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ACUTE AND CHRONIC VASCULAR RESPONSES TO BLOOD FLOW RESTRICTION IN
THE UPPER BODY

A Dissertation Presented in Partial Fulfillment of Requirements for the Degree of
Doctor of Philosophy in Health and Kinesiology
in the Department of Health, Exercise Science, and Recreation Management
The University of Mississippi

May 2018

by James Grant Mouser

ABSTRACT

Blood flow restriction (BFR) with low load exercise increases muscular size and strength. Little is known of vascular adaptations to this training modality, and nothing was known at very low loads. These studies examined cardiovascular responses to high load (70% of one-repetition maximum (1RM)) and very low load (15%1RM) exercise, alone or at two levels of BFR. Study 1: Participants performed unilateral biceps curls using either 15%1RM with no BFR (15/00), 40% of arterial occlusion pressure (AOP) (15/40), or 80%AOP (15/80), or 70%1RM (70/00). Systolic and diastolic blood pressure (SBP, DBP) and blood flow (BF) were measured in the arms during four sets performed to voluntary failure. BF increased in 15/00 (+470.8 (257.6) ml·min⁻¹), 15/40 (325.3 (174.9) ml·min⁻¹), and 70/00 (445.6 (249.3) ml·min⁻¹) following the 2nd set, but not in 15/80. One minute following the 4th set, BF increased in 15/80 (+300.6 (206.4) ml·min⁻¹), with no differences between conditions. SBP rose across all conditions (+10 (11) mmHg), whereas DBP rose in 15/00 (+8 (5) mmHg), 15/40 (+9 (7) mmHg), and 15/80 (+3 (7) mmHg) only. Study 2: Participants trained twice weekly, with one of the four conditions in each arm. Forearm blood flow (FBF), vascular conductance (VC), maximum venous outflow (MVO), venous volume variation (VVV), and venous compliance (C_v) were examined before and after training. FBF and VC increased in 15/80 (+0.520 (0.218) ml·min⁻¹·100ml⁻¹; +8.286 (2.66) ml·mmHg⁻¹) and 70/00 (+0.616 (0.212) ml·min⁻¹·100ml⁻¹; +8.595 (2.60) ml·mmHg⁻¹). MVO increased for all conditions at 60 mmHg (+4.020 (1.416) ml·min⁻¹·100ml⁻¹), and for 15/00 (+6.52 (3.02) ml·min⁻¹·100ml⁻¹) and 15/80 (+11.468 (2.965) ml·min⁻¹·100ml⁻¹) at 80 mmHg. VVV increased at 20 mmHg (+0.075 (0.030) %), 40 mmHg (+0.162 (0.069) %), and 80 mmHg (+0.310 (0.103) %) for all conditions, but decreased for 15/00 (-0.632

(0.200) %) at 60 mmHg. C_v increased across all conditions following training (+0.003 (0.002) $\% \cdot \text{mmHg}^{-1}$). Rating of perceived exertion decreased halfway through training and remained depressed, while discomfort at first decreased at 4 weeks but returned to baseline at 8 weeks. High BFR pressures combined with very low loads result in similar vascular adaptations as high loads with eight weeks of training.

DEDICATION

To Janie and Jim Mouser. Thank you so much.

LIST OF ABBREVIATIONS

1RM	-	one-repetition maximum
AIC	-	Akaike's information criterion
ANOVA	-	analysis of variance
AOP	-	arterial occlusion pressure
BF	-	blood flow
BFR	-	blood flow restriction
BIC	-	Bayesian information criterion
DIA	-	diameter
eNOS	-	endothelial nitric oxide synthase
mmHg	-	millimeter of mercury
MVO	-	maximum venous outflow
SD	-	standard deviation
SE	-	standard error
VC	-	venous compliance
VVV	-	venous volume variation

ACKNOWLEDGEMENTS

Thank you Dr. John Bentley for tirelessly pointing me in the right direction while I was getting my bearings with statistics. Thank you Dr. Paul Loprinzi for stopping and chatting about any little thing and sharing your experiences with me. Thank you Dr. Mark Loftin for injecting a much-needed cheerful attitude into our interactions, both inside and outside of the classroom. Thank you Matt Jessee for being a sounding board whenever I needed to talk. Thank you Scott Dankel for keeping me firmly grounded in my abilities. Thank you Sam Buckner for constantly throwing ideas around and forcing me to think more clearly about their deeper implications. Thank you Kevin Mattocks for keeping me somewhat anchored to the world outside of the lab. Thank you Brittany Counts for all of the great conversations, commiserations, conventions, and casseroles. Thank you Dr. Takashi Abe for the opportunity to learn from your expertise and for pushing me in my abilities with data collection. To Lauren, Pamela, Eveleen, Chris, Caleb, Sam, Jackie, Vokay, Tyler, Amanda, Jeremiah, Ethan, and Emily, thank you for playing a part in this journey.

Thank you Dr. Loenneke for all of the help, encouragement, guidance, enthusiasm, and friendship these last six years. The years since 2012 have been some of the most interesting, productive, and memorable on record. You challenged me not to quit and to push myself further than I thought possible, and I will always be grateful for the experience.

Thank you to the Japanese Society of Wellness and Preventive Medicine for funding part of these studies.

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I: INTRODUCTION

Blood flow restriction is the application of either pneumatic pressure cuffs or elastic wraps to the proximal-most portion of the arms or the legs. When pressure is increased in the cuffs, or similarly when the wraps are tightened, venous pooling begins to occur which causes an increase in the transit time of blood through the limb. During the application of blood flow restriction, low-intensity exercises such as cycling (Abe et al. 2010), walking (Abe et al. 2006), or low-load resistance exercise can be performed (Loenneke et al. 2012a). The combination of blood flow restriction with low-intensity exercises has evidenced viable hypertrophic stimuli in skeletal muscle. Of note, this occurs at intensities and loads that are not typically associated with muscular hypertrophy, such as the loads of > 70% of one-repetition maximum recommended by the American College of Sports Medicine. Because of this, blood flow restriction has been employed in the scientific literature to better understand muscular hypertrophy as it relates to the load being lifted. Further, because the external load being lifted is considered a very light stimulus (20% - 30% of an individual's one-repetition maximum), blood flow restriction has recently appeared in the rehabilitation field as a viable method for increasing or maintaining muscle size and strength following injury or surgery (Tennent et al. 2017).

The muscular adaptation to blood flow restriction is well documented, particularly as it relates to the acute changes seen following resistance exercise. Many studies have examined the decline in force production immediately post-exercise (Loenneke et al. 2013), changes in neuromuscular electrical activity across the exercise protocol (Counts et al. 2016), changes in whole blood lactate concentration following deflation of the cuff (Loenneke et al. 2010), and the acute

muscular swelling response elicited from this mode of exercise (Loenneke et al. 2012c). Further, biochemical analyses have been performed on the intramuscular response to this mode of exercise, investigating muscle protein synthetic pathways (Fry et al. 2010; Gundermann et al. 2012), myostatin gene expression (Laurentino et al. 2012; Santos et al. 2014), and fiber type specific hypertrophy (Nielsen et al. 2012). Considerable interest has also been placed on the hormonal response to blood flow restriction combined with low-load resistance exercise (Takarada et al. 2000; Iida et al. 2007; Inagaki et al. 2011).

Chronically, it has been shown several times that blood flow restriction combined with low-load resistance exercise leads to similar muscular hypertrophy as traditional high-load resistance exercise (Martín-Hernández et al. 2013; Lixandrão et al. 2015). This hypertrophy occurs despite the fact that the pressure applied in most studies is not made relative to each individual. That is, an arbitrary pressure (e.g., 100 mmHg) is applied to each person in the study without respect to either cuff width or limb size, both of which have been shown to affect the pressure at which blood flow will be completely occluded (Loenneke et al. 2015; Jessee et al. 2016a). One such study examining the hypertrophic response to eight weeks of biceps training at both moderate (40% of arterial occlusion pressure) and high (90% of arterial occlusion pressure) levels of blood flow restriction demonstrated results that were not statistically significantly different with respect to muscle hypertrophy, even though the group that trained under 90% of arterial occlusion pressure performed statistically significantly lower total volume than the group trained under 40% of arterial occlusion pressure (Counts et al. 2015). More recent work has shown that low-load resistance exercise under 50% of arterial occlusion pressure elicits similar muscle and strength increases as seen with high-load (75% 1RM) training (Kim et al. 2017).

Although the low loads used with blood flow restriction exercise appear beneficial with

respect to muscular adaptations, especially in populations in which lifting heavy loads is contraindicated, the perception of this type of exercise appears somewhat uncomfortable to the participants during the introductory stages of a training program, although this discomfort appears to decrease with exposure (Kim et al. 2017). Studies examining the perceptual responses to blood flow restriction combined with low-load resistance exercise have shown that higher pressures elicit greater ratings of discomfort (Rossow et al. 2012; Counts et al. 2015). Observations in our laboratory have shown that discomfort ratings are greater toward the end of each rest period between sets, and so studies that examine the discomfort response immediately following each set might not capture an accurate picture of this discomfort.

To test whether the discomfort is more closely associated with the exercise load or the applied pressure, our laboratory has undertaken two studies examining differing pressures at similar loads, and differing loads and similar pressures (Jessee et al. 2017b; Mattocks et al. 2017). We found that for a given pressure, discomfort increases as the load being lifted increases and that for a given load, discomfort increases as pressure increases. It would appear, however, that the load being lifted has a much greater impact on perceived exertion than does the pressure. Conversely, the pressure appears to have a much greater impact on discomfort than does the load being lifted. Higher pressures and loads combine to cause an overall decrease in the amount of exercise volume.

At rest, blood flow to the skeletal muscle is determined by muscle mass: the greater the muscle mass in the limbs, the greater the blood flow to those limbs (Saltin et al. 1998). During exercise, however, the increase in blood flow to the limbs is proportional to the work performed. This is mediated by multiple local as well as systemic factors. Locally, the release of dilatory factors from the skeletal muscle and the arteries themselves cause rapid vasodilation of the conductance arteries supplying the muscle. An increase in local shear stress causes endothelial-derived nitric oxide

synthase (eNOS) to increase production of nitric oxide for release to the smooth muscle surrounding the arteries, causing it to relax further and aid in dilation (Furchgott and Vanhoutte 1989). Systemically, there is an increase in heart rate and cardiac output that occurs following the onset of exercise, further increasing blood flow, shear stress, and vasodilation.

The effects of blood flow restriction combined with low-load resistance exercise on skeletal muscle have been well documented; less known is the blood flow response, both acutely and following training, to this exercise modality. Our laboratory has studied the effects of differing cuff widths on blood flow, as well as the effects of differing pressures applied using the same cuff before exercise, during the rest period between sets, and following blood flow restricted biceps curls. We have found that the hyperemic response, the increase in blood flow due to some stressor, to low-load exercise is blunted in a pressure-dependent manner, with 80% of arterial occlusion pressure allowing a much smaller increase in blood flow than 40% of arterial occlusion pressure, itself decreasing the maximum hyperemia seen in a free flow (i.e. no restriction) condition at the same load (Mouser et al. 2017c). We have also determined that there is not any difference in the hemodynamic responses at rest with respect to commonly used cuff widths as long as the pressures are set relative to the cuff applying the restriction and to the individual (Mouser et al. 2017b).

Several other studies have examined the acute changes in blood flow during the application of blood flow restriction, but these have again used arbitrary pressures. These studies include all participants in blood flow calculations at these arbitrary pressures and thus conclude that a linear decrease in blood flow has occurred (Iida et al. 2005; Takano et al. 2005; Iida et al. 2007). This is misleading, however, as some participants are fully occluded at intermediate pressures used in these studies, whereas some participants never fully occlude. Work performed by the author has shown that, when blood flow is measured during rest at relative pressures in increments of 10% of arterial

occlusion pressure in both seated and supine positions, blood flow decreases in a non-linear manner with pressure (Mouser et al. 2017a). This highlights further the need to prescribe blood flow restriction using relative pressures. At relative pressures, participants are never under full arterial occlusion during exercise. Greater pressures of the kind typically seen with arbitrary values lead to a greater restriction of blood flow, which increases the perceptual response to this type of training. This in turn may decrease willingness to use blood flow restriction in a rehabilitative setting.

The arterial occlusion pressure itself is subject to change acutely across an exercise session. Resting arterial occlusion pressure in the upper body has been linked to the width of the pneumatic cuff, the circumference of the arm to which the pressure cuff is applied, and to the individual's systolic blood pressure (Jessee et al. 2016a). It has been demonstrated once in the lower body that systolic blood pressure increases across an exercise session involving blood flow restriction to a greater degree than that seen with traditional high-load resistance exercise alone (Downs et al. 2014), although the pressures applied to the legs were based off of blood pressure measurements taken in the arm. In the upper body, one study has shown that low-load resistance exercise combined with blood flow restriction elicits a similar blood pressure response as high-load resistance exercise (Brandner et al. 2015). This increase in blood pressure will cause the arterial occlusion pressure immediately following blood flow restriction to increase, to the point that the initial applied pressure, as a percentage of arterial occlusion pressure, decreases by the end of exercise (Barnett et al. 2016). The cardiovascular load imposed by blood flow restriction combined with low-load resistance exercise has raised safety concerns when applying this modality to clinical populations (Spranger et al. 2015; Jessee et al. 2016b). It is currently unknown whether the arterial occlusion pressure measurement taken immediately before exercise in the resting state changes significantly with training.

It is well documented that muscle blood flow is altered with aerobic training, and there are several studies examining the muscle blood flow adaptations that occur with resistance exercise. Capillarization increases near the muscle fibers in order to provide the mitochondria with the oxygen needed to create adenosine triphosphate (ATP). During aerobic training, muscle capillarization increases due to both local metabolic factors as well as local increases in shear stress caused by a systemic increase in blood flow. When combined, capillaries begin budding and growing toward areas of higher metabolic demand through the course of a training program. With resistance exercise, during which shear stresses increase several times above that which occurs with aerobic exercise, an increase in capillarization is seen in the muscle being worked. It is thought that this happens in a pressure-dependent manner, with the increased load causing greater intra-arterial pressure leading to capillary budding and proliferation. While the low loads typically associated with blood flow restriction are not expected to increase intra-arterial pressure to such a degree, it is possible that the application of the pneumatic cuff to a sufficiently high pressure could mimic this pressure response and cause a similar increase in capillarization. In the lower body, exercise training of the knee extensors using 30% of 1RM and 80% of arterial occlusion pressure showed calf vascular conductance to actually decrease following training in comparison with a free-flow (no blood flow restriction) condition using the same loads (Fahs et al. 2014), although the response in the upper body has yet to be documented using elbow flexion. While determinants of blood flow are dissimilar between the upper and lower body, there is no reason to believe that vascular adaptations occur dissimilarly between the two.

Without knowing the acute and training-related changes in blood flow, a clear picture of possible vascular adaptations cannot be seen. Two studies purporting to examine the blood flow response to low-load resistance exercise combined with blood flow restriction have used protocols involving the handgrip exercise, which is entirely novel in the literature and thus possibly not

indicative of typical exercise (Credeur et al. 2010; Hunt et al. 2012). Further, the pressures, cuff locations, and exercise loads used in these studies differed from those commonly seen, and both studies reached differing conclusions as to what occurred with this type of exercise relating to vascular adaptation.

In an effort to further elucidate the perceptual response to differing loads and pressure of blood flow restriction, and to examine more closely the acute and training-induced vascular adaptations to blood flow restriction using very low loads, more research into these areas is required.

Purpose

The purpose of this study was to compare differing levels of blood flow restriction combined with very low-load resistance exercise to high-load resistance exercise as they related to both the acute blood flow response to resistance exercise as well as training-induced vascular adaptations in the upper body. Further, perceptual responses were tracked across the entirety of the study to determine whether there was a lessening of the perceptual response to this mode of exercise with training.

Primary Questions

1. What is the acute hyperemic response to high load resistance exercise and very low load resistance exercise combined with differing levels of blood flow restriction in the upper body and how do they differ?
2. How would eight weeks of twice weekly high load and very low load resistance training combined with differing levels of blood flow restriction in the upper body affect vascular conductance and venous compliance?

Primary Hypotheses

1. The hyperemic response to high-load resistance exercise would be greater than the hyperemic response to very low load resistance exercise combined with differing levels of blood flow restriction in the upper body. At higher relative pressures of blood flow restriction, the hyperemic response would be more severely blunted while the cuff is inflated. The post-exercise, post-deflation hyperemic response will be similar across both moderate and high relative pressures of blood flow restriction when combined with very low load resistance exercise. The very low load condition without blood flow restriction would see a decrease from peak blood flow following exercise.
2. Vascular conductance would increase following eight weeks of training. Vascular conductance would be greater in the high pressure group than in the moderate pressure and no pressure groups, and would be similar to the high load group. Venous compliance would increase following eight weeks of training. Venous compliance would be greater in the high pressure group than in the moderate pressure and no pressure groups as well as the high-load group. Venous compliance would be greater in the moderate pressure group than in the high load group.

Secondary Questions

1. How would blood pressure change acutely with high load, very low load, and very low load combined with differing levels of blood flow restriction exercise?
2. How would resting arterial occlusion pressure change following eight weeks of twice weekly training involving very low loads combined with differing levels of blood flow restriction?
3. How would perceptual responses to this type of exercise change following eight weeks

of twice weekly training involving high loads, very low loads, and very low loads combined with differing levels of blood flow restriction?

Secondary Hypotheses

1. The blood pressure response to high loads and very low loads combined with high relative BFR would not be statistically significantly different. The blood pressure response would not be as great in the very low load with moderate BFR. The very low load with no BFR would see the lowest elevation in blood pressure following exercise.
2. Following eight weeks of twice weekly training using very low loads combined with differing levels of blood flow restriction there would be no change in the resting arterial occlusion pressure.
3. Following eight weeks of twice weekly training using either high loads or very low loads combined with differing levels of blood flow restriction there would be a decrease in the perceptual responses to these types of exercises.

Significance

Relatively little work has examined the vascular response to relative levels of blood flow restriction combined with low load resistance exercise. Because blood flow restriction, as of 2017, is making its way into the rehabilitation setting, and because of the pronounced acute effects of this type of exercise on the cardiovascular system, it is important to elucidate the chronic changes that occur, if any, on the vascular structures of the exercised limbs. If it can be shown that blood flow restriction combined with such low load resistance exercise causes beneficial vascular adaptations in a healthy population, it can then be tested in different populations. As the chronic vascular adaptations to this type of exercise are completely unknown, a complete safety profile of blood flow restriction cannot be made.

Assumptions

1. It was assumed that each participant gave maximum effort during the study.
2. It was assumed that participants honestly answered all screening questionnaires.
3. It was assumed that changes in vascular conductance measures were indicative of changes in the vascular structure.
4. It was assumed that pulsed-wave ultrasound provided an accurate measure of blood flow through the imaged vascular structures.

Delimitations

1. The findings of this study may only be applicable to healthy, college-aged men and women who were not performing resistance training before the study begins.
2. The participants in this study are volunteers and do not represent a true random sample.

Limitations

1. Participants self-reported compliance with the inclusion and exclusion criteria of the study.
2. Participants self-reported testing day compliance with the requirements of the study.
3. Brachial artery diameter was measured with on-screen calipers and not automated edge detection software.
4. Menstrual cycle phase was not tracked for females in the study.

Operational Definitions

1. Arterial Occlusion Pressure (AOP) – The minimum pressure required in a pneumatic cuff to completely occlude the underlying vascular structures in a limb, causing a cessation of blood flow.

2. Blood Flow Restriction (BFR) – The application of pneumatic pressure cuffs or elastic wraps around the proximal-most portion of a limb with the intent to slow blood transit time by occluding vascular return and impeding arterial flow to that limb.
3. Compliance – A measure of the degree to which the veins can dilate in order to store more blood.
4. Conductance – A measure of the amount of swelling induced in a segment of a limb by repeatedly inflating and deflating a collecting cuff as measured by a strain gauge. It is assumed that the increase in limb segment circumference is related to the amount of blood flow entering and completely filling the vasculature in that limb segment.
5. Pulse Wave Velocity – The speed at which the pressure wave generated by the beating heart travels through an artery, typically measured in the carotid, the radial, and/or the femoral arteries.

II: REVIEW OF LITERATURE

Skeletal muscle, a highly metabolically active tissue, is responsible for locomotion and stability, as well as glucose storage and disposal (Mandarino et al. 1993). Blood flow into skeletal muscle is largely dependent upon the local environment (Tschakovsky et al. 2006) and whether work is being performed. The purpose of this literature review will be to examine typical blood flow profiles, the local and systemic controls of blood flow at rest and during exercise, and to examine the vascular adaptations to different types of exercises. A further purpose of this literature review will be to examine the perceptual responses to different types of exercises.

