasoconstriction

Baseline conditions prior to FMD and CPT were not found to be significantly different ($p>0.05$). CPT caused increased BP and decreased FVC in both meal conditions compared to baseline measurements. However, percentage change in FVC was not different ($p>0.05$) between meal conditions. The percentage change in FVC was also not different ($p>0.05$) in males or females between meal conditions. Peak blood pressure response to CPT was also not different ($p>0.05$) in males and females.

Sex Differences Between Meal Conditions

Baseline diameters were found to be significantly higher ($p<0.05$) in males compared to females. Females showed significantly higher ($p<0.05$) %FMD in both meal conditions compared to males. Shear rate AUC was also found to be significantly higher ($p<0.05$) in females compared to males. However, when FMD was normalized to shear AUC, there was no significant difference ($p>0.05$) between sexes. Blood pressure response and Δ%FVC were not significantly different ($p>0.05$) between sexes in response to CPT.

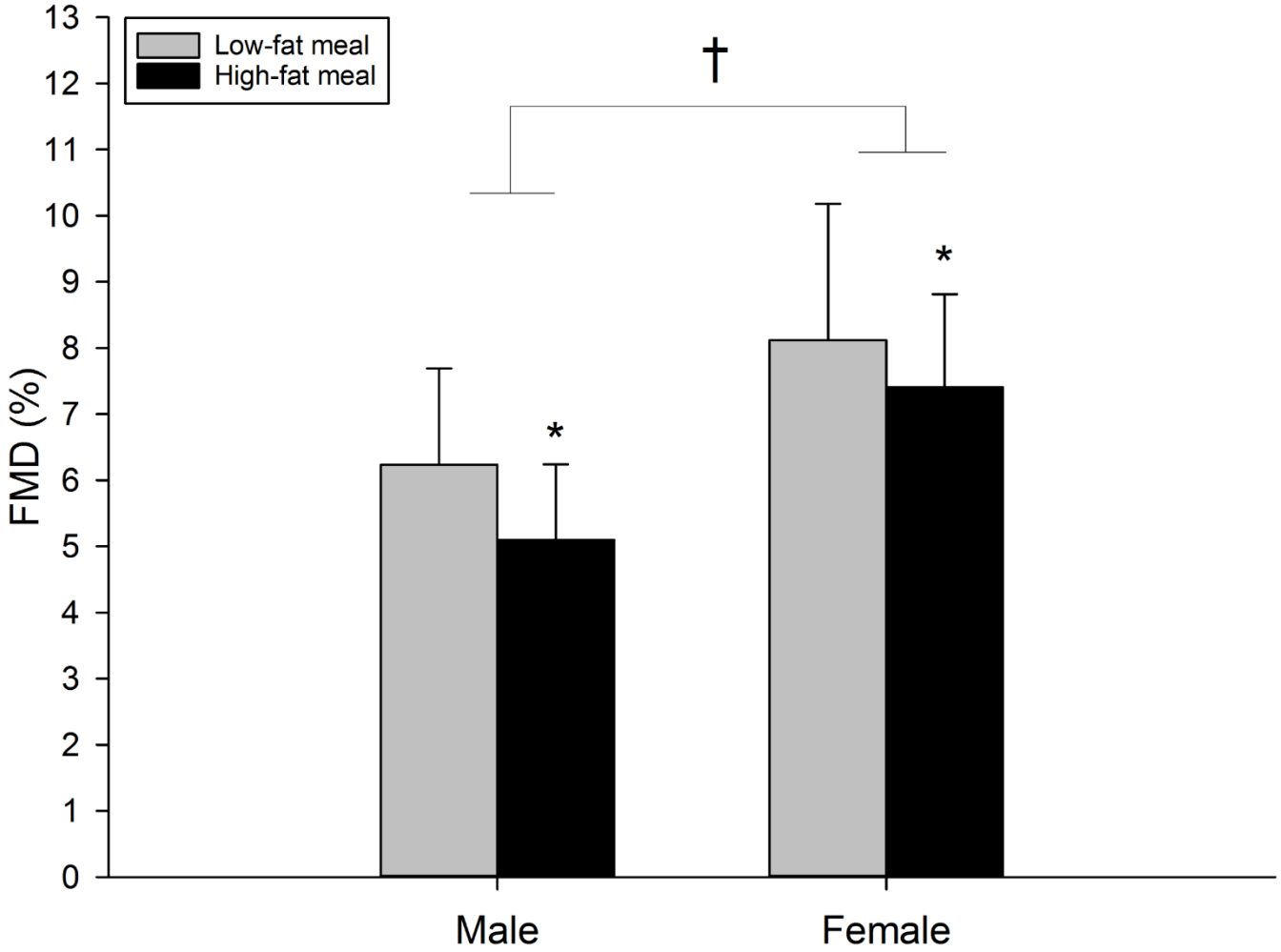

Figure 22. FMD (%) between sex and meal conditions. * Significant difference between meal conditions. † Significant difference between sex. Values are mean ± SD

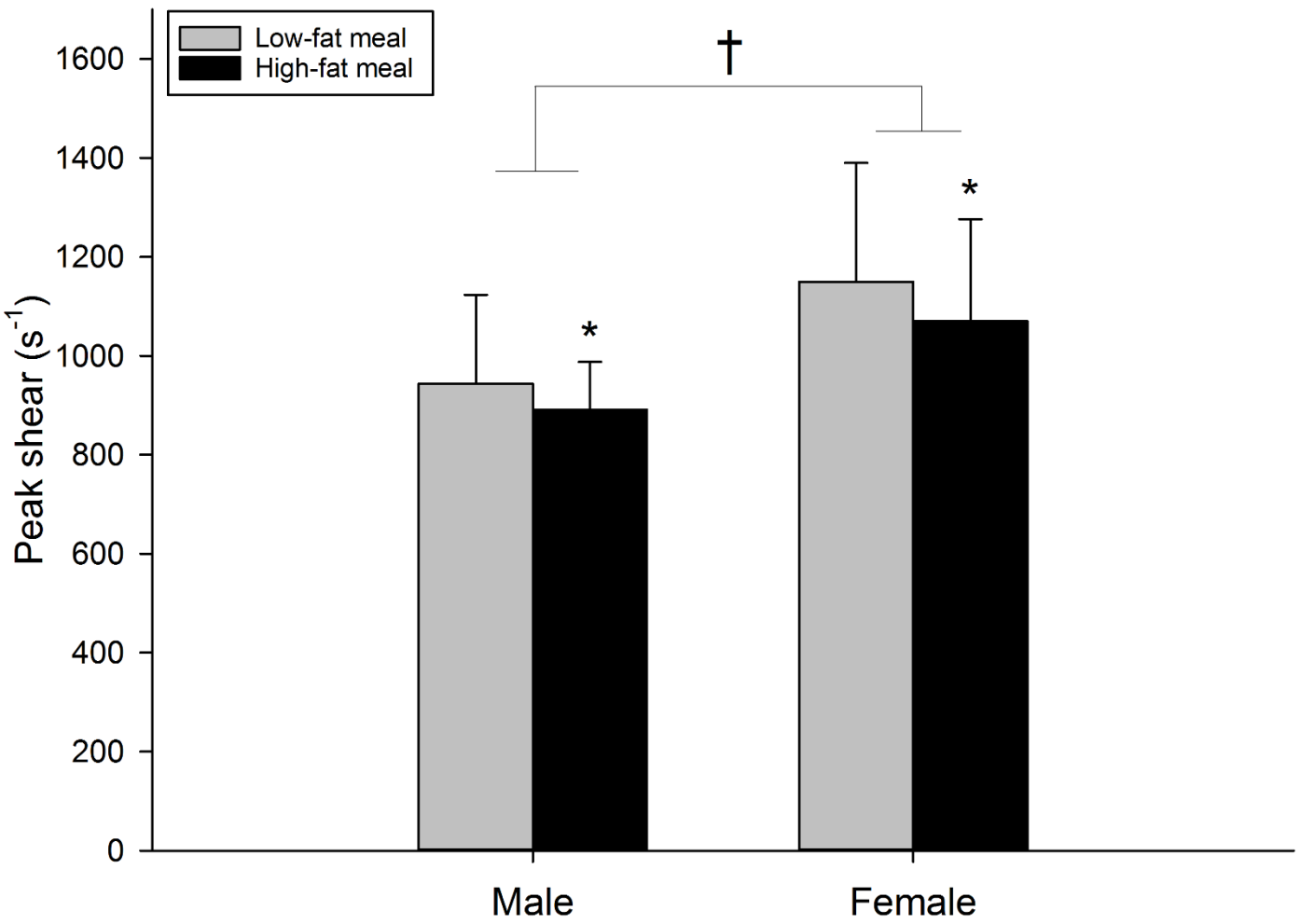

Figure 23. Peak shear (s^{-1}) in response to FMD between sex and meal conditions. * Significant difference between meal conditions. † Significant difference between sex. Values are mean ± SD

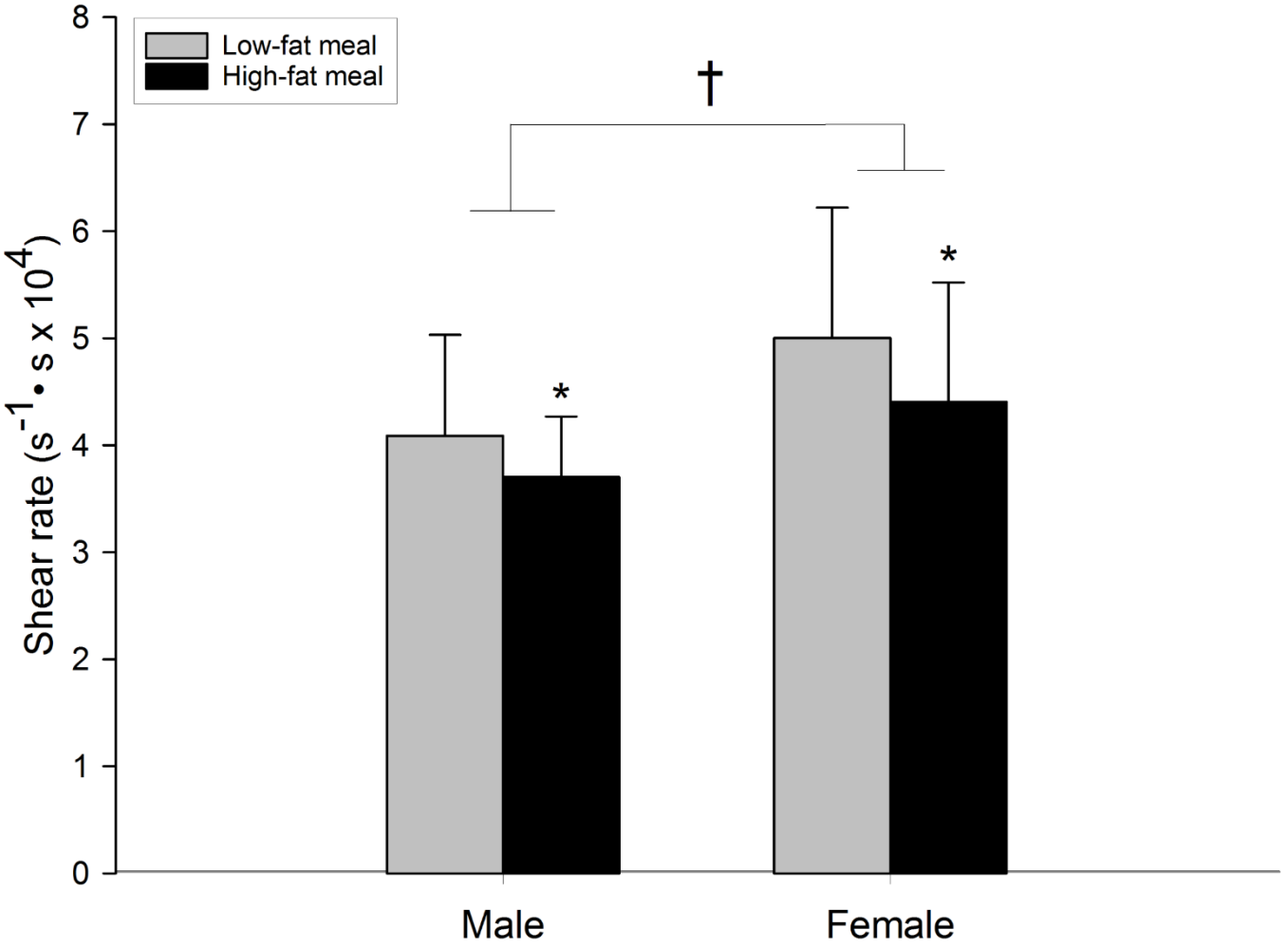

Figure 24. Shear Rate Area Under the Curve (s^{-1}• s x10^4, AUC) in response to FMD between sex and meal conditions. * Significant difference between meal conditions. † Significant difference between sex. Values are mean ± SD