Skeletal Muscle Blood Flow

At rest, the amount of blood flow into the limbs is determined predominantly by the amount of muscle mass present; more muscle mass requires more blood flow in order to provide it with oxygen and nutrients as well as remove metabolic byproducts. Several studies have measured resting blood flow in the upper body. In a study published in 2008 examining shear rates, blood velocities, and volumetric flow in order to understand possible determinants of atherosclerosis, Newcomer and colleagues measured resting blood flow in the brachial and superficial femoral arteries of physically healthy individuals in the supine, seated, and standing positions (Newcomer et al. 2008). That study found that blood flow in the brachial artery remains relatively constant when going from the supine position to standing at between 40 and 45 ml·min⁻¹.

In a 2012 study performed by Ade et al., brachial artery blood flow in the supine position was measured between 57 and 67 ml·min⁻¹ using two separate methods (Ade et al. 2012). Recent

studies performed by our research group have shown resting brachial artery blood flow values of around $60 \text{ ml}\cdot\text{min}^{-1}$ in women and around $100 \text{ ml}\cdot\text{min}^{-1}$ in men while standing (under review), around $70 \text{ ml}\cdot\text{min}^{-1}$ in men and around $25 \text{ ml}\cdot\text{min}^{-1}$ in women while supine (under review), and around $45 \text{ ml}\cdot\text{min}^{-1}$ while seated (Mouser et al. 2017a). From these studies we can see that resting blood flow varies widely across study populations but remains between approximately $40 \text{ ml}\cdot\text{min}^{-1}$ and $100 \text{ ml}\cdot\text{min}^{-1}$ respectively, for men and women.

During exercise, blood flow to the exercising muscle can increase up to 30 times the resting values (Saltin et al. 1998). There is an almost immediate increase in limb blood flow with the initiation of exercise as shown in work performed by Radegran and Saltin in 1998. They measured blood flow in the femoral artery at rest and during the very first voluntary contraction performed at varying workloads and found that blood flow in the artery is blocked during contraction and is increased above baseline during the very first muscle relaxation (Radegran and Saltin 1998). Some of this initial increase in blood flow is due to the emptying of the veins by the muscular contraction. When these veins reopen during relaxation, their internal pressure is greatly reduced, drawing blood from the arterial side more quickly due to the larger pressure gradient. This process has been called the muscle pump, and it facilitates both an increase in local blood flow as well as venous return to the heart during rhythmic muscle contractions.

While the muscle pump and resulting pressure changes across the vascular tree explain the initial increase in local blood flow, additional local responses occur in order to further increase blood flow to the exercising muscle in the upper body. The initial increase in blood flow causes turbulence near the artery walls. This turbulent flow, dubbed shear stress, triggers a cascade in the endothelial cells that line the artery lumen, causing the release of local dilatory factors both into the blood as well as the interstitial space in the arterial walls. Called endothelium-derived relaxing factors (EDRF)

(Furchgott and Vanhoutte 1989), one major factor that has been studied extensively is nitric oxide (NO), which is produced by endothelium nitric oxide synthase (eNOS). The release of NO into the bloodstream decreases platelet accumulation, allowing blood to flow more freely. Release of NO into the intercellular spaces in the artery walls causes relaxation of the smooth muscle, decreasing arterial tone and causing vasodilation. Resistance to blood flow decreases rapidly with increasing artery diameter, and so more blood flow is permitted once eNOS has been activated.

At the same time that local vascular changes occur to permit more blood flow, cardiac output increases due to the increase in heart rate that accompanies exercise. As exercise continues, cardiac output increases further with increasing venous return to the heart. Taken together, each factor will allow for a greater increase in blood flow to the exercising muscles, ensuring that oxygen delivery and waste removal occur at a sufficient rate to sustain exercise.

Chronically, changes in vascular structure and function will occur in order to decrease the shear stress on the arteries. As blood flow increases, so too does shear stress. When this occurs during exercise training shear stress is chronically elevated, which causes capillary growth to occur through the release of a variety of molecular growth factors from the epithelial cells lining the arteries. One such growth factor, vascular endothelial growth factor (VEGF), is released in response to elevated shear stress in order to promote angiogenesis and capillary growth. Capillaries will continue to grow until conductance through a limb is increased enough that shear stress returns to normal levels.

Blood Flow Restriction

Blood flow restriction in its current form relies on external mechanical compression of a portion of the limbs, typically applied using either pneumatic cuffs/tourniquets or elastic bands. This results in a slowing of blood flow through the limbs resulting in venous pooling. Although

blood flow restriction had been experimented with since the late 1960s and 1970s by the man credited with the idea (Sato 2005), it was not mentioned in the research literature until the late 1990s with the publication of a study examining low-resistance isometric contractions under >250 mmHg carried out over four weeks (Shinohara et al. 1998). In that study, healthy men performed isometric contractions of the knee extensors at 40% of their maximal voluntary contraction (MVC) three times per week for four weeks. Following training, the leg that had trained under blood flow restriction saw both greater increases in torque as well as an increase in the rate of torque development.

Prior to this, however, blood flow restriction caused by permanent ligation of the major veins of the limbs had been used to prevent gangrene following obliterative artery surgery in the 1920s and 1930s. In one of the first references to this type of procedure, Brooks and Martin examined the vascular response to venous ligation and noted that gangrene symptoms were relieved in the tissue to which venous drainage had been rerouted (Brooks and Martin 1923). This is attributed to the increased pressure in the venous system upon ligation, which causes the pressure in the capillary beds to increase as well, forcing blood through capillary beds that otherwise are under-utilized. One means by which capillarization occurs is through an increase in local blood flow (Hudlicka et al. 1992; Green et al. 1999), increasing shear stress and causing capillary formation until shear stress is normalized once again. As more capillaries grow, a greater blood supply can reach the damaged tissue, which promoted healing in some cases (Brooks et al. 1934).

Blood flow restriction as a stimulus has been researched at rest, during low-intensity walking, cycling, and resistance exercise. Most commonly, the restrictive stimulus is applied using pneumatic cuffs pressurized by an external air supply. In some cases this setup is as simple as a sphygmomanometer and air bulb, and others a specialized air cuff attached to a dedicated air supply

that can be set to certain pressures and inflated and deflated quickly. One method of restricting blood flow, recently termed practical blood flow restriction, uses elastic wraps to compress the proximal portions of the limbs (Loenneke and Pujol 2009). While this does not allow for any particular pressure to be set easily underneath the wraps, it is a far more inexpensive approach to this type of stimulus and therefore may be of benefit in certain settings in which the specialized equipment is either not available or feasible in the setting (Yamanaka et al. 2012; Luebbers et al. 2014).

In setting the restriction pressure, we have promoted setting the pressure in the cuff relative to both the cuff being used to apply the pressure as well as to the individual to which the cuff will be applied (Jessee et al. 2016b). There are several reasons for this recommendation. The pressure at which blood flow will be fully occluded in the limb, termed the arterial occlusion pressure, is dependent upon several factors. As the width of the pneumatic cuff increases, the pressure at which blood flow ceases decreases. This was noted many times in the human surgical literature (Van Roekel and Thurston 1985; Moore et al. 1987; Levy et al. 1993; Graham et al. 1993). Following extremity surgery in which blood supply to a limb was cut off for long periods of time (>3 hours), pneumatic tourniquets were often inflated to extremely high pressure (>400 mmHg). Following surgery, many patients would experience neuropathy caused by the compression of nerves by the pneumatic cuff. Several researchers set about to examine possible methods for occluding blood flow at the minimum pressure required, which would possibly alleviate these post-operative neuropathies.

Graham and colleagues examined the effects of wider tourniquets on the minimum pressure required to occlude blood flow into the limbs. They found that, as the cuff width increased, the pressure required to occlude blood flow decreased (Graham et al. 1993). Levy also performed a study examining this phenomenon and found that both the width of the cuff as well as the limb

circumference to which the cuff was applied affected the minimum pressure required to occlude blood flow: the wider the cuff, the lower the pressure, the larger the limb, the higher the pressure (Levy et al. 1993). The findings of these two researchers confirm results found by several others (Van Roekel and Thurston 1985; Moore et al. 1987).

Specific to the blood flow restriction literature, several studies have been performed looking at the relationship between cuff width, blood pressure, and limb circumference. In 2015, Loenneke and colleagues carried out a study examining the effects that blood pressure and limb circumference had on determining the minimum pressure required to occlude blood flow into the arms and the legs. Using a 5cm wide cuff, they found that limb circumference, systolic blood pressure, and diastolic blood pressure explained 60.7% of the variance in arterial occlusion pressure in the arms in 171 individuals (Loenneke et al. 2015). A follow-up investigation performed by Jessee et al. in 249 individuals confirmed those results seen by Loenneke et al., finding that arm circumference, systolic blood pressure, diastolic blood pressure, and arm length explained 61.1% of the variance in arterial occlusion pressure using a 5cm wide cuff (Jessee et al. 2016a).

Many studies performed using blood flow restriction use arbitrary pressures such as 100 mmHg or 160 mmHg applied to each individual in the study. As demonstrated above, this is problematic because some participants will be at or above arterial occlusion at certain arbitrary pressures while others may still have partial blood flow. This is even more problematic when considering that the width of the cuff being used to apply the restrictive stimulus sometimes goes unreported. If an arbitrary pressure of 160 mmHg is applied using a 5cm wide cuff, it applies a vastly different stimulus than a 12cm wide cuff at the same pressure for reasons stated above. For these reasons we have recommended the use of relative pressures, or a percentage of the resting arterial occlusion pressure required for each person, measured using the cuff that will be applying the

restriction (Jessee et al. 2016b).

Along similar lines, the material that the cuff is made from has an impact on both the arterial occlusion pressure and the perception of the stimulus. In a study performed in 2012, Rossow and colleagues noted that two cuffs of differing width (5cm and 13.5cm) and differing material (elastic, inelastic nylon) evoked different responses with regard to perceived exertion and discomfort before, during, and following exercise. In 27 healthy individuals, they noted a greater perceived exertion and discomfort during and immediately following exercise in the group using the inelastic wide cuff versus the elastic narrow cuff (Rossow et al. 2012). It is probable that these values are inflated for the wide cuff, as both cuffs were applying 130% of the brachial systolic blood pressure to the legs, and therefore the overall stimulus was greater in the wide cuff. When examining cuffs of similar widths but made of different materials, it has been shown that relative pressures appear to elicit similar fatigue responses regardless of cuff material (Loenneke et al. 2014).

One study performed by Buckner et al. examined the muscular and perceptual response to blood flow restriction combined with low-load resistance exercise in the arms using two similarly-sized cuffs (3.3cm, 5cm) of different material (elastic, inelastic nylon). They found that arterial occlusion pressure was greater in the elastic cuff than in the inelastic cuff, that ratings of perceived exertion was similar between cuffs during exercise, but that ratings of discomfort were higher in the elastic cuff than in the inelastic cuff (Buckner et al. 2016). These findings in opposition to the Rossow study are explained by the similarity in cuff width and the greater pressure required by the elastic cuff to elicit arterial occlusion. Set relative to the occlusion pressure, the elastic cuff was applying a greater pressure to the limb during blood flow restriction.

Surprisingly, very little research has been conducted examining the blood flow response to blood flow restriction. In one of the first studies examining this response in the upper body, Yasuda

and colleagues used pulsed-wave ultrasound to measure blood flow in the arms before the application of 3.3cm elastic cuffs, after the cuffs had been inflated to 100 mmHg and 160 mmHg. In both cases, blood flow decreased below resting values, and then was increased near (but not above) resting values following low-load resistance exercise. There was an increase above resting values one minute following deflation of the cuff, suggesting a hyperemic response to this stimulus. This study noted a greater hyperemic response following cuff deflation in the higher pressure condition (Yasuda et al. 2010a).

Prior to this, blood flow has been measured in the legs on two occasions by Iida's research group in both 2005 and 2007. In both studies, pressures up to 300 mmHg in increments of 50 mmHg were applied to the legs using 6.6 cm wide elastic cuffs. In both studies, the decrease in blood flow appears to follow a linear decline with increasing pressure (Iida et al. 2005, 2007). Similarly, recent work performed by Hunt and colleagues in the arms noted a very linear decrease in brachial artery blood flow with pressure increments of 10 mmHg (Hunt et al. 2016). These studies miss the mark on blood flow decreases with pressure for exactly the same reasons that arbitrary pressures do not provide the same stimulus to each individual. Recent work from our research group has shown that blood flow decreases non-linearly when applying relative pressures. This occurs in the arms while supine (under review) across three differently sized cuffs (5cm, 10cm, 12cm), as well as while seated (Mouser et al. 2017a). At relative pressures between 40% and 90% of the arterial occlusion pressure, total blood flow, while considerably reduced from resting values, remains relatively stable. Were these relative values to be converted to arbitrary values, the decrease would appear more linear, as those who occlude earlier than others, or those who are very close to occlusion pull the average blood flow down, and only the largest individuals will have blood flow at the highest pressures.

When blood flow restriction is applied to the legs rhythmically in which the cuffs are inflated and deflated repeatedly, several notable changes have occurred. In the legs at rest, it has been shown that the muscles distal to the cuffs swell at the same time that whole blood plasma volume decreases. In a 2012 study, Loenneke and colleagues subjected participants to five cycles of inflation/deflation lasting 5 minutes/3 minutes, respectively. Muscle thickness of the quadriceps muscles was measured via B-mode ultrasound and plasma volume was measured via finger stick. That study found that the quadriceps muscles distal to the cuffs swelled from as little as 6% (vastus lateralis) to as much as 22% (rectus femoris). This was accompanied by a decrease in plasma volume of 15% (Loenneke et al. 2012c).

During rest, this stimulus of inflating and deflating the cuffs in the legs has also shown to decrease pulse wave velocity in the femoral and popliteal arteries. Published by Heffernan et al., in 2007, they found that repeatedly inflating a cuff around the thigh to pressures >200 mmHg and then deflating them, in cycles lasting four seconds of inflation and two seconds of deflation, caused a decrease in the pulse wave velocity of blood flow through those arteries (Heffernan et al. 2007). This protocol was chosen as it was deemed similar enough to rhythmic muscular contractions, which have been shown to increase pressures in the muscle and, therefore, on the vasculature, to a similar degree, and that muscular contractions themselves have caused a similar decrease in pulse wave velocity, likely due to the increased blood flow creating a dilatatory response in the affected arteries (Tschakovsky 2004). No published studies have examined blood flow restriction alone in the upper body beyond examining occlusion pressure (Loenneke et al. 2015; Buckner et al. 2016; Jessee et al. 2016a).

Blood flow restriction has also been applied during low-intensity exercise. In 2006, Abe and colleagues published a study in which 18 healthy males performed either slow walking on a treadmill

(50 meters/minute) for five two-minute bouts, with one-minute rests between bouts, twice per day, six days per week, for three weeks, either with or without blood flow restriction. The group that performed the walking training with blood flow restriction observed increases in both leg muscle volume (4%-7%) and maximum strength (8%-10%), whereas the control group that walked without blood flow restriction saw no changes (Abe et al. 2006).

Further the application of blood flow restriction to lower body exercise, Abe, et al. again examined the response to low-intensity exercise combined with blood flow restriction, this time in cycling in 2010. In that study, 19 males were recruited and performed three-times weekly for eight weeks cycle training. Those who received blood flow restriction cycled for 15 minutes at 40% of their VO_2 peak, while those in the control group cycled for 45 minutes at 40% of their VO_2 peak without blood flow restriction. Again, muscle mass and strength increased in the group that performed with blood flow restriction, while no muscular changes were seen in the group that cycled without blood flow restriction (Abe et al. 2010).

More research has been published looking at blood flow restriction combined with low-load resistance exercise. From the very first studies examining blood flow restriction and resistance exercise, the lower body has been studied to a greater degree than the upper body. Beginning with Shinohara's seminal paper in 1998, many research studies have examined the knee extensor muscles, likely because these are the largest, most easily examined muscles in the literature and are prone to displaying large changes with resistance exercise.

As of 2017, it has only been within the last ten or so years that blood flow restriction and resistance exercise in the upper body has become a more widely used model to examine the muscular response to this type of stimulus, although early studies were still prone to using arbitrary pressures applied to each individual without regard for cuff width or limb circumference. One such

study examined the blood flow response to two different, albeit arbitrary, levels of blood flow restriction. In 2010, Yasuda and colleagues examined at blood flow in the brachial artery under the effects of 100 mmHg and 160 mmHg before and immediately following exercise. They noted that blood flow was depressed well below resting values, and did not reach resting values immediately following exercise, although one minute following deflation of the cuff blood flow was increased above resting levels (Yasuda et al. 2010a). This study has two notable findings. First, it shows that blood flow remained below resting levels even following exercise. Second, resting blood flow values in these participants is much higher than any other arm blood flow seen in the literature. Mean values for resting brachial blood flow are near $200 \text{ ml}\cdot\text{min}^{-1}$. This is in stark contrast to several other studies that have seen values anywhere between $40 \text{ ml}\cdot\text{min}^{-1}$ and $100 \text{ ml}\cdot\text{min}^{-1}$ (Newcomer et al. 2008; Ade et al. 2012; Mouser et al. 2017a). In unpublished work from our research group, we found that even under 80% of arterial occlusion pressure, blood flow was increased well above baseline values following exercise. This could signify that the pressures used in the Yasuda study were above arterial occlusion to begin with; however, 100 mmHg has shown to be rarely enough to fully occlude blood flow using the size of cuff which they did. Further, the initial pressure, the amount of pressure that the cuff places on the limb before inflation in certain blood flow restriction apparatuses, was not reported.

More recent work examining blood flow in the limbs has focused on two areas: vascular adaptation to blood flow restriction with resistance exercise and determining pressures as which a certain amount of blood flow will be present. Two studies have examined the chronic response in endothelial function with blood flow restriction. One study performed by Hunt and colleagues in 2012 examined the response to handgrip training undertaken three times weekly for four weeks using 80 mmHg of pressure and 40% of the handgrip 1RM. They determined that flow-mediated dilation, a measure of endothelial function in response to >5 minutes of complete occlusion, did not

change following training (Hunt et al. 2012). Brachial artery diameter did increase following training however, so some vascular adaptations do occur following blood flow restriction with low-load resistance exercise.

A similar study was performed by Credeur et al. in 2010 in which individuals performed handgrip training for four weeks, three times weekly, using 60% of their maximal voluntary contraction while 80 mmHg was applied using a pneumatic cuff. That study found that brachial artery diameter did not change, but brachial artery flow-mediated dilation decreased significantly in the arm receiving blood flow restriction, whereas it increased among participants in the control arm (Credeur et al. 2010). The reason for these discrepant findings are illusive. It is possible that the difference in contraction type (dynamic handgrip exercise performed in the Hunt study, isometric handgrip exercise performed in the Credeur study) can explain these differences. It is also possible that the differences in loads used (40% of 1RM in the Hunt study, 60% of MVC in the Credeur study) contributed to these opposite findings. Similarly, and contrary to typical upper-body models of blood flow restriction, the pneumatic cuffs were placed immediately above the elbow instead of at the most proximal portion of the upper arm. Since measures of flow-mediated dilation are taking toward the middle of the upper arm in the brachial artery, the measured sections were above where the cuff is located. This would be different if the cuff were placed at the proximal portion of the upper arm, as then the brachial artery measurement area would fall distal to the cuff placement. Whether this is important also requires further research.

Another study performed by Hunt and colleagues examined the predictors of a relative decrease in blood flow of 60%. The authors chose this number because previous research observed that pressures which elicited a muscular response tended to decrease blood flow by about 60% from resting levels after application of the cuff. To this end, they measured blood flow during incremental

inflation of a pressure cuff placed over the upper arm. Starting at 60 mmHg and ending at 150 mmHg, in increments of 10 mmHg, blood flow was measured and recorded. Linear regression models were constructed to predict a decrease of 60% in arterial blood flow. They determined that limb circumference is a poor predictor of partial occlusion, even though it plays a much larger role in determining full arterial occlusion. Results of their regression model including limb circumference, systolic blood pressure, diastolic blood pressure, and limb tissue composition explain only 20.6% of the variance in reduction of resting blood flow by 60% (Hunt et al. 2016).

In light of recent findings by our research group, this low level of explained variance is unsurprising. Across relative levels of blood flow ranging from 50% to 90% of arterial occlusion pressure, blood flow is reduced by anywhere from 50% to 60% from resting values (Mouser et al. 2017a). When attempting to predict a relative change, absolute pressures should not be used for reasons mentioned previously.

Several studies in the lower body have examined vascular responses to low-load resistance exercise combined with blood flow restriction; they will be briefly summarized hereafter. A study performed by Fahs et al. measured the change in vascular conductance (a proxy measure of capillarization), and arterial and venous compliance in the calf following six weeks of knee extensor training and found that vascular conductance did not change, arterial compliance decreased, and venous compliance did not change in the limb subjected to blood flow restriction (Fahs et al. 2014). This was a follow-up study performed in which calf vascular conductance did not change acutely in the 45 minutes following the same type of low-load resistance exercise with blood flow restriction (Fahs et al. 2011). Hunt et al. performed a study examining the time-course of vascular adaptation during six weeks of plantar flexion exercise combined with blood flow restriction and found increases in flow-mediated dilation, calf vascular conductance, and popliteal artery diameter (Hunt et

al. 2013). Differences between this study and those performed by Fahs and colleagues are best explained by the specificity of the exercise: knee extension does not directly work the calf muscles whereas plantar flexion does.

Safety

Blood flow restriction induces cardiovascular responses that have yet to be seen with high-load resistance exercise, and so the safety of blood flow restriction is probably dependent upon the exact population in which it is performed. Acutely, blood flow restriction increases heart rate due to a decrease in venous return (Iida et al. 2005). Lower-body blood flow restriction combined with low-load resistance exercise causes an increase in blood pressure above that seen with lower-body high-load exercise (Downs et al. 2014), and so care should be taken if applying this method of training to individuals with compromised cardiac function, although this same blood pressure response is not seen when exercising using blood flow restriction and low loads in the upper body (Brandner et al. 2015). In healthy participants, it does not appear that blood flow restriction increases the likelihood of clot formation, as several levels of the clotting cascade have been examined and found to be unaltered by this stimulus in healthy participants (Madarame et al. 2010; Clark et al. 2011).

Unaccustomed exercise and exercise involving active lengthening of the muscle (eccentric muscle actions) are known to cause muscle damage (Proske and Morgan 2001). This results in prolonged decrements in torque production (Clarkson and Hubal 2002), soreness, as well as prolonged increases in swelling and decreased range of motion (Shellock et al. 1991). It has never been shown reliably that blood flow restriction elicits these same markers of muscle damage (Loenneke et al. 2013; Thiebaud et al. 2014; Sudo et al. 2015).

Mechanisms

There are several mechanisms by which blood flow restriction is thought to exert its effects

on muscles located distal to the cuff. The mechanistic target of rapamycin (mTOR), specifically Complex 1 (mTORC1), upregulates muscle protein synthesis and is implicated in muscle hypertrophy related to mechanical loading in both animals (Bodine et al. 2001) and humans (Gundermann et al. 2014). One target of mTORC1, S6K, is phosphorylated when mTORC1 is activated. When mTORC1 is blocked with rapamycin as in the two previous studies, overload-induced hypertrophy does not occur and muscle protein synthetic rates do not increase to the level seen in controls not given rapamycin. mTOR is upregulated following resistance exercise combined with blood flow restriction (Fry et al. 2010). Similarly, S6K phosphorylation is increased following low-load resistance exercise with blood flow restriction (Fujita et al. 2007). Muscle fractional breakdown rate appears similar following low-load resistance exercise combined with blood flow restriction as in high-load resistance exercise conditions (Gundermann et al. 2014).

Myostatin is a negative regulator of muscle mass; an increase in myostatin will decrease the amount of muscle mass present, and knocking out myostatin or blocking its effects causes an increase in the rate of protein synthesis (Lee 2004). During low-load resistance exercise combined with blood flow restriction, myostatin gene expression is decreased in the hours following exercise (Drummond et al. 2008; Laurentino et al. 2012).

It has been hypothesized that a buildup of metabolites distal to the cuff during blood flow restricted exercise is also partially responsible for the increases in muscle mass seen with this type of exercise. Metabolite activation of Type III and Type IV afferent neurons could produce increased muscle activation above what is typically seen at low intensities (Yasuda et al. 2010b; Loenneke et al. 2011).

The acute swelling response to this type of exercise modality has also been implicated in its hypertrophic stimulus. Acutely, blood flow restriction causes a muscle to swell (Loenneke et al.

2012c). When combined with exercise and a buildup of metabolites, the osmotic gradient created across the muscle cell wall would, in theory, draw that fluid into the muscle cell. It has been hypothesized (Loenneke et al. 2012b) based off of work performed with hepatocytes (Haussinger et al. 1993) that the cells possess a volume sensor that triggers anabolic pathways when cell volume increases. It has been shown that rat muscle, when caused to swell due to an osmotic gradient, downregulates protein catabolism with little change in protein synthesis (Fang et al. 1998), indicating a possible difference in protein metabolism between the two tissues.

Because it is a relatively unexplored area of the field, no studies have examined the mechanisms by which blood flow restriction with low-load resistance exercise may or may not alter vascular structure and function.

Perceptions of Exercise

An individual's perceptual response to exercise can be measured in many ways. Commonly, how much effort they think they are expending during exercise as well as how discomforting the exercise are have been reported as a measure of an exercise's tolerability. It is thought that the lower these ratings, the more likely an individual would be to continue performing that type of exercise.

In the blood flow restriction literature, many research studies have examined the perceptual response to low-load resistance exercise. Some of these studies were designed to answer questions about perceptual responses to cuffs of different materials, such as the Rossow study mentioned previously (Rossow et al. 2012). Another study examining cuffs of different materials, this time in the upper body, compared elastic and inelastic cuffs of similar widths and found that the elastic cuffs elicited a greater discomfort response following each exercise set compared to the inelastic cuffs (Buckner et al. 2016). This could be due in part to the higher pressure applied using the elastic cuffs, as even though the same relative pressures were used, the elastic cuff required a higher pressure to

bring about full arterial occlusion. This is seen in a study performed by Counts and colleagues in which participants trained the elbow flexors using low-load resistance exercise with blood flow restriction of either 40% or 90% of arterial occlusion pressure. Participants consistently rated the higher pressure as more uncomfortable following the second set of exercise (Counts et al. 2016).

When examining very low-load resistance exercise, unpublished work from our research group has shown that discomfort and ratings of perceived exertion increase as load increases and as pressure increases (Jessee et al. 2017a). It is possible that higher pressures that are closer to the arterial occlusion pressure decrease blood flow to such a degree that localized ischemia occurs, which creates a greater degree of discomfort. Similarly, due to the slowed nature of blood transit through the limb during blood flow restriction, a buildup of metabolic byproducts distal to the cuff could also trigger a discomfort response. As noted in the Counts study, the discomfort response is relatively consistent across time, suggesting that it does not diminish with increased exposure. Conversely, two recent studies examining the change in perceptual response to blood flow restriction and resistance exercise showed that the response decreases rapidly across a training program to the point that it is not different from the perceptions of high-load resistance exercise (Kim et al. 2017; Martín-Hernández et al. 2017). With equivocal results, further research is required to examine this.

III: METHODS

Two experiments were performed examining the acute and chronic vascular and perceptual effects of resistance exercise of differing loads with and without blood flow restriction. This chapter describes the methods that were performed during each experiment.

Experiment 1 – Acute Blood Flow Response to Exercise

97 participants (41 females, 38 males) were recruited for this study and visited the laboratory one time. During this visit they were informed of the purpose of the study. Their standing height and body mass were measured and their BMI calculated. If their BMI was greater than 30 and they possessed one or more risk factors for thromboembolism, they were excluded from the study. Following informed consent procedures, they were randomized into one of four total conditions in this study. Their concentric one-repetition maximum was determined for the biceps curl. Following 10 minutes of seated rest, ultrasound measures of blood flow were taken during standing rest from the brachial artery. Immediately following blood flow measurement, resting standing blood pressure was measured in the contralateral arm. Participants then performed four sets of biceps curls according to their group assignment. During the rest period between the second and third set, ultrasound measurements of blood flow were again performed in the exercising arm. Following the fourth and final set, ultrasound measurements of blood flow as well as blood pressure were performed. Participants then left the laboratory.

Experiment 2 – Chronic Vascular Adaptations to Exercise

46 participants (22 females, 24 males) were recruited for this study and visited the laboratory

22 times over the course of 10 weeks. During their first visit they had standing measures of height and body mass taken. If they had a BMI greater than 30 kg/m² and possessed one or more risk factors for thromboembolism they were excluded from the study. Following informed consent procedures, they had each arm randomized into one of four possible training conditions.

Immediately after randomization, they rested supine for 10 minutes. Resting supine blood pressure was measured. Measures of arterial vascular conductance were taken from each forearm. Following a further 10 minutes of supine rest, venous compliance of both arms was measured. During their second visit to the laboratory, at least 24 hours later, their concentric one-repetition maximum in the biceps curl was determined in each arm. During visits four through nineteen (twice weekly), they visited the laboratory for exercise training of each arm according to group assignment, progressing from 1 set on the first day of exercise to 4 sets on the fifth day of exercise. On visits 20 and 21 the same measurements as during the first three visits were again performed. Following the final visit, participants were done with the study.

Inclusion Criteria

1. 18 – 35 years old
2. Recreationally active but not performing resistance training (resistance training two or more times per week) within the last six months
3. Free from orthopedic injury that will prevent or hinder resistance exercise
4. Free from traditional risks of thromboembolism
5. Not taking medication to prevent or treat hypertension
6. Free from symptomatic diseases as determined from a health history questionnaire

Exclusion Criteria

1. Outside of the ages of 18 – 35 years old

2. Currently or within the previous six months performing regular resistance exercise (two or more times per week)
3. Obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) or having one or more risk factors for thromboembolism
 - a. Diagnosed Crohn's or inflammatory bowel disease
 - b. Past fracture of the hip, pelvis, or femur
 - c. Major surgery within the last six months
 - d. Varicose veins
 - e. Personal or family history of deep vein thrombosis or pulmonary embolism
4. Taking medications to prevent or treat hypertension

Body Height and Body Mass

Participants were instructed to remove their shoes, hats, watches, and anything in their pockets. They were instructed to stand on a digital floor scale while staring straight ahead. Their body mass was recorded. They were then instructed to stand on the wall stadiometer platform facing away from the wall. They were instructed to stand as tall as possible and to take a deep breath and hold it while their body height was measured in centimeters and recorded.

Condition and Randomization

Participants had either one (Experiment 1) or both (Experiment 2) arms randomized into one of four possible exercise conditions: 1) High-load resistance exercise (70% of 1RM); 2) Very low load resistance exercise (15% of 1RM); 3) Very low load resistance exercise (15% of 1RM) combined with blood flow restriction at 40% of arterial occlusion pressure; 4) Very low load resistance exercise (15% of 1RM) combined with blood flow restriction at 80% of arterial occlusion pressure.

Randomization was performed using a computer-generated random sequence followed by group counterbalancing so that an equal number of participants were included in each group.

One-Repetition Maximum Determination

Participants stood with their back and heels against a wall. They were given a light weight to use during a warmup set comprising no more than 10 repetitions. They were then handed a weight that was an estimated 50% of their 1RM and performed 3 repetitions with that weight. The weight was then increased to near the estimate of their 1RM, and they performed the concentric portion of the lift. If they were successful the weight was taken from them at the top of the lift. They rested for 90 seconds, more weight was added to the dumbbell and they attempted another concentric-only lift. This was repeated until they were no longer able to perform the lift through a full range of motion with good form. After, the weight was lowered and they performed another attempt. The weight was lowered until they were able to lift it through the full range of motion with good form. The maximum weight they could lift through the full range of motion with good form was recorded as their 1RM. Following five minutes of rest (Experiment 2), the 1RM of their contralateral arm was determined in the same manner.

Arterial Occlusion Pressure Determination

A 5 cm wide nylon pneumatic cuff was placed at the proximal-most portion of the participant's arm and attached to a rapid cuff inflator. A Doppler probe was placed over the radial artery of that arm near the participant's wrist and maneuvered until a pulse could be heard. The cuff was inflated to 50 mmHg and the pressure slowly increased until a pulse was no longer detectable. The minimum pressure required to cause a complete cessation of an audible pulse was recorded as the arterial occlusion pressure.

Blood Pressure Measurement

Following a rest period, participants had blood pressure measured in the arm not performing exercise. An appropriately sized cuff was placed over their upper arm. An automated blood pressure

device measured their blood pressure two times with one minute between measurements. If the measurements were not within 5 mmHg of each other, another measurement was taken following a further one minute of rest. The two closest measurements were averaged and recorded as their resting blood pressure. Following exercise, blood pressure was again measured in the arm not performing exercise using the same equipment one time and recorded as their post-exercise blood pressure.

Exercise Protocols

Participants assigned to the high load resistance exercise group performed four sets of biceps curls at 70% of their 1RM. Each set comprised repetitions to volitional fatigue performed at a cadence of 1 second for the concentric portion of the lift and 1 second for the eccentric portion of the lift. They rested for 90 seconds between sets. Participants assigned to one of the three very low load resistance exercise groups performed four sets of biceps curls at 15% of their 1RM. Each set comprised 90 goal repetitions performed at a cadence of 1 second for the concentric portion of the lift and 1 second for the eccentric portion of the lift. They rested for 30 seconds between sets. If they were assigned to the group that utilized blood flow restriction at 40% of the arterial occlusion pressure, a 5 cm nylon pneumatic cuff was placed at the proximal-most portion of their arm and inflated to 40% of their arterial occlusion pressure.

Similarly, participants assigned to the group that utilized 80% of the arterial occlusion pressure had the same cuff applied in the same location and inflated to 80% of their arterial occlusion pressure. For both groups utilizing blood flow restriction, the pressure was applied before the first set of exercise and the cuff remained inflated until the end of the fourth set of exercise. The weight used during exercise and the number of repetitions performed were recorded for each set of exercise.

Arterial Conductance Measurement

Participants lay supine for 10 minutes on an exam table in a quiet room. One arm was abducted at between 80° and 90° from their body and supported on an arm rest as well as foam blocks. The widest area of their forearm was measured using an inelastic tape measure. A mercury-filled strain gauge was placed around the forearm at this location and held in place with athletic tape. A 5 cm nylon pneumatic cuff was placed over their wrist immediately proximal to their hand and attached to a hand pump. At the same time, a 10 cm nylon pneumatic cuff was placed over their upper arm immediately proximal to their elbow and attached to a rapid cuff inflator. The strain gauge was attached to a Hokanson EC5 which is itself attached to a laptop computer. Before the measurement was taken, the 5 cm cuff at their wrist was inflated to 220 mmHg for 1 minute and remained inflated throughout the measurement protocol. To begin the measurement, the 10 cm cuff was inflated to 50 mmHg for 10 seconds and then deflated for 8 seconds. This repeated up to 8 times until five clear measurements of strain gauge lengthening were complete. The average of the five measurements was recorded and then set relative to the mean arterial pressure.

Venous Volume Variation Measurement

Following measurement of arterial conductance, a further 10 minutes of supine rest occurred, after which venous volume variation measurements were performed. The 5 cm wide cuff was removed from the participant's wrist while the 10 cm wide cuff remained above the elbow. The cuff was inflated to 20 mmHg for 1 minute, followed by inflations of 20 mmHg, 40 mmHg, 60 mmHg, and 80 mmHg for 1, 2, 3, and 4 minutes, respectively. The cuff was deflated for 1 minute between inflation pressures to allow for return to resting flow and prevent edema. Maximum venous outflow and venous volume variation for each pressure were recorded. The maximum volume change of the arm at each inflation pressure determined by the strain gauge was plotted across cuff

pressures, and the slope of the pressure-volume curve was recorded as venous compliance.

Ultrasound Blood Flow Measurement

Participants stood with knees slightly bent facing the investigator. Their arm was supported away from their body at between 30° and 60°, and they were instructed to completely relax their arm and shoulder. Transmission gel was placed on a linear-array ultrasound probe. The probe was positioned over the brachial artery 2-5 cm proximal to the cubital fossa. B-mode ultrasound was adjusted until an image of the brachial artery was clear. Pulse-wave ultrasound was used to measure blood velocity in the brachial artery. The probe was adjusted so that the gate of the ultrasound probe fully insonated the brachial artery at an angle of 60° or less. The gate was adjusted until it encompassed the entire lumen of the brachial artery. At least five consecutive cardiac cycles were recorded at rest. Manufacturer-provided software was used to measure brachial artery diameter and average volumetric blood flow. Ultrasound measurements were performed before exercise, during the rest period following the second set of exercise, and one minute following the conclusion of the fourth set of exercise.

Perceptual Responses

Participants were instructed in how to rate their effort as well as their discomfort using the Rating of Perceived Exertion (RPE) scale as well as the Borg Discomfort 10+ scale. On the RPE scale, participants were informed that 6, the lowest number on the scale, corresponded to them being at rest and not expending any effort at all, while 20 corresponded to maximal effort on their part. They were also instructed that the discomfort scale ranges from 0, which is no discomfort at all, to 10, which is equivalent to the worst discomfort they have ever felt in their life. They were also informed that they could exceed 10 if the exercise-induced discomfort exceeded the worst discomfort they had felt to that point. RPE and Discomfort were taken and recorded before exercise

began. RPE was taken immediately following the end of each set of exercise. Discomfort was taken 10 seconds before the next set of exercise began. This applied to the rest periods following sets 1, 2, and 3. Immediately following set 4, RPE and discomfort were both taken and recorded.

Limitations

Several limitations exist in these studies. In Study 1, participants self-reported refraining from caffeine, food, and water prior to their visit, all of which can impact the cardiovascular and blood flow responses, but these were not monitored. Similarly, participants were asked to refrain from exercise in the 24 hours prior to their visit, but again, these were not monitored. One assumption of the study was that participants would honestly self-report their compliance with the study criteria. One limitation that is often raised in blood flow studies involving women is a lack of control over the menstrual cycle. Recent evidence has demonstrated that vascular reactivity in women is not different across the different phases of the menstrual cycle (Augustine et al. 2018), so we do not perceive this as a limitation. In Study 2, participants were asked not to perform any physical activity outside of the training program, but their compliance with this was not monitored. The amount of effort put into the training by the participants varied greatly. While not measurable empirically, it was noticeable when a participant was not giving maximum effort. The duration of each set of exercise, especially in the case of the very low load conditions, could have affected participant effort. However, 40 participants still completed the entire study.

Statistical Analyses

Mixed model ANOVAs with fixed factors of group and time was performed in order to determine possible differences in the acute blood flow and brachial artery diameter responses to exercise. If no interactions existed, main effects were examined. If an interaction existed, simple effects were examined as needed. Post-hoc comparisons were examined using Least Significant

Difference (LSD).

Forearm arterial conductance and forearm venous compliance were analyzed using mixed model ANOVAs with fixed factors of group and time and either compound symmetry or unstructured covariance types to determine possible differences in the cardiovascular adaptation response to exercise. Both compound symmetry and unstructured models were calculated. Akaike's Information Criteria (AIC) and Schwarz's Bayesian Criteria (BIC) values for both models were compared. The model in which both of those numbers was the smallest, signifying a better fit of the data, was used. This model allowed us to take into account that each participant was providing two conditions to the experiment, and these two conditions were not the same conditions that each participant received. If no interactions existed, main effects were examined. If an interaction existed, simple effects were examined. Post-hoc comparisons were performed (LSD).

Ratings of perceived exertion and discomfort following the first set on the first, ninth, and fifteenth days of training were examined using a mixed model ANOVA with fixed factors of time and condition. This allowed taking into account that each participant contributed two conditions to the experiment, and that these two conditions were not the same for each participant. Interactions and main effects were examined and pairwise comparisons performed (LSD). All statistical analyses were performed using SPSS v23.0. Significance was set at $\alpha = .05$.

IV: RESULTS

Two studies were performed. One study (Study 1) compared the acute hemodynamic responses to high load resistance exercise or very low load resistance exercise, with and without blood flow restriction. Another study (Study 2) examined the effects of either high load resistance exercise or very low load resistance, with and without blood flow restriction, on cardiovascular adaptations such as changes in arterial occlusion pressure, vascular conductance, forearm blood flow, mean venous output, venous capacitance, and venous volume variation. This study also examined possible changes in both perceived exertion and discomfort over time to these four exercise conditions.