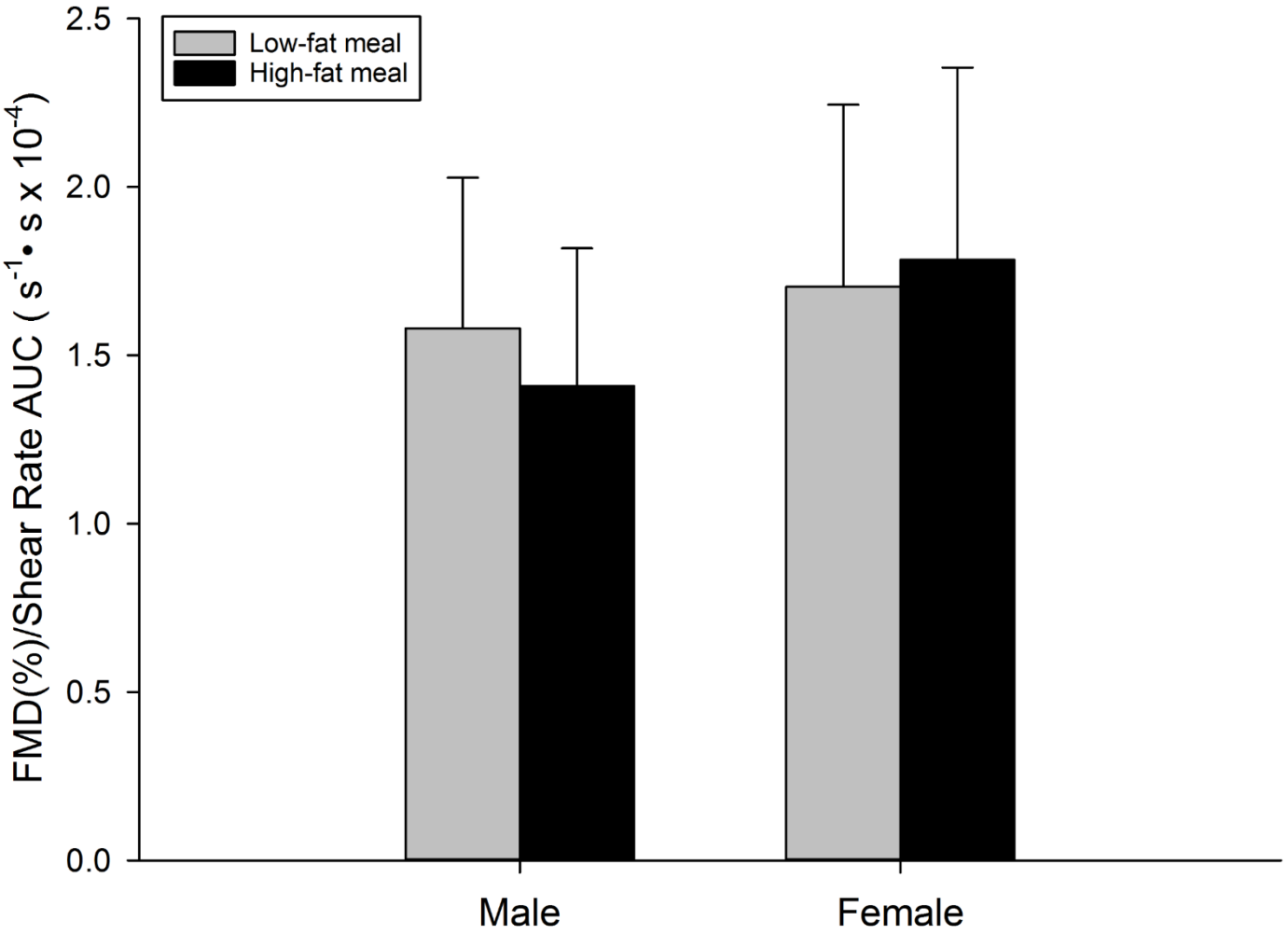

Figure 25. FMD normalized to shear rate AUC (s^{-1}• s x10^{-4}, AUC) between sex and meal conditions. Values are mean ± SD

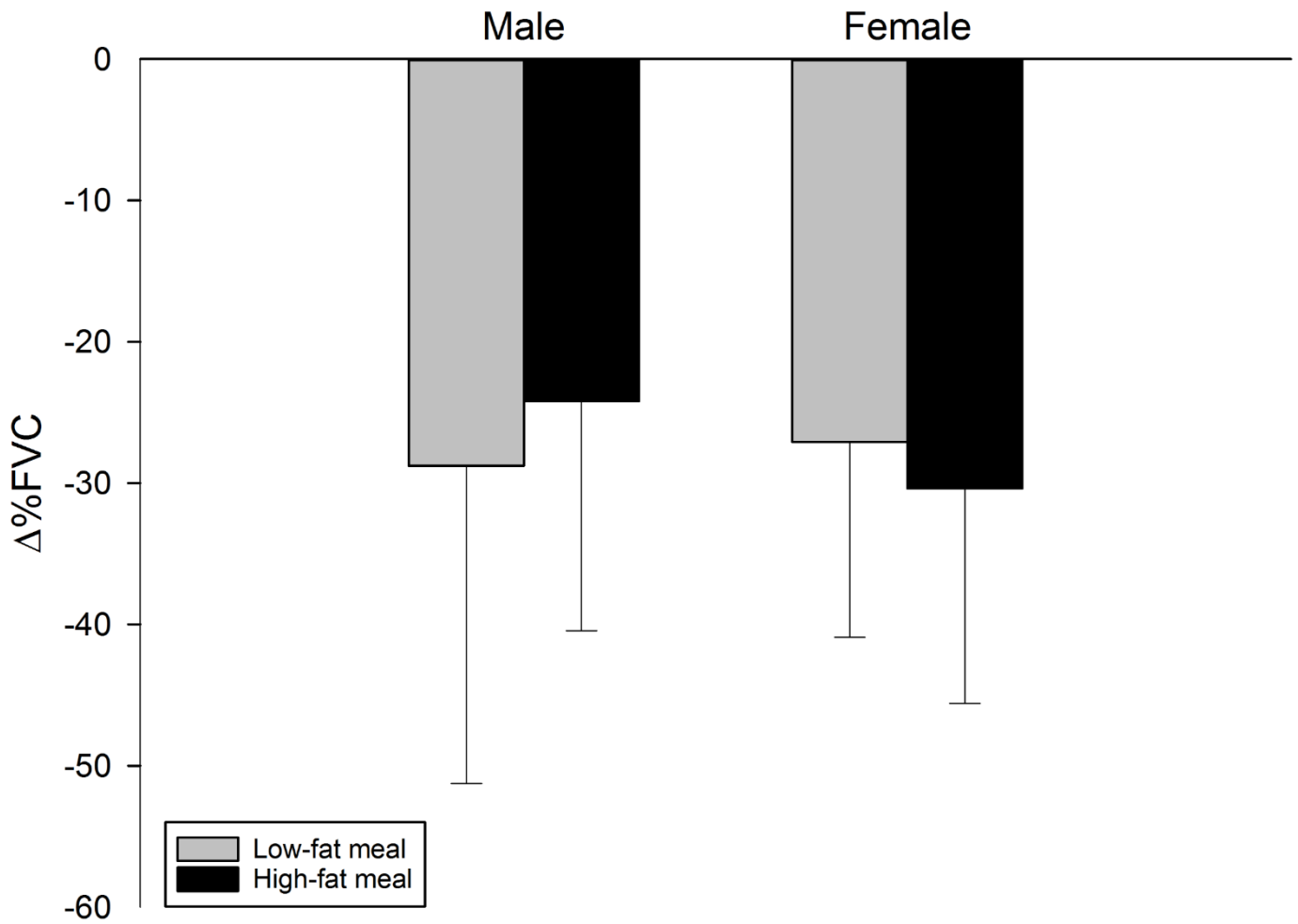

Figure 26. Δ%FVC in response to CPT between sex and meal condition. Values are mean ± SD

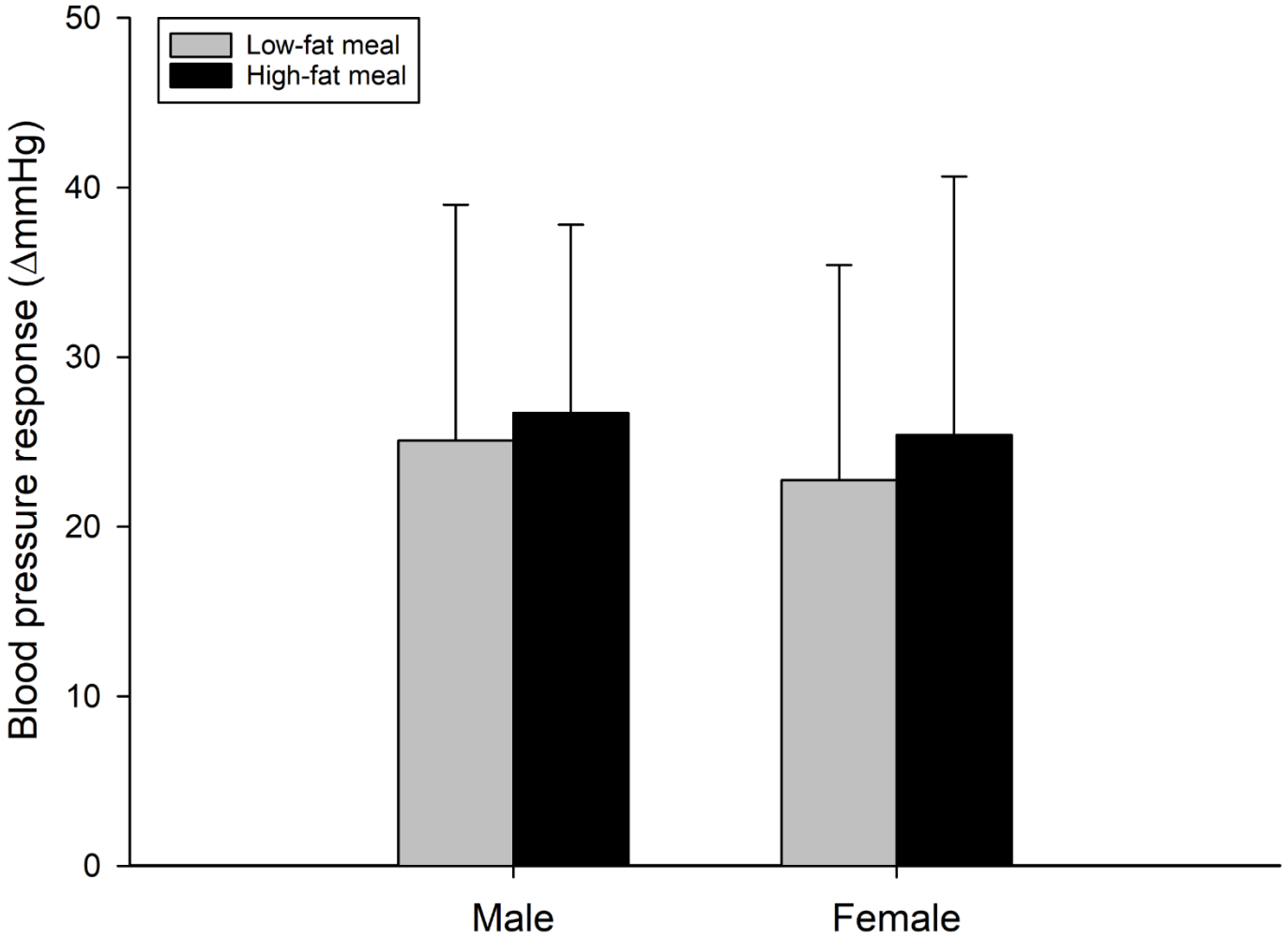

Figure 27. Mean arterial blood pressure response (ΔmmHg) to CPT between sex and meal condition. Values are mean ± SD

Discussion

Main Findings

The purpose of this study was to investigate the effects of HF meal ingestion and sex on sympathetic vasoconstrictor responsiveness and endothelium-mediated vasodilation. It was hypothesized that there would be an augmented sympathetic vasoconstrictor response to CPT in addition to a decline in FMD response after a HF meal as compared to a LF control meal. It was also thought that premenopausal females would show an inherent protection from the insult of a HF meal by showing lower increases in sympathetic vasoconstrictor responsiveness as well as preserved FMD compared to males. Percent FMD was significantly altered by meal and sex. However, contrary to my hypothesis, FVC in response to CPT was not different between meal conditions. There were no observed sex differences in either variable in response to the meals. These results suggest that sympathetic vasoconstriction was not altered in healthy, young males and females after the ingestion of a HF meal. Furthermore, there appeared to be no protective effect of sex on sympathetic vasoconstrictor responsiveness or FMD in females compared to males.

Effect Aerobic Fitness on Vascular Reactivity

Absolute and relative VO_{2max} were not correlated to FMD, normalized FMD or sympathetic vasoconstrictor responsiveness in either meal condition for either sex. Our data indicates that both postprandial endothelial function and sympathetic vasoconstrictor responsiveness were not affected by aerobic fitness. Additionally, males showed significantly lower FMD than females after the ingestion of both meals despite exhibiting higher absolute and relative VO_{2max}, suggesting that higher aerobic fitness was not associated with enhanced endothelial function. This agrees with a previous study that showed that high aerobic fitness did

not provide increased protection against postprandial endothelial dysfunction compared to moderately fit individuals (Ballard et al., 2008). However, there is evidence that highly physically active individuals show maintained FMD after a HF meal compared to sedentary individuals (Johnson et al., 2011). This was corroborated in a later study that showed that chronic physical activity, regardless of training type, showed preserved endothelial function after a HF meal (Das et al., 2018). To my knowledge, this is the first study to examine sympathetic vasoconstrictor responsiveness in response to a HF meal. Our data suggests that postprandial sympathetic vasoconstrictor responsiveness is not affected by aerobic fitness. Collectively, our data indicates that enhanced aerobic fitness does not provide a protective effect against vascular dysfunction caused by a single HF meal. However, the effects of aerobic fitness and chronic exercise training on postprandial vascular function after a HF meal have not been well established and further research may be warranted.