Study 1

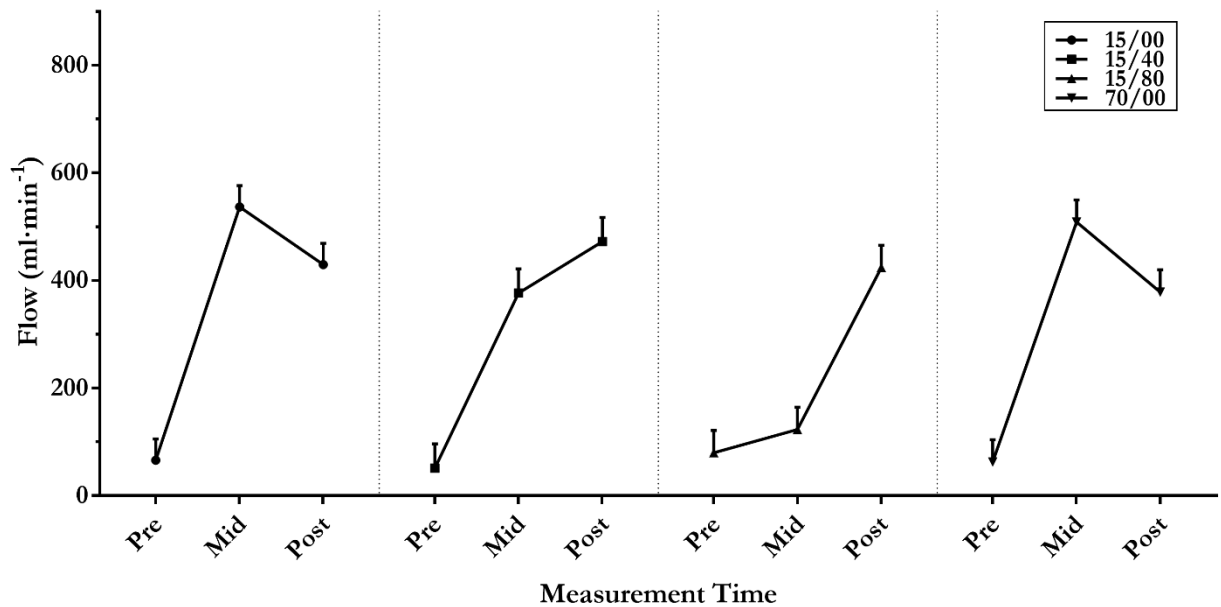
A total of 79 participants (men=38, women=41) completed the entirety of the study with successful measurements at all three time points (15/00: n = 22; 15/40: n = 17; 15/80: n = 20; 70/00: n = 20). There were 19 participants who agreed to participate in the study but either did not return to the laboratory for testing or measurements were unobtainable during their study visit. Participants were on average 22.1 (3.2) years old, with an average height of 1.72 (0.1) m, body mass of 71.2 (13.5) kg, and a BMI of 23.9 (2.8) kg/m². Average elbow flexion 1RM was 15.6 (7.3) kg. Resting systolic pressure averaged 120 (11) mmHg and resting diastolic pressure averaged 80 (8) mmHg. Resting heart rate averaged 81 (14) beats per minute. Values are reported as means (SD)

Blood Flow

Examining the blood flow response across time to the four exercise conditions, Levene's test

was statistically significant for two of the measurement time points (resting: $P = .001$; following set 2: $P < .0005$), indicating a violation of the assumption of homogeneity of variances. Therefore, a linear mixed model ANOVA with fixed factors of condition and time was employed to examine the blood flow response. A statistically significant condition by time interaction was found ($F(6,150) = 13.910$, $P < .0005$). Simple effects were investigated using pairwise comparisons. Across the four conditions within time points, blood flow at rest was not statistically significantly different (15/00: 66.0 (39.6) $\text{ml}\cdot\text{min}^{-1}$; 15/40: 51.4 (44.8) $\text{ml}\cdot\text{min}^{-1}$; 15/80: 79.9 (41.3); 70/00: 63.0 (41.3) $\text{ml}\cdot\text{min}^{-1}$). Following the second set of exercise, blood flow was statistically significantly lower in the 15/80 condition compared to the other conditions (15/00 mean difference: -413.4 (57.0) $\text{ml}\cdot\text{min}^{-1}$, $P < .0005$; 15/40 mean difference: -253.5 (60.9) $\text{ml}\cdot\text{min}^{-1}$, $P < .0005$; 70/00 mean difference: -385.2 (58.4) $\text{ml}\cdot\text{min}^{-1}$, $P < .0005$). Also following the second set of exercise, the 15/40 condition had statistically significantly lower blood flow than the 15/00 (mean difference: -159.9 (59.6) $\text{ml}\cdot\text{min}^{-1}$, $P = .008$) and 70/00 (mean difference: -131.7 (60.9) $\text{ml}\cdot\text{min}^{-1}$, $P = .032$) conditions. One minute following exercise, there were no statistically significant differences in blood flow between groups (15/00: 429.5 (39.4) $\text{ml}\cdot\text{min}^{-1}$; 15/40: 472.2 (44.8) $\text{ml}\cdot\text{min}^{-1}$; 15/80: 424.1 (41.3) $\text{ml}\cdot\text{min}^{-1}$; 70/00: 378.4 (41.3) $\text{ml}\cdot\text{min}^{-1}$) (Table 1, Figure 1).

Figure 1. Changes in brachial artery blood flow across exercise conditions



Brachial Artery Diameter

A repeated measures ANOVA (condition x time) was performed to investigate possible changes in brachial artery diameter during four sets of exercise in all four conditions. No assumptions of the test were violated (Levene's test: $P > .05$; Mauchly's $w = .991$, approximate $\chi^2 = 0.651$, $P = .722$). A statistically significant condition by time interaction was found ($P < .0005$) in the brachial artery response to these modes of exercise. Following pairwise comparisons, there were statistically significant differences were found.

Brachial artery diameter was statistically significantly different between the 15/00 and 15/80 conditions following the second set of exercise (mean difference: 0.06 (0.09) cm, $P = .014$). In the 15/00 and 15/40 conditions, brachial artery diameter increased from resting to the second set of exercise (15/00 mean difference: 0.049 (0.035) cm, $P < .0005$; 15/40 mean difference: 0.052 (0.028) cm, $P < .0005$), from rest to one minute following the final set of exercise (15/00 mean difference:

0.071 (0.035) cm, $P < .0005$; 15/40 mean difference: 0.082 (0.029) cm, $P < .0005$), and from the second set of exercise to one minute following the final set (15/00 mean difference: 0.022 (0.042) cm, $P = .004$; 15/40 mean difference: 0.030 (0.027) cm, $P = .001$).

In the 15/80 condition, there was no statistically significant change in brachial artery diameter from resting to after the second set of exercise (rest to mid mean difference: 0.002 (0.041) cm, $P = .853$), but brachial artery diameter was statistically significantly greater one minute following the final set of exercise than after the second set of exercise (mid to post mean difference: 0.047 (0.034) cm, $P < .0005$) as well as at rest (rest to post mean difference: 0.048 (0.040) cm, $P < .0005$).

In the 70/00 condition, brachial artery diameter at rest was statistically significantly smaller than following the second set of exercise (rest to mid mean difference: 0.037 (0.039) cm, $P < .0005$) as well as one minute following the final set of exercise (rest to post mean difference: 0.044 (0.042) cm, $P < .0005$). However, there was no statistically significant difference in brachial artery diameter in the 70/00 condition from the second set of exercise to one minute following the final set of exercise (mid to post mean difference: 0.007 (0.030) cm, $P = .364$) (Table 1, Figure 2).

Figure 2. Changes in brachial artery diameter across exercise conditions

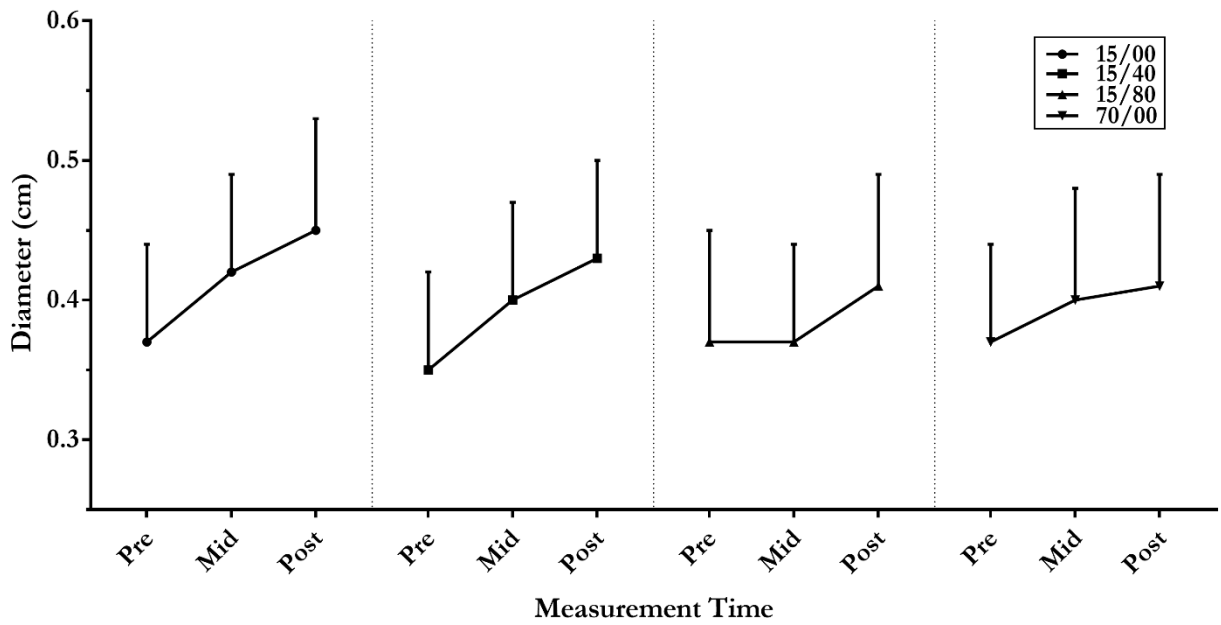


Table 1. Changes in BF and DIA after a bout of resistance exercise in the upper body

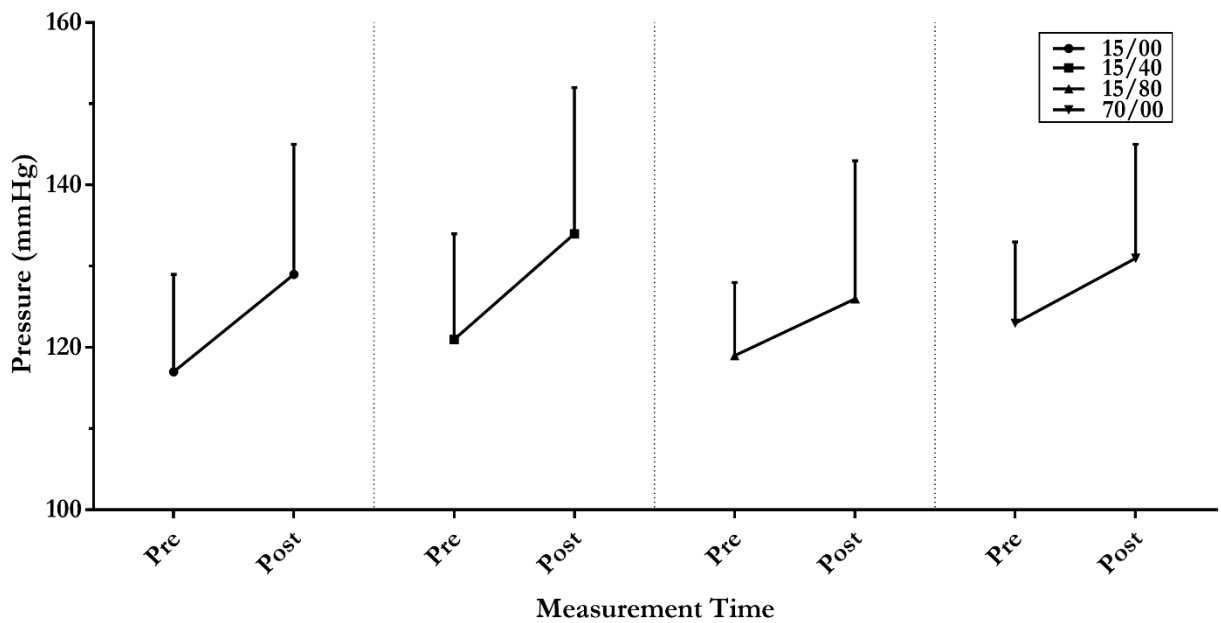
Condition	Pre	Mid	Post
BF^θ			
15/00	66.0 (39.4)	536.7 (39.4) ^{a*}	429.5 (39.4) ^{*ψ}
15/40	51.4 (44.8)	376.8 (44.8) ^{a*}	472.2 (44.8) [*]
15/80	79.9 (41.3)	123.3 (41.3) ^b	424.1 (41.3) ^{*ψ}
70/00	63.0 (41.3)	508.5 (41.3) ^{a*}	378.4 (41.3) ^{*ψ}
Diameter^θ			
15/00	0.37 (0.07)	0.42 (0.07) ^{ac*}	0.45 (0.08) ^{*ψ}
15/40	0.35 (0.07)	0.40 (0.07) ^{bc*}	0.43 (0.07) ^{*ψ}
15/80	0.37 (0.08)	0.37 (0.07) ^b	0.41 (0.08) ^{*ψ}
70/00	0.37 (0.07)	0.40 (0.08) ^{bc*}	0.41 (0.08) [*]

Values of BF are in $\text{ml} \cdot \text{min}^{-1}$ [estimated marginal means (SE)]. Values of Diameter are in cm [means (SD)]. BF: Blood flow; **15/00**: 15% one-repetition maximum (1RM), 0% arterial occlusion pressure (AOP); **15/40**: 15% 1RM, 40% AOP; **15/80**: 15% 1RM, 80% AOP; **70/00**: 70% 1RM, 0% AOP; *: Significantly different from pre ($P < .05$). ψ : Significantly different from mid ($P < .05$); θ : Interaction ($P < .05$). Values marked with different letters are significantly different within that time point ($P < .05$).

Systolic Blood Pressure

For measurements of systolic blood pressure, Levene's test showed that the assumption of homogeneity of variances was violated ($P = .041$), so a linear mixed-model ANOVA with fixed factors of time and condition was performed. Values are reported as means (SD). There was no statistically significant condition by time interaction ($F(3,150) = 0.326, P = .807$), no statistically significant main effect of condition ($F(3,150) = 1.457, P = .229$). At baseline there were no statistically significant differences between groups (15/00: 117 (3) mmHg; 15/40: 121 (13) mmHg; 15/80: 119 (9) mmHg; 70/00: 123 (10) mmHg), nor were their statistically significant differences between groups following exercise (15/00: 129 (16) mmHg; 15/40: 134 (18) mmHg; 15/80: 126 (17) mmHg; 70/00: 131 (14) mmHg). There was a statistically significant main effect of time ($F(1,150) = 21.917, P < .0005$). Overall systolic blood pressure statistically significantly increased from rest to immediately following the final set of exercise (mean change: 10 (11) mmHg, $P < .0005$) (Table 2, Figure 3).

Figure 3. Changes in systolic blood pressure across exercise conditions

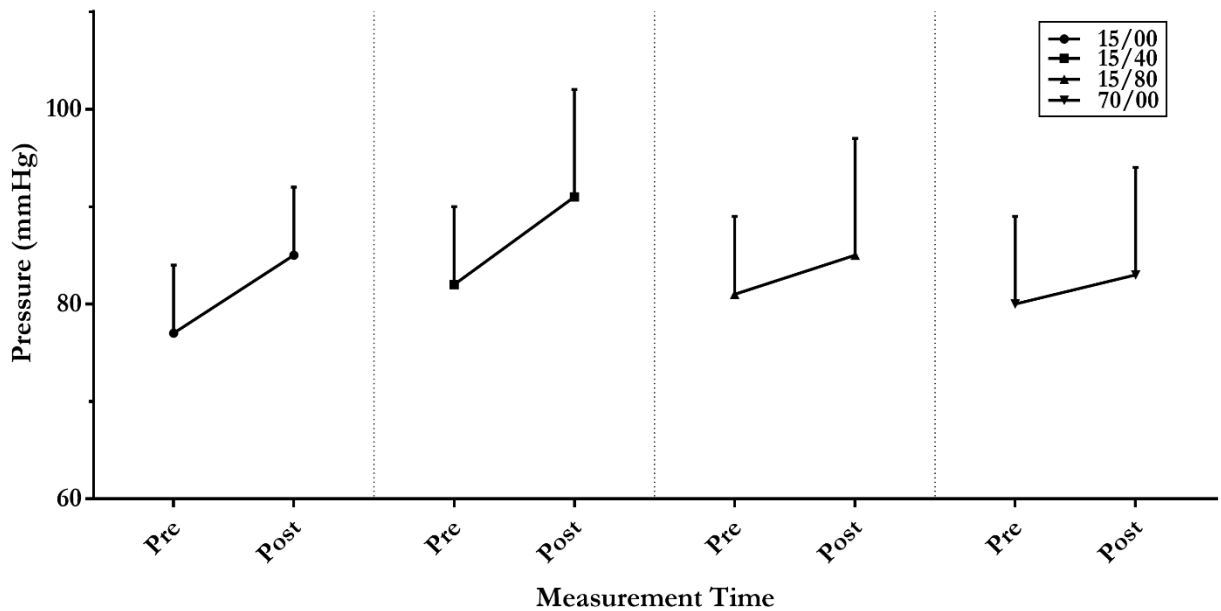


Diastolic Blood Pressure

Levene's test showed no violation of the assumption of homogeneity of variances for diastolic blood pressure ($P > .05$), so a repeated measures (condition x time) ANOVA was used to examine the diastolic blood pressure response from resting to immediately following the final set of exercise. Values reported as means (SD). There was a statistically significant condition by time interaction ($F(3,75) = 4.834, P = .004$). Pairwise comparisons revealed that there were no statistically significant differences between conditions at rest (15/00: 77 (7) mmHg; 15/40: 82 (8) mmHg; 15/80: 81 (8) mmHg; 70/00: 80 (9) mmHg, $P > .05$), but that immediately following exercise, 70/00 was statistically significantly lower than 15/40 (mean difference: -8 (15) mmHg). Within conditions and across time points, all three very low load conditions saw a statistically significant increase in diastolic pressure (15/00: 77 (7) mmHg vs. 85 (7) mmHg, $P < .0005$; 15/40: 82 (8) mmHg vs. 91 (11) mmHg, $P < .0005$; 15/80: 81 (8) mmHg vs. 85 (12) mmHg, $P = .03$), whereas the high load

condition did not see a statistically significant increase in diastolic blood pressure (80 (9) mmHg vs. 83 (11) mmHg, $P = .107$) (Table 2, Figure 4).

Figure 4. Changes in diastolic blood pressure across exercise conditions



Heart Rate

For the analysis of heart rate, Levene's test showed that the assumption of homogeneity of variances was not violated ($P > .05$), so a repeated measures (condition x time) ANOVA was performed to examine the heart rate response from resting to immediately following the final set of exercise. Values reported as means (SD). Results showed that there was no statistically significant condition by time interaction ($F(3,75) = 0.943$, $P = .424$), nor was there a statistically significant main effect of condition ($F(3,75) = 2.505$, $P = .065$). Heart rate was not statistically significantly different between conditions either before (15/00: 76 (14) bpm; 15/40: 81 (16) bpm; 15/80: 87 (10) bpm; 70/00: 79 (15) bpm) or immediately following (15/00: 88 (19) bpm; 15/40: 100 (22) bpm; 15/80: 102 (23) bpm; 70/00: 90 (20) bpm) resistance exercise. There was a statistically significant

main effect of time for heart rate ($F(1,75) = 58.718, P < .0005$). Overall heart rate statistically significantly increased from resting to immediately following exercise, regardless of condition (mean difference: 13 (15) bpm, $P < .0005$) (Table 2, Figure 5).

Figure 5. Changes in heart rate across exercise conditions

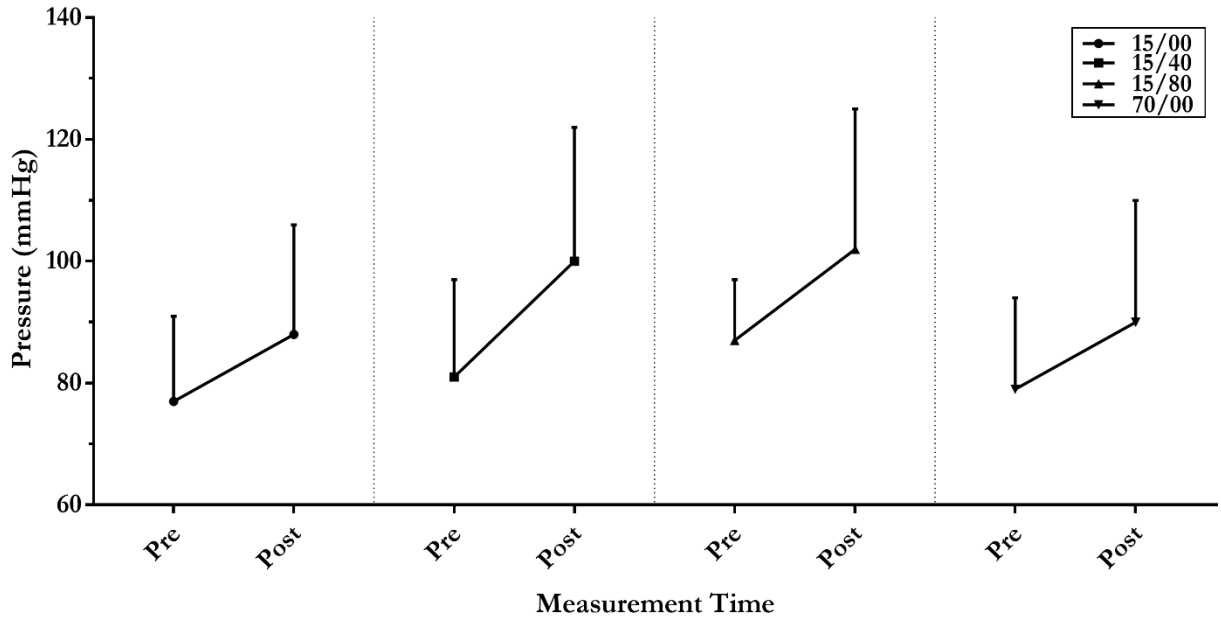


Table 2. Cardiovascular responses to an acute bout of resistance exercise

Condition	Pre	Post	Δ
SBP**			
15/00	117 (12)	129 (16)	12 (13)
15/40	121 (13)	134 (18)	13 (12)
15/80	119 (9)	126 (17)	8 (13)
70/00	123 (10)	131 (14)	8 (9)
DBP			
15/00	77 (7)	85 (7)*	8 (5) ^a
15/40	82 (8)	91 (11)*	9 (7) ^a
15/80	81 (8)	85 (12)*	3 (7) ^a
70/00	80 (9)	83 (11)	2 (7) ^b
HR**			
15/00	77 (14)	88 (18)	11 (11)
15/40	81 (16)	100 (22)	19 (14)
15/80	87 (10)	102 (23)	14 (22)
70/00	79 (15)	90 (20)	11 (14)

Values of SBP and DBP are in mmHg. Values of HR are in beats per minute. Means (SD). SBP: Brachial systolic blood pressure; DBP: Brachial diastolic blood pressure; **15/00**: 15% one-repetition maximum (1RM), 0% arterial occlusion pressure (AOP); **15/40**: 15% 1RM, 40% AOP; **15/80**: 15% 1RM, 80% AOP; **70/00**: 70% 1RM, 0% AOP; **Δ**: Pre to post exercise. *****: Significantly different from pre ($P < .05$); ******: Main effect of time ($P < .05$). **Δ**s marked with different letters represent significant differences in the exercise response ($P < .05$).

Study 2

A total of 40 participants (men = 20, women = 20) completed the study. Two participants (men = 1, women = 1) did not complete the training visits nor did they participate in post testing and their data were excluded from analyses. Post-testing data was not collected on one of the participants (men = 1) due to scheduling conflicts and their values were excluded from the analysis. As each participant performed two different conditions simultaneously, analyses were performed on the following group compositions: 15/00 = 19, 15/40 = 20, 15/80 = 19, 70/00 = 20. Of the 39 who completed every testing session of the study, they were on average 21.5 (2.4) years old, with a stature of 1.72 (0.09) m, with an average body mass of 68.4 (11.5) kg and BMI of 23.0 (2.9) kg/m². Average resting systolic blood pressure at the beginning of the study was 122 (11) mmHg, resting diastolic blood pressure was 69 (10) mmHg, and mean arterial pressure was 87 (9) mmHg. Unless

otherwise noted, values are estimated marginal means (SE).

Forearm Blood Flow

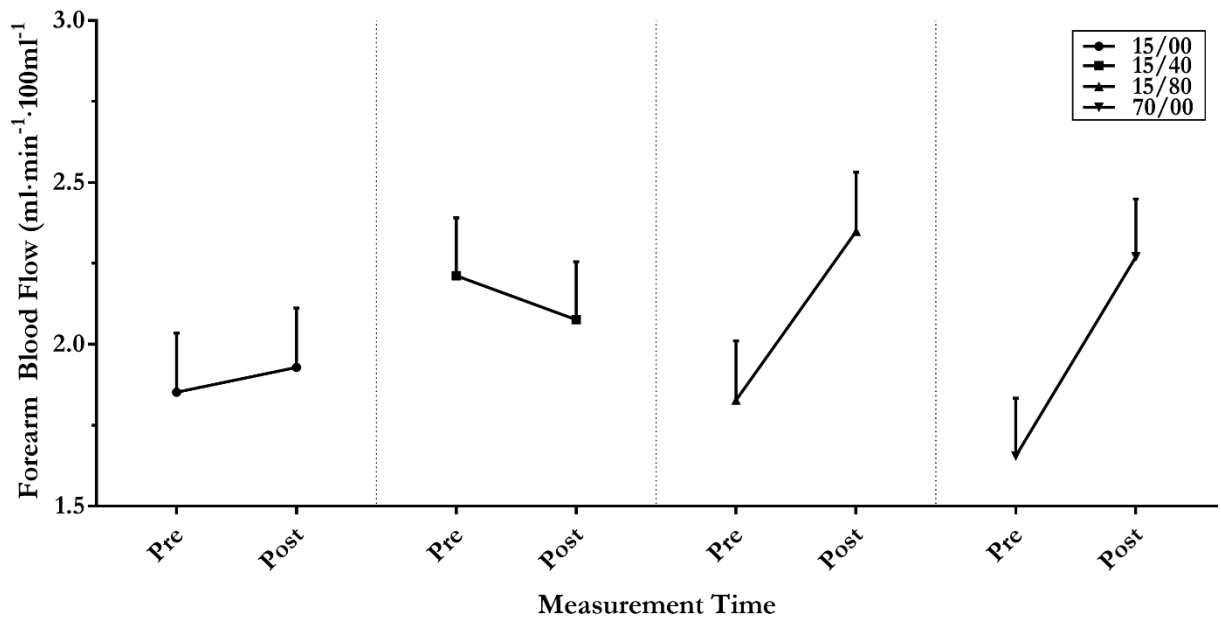
A linear mixed model ANOVA with repeated measures and fixed factors of condition and time using a compound symmetry covariance structure was employed to assess possible forearm blood flow adaptations. This test revealed a statistically significant condition by time interaction ($F(3,110.175) = 2.812, P = .043$). Investigating this interaction showed that the training response in the 15/40 condition was statistically significantly lower than the training response in both the 15/80 (mean difference: $-0.657 (0.303) \text{ ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}, P = .033$) and 70/00 (mean difference: $-0.752 (0.300) \text{ ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}, P = .014$) conditions (Table 3). Within conditions between time points, there were statistically significant increases in forearm blood flow for both the 15/80 (pre to post mean difference: $0.520 (0.218) \text{ ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}, P = .019$) and 70/00 (pre to post mean difference: $0.616 (0.212) \text{ ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}, P = .004$) conditions. Training responses are shown in Figure 6.

Table 3. Forearm BF before and following 8 weeks of elbow flexion training

Condition	Pre	Post	Δ
15/00	1.852 (0.183)	1.929 (0.183)	0.077 (0.218) ^{ab}
15/40	2.212 (0.179)	2.076 (0.179)	-0.137 (0.212) ^b
15/80	1.828 (0.183)	2.349 (0.183)*	0.520 (0.218) ^{ac}
70/00	1.655 (0.179)	2.270 (0.179)*	0.616 (0.212) ^{ac}

Values are in $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$. Estimated Marginal Means (SE). BF: blood flow; **15/00**: 15% one-repetition maximum (1RM), 0% arterial occlusion pressure (AOP); **15/40**: 15% 1RM, 40% AOP; **15/80**: 15% 1RM, 80% AOP; **70/00**: 70% 1RM, 0% AOP; Δ : Pre to post training change. *: Significantly different from pre to post ($P < .05$). Δ s marked with different letters represent significant differences in the training response ($P < .05$).

Figure 6. Changes in forearm blood flow



Forearm Vascular Conductance

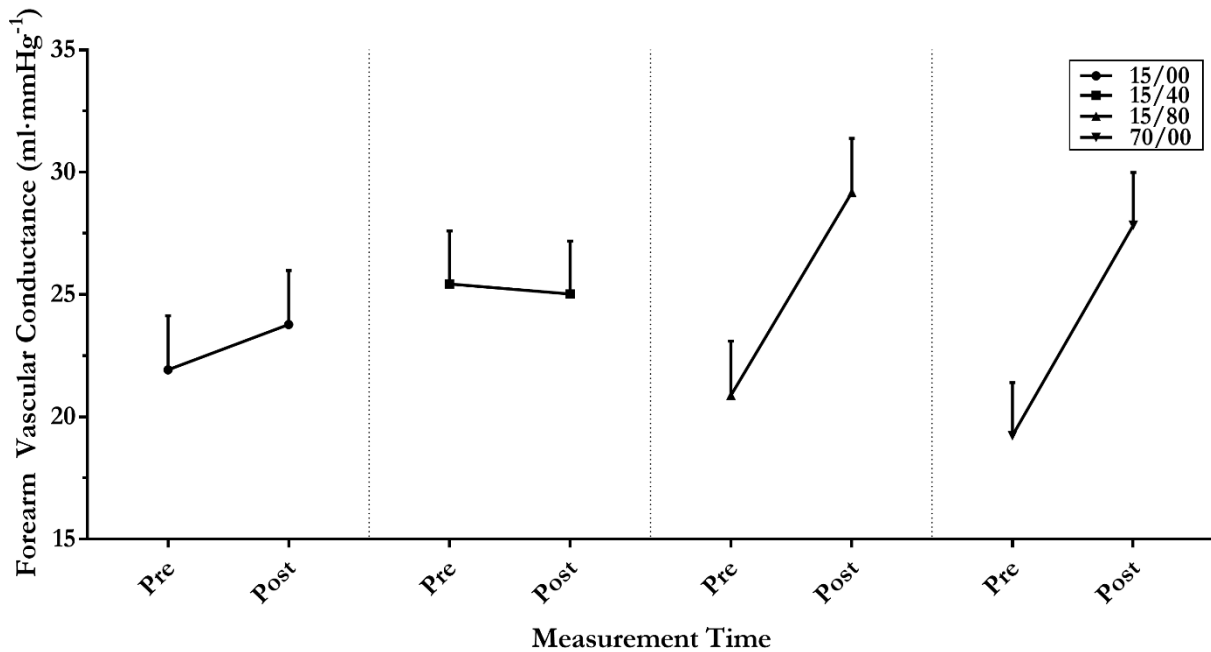
The same linear mixed model ANOVA as before was used to assess possible changes in forearm vascular conductance seen following eight weeks of resistance exercise using a compound symmetry covariance structure. These tests showed a statistically significant condition by time interaction ($F(3,110.208) = 3.034, P = .032$). Pairwise comparisons showed that the training response in the 15/40 condition was statistically significantly different from the response in both the 15/80 (mean difference: $-8.70 (3.72) \text{ ml}\cdot\text{mmHg}^{-1}, P = .021$) and 70/00 (mean difference: $-9.01 (3.67) \text{ ml}\cdot\text{mmHg}^{-1}, P = .016$) conditions (Table 4). There were statistically significant increases in forearm vascular conductance within conditions between time points for both the 15/80 (pre to post mean difference: $8.286 (2.664) \text{ ml}\cdot\text{mmHg}^{-1}, P = .002$) and 70/00 (pre to post mean difference: $8.595 (2.597) \text{ ml}\cdot\text{mmHg}^{-1}, P = .001$) conditions (Table 4). Training related responses are shown in Figure 7.

Table 4. Forearm VC before and following 8 weeks of elbow flexion training

Condition	Pre	Post	Δ
15/00	21.96 (2.22)	23.78 (2.22)	1.813 (2.66) ^{ab}
15/40	25.44 (2.16)	25.02 (2.16)	-0.413 (2.60) ^b
15/80	20.89 (2.22)	29.18 (2.22)*	8.286 (2.66) ^{ac}
70/00	19.24 (2.16)	27.84 (2.16)*	8.595 (2.60) ^{ac}

Values are in $\text{ml}\cdot\text{mmHg}^{-1}$. Estimated Marginal Means (SE). VC: vascular conductance; **15/00**: 15% one-repetition maximum (1RM), 0% arterial occlusion pressure (AOP); **15/40**: 15% 1RM, 40% AOP; **15/80**: 15% 1RM, 80% AOP; **70/00**: 70% 1RM, 0% AOP; Δ : Pre to post training change. *: Significantly different from pre to post ($P < .05$). Δ s marked with different letters represent significant differences in the training response ($P < .05$).

Figure 7. Changes in forearm vascular conductance



Maximum Venous Outflow (MVO)

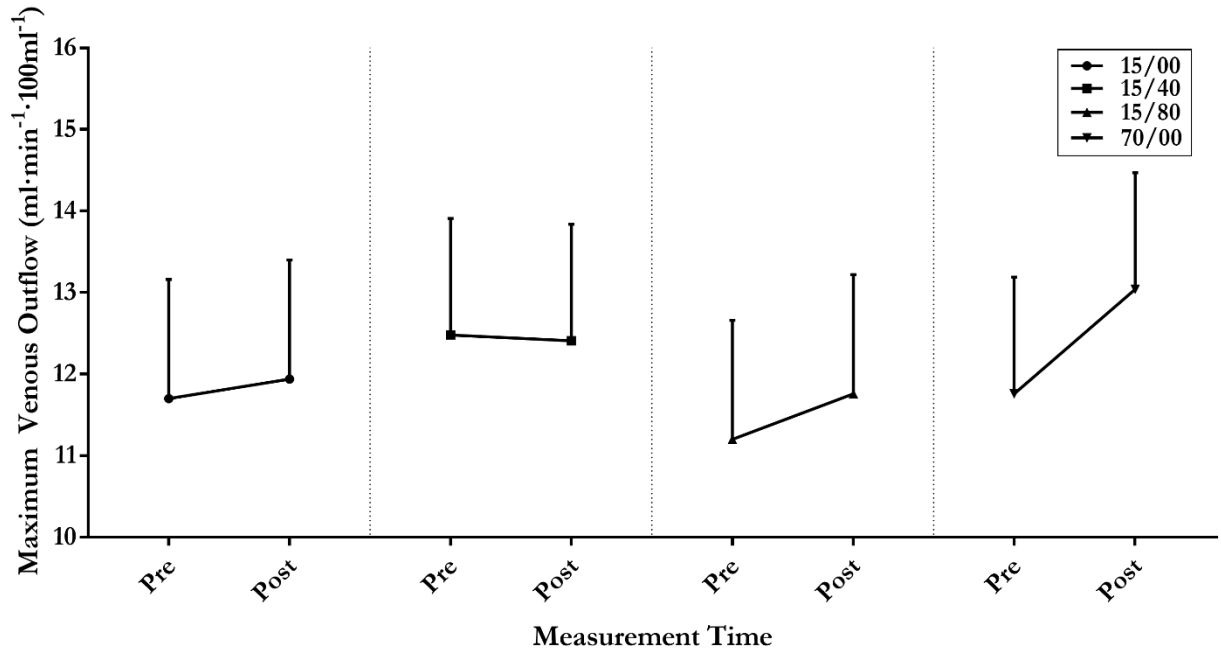
Maximum venous outflow both before and following eight weeks of resistance exercise was analyzed at four different levels (20 mmHg, 40 mmHg, 60 mmHg, 80 mmHg), each using the same linear mixed model ANOVA as before with a compound symmetry covariance structure. Analyses were performed on all available data, excluding values where measurement error / participant

movement disallowed the recording of values. Group sizes are therefore listed here: 20 mmHg (both pre and post measurements: 15/00 = 19, 15/40 = 20; 15/80 = 19, 70/00 = 20); 40 mmHg (both pre and post measurements: 15/00 = 19, 15/40 = 20; 15/80 = 19, 70/00 = 20); 60 mmHg (pre: 15/00 = 19, 15/40 = 20, 15/80 = 19, 70/00 = 20; post: 15/00 = 19, 15/40 = 20, 15/80 = 19, 70/00 = 19); 80 mmHg (pre: 15/00 = 19, 15/40 = 20, 15/80 = 19, 70/00 = 20; post: 15/00 = 18, 15/40 = 19, 15/80 = 19, 70/00 = 19).

MVO at 20 mmHg

There was no statistically significant condition by time interaction ($F(3,110.121) = 0.155, P = .926$), nor were there statistically significant main effects of either condition ($F(3,125.075) = 0.295, P = .829$) or time ($F(1,110.121) = 0.460, P = .499$). Maximum venous outflow at 20 mmHg remained statistically unchanged from before (15/00: 11.70 (1.46) $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$; 15/40: 12.48 (1.43) $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$; 15/80: 11.20 (1.46) $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$; 70/00: 11.77 (1.43) $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$) to after (15/00: 11.94 (1.46) $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$; 15/40: 12.41 (1.43) $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$; 15/80: 11.76 (1.46) $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$; 70/00: 13.04 (1.43) $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$) eight weeks of resistance exercise (Table 5, Figure 8).

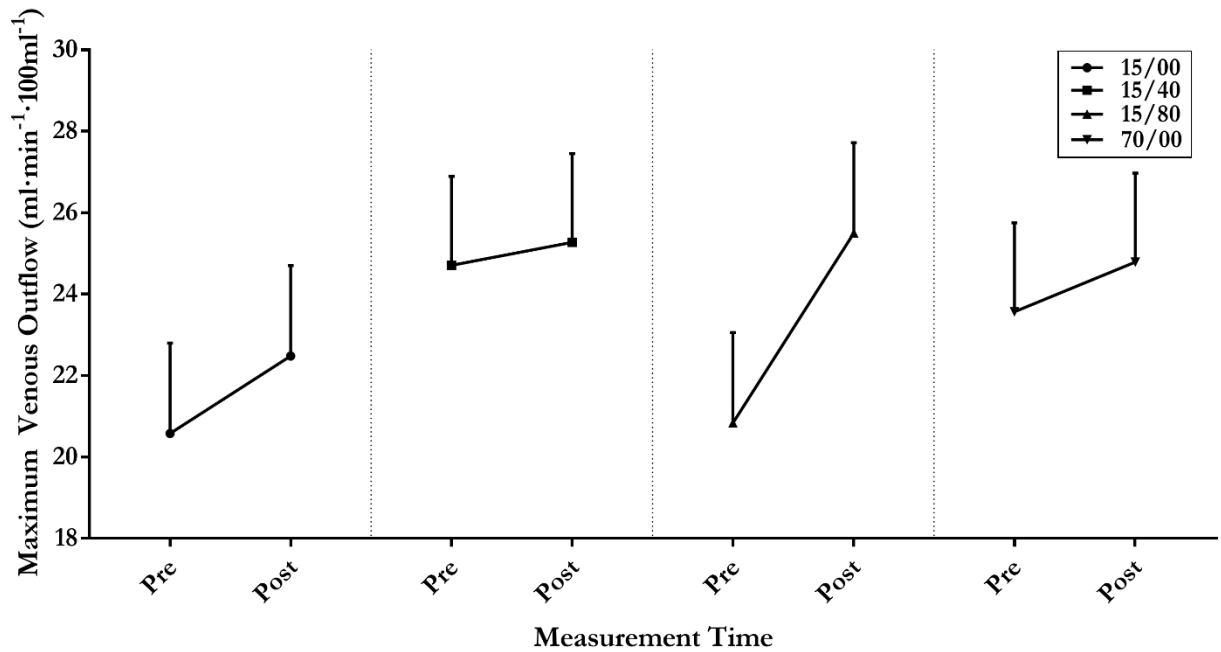
Figure 8. Changes in maximum venous outflow at 20 mmHg following training



MVO at 40 mmHg

There was no statistically significant condition by time interaction ($F(3,110.360) = 0.607, P = .612$), nor were there statistically significant main effects of either condition ($F(3,126.225) = 1.262, P = .290$) or time ($F(1,110.360) = 3.278, P = .073$). Maximum venous outflow at 40 mmHg remained statistically unchanged from before (15/00: 20.58 (2.22) ml·min⁻¹·100ml⁻¹; 15/40: 24.71 (2.18) ml·min⁻¹·100ml⁻¹; 15/80: 20.84 (2.22) ml·min⁻¹·100ml⁻¹; 70/00: 23.57 (2.18) ml·min⁻¹·100ml⁻¹) to after (15/00: 22.48 (2.22) ml·min⁻¹·100ml⁻¹; 15/40: 25.27 (2.18) ml·min⁻¹·100ml⁻¹; 15/80: 25.50 (2.22) ml·min⁻¹·100ml⁻¹; 70/00: 24.79 (2.18) ml·min⁻¹·100ml⁻¹) eight weeks of resistance exercise (Table 5, Figure 9).