Effect of Meal Ingestion on FMD

In the present study, postprandial endothelial function was measured by FMD to corroborate previous reports of endothelial dysfunction following a HF meal. FMD, being a NO-mediated technique, also served as an assay of NO bioavailability. As expected, both males and females exhibited an increase in brachial artery diameter during reactive hyperemia. Consistent with previous studies, percent change in FMD was significantly lowered (Figure 22) after the HF meal 2-hours after meal ingestion compared to the LF meal condition, which is sufficient time to induce significant changes in brachial artery FMD (Bae et al., 2001; Faulk & Bartholomew, 2012; Jakulj et al., 2007; Patik et al., 2018; Tsai et al., 2004; Tucker et al., 2018; Vogel et al., 1997) and report significant PPL (Bae et al., 2001; Faulk & Bartholomew, 2012; Jakulj et al., 2007; Tsai et al., 2004; Vogel et al., 1997). In addition to changes in FMD, shear rate AUC was

also found to be significantly different (Figure 24) between meal conditions with the HF meal condition showing significantly diminished shear rate following cuff release compared to the LF meal. This is in agreement with Poitras and colleagues (2014), who noted a significant effect of meal on shear stress AUC 2 hours postprandial between LF and HF meal conditions during FMD (Poitras et al., 2014). In contrast, Harris and colleagues (2012) found no difference between pre- and post-meal shear rate with the ingestion of a HF meal. They further reported, that the decline in FMD was preserved post-meal when FMD is normalized to shear rate AUC (Harris et al., 2012). This contradicts the findings in the current study as normalizing brachial artery FMD to cumulative shear rate stimulus abolished the difference in FMD between meal conditions (Figure 25). This indicates the observed difference in %FMD is dependent on shear rate following the release of the cuff. While normalization of FMD to shear AUC as a ratio has been used to determine independent differences in endothelial function, there is currently no universally accepted method to account for differences in reactive hyperemia shear stress stimulus (Pyke & Tschakovsky, 2005). As such, the majority of studies examining HF meal ingestion have reported only percentage change in FMD, without normalizing to shear stress. Further study into the influence of shear on postprandial FMD may help further elucidate the effects of a HF meal.

Effect of Meal Ingestion on Sympathetic Vasoconstriction

Meal ingestion has been shown to increase sympathetic activity in the periphery (Berne et al., 1989; Fagius & Berne, 1994; Scott et al., 2013; Vaz et al., 1995). The entrance of nutrients into the gastrointestinal tract is part of a dual mechanism responsible for the increase in MSNA after food ingestion (Fagius & Berne, 1994; Fagius, 2003). Insulin also seems to be responsible at least in part for the increase in MSNA observed after pure carbohydrate or mixed meal consumption (Fagius, 2003). This seems to be strictly limited to food as water ingestion does not

increase sympathetic activity (Fagius & Berne, 1994). Meal composition seems to mediate the increase in sympathetic outflow. Fagius and Berne (1994) provided evidence of the role of meal composition by demonstrating that a mixed meal caused an intermediary increase between meals of pure carbohydrate and pure fat/protein. Pure carbohydrate ingestion elicited the strongest incidence of burst activity compared to other types of fuels due to the corresponding increase in circulating insulin and its sympathoexcitatory properties (Fagius & Berne, 1994). This peripheral increase in MSNA may elicit vasoconstriction, higher vascular resistance, and elevated blood pressure in the postprandial state. Given the importance of NO as a mediator of the inhibition of vasoconstriction in skeletal muscle vascular beds, we hypothesized that a HF meal would augment peripheral sympathetic vasoconstriction through decreased NO bioavailability (Casey et al., 2010; Chavoshan et al., 2002; Huang et al., 1995; Jendzjowsky, N. G. & DeLorey, 2013a; Jendzjowsky, N. G. & Delorey, 2013b; Lamping & Faraci, 2003; Thomas & Victor, 1998; Wray et al., 2011). In the current study, we found no significant effect of a HF meal compared to a LF meal on peripheral vasoconstriction as measured by the percentage change in FVC in response to CPT (Figure 26). While it has been previously suggested that meal ingestion increases MSNA, the similar baseline MAP, HR, and FVC suggest that sympathetic outflow was similar between meals (Fagius & Berne, 1994). Furthermore, the similar sympathetic vasoconstrictor responsiveness.in the two meal conditions, suggests that neurovascular control of the peripheral circulation was not altered by ingestion of a HF meal.

We also found no significant difference in the blood pressure response to a CPT between meal conditions (Figure 27). This is in agreement with a study conducted by Sauder and colleagues (2012), who found no significant difference in the change in blood pressure or vascular resistance in response to acute cold stress, 2 hours after HF meal ingestion (Sauder,

Johnston, Skulas-Ray, Campbell, & West, 2012). However, this was contrary to their previous study, where they found that a single HF meal, compared to a LF control meal, caused increased blood pressure reactivity during CPT (Jakulj et al., 2007). The authors found higher total peripheral resistance in response to CPT accompanying the HF meal, indicating increased systemic postprandial vasoconstriction (Jakulj et al., 2007). While the meals were designed to be as similar as possible to their previous study, differences in food preparation and attempts to minimize disparities in macronutrient content between meals may have altered the effects of the meals (Sauder et al., 2012). Additionally, a separate study found that a HF meal increased mean arterial pressure reactivity compared to a LF meal (Faulk & Bartholomew, 2012). Although there is some evidence that suggests that HF meal ingestion may affect cardiovascular reactivity and peripheral vasoconstriction, there have been no studies that have directly measured the effect of a HF meal on vasoconstriction. However, our results suggest that a HF meal does not augment peripheral vasoconstriction compared to an iso-caloric LF meal in healthy, young adults.

Influence of Sex on Postprandial Cardiovascular Function

Previous studies have suggested that sex modulates vascular response (Bloomer et al., 2009; Bloomer & Lee, 2013; Harris et al., 2012; Hashimoto et al., 1995; Schillaci et al., 2001; Thom et al., 2016). FMD during different stages of the menstrual cycle shows a phasic response, with the luteal and follicular stages showing significantly higher FMD response compared to the menses stage, suggesting this sex difference is driven by the level of circulating hormone (Harris et al., 2012; Hashimoto et al., 1995). Several studies have pointed towards a sex-specific difference in vascular response to a HF meal, suggesting that premenopausal females display an inherent protection from the insult of a HF meal (Harris et al., 2012; Schillaci et al., 2001). Schillaci and colleagues (2001) found that premenopausal women did not exhibit a decline

postprandial FMD in response to the insult of a HF meal. Harris and colleagues (2012) also found this inherent protection to HF meal ingestion in young females when FMD was taken before and after a HF meal at multiple points in the menstrual cycle. While women did show phasic differences in response, pre- and post-meal FMD were similar at all points of the cycle (Harris et al., 2012). This is in contrast to young males, who showed a 50% reduction following HF meal ingestion (Harris et al., 2012). Both authors suggest that estrogen may exert a protective effect on the endothelium in young females (Harris et al., 2012; Schillaci et al., 2001). However, this has not been established and there is evidence that estradiol does not have a significant effect on circulating TRG, oxidative stress, or inflammation (Bell & Bloomer, 2010). More detailed research may be warranted to establish the effect of levels of circulating sex hormone on postprandial vascular function. Bloomer & Lee (2013) suggest that elevated mean levels of ovarian hormones may partly account for lower oxidative stress along with blunted TRG levels in females after acute HF meal ingestion that diminishes postprandial oxidative stress (Bloomer & Lee, 2013). Cumulatively, these studies suggest that females display an inherent protection against the insult of a HF meal. In the current study, females showed significantly higher FMD (Figure 22) and shear rate AUC (Figure 24) compared to males in both meal conditions. This increase in shear rate is consistent with a study that observed premenopausal females exhibiting a greater shear stimulus, which can possibly be attributed to generally smaller arterial dimensions (Harris et al., 2012). However, when normalized to shear rate AUC during the first 90s after cuff occlusion there was no significant difference between sex in FMD/Shear rate AUC (Figure 25). This suggests that the increased shear stimulus in females may drive the increased FMD. However, our results do not suggest an inherent protective effect against the insult of a HF meal in females compared to males.

Young women are generally characterized by lower resting blood pressures and MSNA (Hart, E. C. J. & Charkoudian, 2014), suggesting that sex also modulates sympathetic regulation of vascular resistance and blood pressure (Hart, E. C. J. & Charkoudian, 2014; Hogarth et al., 2007; Just & DeLorey, 2017). It has also been proposed that women display altered neurovascular transduction (Hogarth et al., 2007; Just & DeLorey, 2017). Young females have shown a blunted sympathetic vasoconstrictor response compared to males when exposed to a variety of different stimuli (Hart, E. C. J. & Charkoudian, 2014; Hogarth et al., 2007). While the mechanism is not clearly defined, a protective effect of estradiol (Charkoudian et al., 2017; Hart, E. C. et al., 2011; Hart, E. C. J. & Charkoudian, 2014) or augmented β-adrenergic receptor activity reducing the transduction of MSNA into peripheral vascular resistance in healthy, young women (Hart, E. C. et al., 2011; Hart, E. C., Joyner, Wallin, & Charkoudian, 2012; Hart, E. C. J. & Charkoudian, 2014; Kneale et al., 2000) have been implicated in sex-specific differences. While there seems to be a sex-specific difference in sympathetic activity at rest (Hart, E. C. J. & Charkoudian, 2014; Hogarth et al., 2007; Just & DeLorey, 2017), this is not demonstrated in the postprandial phase to my knowledge. The current study investigated the influence of a HF meal in response to CPT in both men and women. However, contrary to my hypothesis, we saw no difference in postprandial FVC percentage or MAP for either meal condition during CPT between sex (Figure 26). This suggests that there is no sex-specific difference in sympathetic vasoconstriction with acute cold stress due to the ingestion of a HF meal.

Integrative Postprandial Vascular Response to a HF Meal

A HF meal decreased FMD compared to the LF meal condition in both males and females, suggesting that there is an acute reduction in endothelial function following consumption of a high fat meal. Additionally, the HF meal caused a significant decrease in shear

rate in males and females. The abolishment of meal differences in FMD when normalized to shear rate seems to indicate that this is driven by a decrease in the magnitude of the vasodilatory stimulus as opposed to a decrease in NO bioavailability. If NO bioavailability was not influenced by the ingestion of a HF meal, NO-mediated inhibition of sympathetic vasoconstriction would not be expected to be different between meal conditions. Consistent with this notion, postprandial sympathetic vasoconstrictor responsiveness was not different between the HF and LF meals in either sex. It is also possible that NO is not a significant contributor to the inhibition of sympathetic vasoconstriction in human skeletal muscle at rest. Several studies in rodents have provided evidence of NO-mediated sympathetic vasoconstriction in resting skeletal muscle (Häbler, Wasner, & Jänig, 1997; Jendzjowsky, N. G. & DeLorey, 2013a). However, similar evidence in humans is lacking. For example, Dinenno & Joyner (2004) found that vasoconstrictor responsiveness to the infusion of selective α-adrenergic receptor agonists was unaffected by NOS blockade in the resting human forearm (Dinenno & Joyner, 2004). Furthermore, exogenous NO administration did not blunt α-adrenergic vasoconstriction in the resting human forearm (Rosenmeier, Fritzlar, Dinenno, & Joyner, 2003). In summary, the lack of a difference in sympathetic vasoconstrictor responsiveness between meal conditions suggests that neurovascular control was not altered by consumption of a HF meal.

Conclusions

Percent change in FMD was significantly changed by HF meal ingestion, however, this difference was abolished when normalized to shear rate stimulus. Sympathetic vasoconstriction measured by the decrease in FVC as well as blood pressure response to CPT were not significantly altered between meals. There were differences in FMD and peak shear between sexes. However, FMD/shear rate AUC was not different between sex. Δ%FVC and blood

pressure response during CPT did not show a difference between sexes. This suggests that premenopausal females do not exhibit a sex-specific protective effect against either reductions in postprandial endothelium-mediated vasodilation or increases in sympathetic vasoconstriction after a HF meal compared to men. The data collected from this study further suggests that a HF meal does seem to affect endothelium-mediated vasodilation but does not significantly alter sympathetic vasoconstriction in healthy young males and females.

References

Bae, J. H., Bassenge, E., Kim, K. B., Kim, Y. N., Kim, K. S., Lee, H. J., . . . Schwemmer, M. (2001). Postprandial hypertriglyceridemia impairs endothelial function by enhanced oxidant stress. *Atherosclerosis, 155*(2), 517-523.

Ballard, K. D., Miller, J. J., Robinson, J. H., & Olive, J. L. (2008). Aerobic capacity and postprandial flow mediated dilation. *International Journal of Exercise Science, 1*(4), 163-176.

Bell, H. K., & Bloomer, R. J. (2010). Impact of serum estradiol on postprandial lipemia, oxidative stress, and inflammation across a single menstrual cycle. *Gender Medicine, 7*(2), 166-178. doi:10.1016/j.genm.2010.03.001

Berne, C., Fagius, J., & Niklasson, F. (1989). Sympathetic response to oral carbohydrate administration. evidence from microelectrode nerve recordings. *The Journal of Clinical Investigation, 84*(5), 1403-1409. doi:10.1172/JCI114313

Bloomer, R. J., Ferebee, D. E., Fisher-Wellman, K. H., Quindry, J. C., & Schilling, B. K. (2009). Postprandial oxidative stress: Influence of sex and exercise training status. *Medicine and Science in Sports and Exercise, 41*(12), 2111-2119. doi:10.1249/MSS.0b013e3181a9e832

Bloomer, R. J., & Lee, S. (2013). Women experience lower postprandial oxidative stress compared to men. *SpringerPlus, 2*, 553. doi:10.1186/2193-1801-2-553

Buckwalter, J. B., & Clifford, P. S. (2001). The paradox of sympathetic vasoconstriction in exercising skeletal muscle. *Exercise and Sport Sciences Reviews, 29*(4), 159-163.