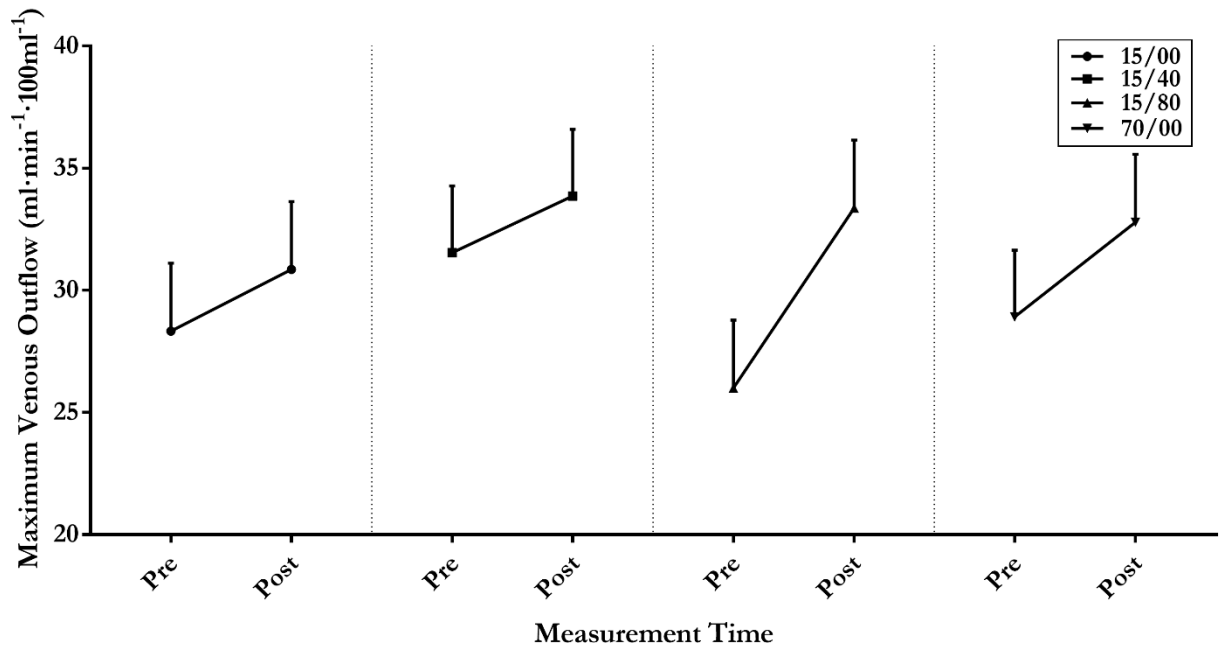
Figure 9. Changes in maximum venous outflow at 40 mmHg following training



MVO at 60 mmHg

There was no statistically significant condition by time interaction ($F(3,109.387) = 0.677, P = .568$), nor was there a statistically significant main effect of condition ($F(3,123.968) = 0.786, P = .504$). There was a statistically significant main effect of time ($F(1,109.387) = 8.052, P = .005$) with overall maximum venous outflow across time increasing (pre to post mean difference: $4.020 (1.416) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$) following eight weeks of resistance exercise. Maximum venous outflow at 60 mmHg was not different between groups either before (15/00: $28.33 (2.78) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$; 15/40: $31.54 (2.73) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$; 15/80: $26.00 (2.78) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$; 70/00: $28.91 (2.73) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$) or after (15/00: $30.85(2.78) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$; 15/40: $33.86 (2.73) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$; 15/80: $33.37 (2.78) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$; 70/00: $32.79 (2.78) \text{ ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$) eight weeks of resistance training (Table 5, Figure 10).

Figure 10. Changes in maximum venous outflow at 60 mmHg following training



MVO 80 mmHg

There was a statistically significant condition by time interaction ($F(3,107.773) = 3.029, P = .033$). Pairwise comparisons revealed that the training response in the 15/80 condition was statistically greater than the training response in both the 15/40 (mean difference: 11.22 (4.18) ml·min⁻¹·100ml⁻¹, $P = .008$) and 70/00 (mean difference: 10.01 (4.18) ml·min⁻¹·100ml⁻¹, $P = .018$) conditions. Within conditions between time points there were statistically significant differences, with maximum venous outflow increasing in both the 15/00 (pre to post mean difference: 6.527 (3.022) ml·min⁻¹·100ml⁻¹, $P = .033$) and 15/80 (pre to post mean difference: 11.468 (2.965) ml·min⁻¹·100ml⁻¹, $P < .0005$) conditions (Table 5, Figure 11).

Figure 11. Changes in maximum venous outflow at 80 mmHg following training

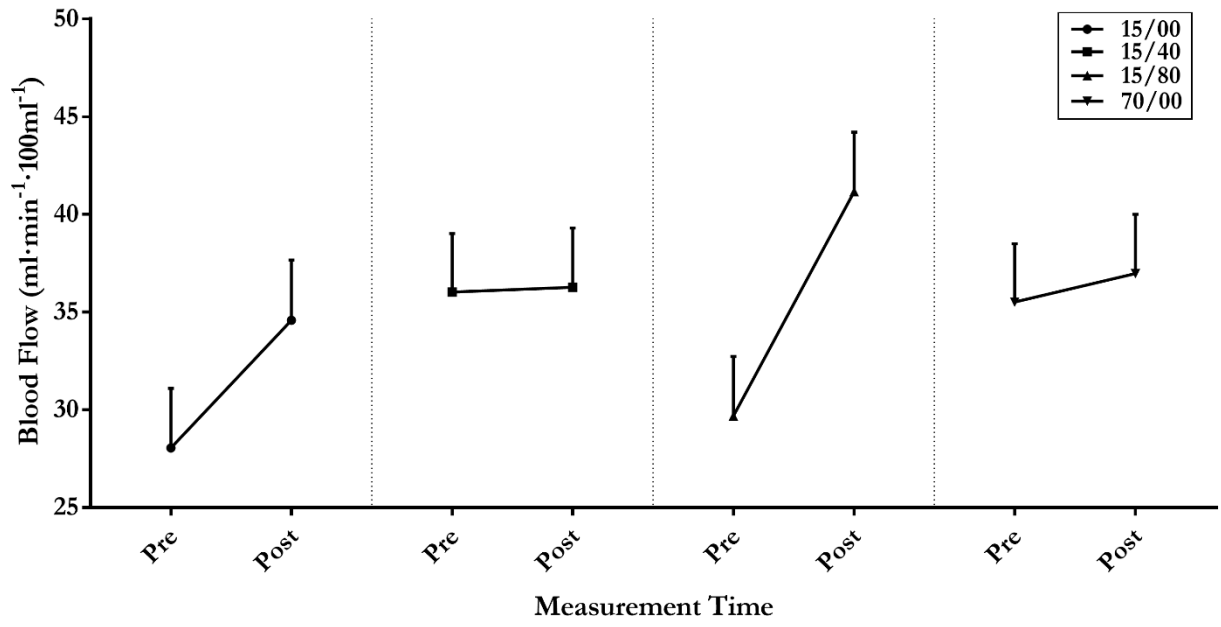


Table 5. Forearm MVO before and following 8 weeks of elbow flexion training

Pressure	Condition	Pre	Post	Δ
20	15/00	11.70 (1.46)	11.94 (1.46)	0.24 (1.51)
	15/40	12.48 (1.43)	12.41 (1.43)	-0.07 (1.47)
	15/80	11.20 (1.46)	11.76 (1.46)	0.56 (1.51)
	70/00	11.76 (1.43)	13.04 (1.43)	1.28 (1.47)
	40	15/00	20.58 (2.22)	22.48 (2.22)
40	15/40	24.71 (2.18)	25.27 (2.18)	0.56 (2.28)
	15/80	20.84 (2.22)	25.50 (2.22)	4.66 (2.33)
	70/00	23.57 (2.18)	24.79 (2.18)	1.21 (2.28)
	60**	15/00	28.33 (2.78)	30.85 (2.78)
60**	15/40	31.54 (2.73)	33.86 (2.73)	2.32 (2.79)
	15/80	26.00 (2.78)	33.37 (2.78)	7.37 (2.86)
	70/00	28.91 (2.73)	32.79 (2.78)	3.87 (2.83)
	80 ^Θ	15/00	28.05 (3.04)	34.58 (3.08)*
80 ^Θ	15/40	36.02 (2.99)	36.27 (3.03)	0.25 (2.94) ^a
	15/80	29.69 (3.04)	41.16 (3.04)*	11.46 (2.97) ^{bc}
	70/00	35.51 (2.98)	36.97 (3.03)	1.45 (2.94) ^a

Values are in $\text{ml} \cdot \text{min}^{-1} \cdot 100\text{ml}^{-1}$. **Estimated Marginal Means (SE)**. **MVO**: maximum venous outflow; **15/00**: 15% one-repetition maximum (1RM), 0% arterial occlusion pressure (AOP); **15/40**: 15% 1RM, 40% AOP; **15/80**: 15% 1RM, 80% AOP; **70/00**: 70% 1RM, 0% AOP; **Δ** : Pre to post training change. *****: Significantly different from pre to post ($P < .05$); ******: Main effect of time ($P < .05$); **Θ** : Interaction ($P < .05$). **Δ s** marked with different letters represent significant differences in the training response ($P < .05$).

Venous Volume Variation (VVV)

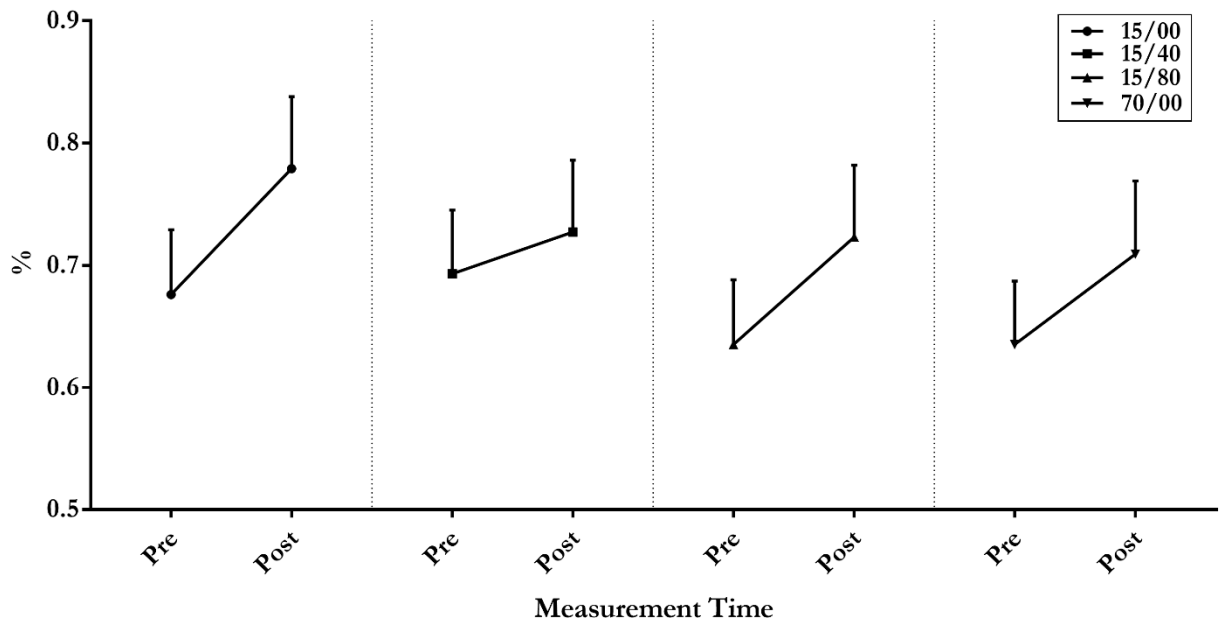
The same linear mixed model ANOVA was used to examine changes in venous volume variation as well as the venous compliance slope following eight weeks of resistance exercise. Similarly to maximum venous outflow, venous volume variation was measured at 20 mmHg, 40 mmHg, 60 mmHg, and 80 mmHg. Unstructured covariance analyses were used for venous volume variation at 20 mmHg, 40 mmHg, and 80 mmHg, while a compound symmetry covariance structure was used for venous volume variation at 60 mmHg. Analyses were performed on all available data, excluding values where measurement error / participant movement disallowed the recording of

values. Group sizes are therefore listed here: 20 mmHg (both pre and post measurements: 15/00 = 19, 15/40 = 20; 15/80 = 19, 70/00 = 20); 40 mmHg (both pre and post measurements: 15/00 = 19, 15/40 = 20; 15/80 = 19, 70/00 = 20); 60 mmHg (pre: 15/00 = 19, 15/40 = 20, 15/80 = 19, 70/00 = 20; post: 15/00 = 19, 15/40 = 20, 15/80 = 19, 70/00 = 19); 80 mmHg (pre: 15/00 = 19, 15/40 = 20, 15/80 = 19, 70/00 = 20; post: 15/00 = 18, 15/40 = 19, 15/80 = 19, 70/00 = 19).

VVV at 20 mmHg

There was no statistically significant condition by time interaction ($F(3,48.383) = 0.536, P = .660$), nor was there a main effect of condition for venous volume variation at 20 mmHg ($F(3,40.075) = 0.587, P = .627$). Venous volume variation at 20 mmHg was not statistically significantly different between conditions either before (15/00: 0.694 (0.063) %; 15/40: 0.692 (0.062) %; 15/80: 0.606 (0.063); 70/00: 0.648 (0.062) %) or following (15/00: 0.763 (0.063) %; 15/40: 0.742 (0.062) %; 15/80: 0.706 (0.063) %; 70/00: 0.708 (0.062) %) eight weeks of resistance training. There was a statistically significant main effect of time ($F(1,35.006) = 6.159, P = .018$), with overall venous volume variation increasing (mean difference: 0.075 (0.030) % following eight weeks of resistance exercise (Table 6, Figure 12).

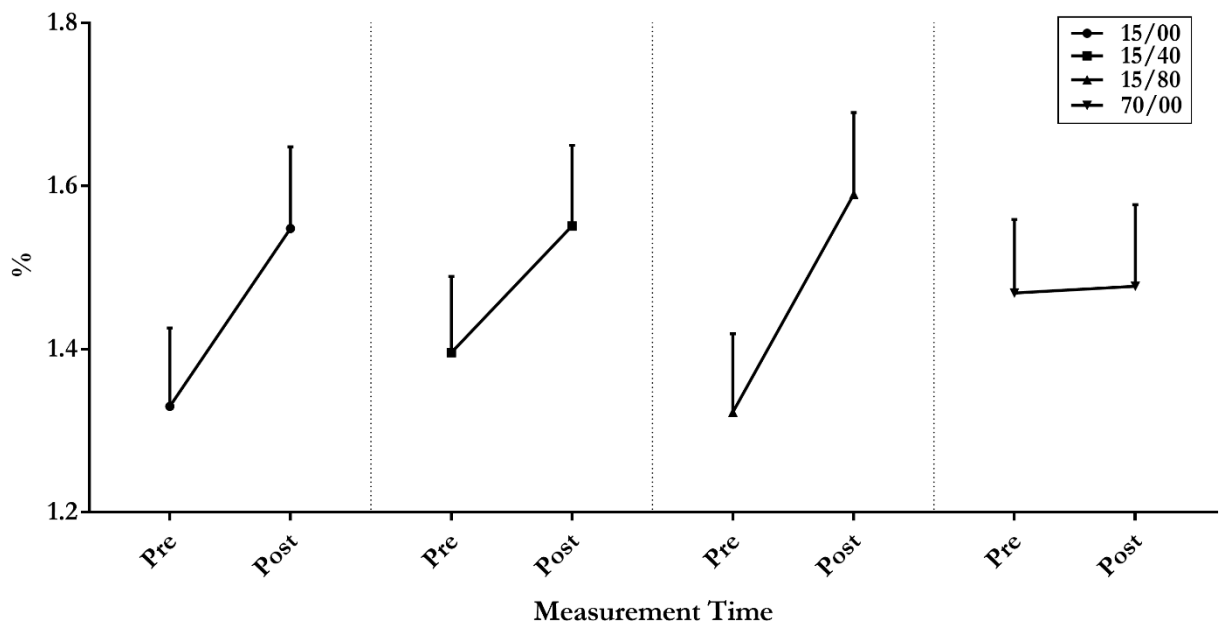
Figure 12. Changes in venous volume variation at 20 mmHg following training



VVV at 40 mmHg

There was no statistically significant condition by time interaction ($F(3,53.127) = 1.157, P = .335$), nor was there a statistically significant main effect of condition ($F(3,42.951) = 0.090, P = .965$). There was a statistically significant main effect of time ($F(1,34.390) = 5.580, P = .024$), with venous volume variation at 40 mmHg increasing (mean difference: 0.162 (0.069) %) following eight weeks of resistance exercise (Table 6, Figure 13).

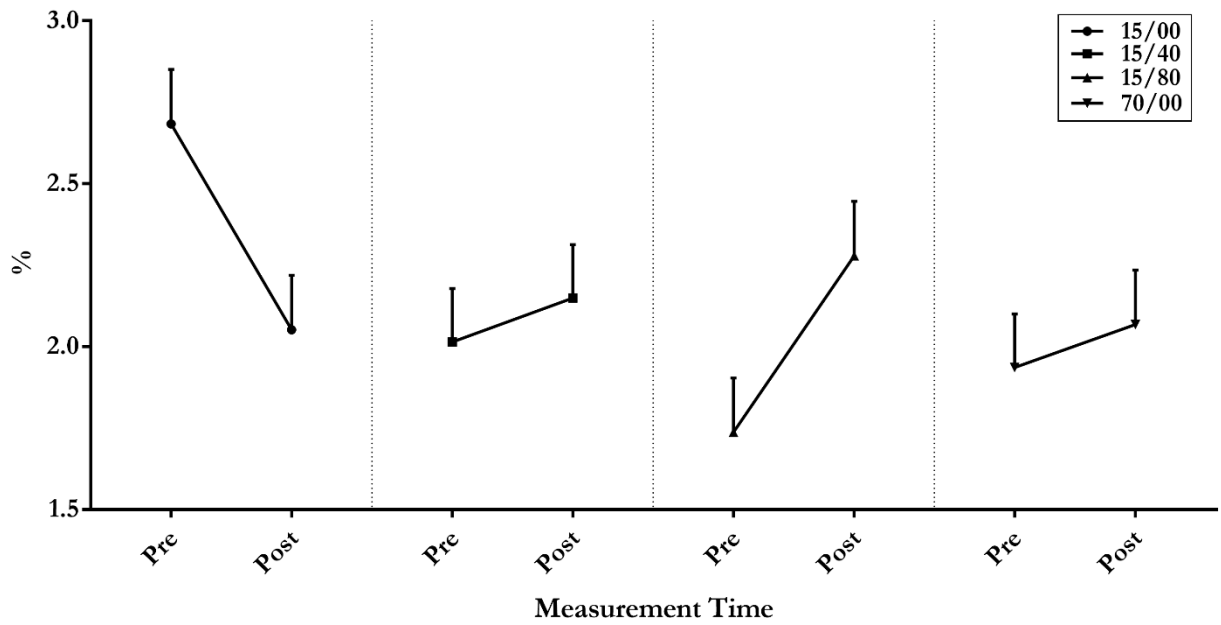
Figure 13. Changes in venous volume variation at 40 mmHg following training



VVV at 60 mmHg

There was a statistically significant condition by time interaction ($F(3,109.228) = 5.996, P = .001$). Pairwise comparisons showed that the training response in the 15/00 was different from the training response in the 15/40 (mean difference: $-0.767 (0.280) \%$, $P = .007$), 15/80 (mean difference: $-1.174 (0.283) \%$, $P < .0005$), and 70/00 ($-0.764 (0.282) \%$, $P = .008$) conditions. Within conditions and between time points, venous volume variation at 60 mmHg statistically significantly decreased in the 15/00 condition (pre to post mean difference: $-0.632 (0.200) \%$, $P = .002$), while it statistically significantly increased in the 15/80 condition (pre to post mean difference: $0.542 (0.200) \%$, $P = .008$) following eight weeks of resistance training (Table 6, Figure 14).

Figure 14. Changes in venous volume variation at 60 mmHg following training



VVV at 80 mmHg

There was no statistically significant condition by time interaction ($F(3,41.308) = 1.611, P = .201$), nor was there a significant main effect of condition ($F(3,39.420) = 0.485, P = .695$), but there was a statistically significant main effect of time ($F(1,35.973) = 9.068, P = .005$), with overall venous volume variation at 80 mmHg increasing (mean difference: 0.310 (0.103) %) following eight weeks of resistance training (Table 6, Figure 15).