Burns, S. F., Miyashita, M., & Stensel, D. J. (2015). High-intensity interval exercise and postprandial triacylglycerol. *Sports Medicine (Auckland, N.Z.), 45*(7), 957-968. doi:10.1007/s40279-015-0327-6

Casey, D. P., Madery, B. D., Curry, T. B., Eisenach, J. H., Wilkins, B. W., & Joyner, M. J. (2010). Nitric oxide contributes to the augmented vasodilatation during hypoxic exercise. *The Journal of Physiology, 588*(Pt 2), 373-385. doi:10.1113/jphysiol.2009.180489

Charkoudian, N., Hart, E. C. J., Barnes, J. N., & Joyner, M. J. (2017). Autonomic control of body temperature and blood pressure: Influences of female sex hormones. *Clinical Autonomic Research: Official Journal of the Clinical Autonomic Research Society, 27*(3), 149-155. doi:10.1007/s10286-017-0420-z

Chavoshan, B., Sander, M., Sybert, T. E., Hansen, J., Victor, R. G., & Thomas, G. D. (2002). Nitric oxide-dependent modulation of sympathetic neural control of oxygenation in exercising human skeletal muscle. *The Journal of Physiology, 540*(Pt 1), 377-386.

Corretti, M. C., Anderson, T. J., Benjamin, E. J., Celermajer, D., Charbonneau, F., Creager, M. A., . . . Vogel, R. (2002). Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the international brachial artery reactivity task force. *Journal of the American College of Cardiology, 39*(2), 257-265.

Das, E. K., Lai, P. Y., Robinson, A. T., Pleuss, J., Ali, M. M., Haus, J. M., . . . Phillips, S. A. (2018). Regular aerobic, resistance, and cross-training exercise prevents reduced vascular function following a high sugar or high fat mixed meal in young healthy adults. *Frontiers in Physiology, 9*, 183. doi:10.3389/fphys.2018.00183

Dinenno, F. A., & Joyner, M. J. (2004). Combined NO and PG inhibition augments alpha-adrenergic vasoconstriction in contracting human skeletal muscle. *American Journal of Physiology.Heart and Circulatory Physiology, 287*(6), 2576. doi:10.1152/ajpheart.00621.2004 [doi]

D'Urzo, K. A., King, T. J., Williams, J. S., Silvester, M. D., & Pyke, K. E. (2018). The impact of menstrual phase on brachial artery flow-mediated dilatation during handgrip exercise in healthy premenopausal women. *Experimental Physiology, 103*(2), 291-302. doi:10.1113/EP086311

Emerson, S. R., Kurti, S. P., Harms, C. A., Haub, M. D., Melgarejo, T., Logan, C., & Rosenkranz, S. K. (2017). Magnitude and timing of the postprandial inflammatory response to a high-fat meal in healthy adults: A systematic review. *Advances in Nutrition (Bethesda, Md.), 8*(2), 213-225. doi:10.3945/an.116.014431

Fagius, J. (2003). Sympathetic nerve activity in metabolic control--some basic concepts. *Acta Physiologica Scandinavica, 177*(3), 337-343. doi:10.1046/j.1365-201X.2003.01086.x

Fagius, J., & Berne, C. (1994). Increase in muscle nerve sympathetic activity in humans after food intake. *Clinical Science (London, England: 1979), 86*(2), 159-167.

Faulk, K. E., & Bartholomew, J. B. (2012). The moderating effect of physical activity on cardiovascular reactivity following single fat feedings. *Psychophysiology, 49*(1), 145-149. doi:10.1111/j.1469-8986.2011.01283.x

Fuller, K. N. Z., Summers, C. M., & Valentine, R. J. (2017). Effect of a single bout of aerobic exercise on high-fat meal-induced inflammation. *Metabolism: Clinical and Experimental, 71*, 144-152. doi:10.1016/j.metabol.2017.03.001

Fung, T. T., Rimm, E. B., Spiegelman, D., Rifai, N., Tofler, G. H., Willett, W. C., & Hu, F. B. (2001). Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. *The American Journal of Clinical Nutrition, 73*(1), 61-67. doi:10.1093/ajcn/73.1.61 [doi]

Gamboa, A., Shibao, C., Diedrich, A., Choi, L., Pohar, B., Jordan, J., . . . Biaggioni, I. (2007). Contribution of endothelial nitric oxide to blood pressure in humans. *Hypertension (Dallas, Tex.: 1979), 49*(1), 170-177. doi:10.1161/01.HYP.0000252425.06216.26

Häbler, H. J., Wasner, G., & Jänig, W. (1997). Attenuation of neurogenic vasoconstriction by nitric oxide in hindlimb microvascular beds of the rat in vivo. *Hypertension (Dallas, Tex.: 1979), 30*(4), 957-961. doi:10.1161/01.hyp.30.4.957

Harris, R. A., Tedjasaputra, V., Zhao, J., & Richardson, R. S. (2012). Premenopausal women exhibit an inherent protection of endothelial function following a high-fat meal. *Reproductive Sciences (Thousand Oaks, Calif.), 19*(2), 221-228. doi:10.1177/1933719111418125

Hart, E. C., Charkoudian, N., Wallin, B. G., Curry, T. B., Eisenach, J., & Joyner, M. J. (2011). Sex and ageing differences in resting arterial pressure regulation: The role of the beta-adrenergic receptors. *The Journal of Physiology, 589*(Pt 21), 5285-5297. doi:10.1113/jphysiol.2011.212753 [doi]

Hart, E. C., Joyner, M. J., Wallin, B. G., & Charkoudian, N. (2012). Sex, ageing and resting blood pressure: Gaining insights from the integrated balance of neural and haemodynamic factors. *The Journal of Physiology, 590*(9), 2069-2079. doi:10.1113/jphysiol.2011.224642 [doi]

Hart, E. C. J., & Charkoudian, N. (2014). Sympathetic neural regulation of blood pressure: Influences of sex and aging. *Physiology (Bethesda, Md.), 29*(1), 8-15. doi:10.1152/physiol.00031.2013

Hashimoto, M., Akishita, M., Eto, M., Ishikawa, M., Kozaki, K., Toba, K., . . . Ouchi, Y. (1995). Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation, 92*(12), 3431-3435.

Hogarth, A. J., Mackintosh, A. F., & Mary, David A. S. G. (2007). Gender-related differences in the sympathetic vasoconstrictor drive of normal subjects. *Clinical Science (London, England: 1979), 112*(6), 353-361. doi:10.1042/CS20060288

Huang, P. L., Huang, Z., Mashimo, H., Bloch, K. D., Moskowitz, M. A., Bevan, J. A., & Fishman, M. C. (1995). Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature, 377*(6546), 239-242. doi:10.1038/377239a0

Jakulj, F., Zernicke, K., Bacon, S. L., van Wielingen, L. E., Key, B. L., West, S. G., & Campbell, T. S. (2007). A high-fat meal increases cardiovascular reactivity to psychological stress in healthy young adults. *The Journal of Nutrition, 137*(4), 935-939. doi:10.1093/jn/137.4.935

Jendzjowsky, N. G., & DeLorey, D. S. (2013a). Role of neuronal nitric oxide in the inhibition of sympathetic vasoconstriction in resting and contracting skeletal muscle of healthy rats. *Journal of Applied Physiology (Bethesda, Md.: 1985), 115*(1), 97-106. doi:10.1152/japplphysiol.00250.2013

Jendzjowsky, N. G., & Delorey, D. S. (2013b). Short-term exercise training enhances functional sympatholysis through a nitric oxide-dependent mechanism. *The Journal of Physiology, 591*(6), 1535-1549. doi:10.1113/jphysiol.2012.238998

Johnson, B. D., Padilla, J., Harris, R. A., & Wallace, J. P. (2011). Vascular consequences of a high-fat meal in physically active and inactive adults. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme, 36*(3), 368-375. doi:10.1139/H11-028

Just, T. P., & DeLorey, D. S. (2017). Sex differences in sympathetic vasoconstrictor responsiveness and sympatholysis. *Journal of Applied Physiology (Bethesda, Md.: 1985), 123*(1), 128-135. doi:10.1152/japplphysiol.00139.2017

Kneale, B. J., Chowienczyk, P. J., Brett, S. E., Coltart, D. J., & Ritter, J. M. (2000). Gender differences in sensitivity to adrenergic agonists of forearm resistance vasculature. *Journal of the American College of Cardiology, 36*(4), 1233-1238.

Lamping, K., & Faraci, F. (2003). Enhanced vasoconstrictor responses in eNOS deficient mice. *Nitric Oxide: Biology and Chemistry, 8*(4), 207-213.

Lerman, A., Sandok, E. K., Hildebrand, F. L., & Burnett, J. C. (1992). Inhibition of endothelium-derived relaxing factor enhances endothelin-mediated vasoconstriction. *Circulation, 85*(5), 1894-1898.

Moncada, S., & Higgs, E. A. (2006). The discovery of nitric oxide and its role in vascular biology. *British Journal of Pharmacology, 147 Suppl 1*, 193. doi:10.1038/sj.bjp.0706458

Padilla, J., Harris, R. A., Fly, A. D., Rink, L. D., & Wallace, J. P. (2006). The effect of acute exercise on endothelial function following a high-fat meal. *European Journal of Applied Physiology, 98*(3), 256-262. doi:10.1007/s00421-006-0272-z

Patik, J. C., Tucker, W. J., Curtis, B. M., Nelson, M. D., Nasirian, A., Park, S., & Brothers, R. M. (2018). Fast-food meal reduces peripheral artery endothelial function but not cerebral vascular hypercapnic reactivity in healthy young men. *Physiological Reports, 6*(18), e13867. doi:10.14814/phy2.13867

Poitras, V. J., Slattery, D. J., Levac, B. M., Fergus, S., Gurd, B. J., & Pyke, K. E. (2014). The combined influence of fat consumption and repeated mental stress on brachial artery flow-mediated dilatation: A preliminary study. *Experimental Physiology, 99*(4), 715-728. doi:10.1113/expphysiol.2013.077131

Pyke, K. E., & Tschakovsky, M. E. (2005). The relationship between shear stress and flow-mediated dilatation: Implications for the assessment of endothelial function. *The Journal of Physiology, 568*(Pt 2), 357-369. doi:10.1113/jphysiol.2005.089755

Rosenmeier, J. B., Fritzlar, S. J., Dinenno, F. A., & Joyner, M. J. (2003). Exogenous NO administration and alpha-adrenergic vasoconstriction in human limbs. *Journal of Applied Physiology (Bethesda, Md.: 1985), 95*(6), 2370-2374. doi:10.1152/japplphysiol.00634.2003 [doi]

Rowell, L. B. (1993). *Human vascular control*

. New York: Oxford University Press.

Rudolph, T. K., Ruempler, K., Schwedhelm, E., Tan-Andresen, J., Riederer, U., Böger, R. H., & Maas, R. (2007). Acute effects of various fast-food meals on vascular function and cardiovascular disease risk markers: The hamburg burger trial. *The American Journal of Clinical Nutrition, 86*(2), 334-340. doi:10.1093/ajcn/86.2.334

Sandoo, A., van Zanten, J. J., Metsios, G. S., Carroll, D., & Kitas, G. D. (2010). The endothelium and its role in regulating vascular tone. *The Open Cardiovascular Medicine Journal, 4*, 302-312. doi:10.2174/1874192401004010302 [doi]

Sauder, K. A., Johnston, E. R., Skulas-Ray, A. C., Campbell, T. S., & West, S. G. (2012). Effect of meal content on heart rate variability and cardiovascular reactivity to mental stress. *Psychophysiology, 49*(4), 470-477. doi:10.1111/j.1469-8986.2011.01335.x

Schillaci, G., Marchesi, S., Siepi, D., Lupattelli, G., Vaudo, G., Pasqualini, L., & Mannarino, E. (2001). Gender differences in postprandial endothelial function. *The American Journal of Cardiology, 87*(11), 1323-1325.

Scott, E. M., Greenwood, J. P., Pernicova, I., Law, G. R., Gilbey, S. G., Kearney, M. T., & Mary, David A S G. (2013). Sympathetic activation and vasoregulation in response to carbohydrate ingestion in patients with congestive heart failure. *The Canadian Journal of Cardiology, 29*(2), 236-242. doi:10.1016/j.cjca.2012.03.020

Seals, D. R. (1991). Sympathetic neural adjustments to stress in physically trained and untrained humans. *Hypertension (Dallas, Tex.: 1979), 17*(1), 36-43.

Teeman, C. S., Kurti, S. P., Cull, B. J., Emerson, S. R., Haub, M. D., & Rosenkranz, S. K. (2016). Postprandial lipemic and inflammatory responses to high-fat meals: A review of the roles of acute and chronic exercise. *Nutrition & Metabolism, 13*, 80. doi:10.1186/s12986-016-0142-6

Thijssen, D. H. J., Black, M. A., Pyke, K. E., Padilla, J., Atkinson, G., Harris, R. A., . . . Green, D. J. (2011). Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *American Journal of Physiology. Heart and Circulatory Physiology, 300*(1), 2. doi:10.1152/ajpheart.00471.2010

Thom, N. J., Early, A. R., Hunt, B. E., Harris, R. A., & Herring, M. P. (2016). Eating and arterial endothelial function: A meta-analysis of the acute effects of meal consumption on flow-mediated dilation. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity, 17*(11), 1080-1090. doi:10.1111/obr.12454

Thomas, G. D., & Segal, S. S. (2004). Neural control of muscle blood flow during exercise. *Journal of Applied Physiology (Bethesda, Md.: 1985), 97*(2), 731-738. doi:10.1152/japplphysiol.00076.2004 [doi]

Thomas, G. D., & Victor, R. G. (1998). Nitric oxide mediates contraction-induced attenuation of sympathetic vasoconstriction in rat skeletal muscle. *The Journal of Physiology, 506 (Pt 3)*, 817-826.