Figure 15. Changes in venous volume variation at 80 mmHg following training

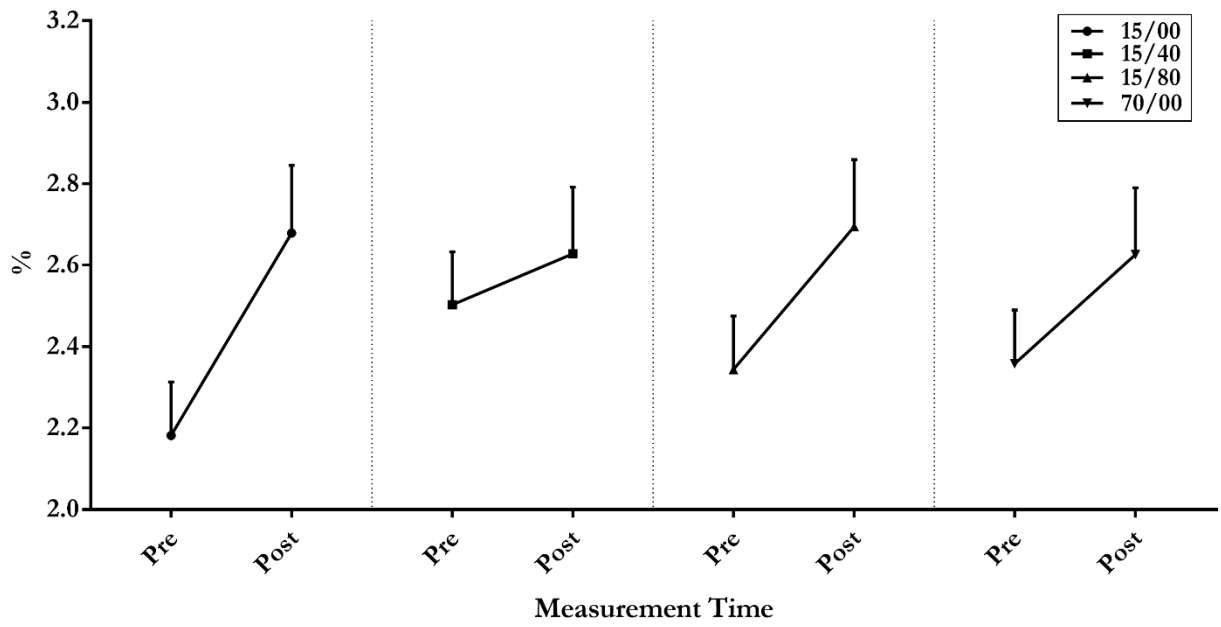


Table 6. Forearm VVV and compliance before and following 8 weeks of elbow flexion training

Pressure	Condition	Pre	Post	Δ
20**	15/00	0.676 (0.053)	0.779 (0.059)	0.103 (0.047)
	15/40	0.693 (0.052)	0.727 (0.059)	0.034 (0.046)
	15/80	0.635 (0.053)	0.723 (0.059)	0.088 (0.047)
	70/00	0.635 (0.052)	0.709 (0.060)	0.074 (0.047)
40**	15/00	1.330 (0.096)	1.548 (0.100)	0.219 (0.117)
	15/40	1.396 (0.093)	1.551 (0.099)	0.155 (0.113)
	15/80	1.323 (0.096)	1.590 (0.100)	0.266 (0.117)
	70/00	1.469 (0.090)	1.477 (0.100)	0.007 (0.112)
60^θ	15/00	2.684 (0.167) ^ψ	2.052 (0.167)*	-0.632 (0.200) ^a
	15/40	2.014 (0.164)	2.149 (0.164)	0.135 (0.195) ^b
	15/80	1.737 (0.167)	2.279 (0.167)*	0.542 (0.200) ^b
	70/00	1.936 (0.164)	2.068 (0.167)	0.132 (0.198) ^b
80**	15/00	2.182 (0.131)	2.678 (0.166)	0.496 (0.148)
	15/40	2.503 (0.130)	2.628 (0.164)	0.125 (0.149)
	15/80	2.344 (0.131)	2.695 (0.164)	0.351 (0.147)
	70/00	2.358 (0.132)	2.626 (0.164)	0.267 (0.152)
VC**	15/00	0.028 (0.002)	0.031 (0.002)	0.003 (0.002)
	15/40	0.030 (0.002)	0.031 (0.002)	0.001 (0.002)
	15/80	0.028 (0.002)	0.033 (0.002)	0.005 (0.002)
	70/00	0.027 (0.002)	0.031 (0.002)	0.004 (0.002)

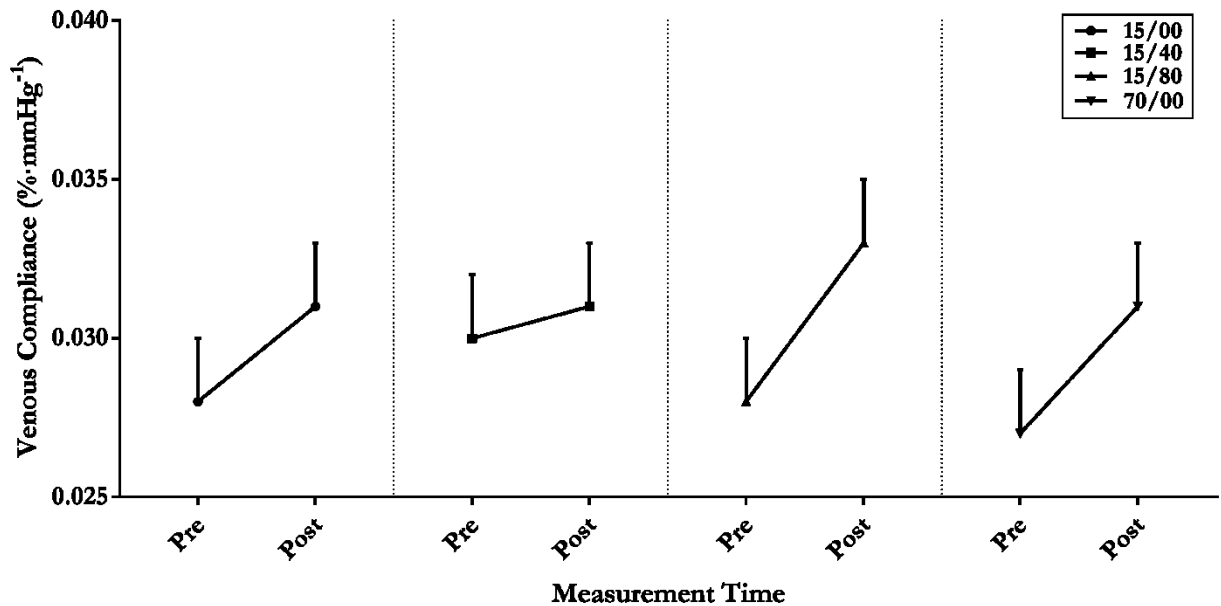
Values are % Δ from resting. Means (SE). 15/00: 15% one-repetition maximum (1RM), 0% arterial occlusion pressure (AOP); **15/40:** 15% 1RM, 40% AOP; **15/80:** 15% 1RM, 80% AOP; **70/00:** 70% 1RM, 0% AOP; **Δ :** Pre to post training change; **VC:** Venous compliance, units are %·mmHg⁻¹; **VVV:** venous volume variation. *: Significantly different from pre ($P < .05$); **: Main effect of time ($P < .05$); **θ :** Interaction ($P < .05$). **Δ s** marked with different letters represent significant differences in the training response ($P < .05$).

Venous Compliance (VC)

A mixed model ANOVA with fixed factors of time and condition using unstructured covariance was used to examine venous compliance. There was no statistically significant condition by time interaction ($F(3,40.096) = 0.458, P = .713$), nor was there a statistically significant main effect of condition ($F(3,43.904) = 0.318, P = .813$) but there was a statistically significant main effect of time ($F(1,36.973) = 4.338, P = .044$), with overall venous compliance increasing across time

(mean difference: 0.003 (0.002) %·mmHg⁻¹) (Table 6, Figure 16).

Figure 16. Changes in venous compliance following training

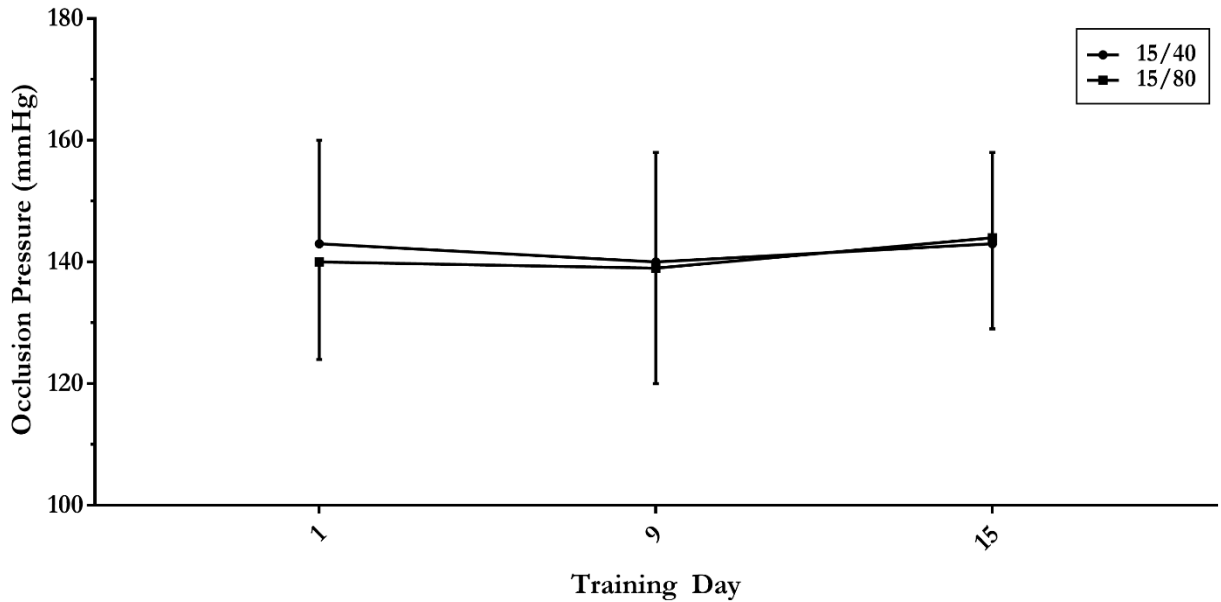


Arterial Occlusion Pressure

Resting arterial occlusion pressures in the 15/40 and 15/80 conditions were investigated across three time points of the study (Days 1, 9, and 15). Levene's test showed that the assumption of homogeneity of variance was not violated ($P > .05$), so a repeated measures ANOVA analysis was performed on each condition individually. For the 15/40 condition the assumption of sphericity was not violated ($P = .175$), so no corrections were made to the degrees of freedom of the omnibus test ($\epsilon = 1.0$). There was no statistically significant main effect of time ($F(2,40) = 0.793$, $P = .459$). For the 15/80 condition the assumption of sphericity was also not violated ($P = .051$), so no corrections were made to the degrees of freedom of the omnibus test ($\epsilon = 1.0$). There was no statistically significant main effect of time ($F(2,38) = 2.461$, $P = .099$). Values remained unchanged from before training (15/40: 143 (17) mmHg; 15/80: 140 (16) mmHg), prior to the ninth training visit (15/40:

140 (18) mmHg; 15/80: 139 (19) mmHg), and prior to the fifteenth training visit (15/40: 143 (15) mmHg; 15/80: 144 (15) mmHg) (Figure 17).

Figure 17. Changes in arterial occlusion pressure following training

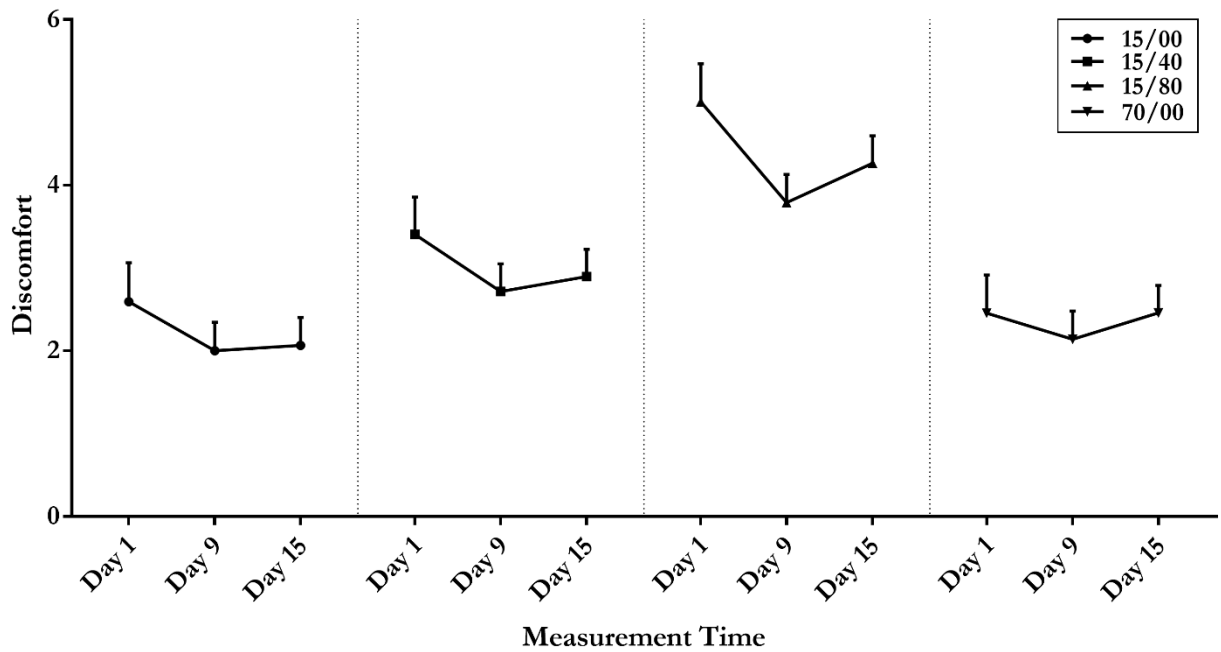


Discomfort

Discomfort was analyzed from three time points throughout the study using a linear mixed model with fixed factors of condition and time and unstructured covariance. There was no statistically significant condition by time interaction ($F(6,62.387) = 1.008, P = .429$), but there were statistically significant main effects of both time ($F(2,37.617) = 7.591, P = .002$) and condition ($F(3,44.468) = 17.824, P < .0005$). Pairwise comparisons revealed that the 15/40 condition experienced statistically greater discomfort than the 15/00 condition (mean difference: 0.785 (0.320), $P = .018$) and the 70/00 condition (mean difference: 0.655 (0.325) $P = .050$). The 15/80 condition experienced statistically greater overall discomfort than the 15/00 (mean difference: 2.133 (0.337)), 15/40 (mean difference: 1.348 (0.321)), and 70/00 (2.003 (0.319)) conditions. Discomfort following

the first set of exercise on the 9th visit was statistically significantly lower than following the first set of exercise on the 1st visit (mean difference: -0.703 (0.216), $P = .002$) as well as following the first set of exercise on the 15th visit (mean difference: -0.260 (0.099), $P = .013$). Discomfort values for all conditions at all time points are found in Table 7 and visualized in Figure 18.

Figure 18. Ratings of discomfort during eight weeks of resistance exercise



RPE

Ratings of perceived exertion were analyzed at three time points throughout the study using a linear mixed model with fixed factors of time and condition and unstructured covariance. There was no statistically significant condition by time interaction ($F(6,56.496) = 1.686$, $P = .141$). There were statistically significant main effects of both time ($F(2,37.522) = 4.817$, $P = .014$) and condition ($F(3,44.278) = 23.928$, $P < .0005$). Participants rated lower exertion scores in the 15/00 condition compared to the 15/40 (mean difference (-0.844 (0.333), $P = .015$), 15/80 (mean difference: -2.646 (0.351), $P < .0005$), and 70/00 (mean difference: -2.231 (0.346), $P < .0005$) conditions. Participants

rated lower exertion scores in the 15/40 condition compared to the 15/80 (mean difference: -1.802 (0.336), $P < .0005$) and 70/00 (-1.387 (0.339), $P < .0005$) conditions. Participants in the 15/80 and 70/00 conditions did not rate their exertion differently (mean difference: 0.415 (0.334), $P = .222$). Perceived exertion was greatest following the first set of exercise on the 1st day of training compared to immediately after the first set of exercise on the 9th day (mean difference: 1.074 (0.425), $P = .016$) as well as immediately after the first set of exercise on the 15th day of training (mean difference: 1.304 (0.428), $P = .004$). All RPE values are found in Table 7 and visualized in Figure 19.

Figure 19. Ratings of perceive exertion during eight weeks of resistance exercise

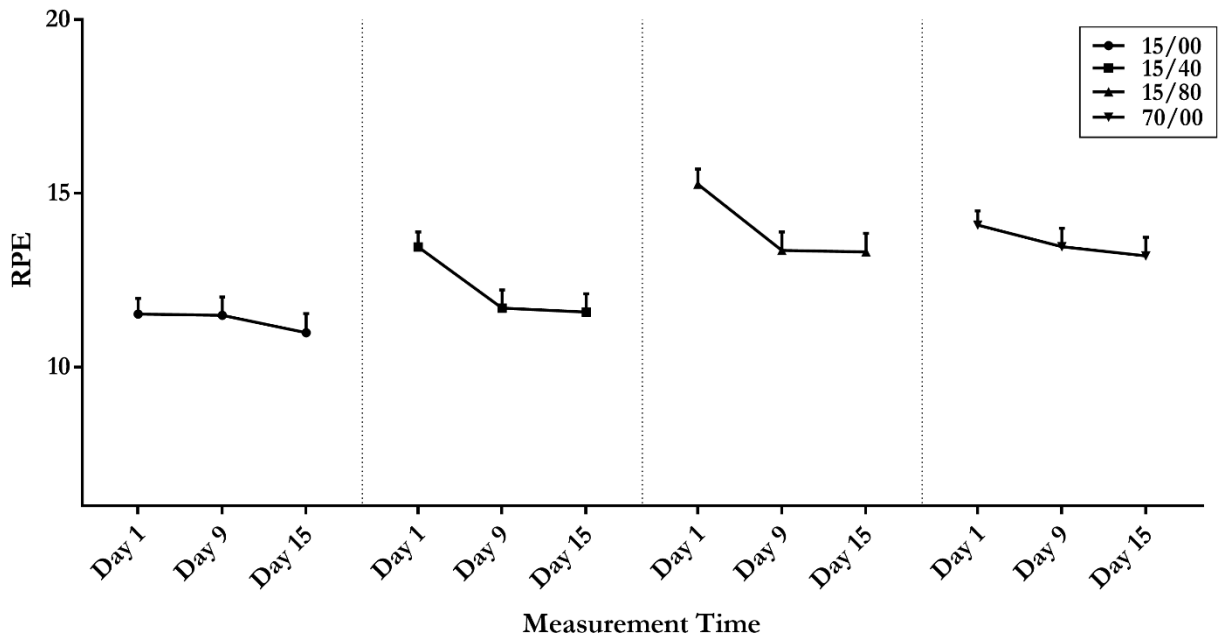


Table 7. RPE and discomfort during eight weeks of resistance training

Condition	Pre	Mid	Post
Disc.			
15/00^a	2.595 (0.468)	2.002 (0.344) ^ψ	2.066 (0.337)
15/40^b	3.406 (0.452)	2.716 (0.335) ^ψ	2.898 (0.327)
15/80^c	5.007 (0.460)	3.790 (0.340) ^ψ	4.266 (0.332)
70/00^a	2.455 (0.460)	2.141 (0.339) ^ψ	2.458(0.332)
RPE			
15/00^a	11.562 (0.495)*	11.482 (0.558)	11.012 (0.572)
15/40^b	13.372 (0.476)*	11.664 (0.546)	11.555 (0.557)
15/80^c	15.301 (0.486)*	13.366 (0.551)	13.328 (0.564)
70/00^c	14.067 (0.485)*	13.493 (0.555)	13.191 (0.564)

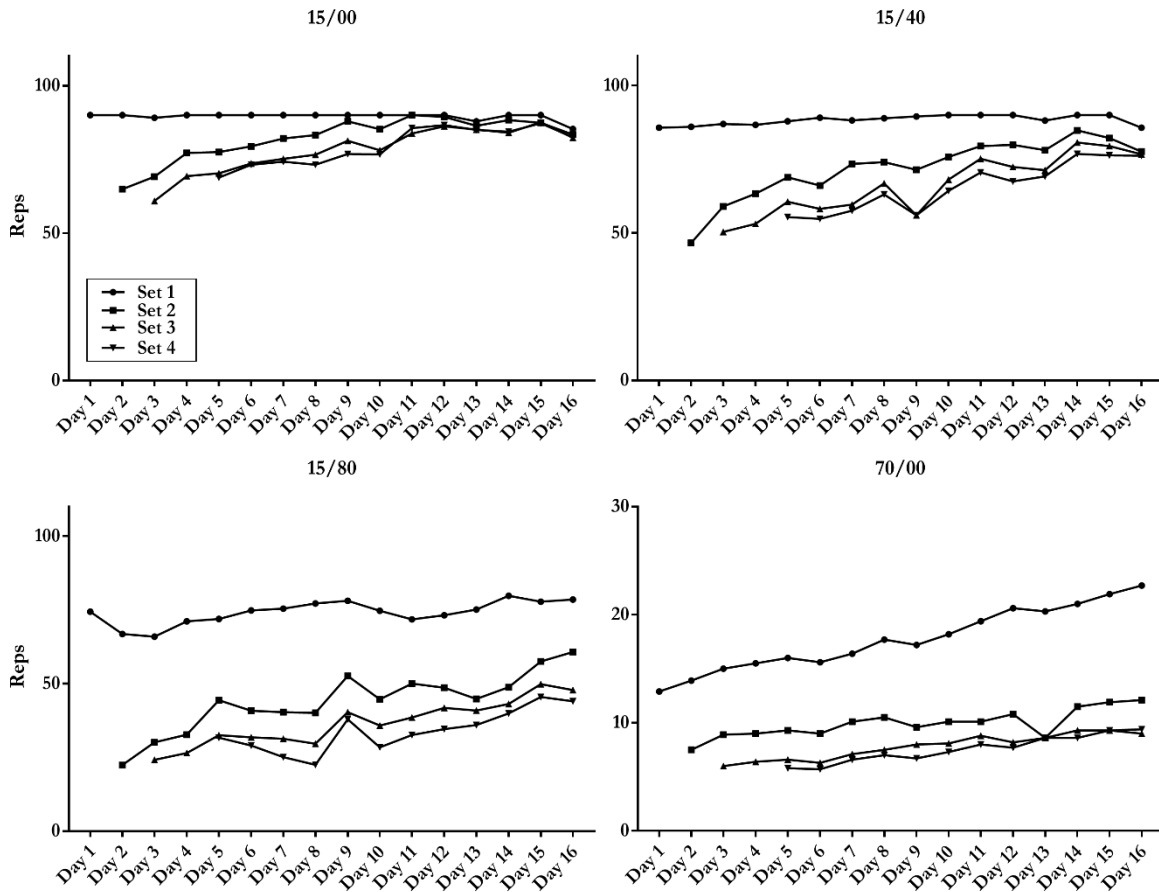
Values are in ml·min⁻¹. Means (SD). Disc.: discomfort; **RPE:** ratings of perceived exertion; **15/00:** 15% one-repetition maximum (1RM), 0% arterial occlusion pressure (AOP); **15/40:** 15% 1RM, 40% AOP; **15/80:** 15% 1RM, 80% AOP; **70/00:** 70% 1RM, 0% AOP; *****: Significant differences between pre and all other time points ($P < .05$). **ψ**: Significant differences between mid and all other time points ($P < .05$). Conditions marked with different letters are significantly different ($P < .05$).