Toda, N., & Okamura, T. (2003). The pharmacology of nitric oxide in the peripheral nervous system of blood vessels. *Pharmacological Reviews, 55*(2), 271-324. doi:10.1124/pr.55.2.3

Toda, N., & Okamura, T. (2015). Recent advances in research on nitrergic nerve-mediated vasodilatation. *Pflugers Archiv: European Journal of Physiology, 467*(6), 1165-1178. doi:10.1007/s00424-014-1621-0

Tsai, W., Li, Y., Lin, C., Chao, T., & Chen, J. (2004). Effects of oxidative stress on endothelial function after a high-fat meal. *Clinical Science (London, England: 1979), 106*(3), 315-319. doi:10.1042/CS20030227

Tucker, W. J., Sawyer, B. J., Jarrett, C. L., Bhammar, D. M., Ryder, J. R., Angadi, S. S., & Gaesser, G. A. (2018). High-intensity interval exercise attenuates but does not eliminate endothelial dysfunction after a fast food meal. *American Journal of Physiology. Heart and Circulatory Physiology, 314*(2), H188-H194. doi:10.1152/ajpheart.00384.2017

Tushuizen, M. E., Nieuwland, R., Scheffer, P. G., Sturk, A., Heine, R. J., & Diamant, M. (2006). Two consecutive high-fat meals affect endothelial-dependent vasodilation, oxidative stress and cellular microparticles in healthy men. *Journal of Thrombosis and Haemostasis: JTH, 4*(5), 1003-1010. doi:10.1111/j.1538-7836.2006.01914.x

Vaz, M., Turner, A., Kingwell, B., Chin, J., Koff, E., Cox, H., . . . Esler, M. (1995). Postprandial sympatho-adrenal activity: Its relation to metabolic and cardiovascular events and to changes in meal frequency. *Clinical Science (London, England: 1979), 89*(4), 349-357.

Victor, R. G., Leimbach, W. N., Seals, D. R., Wallin, B. G., & Mark, A. L. (1987). Effects of the cold pressor test on muscle sympathetic nerve activity in humans. *Hypertension (Dallas, Tex.: 1979), 9*(5), 429-436.

Vogel, R. A., Corretti, M. C., & Plotnick, G. D. (1997). Effect of a single high-fat meal on endothelial function in healthy subjects. *The American Journal of Cardiology, 79*(3), 350-354.

Wray, D. W., Witman, M. A. H., Ives, S. J., McDaniel, J., Fjeldstad, A. S., Trinity, J. D., . . . Richardson, R. S. (2011). Progressive handgrip exercise: Evidence of nitric oxide-dependent vasodilation and blood flow regulation in humans. *American Journal of Physiology. Heart and Circulatory Physiology, 300*(3), 1101. doi:10.1152/ajpheart.01115.2010

Chapter 3: General Discussion

Introduction

Habitual consumption of a high-fat diet induces a state of chronic vascular dysfunction and has important implications for the long-term development of atherosclerosis and CVD. Even singular HF meals have been found to cause decreased endothelial function, often measured by decreased FMD, for several hours after the ingestion of the meal. It is currently thought that a HF meal raises levels of circulating TRG and causes higher rates of lipid oxidation, which increases oxidative stress and decrease NO bioavailability. In addition to its role in endothelium-mediated vasodilation, NO is also a mediator of peripheral sympathetic vasoconstriction. Increased sympathetic vasoconstriction, in addition to reduced vasodilation, may further exacerbate the development of vascular disease. This may also be altered by biological sex. Females have been shown to exhibit lower blood pressure and sympathetic outflow than males at rest (Hart & Charkoudian, 2014). There is also evidence that females have protected endothelial function after a HF meal compared to males (Harris, Tedjasaputra, Zhao, & Richardson, 2012; Schillaci et al., 2001). This sex-specific difference in vascular function after a HF meal may also influence sympathetic vasoconstriction. Thus, this study aimed to investigate the effects of a HF meal and sex on sympathetic vasoconstrictor responsiveness. We found that a HF meal does not appear to increase sympathetic vasoconstriction compared to a LF meal, despite causing an acute reduction in endothelial function in both males and females. Our study also showed a lack of sex-specific protection against a HF meal in young females compared to males, both in regards to sympathetic vasoconstriction and FMD.

Experimental Considerations and Limitations

There are several limitations to the current study. We chose to compare two different meal conditions in order to compare postprandial function as opposed to comparing to a pre-meal fasted condition to monitor baseline FMD and CPT response. This study design was meant to highlight physiological differences in postprandial response between meals of different macronutrient content. However, by not including a pre-meal baseline, we somewhat limited our ability to compare against some previous studies in the literature. Additionally, vasoconstriction measured at the brachial may not be reflective of other vascular beds, including the mesenteric vascular bed. It could be that there was an enhanced vasoconstrictor response in the mesentery. Someya and colleagues (2010) investigated the effect of mental stress on postprandial splanchnic blood flow (Someya, Endo, Fukuba, Hirooka, & Hayashi, 2010). They discovered that while stress caused vasoconstriction in the superior mesenteric artery at rest, this constriction seemed to be overridden by the increase in postprandial blood flow (Someya et al., 2010). However, there are several differences between our studies. First, our HF meal was significantly higher in fat and caloric content. It could be that a larger meal with higher fat content may significant increase the level of circulating TRG and reduce NO bioavailability to the point that the resulting vasoconstriction overcomes the increase in mesenteric blood flow following a meal. Secondly, cold stress elicits a different reaction than mental stress. The cold pressor test induces an involuntary increase in sympathetic outflow mediated by peripheral type III and IV afferent fibers in response to both pain and thermoregulatory stress (Rowell, 1993). In contrast, increased sympathetic outflow from mental stress is mainly caused by central activation and stimulation of β-adrenergic receptors (Hassellund, Flaa, Sandvik, Kjeldsen, & Rostrup, 2010; Montoya, Brody, Beck, Veit, & Rau, 1997). While both increase sympathetic activity, different mechanisms of

sympathetic activation for CPT and mental stress tasks may cause differing degrees of mesenteric vasoconstriction. However, this has not been examined to my knowledge. Further investigation into the effect of macronutrient composition of a meal on mesenteric vascular function may be merited.

Another possible limitation to this study could have been differences in meal macronutrient composition. The meals in this study were modeled from previous literature and have been shown to induce endothelial dysfunction in the HF condition but not in the LF condition. These meals were also selected as they were thought to be representative of a meal that may be consumed on a regular basis. Differences in sugar and carbohydrate content may be in part responsible for the lack of difference between meals. Fagius and Berne (1994) have previously demonstrated that ingestion of a pure carbohydrate increased MSNA to a greater degree than mixed, pure protein, or pure fat meals. This was linked to an increase in plasma insulin levels (Fagius & Berne, 1994). It may be possible that our HF and LF meal conditions influenced vasoconstriction via different mechanisms. While the HF meal may reduce NO bioavailability and disrupt NO-mediated sympathetic vasoconstriction inhibition, the LF meal may increase vasoconstriction through increased MSNA burst activity due to a higher carbohydrate composition and plasma insulin levels. It is also conceivable that increased insulin levels oppose sympathetic vasoconstriction, as insulin is a known vasodilator (Anderson, Hoffman, Balon, Sinkey, & Mark, 1991). However, as we did not directly measure MSNA or insulin during this experiment, a definitive claim cannot be made to this effect, and more research may be warranted to further examine the effect of a HF meal on sympathetic vasoconstriction. Finally, there is the possibility that the current meal may not have contained

enough fat or caloric content to elicit a significant difference in NO bioavailability or sympathetic vasoconstriction.

Vitamin supplementation and diet leading up to the study was not monitored. There is evidence that vitamin C and E provide vascular protection to acute HF meal ingestion by reducing oxidative stress due to their antioxidant properties (Bae et al., 2003; Plotnick, Corretti, & Vogel, 1997; Yim et al., 2012). While our LF meal condition contained orange juice, which is high in vitamin C, this does not appear to have a beneficial antioxidant effect in our study or others (Poitras et al., 2014; Vogel, Corretti, & Plotnick, 1997). Plotnick and colleagues (1997) provided evidence that endothelial dysfunction induced by a HF meal was blocked by pretreatment with vitamin C and E (Plotnick et al., 1997). Bae and colleagues (2003) corroborated this finding, noting no difference in the percentage change in FMD between a LF meal and a HF meal supplemented with vitamin E. This suggests that vitamin E provides a protective effect, preventing endothelial dysfunction (Bae et al., 2003). Yim and colleagues (2012) found that 14 days of vitamin supplementation abolished the significant decrease in blood flow response in Koreans compared to Caucasians (Yim et al., 2012). Collectively, these data suggest that vitamin supplementation seems to have an important effect on postprandial endothelial dysfunction. We did not ask subjects about current vitamin supplementation nor did we ask subjects to abstain from vitamins prior to participation, hence we cannot rule out the potential protective influence of vitamin C and E on oxidative stress and endothelial function during this study. While vitamin supplementation could have influenced the vascular response to the meals, the concentration of vitamin C contained within the meals do not seem to be sufficient to significantly alter our results (Poitras et al., 2014; Vogel et al., 1997). It is also possible that previous dietary habits may have an effect on acute vascular response to HF consumption.

Prolonged exposure to a more "westernized diet" may reduce the acute endothelial dysfunction compared to subjects who typically consume a diet lower in fat. Further study may be useful in determining whether a HF meal has the same effects after an acclimatization period to higher fat content.

Blood chemistry measurements were not taken during this study. Although this cannot be definitively stated in the results of this study, there is evidence that the HF meal given in this study was sufficient to elicit an increase in serum triglycerides (Bae et al., 2003; Plotnick et al., 1997; Tsai, Li, Lin, Chao, & Chen, 2004; Vogel et al., 1997). Bae and colleagues (2001) found that a HF meal also increased superoxide anion production while a LF meal did not, indicating an increase in oxidative stress. This was supported by a later study that found a HF meal was associated with depletion of the serum antioxidant enzyme, plasma glutathione peroxidase, and increased secretion of 8-epi-prostaglandin, a free-radical catalyzed product of oxidation (Tsai, Li, Lin, Chao, & Chen, 2004). These results, in addition to decreased postprandial FMD, seem to support the hypothesis that decreased NO and increased oxidative stress are both important to postprandial vascular function. However, these studies used different meals than the HF meal that was consumed in this study. Despite similar fat content, it is possible that differences in the type of food and preparation of meals with similar macronutrients may differently influence blood chemistry markers.

Future Directions

NO is known to downregulate the production and release of endothelin-1 (ET-1), a potent vasoconstrictor released by the endothelium to maintain normal vascular tone (Rajendran et al., 2013; Sandoo, van Zanten, Metsios, Carroll, & Kitas, 2010; Vanhoutte, Shimokawa, Feletou, & Tang, 2017). In addition to being a potent vasodilator, ET-1 plays a role in stimulating central

and peripheral SNS activity by binding endothelin type-A receptors, which increases sympathoexcitatory signaling and catecholamine release (Bruno et al., 2012). As such, a decline in circulating NO, and the corresponding increase in ET-1, are major characteristics of essential hypertension and endothelial dysfunction (Godo & Shimokawa, 2017; Khaddaj Mallat, Mathew John, Kendrick, & Braun, 2017; Rajendran et al., 2013; Sandoo et al., 2010; Vanhoutte et al., 2017). Decreases in NO bioavailability seems to cause ET-1 to have a more prominent role in vascular tone with higher ET-1 stimulating increased smooth muscle contractile response resulting in vasoconstriction (Godo & Shimokawa, 2017; Khaddaj Mallat et al., 2017; Lamping & Faraci, 2003; Lerman, Sandok, Hildebrand, & Burnett, 1992; Rajendran et al., 2013; Sandoo et al., 2010; Vanhoutte et al., 2017). This may be of note considering the proposed mechanism of postprandial dysfunction after a HF meal involves reduced NO bioavailability. Mundy and colleagues (2007) found that increased dietary fat intake was associated with increased angiotensin and endothelin type-A receptors in mice. Higher fat intake also seemed to increase reactivity to vasoconstrictor substances, shown by an increased vasoconstrictor effect in response to acetylcholine in the aorta (Mundy et al., 2007). This may indicate a possible role for ET-1 in postprandial vascular dysfunction after a HF meal. This has not been investigated to my knowledge and may merit further research.

While there are studies that have looked at the effect of a HF meal effect on vascular reactivity, these studies have focused primarily on indirect changes such as blood pressure and peripheral resistance (Jakulj et al., 2007; Sauder, Johnston, Skulas-Ray, Campbell, & West, 2012). Direct methods of MSNA measurement, such as microneurography, have also been employed to describe the effect of a HF meal (Fagius & Berne, 1994). Our present study used the decline in FVC during CPT as an index of vasoconstrictor response in the brachial artery.

However, we did not use any direct measures of sympathetic activity. It may be beneficial to use both direct and indirect measures of sympathetic activity in order to obtain a more complete picture of possible postprandial effects.

The effects of aerobic fitness on postprandial vascular function has not been well established. Ballard and colleagues (2008) found that there was no significant difference in postprandial FMD in response to a HF meal in highly trained compared to moderately trained individuals, suggesting that high aerobic capacity may not be necessary to maintain endothelial function (Ballard, Miller, Robinson, & Olive, 2008). However, there are no studies, to my knowledge, that have examined the effect of low aerobic fitness. Johnson and colleagues (2011) found that inactive adults have a significant decrease in FMD after a HF meal, while FMD in regularly active individuals was unchanged (Johnson, Padilla, Harris, & Wallace, 2011). This was corroborated by a later study by Das and colleagues (2018), who found that regular physical activity, whether that was aerobic, resistance, or cross-training, prevented reductions in postprandial FMD compared to sedentary individuals (Das et al., 2018). However, neither of these studies reported aerobic fitness of sedentary individuals. It may be possible that there is a lower limit of aerobic fitness that prevents the decline in postprandial endothelial function. However, more research would be required to determine the potential role of low aerobic fitness.

Our data suggests that peak shear and shear rate AUC is lower with HF meal ingestion compared to the LF condition in both young males and females. Using similar meal conditions, Poitras and colleagues (2014) reported a lowered shear stress stimuli 2-hours postprandial during HF meal compared to LF (Poitras et al., 2014). This may be due to a change in blood or plasma viscosity after acute HF ingestion. Hyperlipidemia may increase plasma viscosity compared to healthy subjects (Irace et al., 2014). However, there is conflicting evidence in the literature about

the effect of HF meal ingestion on plasma and serum viscosity with some studies reporting increased viscosity (Schütz, Schuff-Werner, Güttner, Schulz, & Armstrong, 1993) while others found no significant difference (Charm, Mccomis, Tejada, & Kurland, 1963; Tangney, Hafner, McQuiston, Domas, & Rosenson, 1997). This may account for the significant difference in shear rate noted between meal conditions. It is important to note that we used shear rate in this study as opposed to shear stress as we did not directly measure blood viscosity. Shear rate, a function of blood velocity and vessel diameter only, does not account for blood viscosity. It may be possible that increased blood viscosity lowers velocity and causes a decrease in shear rate. However, this cannot be definitely stated in our results. There is currently very little research regarding the effect of meal content on shear and further study may expand our understanding of the mechanisms involved in vascular function following acute HF meal ingestion.

Conclusion

In conclusion, we found that sympathetic vasoconstrictor responsiveness and blood pressure response during CPT were not different between meal conditions. This was true for both males and females, suggesting that premenopausal females do not exhibit a sex-specific protection in sympathetic vasoconstriction after a HF meal. As expected, the results of this study suggest that HF meal ingestion acutely reduces endothelial function as measured by FMD. Interestingly, we found that HF meal ingestion also decreased shear rate AUC compared to the LF control meal. In addition to a possible reduction in NO bioavailability, decreased shear rate after a HF meal may possibly contribute to the decline in FMD. These results suggest that a single HF meal does not alter sympathetic vasoconstrictor responsiveness to a unilateral CPT compared to an iso-caloric LF meal in healthy young males and females.

References

Anderson, E. A., Hoffman, R. P., Balon, T. W., Sinkey, C. A., & Mark, A. L. (1991). Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *The Journal of Clinical Investigation, 87*(6), 2246-2252. doi:10.1172/JCI115260

Bae, J. H., Schwemmer, M., Lee, I. K., Lee, H. J., Park, K. R., Kim, K. Y., & Bassenge, E. (2003). Postprandial hypertriglyceridemia-induced endothelial dysfunction in healthy subjects is independent of lipid oxidation. *International Journal of Cardiology, 87*(2-3), 259-267. doi:S0167527302003479 [pii]

Ballard, K. D., Miller, J. J., Robinson, J. H., & Olive, J. L. (2008). Aerobic capacity and postprandial flow mediated dilation. *International Journal of Exercise Science, 1*(4), 163-176.

Bruno, R. M., Ghiadoni, L., Seravalle, G., Dell'oro, R., Taddei, S., & Grassi, G. (2012). Sympathetic regulation of vascular function in health and disease. *Frontiers in Physiology, 3*, 284. doi:10.3389/fphys.2012.00284

Charm, S., Mccomis, W., Tejada, C., & Kurland, G. (1963). Effect of a fatty meal on whole blood and plasma viscosity. *Journal of Applied Physiology, 18*, 1217-1220. doi:10.1152/jappl.1963.18.6.1217

Das, E. K., Lai, P. Y., Robinson, A. T., Pleuss, J., Ali, M. M., Haus, J. M., . . . Phillips, S. A. (2018). Regular aerobic, resistance, and cross-training exercise prevents reduced vascular function following a high sugar or high fat mixed meal in young healthy adults. *Frontiers in Physiology, 9*, 183. doi:10.3389/fphys.2018.00183

Fagius, J., & Berne, C. (1994). Increase in muscle nerve sympathetic activity in humans after food intake. *Clinical Science (London, England: 1979), 86*(2), 159-167.

Godo, S., & Shimokawa, H. (2017). Endothelial functions. *Arteriosclerosis, Thrombosis, and Vascular Biology, 37*(9), e108-e114. doi:10.1161/ATVBAHA.117.309813

Harris, R. A., Tedjasaputra, V., Zhao, J., & Richardson, R. S. (2012). Premenopausal women exhibit an inherent protection of endothelial function following a high-fat meal. *Reproductive Sciences (Thousand Oaks, Calif.), 19*(2), 221-228. doi:10.1177/1933719111418125

Hart, E. C. J., & Charkoudian, N. (2014). Sympathetic neural regulation of blood pressure: Influences of sex and aging. *Physiology (Bethesda, Md.), 29*(1), 8-15. doi:10.1152/physiol.00031.2013

Hassellund, S. S., Flaa, A., Sandvik, L., Kjeldsen, S. E., & Rostrup, M. (2010). Long-term stability of cardiovascular and catecholamine responses to stress tests: An 18-year follow-up study. *Hypertension (Dallas, Tex.: 1979), 55*(1), 131-136. doi:10.1161/HYPERTENSIONAHA.109.143164 [doi]

Irace, C., Carallo, C., Scavelli, F., Esposito, T., De Franceschi, M. S., Tripolino, C., & Gnasso, A. (2014). Influence of blood lipids on plasma and blood viscosity. *Clinical Hemorheology and Microcirculation, 57*(3), 267-274. doi:10.3233/CH-131705

Jakulj, F., Zernicke, K., Bacon, S. L., van Wielingen, L. E., Key, B. L., West, S. G., & Campbell, T. S. (2007). A high-fat meal increases cardiovascular reactivity to psychological stress in healthy young adults. *The Journal of Nutrition, 137*(4), 935-939. doi:10.1093/jn/137.4.935

Johnson, B. D., Padilla, J., Harris, R. A., & Wallace, J. P. (2011). Vascular consequences of a high-fat meal in physically active and inactive adults. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme, 36*(3), 368-375. doi:10.1139/H11-028

Khaddaj Mallat, R., Mathew John, C., Kendrick, D. J., & Braun, A. P. (2017). The vascular endothelium: A regulator of arterial tone and interface for the immune system. *Critical Reviews in Clinical Laboratory Sciences, 54*(7-8), 458-470. doi:10.1080/10408363.2017.1394267

Lamping, K., & Faraci, F. (2003). Enhanced vasoconstrictor responses in eNOS deficient mice. *Nitric Oxide: Biology and Chemistry, 8*(4), 207-213.

Lerman, A., Sandok, E. K., Hildebrand, F. L., & Burnett, J. C. (1992). Inhibition of endothelium-derived relaxing factor enhances endothelin-mediated vasoconstriction. *Circulation, 85*(5), 1894-1898.

Montoya, P., Brody, S., Beck, K., Veit, R., & Rau, H. (1997). Differential beta- and alpha-adrenergic activation during psychological stress. *European Journal of Applied Physiology and Occupational Physiology, 75*(3), 256-262. doi:10.1007/s004210050157 [doi]

Mundy, A. L., Haas, E., Bhattacharya, I., Widmer, C. C., Kretz, M., Hofmann-Lehmann, R., . . . Barton, M. (2007). Fat intake modifies vascular responsiveness and receptor expression of vasoconstrictors: Implications for diet-induced obesity. *Cardiovascular Research, 73*(2), 368-375. doi:S0008-6363(06)00507-4 [pii]

Plotnick, G. D., Corretti, M. C., & Vogel, R. A. (1997). Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal. *Jama, 278*(20), 1682-1686.

Poitras, V. J., Slattery, D. J., Levac, B. M., Fergus, S., Gurd, B. J., & Pyke, K. E. (2014). The combined influence of fat consumption and repeated mental stress on brachial artery flow-mediated dilatation: A preliminary study. *Experimental Physiology, 99*(4), 715-728. doi:10.1113/expphysiol.2013.077131

Rajendran, P., Rengarajan, T., Thangavel, J., Nishigaki, Y., Sakthisekaran, D., Sethi, G., & Nishigaki, I. (2013). The vascular endothelium and human diseases. *International Journal of Biological Sciences, 9*(10), 1057-1069. doi:10.7150/ijbs.7502

Rowell, L. B. (1993). *Human vascular control*

. New York: Oxford University Press.

Sandoo, A., van Zanten, J. J., Metsios, G. S., Carroll, D., & Kitas, G. D. (2010). The endothelium and its role in regulating vascular tone. *The Open Cardiovascular Medicine Journal, 4*, 302-312. doi:10.2174/1874192401004010302 [doi]

Sauder, K. A., Johnston, E. R., Skulas-Ray, A. C., Campbell, T. S., & West, S. G. (2012). Effect of meal content on heart rate variability and cardiovascular reactivity to mental stress. *Psychophysiology, 49*(4), 470-477. doi:10.1111/j.1469-8986.2011.01335.x

Schillaci, G., Marchesi, S., Siepi, D., Lupattelli, G., Vaudo, G., Pasqualini, L., & Mannarino, E. (2001). Gender differences in postprandial endothelial function. *The American Journal of Cardiology, 87*(11), 1323-1325.

Schütz, E., Schuff-Werner, P., Güttner, Y., Schulz, S., & Armstrong, V. W. (1993). Investigations into the haemorheological significance of postprandial and fasting hypertriglyceridaemia. *European Journal of Clinical Investigation, 23*(5), 270-276. doi:10.1111/j.1365-2362.1993.tb00773.x

Someya, N., Endo, M. Y., Fukuba, Y., Hirooka, Y., & Hayashi, N. (2010). Effects of a mental task on splanchnic blood flow in fasting and postprandial conditions. *European Journal of Applied Physiology, 108*(6), 1107-1113. doi:10.1007/s00421-009-1316-y

Tangney, C. C., Hafner, J. M., McQuiston, B. D., Domas, A. J., & Rosenson, R. S. (1997). Postprandial changes in plasma and serum viscosity and plasma lipids and lipoproteins after an acute test meal. *The American Journal of Clinical Nutrition, 65*(1), 36-40. doi:10.1093/ajcn/65.1.36 [doi]

Tsai, W., Li, Y., Lin, C., Chao, T., & Chen, J. (2004). Effects of oxidative stress on endothelial function after a high-fat meal. *Clinical Science (London, England: 1979), 106*(3), 315-319. doi:10.1042/CS20030227

Vanhoutte, P. M., Shimokawa, H., Feletou, M., & Tang, E. H. C. (2017). Endothelial dysfunction and vascular disease - a 30th anniversary update. *Acta Physiologica (Oxford, England), 219*(1), 22-96. doi:10.1111/apha.12646

Vogel, R. A., Corretti, M. C., & Plotnick, G. D. (1997). Effect of a single high-fat meal on endothelial function in healthy subjects. *The American Journal of Cardiology, 79*(3), 350-354.

Yim, J., Petrofsky, J., Berk, L., Daher, N., Lohman, E., Moss, A., & Cavalcanti, P. (2012). Protective effect of anti-oxidants on endothelial function in young korean-asians compared to caucasians. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 18*(8), CR467-479. doi:10.12659/msm.883266

Works Cited

Anderson, E. A., Hoffman, R. P., Balon, T. W., Sinkey, C. A., & Mark, A. L. (1991). Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *The Journal of Clinical Investigation, 87*(6), 2246-2252. doi:10.1172/JCI115260

Bae, J. H., Schwemmer, M., Lee, I. K., Lee, H. J., Park, K. R., Kim, K. Y., & Bassenge, E. (2003). Postprandial hypertriglyceridemia-induced endothelial dysfunction in healthy subjects is independent of lipid oxidation. *International Journal of Cardiology, 87*(2-3), 259-267. doi:S0167527302003479 [pii]

Ballard, K. D., Miller, J. J., Robinson, J. H., & Olive, J. L. (2008). Aerobic capacity and postprandial flow mediated dilation. *International Journal of Exercise Science, 1*(4), 163-176.

Barton, M., Baretella, O., & Meyer, M. R. (2012). Obesity and risk of vascular disease: Importance of endothelium-dependent vasoconstriction. *British Journal of Pharmacology, 165*(3), 591-602. doi:10.1111/j.1476-5381.2011.01472.x

Bauer, V., & Sotníková, R. (2010). Nitric oxide--the endothelium-derived relaxing factor and its role in endothelial functions. *General Physiology and Biophysics, 29*(4), 319-340.

Bell, H. K., & Bloomer, R. J. (2010). Impact of serum estradiol on postprandial lipemia, oxidative stress, and inflammation across a single menstrual cycle. *Gender Medicine, 7*(2), 166-178. doi:10.1016/j.genm.2010.03.001

Berne, C., Fagius, J., & Niklasson, F. (1989). Sympathetic response to oral carbohydrate administration. evidence from microelectrode nerve recordings. *The Journal of Clinical Investigation, 84*(5), 1403-1409. doi:10.1172/JCI114313

Bloomer, R. J., & Fisher-Wellman, K. H. (2010). Lower postprandial oxidative stress in women compared with men. *Gender Medicine, 7*(4), 340-349. doi:10.1016/j.genm.2010.07.001 [doi]

Bloomer, R. J., Ferebee, D. E., Fisher-Wellman, K. H., Quindry, J. C., & Schilling, B. K. (2009). Postprandial oxidative stress: Influence of sex and exercise training status. *Medicine and Science in Sports and Exercise, 41*(12), 2111-2119. doi:10.1249/MSS.0b013e3181a9e832

Bloomer, R. J., & Lee, S. (2013). Women experience lower postprandial oxidative stress compared to men. *SpringerPlus, 2*, 553. doi:10.1186/2193-1801-2-553

Bruno, R. M., Ghiadoni, L., Seravalle, G., Dell'oro, R., Taddei, S., & Grassi, G. (2012). Sympathetic regulation of vascular function in health and disease. *Frontiers in Physiology, 3*, 284. doi:10.3389/fphys.2012.00284

Buckwalter, J. B., & Clifford, P. S. (2001). The paradox of sympathetic vasoconstriction in exercising skeletal muscle. *Exercise and Sport Sciences Reviews, 29*(4), 159-163.

Burns, S. F., Miyashita, M., & Stensel, D. J. (2015). High-intensity interval exercise and postprandial triacylglycerol. *Sports Medicine (Auckland, N.Z.), 45*(7), 957-968. doi:10.1007/s40279-015-0327-6

Casey, D. P., Madery, B. D., Curry, T. B., Eisenach, J. H., Wilkins, B. W., & Joyner, M. J. (2010). Nitric oxide contributes to the augmented vasodilatation during hypoxic exercise. *The Journal of Physiology, 588*(Pt 2), 373-385. doi:10.1113/jphysiol.2009.180489

Charkoudian, N., Hart, E. C. J., Barnes, J. N., & Joyner, M. J. (2017). Autonomic control of body temperature and blood pressure: Influences of female sex hormones. *Clinical Autonomic Research: Official Journal of the Clinical Autonomic Research Society, 27*(3), 149-155. doi:10.1007/s10286-017-0420-z

Charm, S., Mccomis, W., Tejada, C., & Kurland, G. (1963). Effect of a fatty meal on whole blood and plasma viscosity. *Journal of Applied Physiology, 18*, 1217-1220. doi:10.1152/jappl.1963.18.6.1217

Chavoshan, B., Sander, M., Sybert, T. E., Hansen, J., Victor, R. G., & Thomas, G. D. (2002). Nitric oxide-dependent modulation of sympathetic neural control of oxygenation in exercising human skeletal muscle. *The Journal of Physiology, 540*(Pt 1), 377-386.

Clarkson, P., Montgomery, H. E., Mullen, M. J., Donald, A. E., Powe, A. J., Bull, T., . . . Deanfield, J. E. (1999). Exercise training enhances endothelial function in young men. *Journal of the American College of Cardiology, 33*(5), 1379-1385. doi:S0735-1097(99)00036-4 [pii]

Corretti, M. C., Anderson, T. J., Benjamin, E. J., Celermajer, D., Charbonneau, F., Creager, M. A., . . . Vogel, R. (2002). Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the international brachial artery reactivity task force. *Journal of the American College of Cardiology, 39*(2), 257-265.

Das, E. K., Lai, P. Y., Robinson, A. T., Pleuss, J., Ali, M. M., Haus, J. M., . . . Phillips, S. A. (2018). Regular aerobic, resistance, and cross-training exercise prevents reduced vascular function following a high sugar or high fat mixed meal in young healthy adults. *Frontiers in Physiology, 9*, 183. doi:10.3389/fphys.2018.00183

Dinenno, F. A., & Joyner, M. J. (2004). Combined NO and PG inhibition augments alpha-adrenergic vasoconstriction in contracting human skeletal muscle. *American Journal of Physiology.Heart and Circulatory Physiology, 287*(6), 2576. doi:10.1152/ajpheart.00621.2004 [doi]

Durand, S., Davis, S. L., Cui, J., & Crandall, C. G. (2005). Exogenous nitric oxide inhibits sympathetically mediated vasoconstriction in human skin. *The Journal of Physiology, 562*(Pt 2), 629-634. doi:jphysiol.2004.075747 [pii]

D'Urzo, K. A., King, T. J., Williams, J. S., Silvester, M. D., & Pyke, K. E. (2018). The impact of menstrual phase on brachial artery flow-mediated dilatation during handgrip exercise in healthy premenopausal women. *Experimental Physiology, 103*(2), 291-302. doi:10.1113/EP086311

Emerson, S. R., Kurti, S. P., Harms, C. A., Haub, M. D., Melgarejo, T., Logan, C., & Rosenkranz, S. K. (2017). Magnitude and timing of the postprandial inflammatory response to a high-fat meal in healthy adults: A systematic review. *Advances in Nutrition (Bethesda, Md.), 8*(2), 213-225. doi:10.3945/an.116.014431

Fagius, J. (2003). Sympathetic nerve activity in metabolic control--some basic concepts. *Acta Physiologica Scandinavica, 177*(3), 337-343. doi:10.1046/j.1365-201X.2003.01086.x

Fagius, J., & Berne, C. (1994). Increase in muscle nerve sympathetic activity in humans after food intake. *Clinical Science (London, England: 1979), 86*(2), 159-167.

Faulk, K. E., & Bartholomew, J. B. (2012). The moderating effect of physical activity on cardiovascular reactivity following single fat feedings. *Psychophysiology, 49*(1), 145-149. doi:10.1111/j.1469-8986.2011.01283.x

Fukai, T., Siegfried, M. R., Ushio-Fukai, M., Cheng, Y., Kojda, G., & Harrison, D. G. (2000). Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. *The Journal of Clinical Investigation, 105*(11), 1631-1639. doi:10.1172/JCI9551 [doi]

Fuller, K. N. Z., Summers, C. M., & Valentine, R. J. (2017). Effect of a single bout of aerobic exercise on high-fat meal-induced inflammation. *Metabolism: Clinical and Experimental, 71*, 144-152. doi:10.1016/j.metabol.2017.03.001

Fung, T. T., Rimm, E. B., Spiegelman, D., Rifai, N., Tofler, G. H., Willett, W. C., & Hu, F. B. (2001). Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. *The American Journal of Clinical Nutrition, 73*(1), 61-67. doi:10.1093/ajcn/73.1.61 [doi]

Gamboa, A., Shibao, C., Diedrich, A., Choi, L., Pohar, B., Jordan, J., . . . Biaggioni, I. (2007). Contribution of endothelial nitric oxide to blood pressure in humans. *Hypertension (Dallas, Tex.: 1979), 49*(1), 170-177. doi:10.1161/01.HYP.0000252425.06216.26

Godo, S., & Shimokawa, H. (2017). Endothelial functions. *Arteriosclerosis, Thrombosis, and Vascular Biology, 37*(9), e108-e114. doi:10.1161/ATVBAHA.117.309813

Green, D. J., & Smith, K. J. (2018). Effects of exercise on vascular function, structure, and health in humans. *Cold Spring Harbor Perspectives in Medicine, 8*(4), 10.1101/cshperspect.a029819. doi:a029819 [pii]

Green, D. J., Spence, A., Halliwill, J. R., Cable, N. T., & Thijssen, D. H. (2011). Exercise and vascular adaptation in asymptomatic humans. *Experimental Physiology, 96*(2), 57-70. doi:10.1113/expphysiol.2009.048694 [doi]

Green, D. J., Dawson, E. A., Groenewoud, H. M. M., Jones, H., & Thijssen, D. H. J. (2014). Is flow-mediated dilation nitric oxide mediated?: A meta-analysis. *Hypertension (Dallas, Tex.: 1979), 63*(2), 376-382. doi:10.1161/HYPERTENSIONAHA.113.02044

Häbler, H. J., Wasner, G., & Jänig, W. (1997). Attenuation of neurogenic vasoconstriction by nitric oxide in hindlimb microvascular beds of the rat in vivo. *Hypertension (Dallas, Tex.: 1979), 30*(4), 957-961. doi:10.1161/01.hyp.30.4.957

Harris, R. A., Nishiyama, S. K., Wray, D. W., & Richardson, R. S. (2010). Ultrasound assessment of flow-mediated dilation. *Hypertension (Dallas, Tex.: 1979), 55*(5), 1075-1085. doi:10.1161/HYPERTENSIONAHA.110.150821

Harris, R. A., Tedjasaputra, V., Zhao, J., & Richardson, R. S. (2012). Premenopausal women exhibit an inherent protection of endothelial function following a high-fat meal.

Reproductive Sciences (Thousand Oaks, Calif.), 19(2), 221-228. doi:10.1177/1933719111418125

Hart, E. C., Charkoudian, N., Wallin, B. G., Curry, T. B., Eisenach, J., & Joyner, M. J. (2011). Sex and ageing differences in resting arterial pressure regulation: The role of the beta-adrenergic receptors. *The Journal of Physiology, 589*(Pt 21), 5285-5297. doi:10.1113/jphysiol.2011.212753 [doi]

Hart, E. C., Joyner, M. J., Wallin, B. G., & Charkoudian, N. (2012). Sex, ageing and resting blood pressure: Gaining insights from the integrated balance of neural and haemodynamic factors. *The Journal of Physiology, 590*(9), 2069-2079. doi:10.1113/jphysiol.2011.224642 [doi]

Hart, E. C. J., & Charkoudian, N. (2014). Sympathetic neural regulation of blood pressure: Influences of sex and aging. *Physiology (Bethesda, Md.), 29*(1), 8-15. doi:10.1152/physiol.00031.2013

Hashimoto, M., Akishita, M., Eto, M., Ishikawa, M., Kozaki, K., Toba, K., . . . Ouchi, Y. (1995). Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation, 92*(12), 3431-3435.

Hassellund, S. S., Flaa, A., Sandvik, L., Kjeldsen, S. E., & Rostrup, M. (2010). Long-term stability of cardiovascular and catecholamine responses to stress tests: An 18-year follow-up study. *Hypertension (Dallas, Tex.: 1979), 55*(1), 131-136. doi:10.1161/HYPERTENSIONAHA.109.143164 [doi]

Hogarth, A. J., Mackintosh, A. F., & Mary, David A. S. G. (2007). Gender-related differences in the sympathetic vasoconstrictor drive of normal subjects. *Clinical Science (London, England: 1979), 112*(6), 353-361. doi:10.1042/CS20060288

Huang, P. L., Huang, Z., Mashimo, H., Bloch, K. D., Moskowitz, M. A., Bevan, J. A., & Fishman, M. C. (1995). Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature, 377*(6546), 239-242. doi:10.1038/377239a0

Irace, C., Carallo, C., Scavelli, F., Esposito, T., De Franceschi, M. S., Tripolino, C., & Gnasso, A. (2014). Influence of blood lipids on plasma and blood viscosity. *Clinical Hemorheology and Microcirculation, 57*(3), 267-274. doi:10.3233/CH-131705

Jakulj, F., Zernicke, K., Bacon, S. L., van Wielingen, L. E., Key, B. L., West, S. G., & Campbell, T. S. (2007). A high-fat meal increases cardiovascular reactivity to psychological stress in healthy young adults. *The Journal of Nutrition, 137*(4), 935-939. doi:10.1093/jn/137.4.935

Jendzjowsky, N. G., Just, T. P., & DeLorey, D. S. (2014). Exercise training augments neuronal nitric oxide synthase-mediated inhibition of sympathetic vasoconstriction in contracting skeletal muscle of rats. *The Journal of Physiology, 592*(21), 4789-4802. doi:10.1113/jphysiol.2014.278846 [doi]

Jendzjowsky, N. G., & DeLorey, D. S. (2013a). Role of neuronal nitric oxide in the inhibition of sympathetic vasoconstriction in resting and contracting skeletal muscle of healthy rats. *Journal of Applied Physiology (Bethesda, Md.: 1985), 115*(1), 97-106. doi:10.1152/japplphysiol.00250.2013

Jendzjowsky, N. G., & Delorey, D. S. (2013b). Short-term exercise training enhances functional sympatholysis through a nitric oxide-dependent mechanism. *The Journal of Physiology, 591*(6), 1535-1549. doi:10.1113/jphysiol.2012.238998

Johnson, B. D., Padilla, J., Harris, R. A., & Wallace, J. P. (2011). Vascular consequences of a high-fat meal in physically active and inactive adults. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme, 36*(3), 368-375. doi:10.1139/H11-028

Just, T. P., & DeLorey, D. S. (2017). Sex differences in sympathetic vasoconstrictor responsiveness and sympatholysis. *Journal of Applied Physiology (Bethesda, Md.: 1985), 123*(1), 128-135. doi:10.1152/japplphysiol.00139.2017

Kasikcioglu, E., Oflaz, H., Kasikcioglu, H. A., Kayserilioglu, A., Umman, S., & Meric, M. (2005). Endothelial flow-mediated dilatation and exercise capacity in highly trained endurance athletes. *The Tohoku Journal of Experimental Medicine, 205*(1), 45-51. doi:JST.JSTAGE/tjem/205.45 [pii]

Khaddaj Mallat, R., Mathew John, C., Kendrick, D. J., & Braun, A. P. (2017). The vascular endothelium: A regulator of arterial tone and interface for the immune system. *Critical Reviews in Clinical Laboratory Sciences, 54*(7-8), 458-470. doi:10.1080/10408363.2017.1394267

Kneale, B. J., Chowienczyk, P. J., Brett, S. E., Coltart, D. J., & Ritter, J. M. (2000). Gender differences in sensitivity to adrenergic agonists of forearm resistance vasculature. *Journal of the American College of Cardiology, 36*(4), 1233-1238.

Lamping, K., & Faraci, F. (2003). Enhanced vasoconstrictor responses in eNOS deficient mice. *Nitric Oxide: Biology and Chemistry, 8*(4), 207-213.

Lehoux, S., & Jones, E. A. (2016). Shear stress, arterial identity and atherosclerosis. *Thrombosis and Haemostasis, 115*(3), 467-473. doi:10.1160/TH15-10-0791 [doi]

Lerman, A., Sandok, E. K., Hildebrand, F. L., & Burnett, J. C. (1992). Inhibition of endothelium-derived relaxing factor enhances endothelin-mediated vasoconstriction. *Circulation, 85*(5), 1894-1898.

Li, X., Yang, Q., Wang, Z., & Wei, D. (2014). Shear stress in atherosclerotic plaque determination. *DNA and Cell Biology, 33*(12), 830-838. doi:10.1089/dna.2014.2480 [doi]

Limberg, J. K., Johansson, R. E., Peltonen, G. L., Harrell, J. W., Kellawan, J. M., Eldridge, M. W., . . . Schrage, W. G. (2016). B-adrenergic-mediated vasodilation in young men and women: Cyclooxygenase restrains nitric oxide synthase. *American Journal of Physiology. Heart and Circulatory Physiology, 310*(6), 756. doi:10.1152/ajpheart.00886.2015

Lopes Krüger, R., Costa Teixeira, B., Boufleur Farinha, J., Cauduro Oliveira Macedo, R., Pinto Boeno, F., Rech, A., . . . Reischak-Oliveira, A. (2016). Effect of exercise intensity on postprandial lipemia, markers of oxidative stress, and endothelial function after a high-fat meal. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme, 41*(12), 1278-1284. doi:10.1139/apnm-2016-0262

Moncada, S., & Higgs, E. A. (2006). The discovery of nitric oxide and its role in vascular biology. *British Journal of Pharmacology, 147 Suppl 1*, 193. doi:10.1038/sj.bjp.0706458

Montoya, P., Brody, S., Beck, K., Veit, R., & Rau, H. (1997). Differential beta- and alpha-adrenergic activation during psychological stress. *European Journal of Applied Physiology and Occupational Physiology, 75*(3), 256-262. doi:10.1007/s004210050157 [doi]

Morbiducci, U., Kok, A. M., Kwak, B. R., Stone, P. H., Steinman, D. A., & Wentzel, J. J. (2016). Atherosclerosis at arterial bifurcations: Evidence for the role of haemodynamics and geometry. *Thrombosis and Haemostasis, 115*(3), 484-492. doi:10.1160/TH15-07-0597 [doi]

Mundy, A. L., Haas, E., Bhattacharya, I., Widmer, C. C., Kretz, M., Hofmann-Lehmann, R., . . . Barton, M. (2007). Fat intake modifies vascular responsiveness and receptor expression of vasoconstrictors: Implications for diet-induced obesity. *Cardiovascular Research, 73*(2), 368-375. doi:S0008-6363(06)00507-4 [pii]

Nase, G. P., & Boegehold, M. A. (1996). Nitric oxide modulates arteriolar responses to increased sympathetic nerve activity. *The American Journal of Physiology, 271*(3 Pt 2), 860. doi:10.1152/ajpheart.1996.271.3.H860 [doi]

O'Sullivan, S. E., & Bell, C. (2001). Training reduces autonomic cardiovascular responses to both exercise-dependent and -independent stimuli in humans. *Autonomic Neuroscience : Basic & Clinical, 91*(1-2), 76-84. doi:S1566-0702(01)00288-0 [pii]

Padilla, J., Harris, R. A., Fly, A. D., Rink, L. D., & Wallace, J. P. (2006). The effect of acute exercise on endothelial function following a high-fat meal. *European Journal of Applied Physiology, 98*(3), 256-262. doi:10.1007/s00421-006-0272-z

Patik, J. C., Tucker, W. J., Curtis, B. M., Nelson, M. D., Nasirian, A., Park, S., & Brothers, R. M. (2018). Fast-food meal reduces peripheral artery endothelial function but not cerebral vascular hypercapnic reactivity in healthy young men. *Physiological Reports, 6*(18), e13867. doi:10.14814/phy2.13867

Pellinger, T. K., & Halliwill, J. R. (2007). Effect of propranolol on sympathetically mediated leg vasoconstriction in humans. *The Journal of Physiology, 583*(Pt 2), 797-809. doi:10.1113/jphysiol.2007.137422

Plotnick, G. D., Corretti, M. C., & Vogel, R. A. (1997). Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal. *Jama, 278*(20), 1682-1686.

Poitras, V. J., Slattery, D. J., Levac, B. M., Fergus, S., Gurd, B. J., & Pyke, K. E. (2014). The combined influence of fat consumption and repeated mental stress on brachial artery flow-mediated dilatation: A preliminary study. *Experimental Physiology, 99*(4), 715-728. doi:10.1113/expphysiol.2013.077131

Pyke, K. E., & Tschakovsky, M. E. (2005). The relationship between shear stress and flow-mediated dilatation: Implications for the assessment of endothelial function. *The Journal of Physiology, 568*(Pt 2), 357-369. doi:10.1113/jphysiol.2005.089755

Rajendran, P., Rengarajan, T., Thangavel, J., Nishigaki, Y., Sakthisekaran, D., Sethi, G., & Nishigaki, I. (2013). The vascular endothelium and human diseases. *International Journal of Biological Sciences, 9*(10), 1057-1069. doi:10.7150/ijbs.7502

Rosenmeier, J. B., Fritzlar, S. J., Dinenno, F. A., & Joyner, M. J. (2003). Exogenous NO administration and alpha-adrenergic vasoconstriction in human limbs. *Journal of Applied Physiology (Bethesda, Md.: 1985), 95*(6), 2370-2374. doi:10.1152/japplphysiol.00634.2003 [doi]

Rowell, L. B. (1993). *Human vascular control*. New York: Oxford University Press.

Rudolph, T. K., Ruempler, K., Schwedhelm, E., Tan-Andresen, J., Riederer, U., Böger, R. H., & Maas, R. (2007). Acute effects of various fast-food meals on vascular function and cardiovascular disease risk markers: The hamburg burger trial. *The American Journal of Clinical Nutrition, 86*(2), 334-340. doi:10.1093/ajcn/86.2.334

Sandoo, A., van Zanten, J. J., Metsios, G. S., Carroll, D., & Kitas, G. D. (2010). The endothelium and its role in regulating vascular tone. *The Open Cardiovascular Medicine Journal, 4*, 302-312. doi:10.2174/1874192401004010302 [doi]

Sauder, K. A., Johnston, E. R., Skulas-Ray, A. C., Campbell, T. S., & West, S. G. (2012). Effect of meal content on heart rate variability and cardiovascular reactivity to mental stress. *Psychophysiology, 49*(4), 470-477. doi:10.1111/j.1469-8986.2011.01335.x

Schillaci, G., Marchesi, S., Siepi, D., Lupattelli, G., Vaudo, G., Pasqualini, L., & Mannarino, E. (2001). Gender differences in postprandial endothelial function. *The American Journal of Cardiology, 87*(11), 1323-1325.

Schütz, E., Schuff-Werner, P., Güttner, Y., Schulz, S., & Armstrong, V. W. (1993). Investigations into the haemorheological significance of postprandial and fasting

hypertriglyceridaemia. *European Journal of Clinical Investigation, 23*(5), 270-276. doi:10.1111/j.1365-2362.1993.tb00773.x

Scott, E. M., Greenwood, J. P., Pernicova, I., Law, G. R., Gilbey, S. G., Kearney, M. T., & Mary, David A S G. (2013). Sympathetic activation and vasoregulation in response to carbohydrate ingestion in patients with congestive heart failure. *The Canadian Journal of Cardiology, 29*(2), 236-242. doi:10.1016/j.cjca.2012.03.020

Seals, D. R. (1991). Sympathetic neural adjustments to stress in physically trained and untrained humans. *Hypertension (Dallas, Tex.: 1979), 17*(1), 36-43.

Shah, Y., Bass, L., Davison, G. W., Seigler, N., Pollock, J. S., Thomas, J., & Harris, R. A. (2017). BH4 improves postprandial endothelial function after a high-fat meal in men and postmenopausal women. *Menopause (New York, N.Y.), 24*(5), 555-562. doi:10.1097/GME.0000000000000785

Someya, N., Endo, M. Y., Fukuba, Y., Hirooka, Y., & Hayashi, N. (2010). Effects of a mental task on splanchnic blood flow in fasting and postprandial conditions. *European Journal of Applied Physiology, 108*(6), 1107-1113. doi:10.1007/s00421-009-1316-y

Tangney, C. C., Hafner, J. M., McQuiston, B. D., Domas, A. J., & Rosenson, R. S. (1997). Postprandial changes in plasma and serum viscosity and plasma lipids and lipoproteins after an acute test meal. *The American Journal of Clinical Nutrition, 65*(1), 36-40. doi:10.1093/ajcn/65.1.36 [doi]

Teeman, C. S., Kurti, S. P., Cull, B. J., Emerson, S. R., Haub, M. D., & Rosenkranz, S. K. (2016). Postprandial lipemic and inflammatory responses to high-fat meals: A review of the roles of acute and chronic exercise. *Nutrition & Metabolism, 13*, 80. doi:10.1186/s12986-016-0142-6

Tesfamariam, B., Weisbrod, R. M., & Cohen, R. A. (1987). Endothelium inhibits responses of rabbit carotid artery to adrenergic nerve stimulation. *The American Journal of Physiology, 253*(4 Pt 2), 792. doi:10.1152/ajpheart.1987.253.4.H792 [doi]

Thijssen, D. H. J., Black, M. A., Pyke, K. E., Padilla, J., Atkinson, G., Harris, R. A., . . . Green, D. J. (2011). Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *American Journal of Physiology. Heart and Circulatory Physiology, 300*(1), 2. doi:10.1152/ajpheart.00471.2010

Thom, N. J., Early, A. R., Hunt, B. E., Harris, R. A., & Herring, M. P. (2016). Eating and arterial endothelial function: A meta-analysis of the acute effects of meal consumption on flow-mediated dilation. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity, 17*(11), 1080-1090. doi:10.1111/obr.12454

Thomas, G. D., & Segal, S. S. (2004). Neural control of muscle blood flow during exercise. *Journal of Applied Physiology (Bethesda, Md.: 1985), 97*(2), 731-738. doi:10.1152/japplphysiol.00076.2004 [doi]

Thomas, G. D., & Victor, R. G. (1998). Nitric oxide mediates contraction-induced attenuation of sympathetic vasoconstriction in rat skeletal muscle. *The Journal of Physiology, 506 (Pt 3)*, 817-826.

Toda, N., & Okamura, T. (2003). The pharmacology of nitric oxide in the peripheral nervous system of blood vessels. *Pharmacological Reviews, 55*(2), 271-324. doi:10.1124/pr.55.2.3

Toda, N., & Okamura, T. (2015). Recent advances in research on nitrergic nerve-mediated vasodilatation. *Pflugers Archiv: European Journal of Physiology, 467*(6), 1165-1178. doi:10.1007/s00424-014-1621-0

Tsai, W., Li, Y., Lin, C., Chao, T., & Chen, J. (2004). Effects of oxidative stress on endothelial function after a high-fat meal. *Clinical Science (London, England: 1979), 106*(3), 315-319. doi:10.1042/CS20030227

Tucker, W. J., Sawyer, B. J., Jarrett, C. L., Bhammar, D. M., Ryder, J. R., Angadi, S. S., & Gaesser, G. A. (2018). High-intensity interval exercise attenuates but does not eliminate endothelial dysfunction after a fast food meal. *American Journal of Physiology. Heart and Circulatory Physiology, 314*(2), H188-H194. doi:10.1152/ajpheart.00384.2017

Tushuizen, M. E., Nieuwland, R., Scheffer, P. G., Sturk, A., Heine, R. J., & Diamant, M. (2006). Two consecutive high-fat meals affect endothelial-dependent vasodilation, oxidative stress and cellular microparticles in healthy men. *Journal of Thrombosis and Haemostasis: JTH, 4*(5), 1003-1010. doi:10.1111/j.1538-7836.2006.01914.x

Vanhoutte, P. M., Shimokawa, H., Feletou, M., & Tang, E. H. C. (2017). Endothelial dysfunction and vascular disease - a 30th anniversary update. *Acta Physiologica (Oxford, England), 219*(1), 22-96. doi:10.1111/apha.12646

Vaz, M., Turner, A., Kingwell, B., Chin, J., Koff, E., Cox, H., . . . Esler, M. (1995). Postprandial sympatho-adrenal activity: Its relation to metabolic and cardiovascular events and to changes in meal frequency. *Clinical Science (London, England: 1979), 89*(4), 349-357.

Victor, R. G., Leimbach, W. N., Seals, D. R., Wallin, B. G., & Mark, A. L. (1987). Effects of the cold pressor test on muscle sympathetic nerve activity in humans. *Hypertension (Dallas, Tex.: 1979), 9*(5), 429-436.

Vogel, R. A., Corretti, M. C., & Plotnick, G. D. (1997). Effect of a single high-fat meal on endothelial function in healthy subjects. *The American Journal of Cardiology, 79*(3), 350-354.

Wray, D. W., Witman, M. A. H., Ives, S. J., McDaniel, J., Fjeldstad, A. S., Trinity, J. D., . . . Richardson, R. S. (2011). Progressive handgrip exercise: Evidence of nitric oxide-dependent vasodilation and blood flow regulation in humans. *American Journal of Physiology. Heart and Circulatory Physiology, 300*(3), 1101. doi:10.1152/ajpheart.01115.2010

Yim, J., Petrofsky, J., Berk, L., Daher, N., Lohman, E., Moss, A., & Cavalcanti, P. (2012). Protective effect of anti-oxidants on endothelial function in young korean-asians compared to caucasians. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 18*(8), CR467-479. doi:10.12659/msm.883266