Exercise Volume

Although not statistically analyzed, total exercise volume is displayed below (Figure 20).

Repetitions across time tended to increase for each set in each condition with the exception of the 15/00 condition during Set 1, which remained at or near 90 repetitions each training day for the large majority of participants in that condition.

Figure 20. Exercise volume across eight weeks of upper body resistance exercise



V: DISCUSSION

These studies were conducted to examine the cardiovascular responses and vascular adaptations to four different types of resistance exercise in the upper body, both with and without blood flow restriction. One study involved monitoring the acute cardiovascular responses to very low load resistance training at multiple different pressures of blood flow restriction. The main findings of this study were that:

- Exercise-induced hyperemia is decreased with application of blood flow restriction
- The magnitude of this decrease is pressure dependent
- Following exercise and cuff deflation, blood flow was not different between conditions
- Systolic blood pressure and heart rate increase regardless of exercise condition
- Diastolic blood pressure increased in all but the high load condition

The second study investigated the training-related adaptations that occurred at the vascular level in the forearm, as well as the perceptual responses to exercise, following eight weeks of twice-weekly resistance training in the same four conditions. The main findings of this study were that:

- Forearm blood flow and vascular conductance tended to increase after training
- This increase was greatest in the high pressure and high load conditions
- Venous volume variation increased at all pressures for almost all conditions after training
- Venous compliance increased across all conditions after training
- Perceived exertion decreased over the course of training
- Discomfort first decreased, then increased over the course of training

Study One

Blood flow and artery diameter

Similar to previous work performed in our laboratory (Mouser et al. 2017c), the exercise-induced hyperemic response was decreased in those who received the highest blood flow restriction pressures. Following the second set of exercise, blood flow increased in the 15/00, 15/40, and 70/00 conditions, while it was not statistically significantly increased in the 15/80 condition. This lack of an exercise-induced hyperemic response at the higher blood flow restriction pressure demonstrates that enough external pressure is being applied to prevent more blood from entering the artery. When examined with the lack of a statistically significant increase in brachial artery diameter following the second set of exercise in the 15/80 condition, we hypothesize that the external pressure is high enough to the point that it prevents the increase in blood flow needed to increase the shear rate, which would then prevent dilation of the brachial artery until the pressure in the cuff is released. Since wall shear stress caused by hyperemia is implicated in vasodilation, it is plausible that the 15/80 condition blocked any significant amount of hyperemia during cuff inflation, and the muscular contractions required at only 15% of 1RM were not enough to mechanically stimulate arterial dilation. In all other conditions (including 15/40), brachial artery diameter increased following the second set of exercise, leading us to conclude that the highest blood flow restriction pressures used in this study almost fully block the exercise-induced hyperemic response to resistance exercise.

Following exercise and the deflation of the cuff, blood flow was not statistically significantly different across any of the conditions. In cases where it was first depressed due to the cuff application, blood flow increased following release of the cuff. This is also in line with work performed previously in our laboratory at 30% of 1RM: blood flow is not different across conditions

one minute following exercise. If blood flow is matched to metabolic demand during and following exercise as has been shown (Corcondilas et al. 1964), then one could hypothesize that all four conditions resulted in a similar metabolic demand on the muscle, but that this demand was met at different time points. Blood flow in the unrestricted conditions, in which it is expected that blood flow is only limited briefly during muscular contraction, decreased from its peak following the second set of exercise, signifying that the metabolic demand of the muscle was being adequately supplied during and following exercise. In the restricted conditions, however, blood flow increased from the second set of exercise in which restriction was still present, to its peak at one minute following cuff deflation and the end of exercise, demonstrating that blood flow during exercise was insufficient to fully meet metabolic demands, and therefore had to increase. That none of the conditions were different from each other at one minute following exercise, combined with the different post-exercise blood flow responses, can be taken to show that, in the unrestricted conditions, metabolic demand was being met during and immediately following exercise, whereas metabolic demand was only partially met during exercise in the restricted conditions and the majority of the metabolic demand was made up for post exercise.

It should be noted that the sample size of the 15/40 condition was skewed in favor of women (women=10, men=7), and this could have artificially lowered the absolute mean values of blood flow. At rest, following exercise, and during exercise recovery, women tend to have lower absolute blood flow values than men (Mouser et al. 2017c).

Blood pressure

Regardless of condition, systolic blood pressure increased following four sets of resistance exercise in the upper body. This is similar to the findings of Brandner and colleagues to a degree. In their study during which 20% of 1RM with either continuous or intermittent blood flow restriction

were compared to 20% 1RM with no blood flow restriction as well as 80% of 1RM, systolic blood pressure increased across the exercise protocol of four sets (Brandner et al. 2015). What separates our findings from that of the Brandner study was the lack of difference we saw between conditions. Whereas high load and intermittent blood flow restriction elicited the largest increases in systolic blood pressure, there were no group differences in the systolic blood pressure response in the present study. This could be attributable in the present study to the lower weight used, or perhaps the much higher volume of exercise performed, regardless of condition, caused a rise in systolic blood pressure, as participants in Brandner's study performed a defined number of repetitions per set; in this study, participants performed to muscular failure.

Contrary to the Brandner study, diastolic blood pressure increased following four sets of resistance exercise in all but the 70/00 condition, which remained unchanged from rest. This may provide some basis to state that the total volume of exercise completed played a larger role in the blood pressure response, as less volume was completed in the 70/00 condition overall than in the other conditions due to the differences in repetition ranges performed in each condition. Perhaps a higher volume of exercise performed in the upper body combined with the lower load activated the exercise pressor reflex to a greater degree than at lower volumes with higher loads, and this occurred whether or not blood flow restriction was applied in these very low load conditions. The decreased venous return would require greater work by the heart, which could increase diastolic pressure. Whereas Brandner et al. saw the greatest increases in diastolic pressure in the high load condition, we saw no increase. This is almost certainly due to the difference in our high load protocol compared to theirs. Each set was performed with a higher relative load in the aforementioned study, so we hypothesize that this change in relative load is responsible for the differences in diastolic blood pressure response seen between the two studies.

Study Two

Forearm blood flow and vascular conductance

A unique finding of this study was that both forearm blood flow (in milliliters of blood per minute per 100 ml of forearm tissue [$\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ml}^{-1}$]) and forearm vascular conductance (in milliliters of blood per millimeter of mercury of pressure [$\text{ml}\cdot\text{mmHg}^{-1}$]) increased only in the 15/80 and 70/00 conditions following eight weeks of twice-weekly resistance exercise in the upper body. This is significant for several reasons.

First, blood flow and vascular conductance measurement using mercury strain gauge plethysmography necessitates the distal portion of the limb, in this case the forearm, be measured, as the bicep does not allow enough space for both a proximal and distal inflation cuff. The forearm is also less involved in very low load resistance training: the flexor muscles of the wrist and hand must only grasp and hold 15% of the 1RM. This is not the case in the high load condition in which the hand must grasp and hold 70% of the 1RM. It is therefore not surprising that increases in blood flow and vascular conductance were seen in the 70/00 condition: those muscles had to maintain the hand's grasp on the weight throughout the entire training regimen. What is surprising is that the 15/80 condition saw equally large increases in blood flow and vascular conductance as did the 70/00 condition. We can ascribe this change in blood flow and vascular conductance in the 15/80 condition to the high relative pressure being applied by the blood flow restriction, as the 15/00 condition saw no increase in blood flow or vascular conductance and was lifting a similarly light weight.

It has been hypothesized before that, in order to see muscular hypertrophy with very low loads, higher pressures of blood flow restriction are needed (Lixandrão et al. 2015). This could be due to the need to recruit more muscle fibers at such low loads, and by restricting a larger amount of

blood flow during exercise while exercising with very low loads, the metabolic demands of the motor units are not being met and so more are recruited. If this is the case, then the recruitment of a larger number of muscle fibers may cause a greater increase in muscle-produced VEGF (Hoier and Hellsten 2014), providing a greater angiogenic stimulus. A study published recently examining the acute angiogenic signaling responses to blood flow restricted knee extension showed that VEGF mRNA was increased at 2h and 4h following exercise when compared to a control group exercising at the same relative low load without blood flow restriction (Ferguson et al. 2018), so this reasoning seems sound.

At the same time, it has been proposed that restricting blood flow by venous occlusion may increase circumferential wall stress at the arterioles and capillaries by causing a pressure increase on the venous side of the circulation, where it is traditionally lower than the arterial side (Price and Skalak 1994). Localized increases in circumferential sheer stress are thought to signal growth factor release that causes capillary budding and growth in order to increase the overall cross sectional area of the capillary bed, thereby reducing resistance to blood flow and lowering the local pressure. With the likely increase in circulating VEGF combined with local stimuli, we have a probable explanation for the increased blood flow and vascular conductance seen in this study.

Maximum venous outflow, venous capacitance, and venous volume variation

The major findings of this study relating to the venous circulation were that maximum venous outflow was unaffected at the first two measurement pressures of 20 mmHg and 40 mmHg. Overall, each condition increases maximum venous outflow at 60 mmHg, and that 15/00 and 15/80 increased maximum venous outflow at 80 mmHg. Venous volume variation, the amount of change in the volume of the veins under a given measurement pressure, increased at all four measurement pressures, with the single exception of the 15/00 condition at 60 mmHg, which decreased to a large

degree. Venous compliance, the change in venous volume variation per mmHg of measurement pressure, also called the volume-pressure curve, increased due to training regardless of condition. There are several possible explanations for these findings.

Maximum venous outflow can be thought of as the speed with which the veins can empty when resistance to flow has been rapidly removed. As such, it is related to the ability of the vein to dilate once the measurement cuff has been deflated and can be moderated by factors such as venous tone and the presence or absence of nitric oxide (Green et al. 2017). Similar to the changes in maximum venous outflow seen by Iida and colleagues in the legs following blood flow restriction during walk training, we saw an increase in maximum venous outflow at 80 mmHg (Iida et al. 2011) in both the 15/00 and 15/80 conditions. Regarding the specificity of the measure, this observation is plausible for the 15/80 condition: the pressures used to reach 80% of arterial occlusion pressure were higher than 80 mmHg, so this training study routinely pushed venous pressure above those levels. Similarly at 60 mmHg, where there was an overall effect of time, this is largely driven by the 15/80 condition. The change seen in the 15/00 condition at 80 mmHg is perplexing in that the same reasoning in the 15/80 condition cannot apply to it: there was no applied pressure that was much higher than the measurement pressure, and the 15/40 condition did not see a similar change at 80 mmHg.

The average pressure applied in the 15/80 group was 114 (11) mmHg, and in the 15/40 condition it was 58 (6) mmHg. Since we did not see a similar increase in maximum venous outflow with the 15/40 condition, we speculate that applied pressures higher than the measurement pressure are required in order to see adaptations. Future research should examine the pressure-adaptation relationship to test this hypothesis. Iida and colleagues also examined whether these changes with slow walking during blood flow restriction changed hydrostatic gradients throughout the body by

examining the vascular response in the arms as well and found no changes following training (Iida et al. 2011). They hypothesized that these changes in pressure that would alter venous function are strictly local.

The increase in venous volume variation was greater following resistance exercise for all but one group at one measurement time point. This would suggest that lifting weights, even very low loads, is enough to raise the blood flow in the veins to a degree that causes adaptations. Combined with blood flow restriction, which hypothetically would raise the pressure in the veins to that of the cuff and higher, and the increase in maximum venous outflow that occurs following cuff deflation, structural changes to the veins themselves in the form of an upward shifting elastin:collagen ratio would not be out of the realm of possibility. It has been shown in rats that the elastin:collagen ratio is associated with the amount of blood flow present in both the arteries and the veins (Basu et al. 2010), with greater blood flow associated with a higher elastin:collagen ratio. When blood flow is present at higher values in the vasculature, the amount of elastin present tends to increase. Performing continuous resistance exercise, even combined with blood flow restriction, increases arterial blood flow which must then pass through the venous circulation. Regularly increasing the blood flow through the veins via exercise seems a plausible mechanism by which venous capacitance increases.

Venous compliance, the increase in venous volume variation per mmHg of measurement pressure, increased following exercise in the present study. This is in line with the results of the Iida walking study, in which blood flow restriction combined with walking significantly increased venous compliance (Iida et al. 2011). It is, however, contrary to the results seen by Fahs and colleagues, in which venous compliance in the calves did not change following blood flow restricted leg exercises (Fahs et al. 2014). There could be structural differences between the arms and the legs that account

for the different values of venous compliance seen in the two studies. Iida saw pre-training venous compliance measures of $0.0518 - 0.0686 \text{ ml} \cdot 100\text{ml}^{-1} \cdot \text{mmHg}^{-1}$. This is greater than those seen in the present study, which range from $0.028 - 0.030 \text{ ml} \cdot 100\text{ml}^{-1} \cdot \text{mmHg}^{-1}$. A study performed using 18 days of head down tilt showed that venous compliance decreased in the legs and remained unchanged in the arms, which could point to differences between the limbs in either morphology or adaptation (Bleeker et al. 2004). Likely, it is a difference in the activation of the muscles during each type of exercise. While walking as in the Iida study, the calves are regularly contracting and relaxing. During knee extensions as in the Fahs study, the calves may or may not be contracting depending on the execution of the task. During elbow flexion as in this study, the muscles of the forearm are constantly contracted in order to hold the weight in the hand.

Arterial occlusion pressure

The arterial occlusion pressure remained unchanged across the course of the study in the two groups of participants receiving blood flow restriction. Since arm circumference and systolic blood pressure play a determinant role in the arterial occlusion pressure for a cuff of a given size (Loenneke et al. 2015; Jessee et al. 2016a), it seemed unlikely that the occlusion pressure would change significantly across eight weeks of twice-weekly resistance exercise. Although unexamined in the present study, the aggregated mean arterial pressure decreased from before to after eight weeks of resistance training. Combined with any hypertrophy seen, these two changes could have cancelled each other in the final determination of arterial occlusion pressure. More likely, though, is that arm circumference did not change enough to meaningfully impact this pressure. Moving forward, it appears that daily measures of arterial occlusion pressure are not required and instead could be tested every several weeks of a training study to confirm this is not shifting.

Discomfort and ratings of perceived exertion

The discomfort response as measured at three time points in the study saw the lowest discomfort reported at the 9th visit for all groups. Participant discomfort and perceived exertion were analyzed following the first set of exercise only, as on the 1st visit participants performed only one set of exercise, increasing to four sets of exercise by the 5th visit. The 1st and 15th visits were rated similarly uncomfortable. This is different to the results seen by Kim and colleagues, in which the discomfort associated with blood flow restriction decreased across the duration of the training study (Kim et al. 2017). Another study examining the pain response to repeated exposure to blood flow restriction showed that the pain response decreased across repeated exposure (Martín-Hernández et al. 2017). The differences in exercise protocols and blood flow restriction pressures could explain this discrepancy. Total volume continued to increase across the duration of the present study for each group, and it could be that increasing the number of repetitions performed continuously caused an increase in discomfort toward the end of the training period, as each set was performed to or near to muscular failure. In the Martín-Hernandez study, participants maintained the same volume across all training bouts, and in the Kim study, although volume was increased by retesting the 1RM every two weeks, the participants still performed a set number of repetitions in each exercise. In aerobic exercise, time to exhaustion is linked with perception of effort (Marcora and Staiano 2010), and the increase in number of repetitions performed, concomitant with the decrease in perception of effort, would have allowed the participants to perform more repetitions per set, which could increase discomfort due to metabolite accumulation in the muscle. Participants in the 15/80 condition consistently rated their exercise sets as being more uncomfortable than all other conditions, which was to be expected as higher pressures are associated with greater discomfort in blood flow restriction (Mattocks et al. 2017).

Perceived exertion was highest for all groups following the 1st set of the 1st day of training, after which it decreased and remained so until the end of the training period, even with a concomitant increase in repetitions. This can be explained by the likely adaptations occurring in the muscle. Endurance increased across the study, allowing for more repetitions to be performed. At the same time, the weight was never increased, so as the participants adapted to lifting more repetitions with the same weight, they perceived the relative exertion as lower than when they began the training program. It is also possible that central fatigue, a decrease in neural drive to the muscle, decreased across the duration of the study since, as mentioned before, the weight was kept constant throughout the study. Marcora and colleagues propose what they call task disengagement, i.e., “the participant gives up” (Marcora and Staiano 2010) during high intensity aerobic exercise to failure. By measuring muscle force before and immediately after an exhaustive bout of aerobic exercise, the authors determined that the decrease in muscle force due to the exercise bout was not sufficient to show that the muscles had failed completely. This implicated the descending drive from the brain as a reason that the participants ended the protocol when they did. Although these tests were not high intensity aerobic exercise as performed in the Marcora study, descending drive across the duration of the study could have adapted to allow the participants to lift a greater volume over time.

VI: CONCLUSION

The purpose of these studies was to examine the acute hemodynamic response to four different types of resistance exercise (very low load at 15% 1RM, very low load at 15% 1RM combined with blood flow restriction at 40% or 80% of arterial occlusion pressure, and high load at 70% 1RM) in the upper body, as well as to evaluate the training-induced adaptations that occur in the vascular tree of the forearm in these same four conditions. We found that exercise-induced hyperemia is blunted when blood flow restriction is applied at relative levels in the upper body, that this hyperemia is blunted in a pressure-dependent manner, and that blood pressure increases in almost all exercise conditions. Following training, vascular conductance increased in the forearms to a greater degree in the high pressure and high load conditions, maximum venous outflow increased only at the higher measurement pressures, venous compliance increased following resistance training regardless of condition, and while the perception of exertion decreased across the duration of the training program, the perception of discomfort first decreased, and then increased across that same time.

Hypotheses

H₁

We hypothesized that the hyperemic response to high load exercise would be the greatest of the four conditions. While not statistically significantly different from the 70/00 condition, the 15/00 condition saw the greatest increase in blood flow following the second set of exercise. We further hypothesized that the hyperemic response would be blunted in relation to the amount of

pressure applied during blood flow restriction, which is what we observed: the 15/40 condition had greater blood flow following the second set of exercise than did the 15/80 condition. We also hypothesized that post-exercise, post-deflation blood flow would not be statistically significantly different across groups, which is what occurred. Finally, we hypothesized that blood flow in the 15/00 condition would decrease from a peak following the second set of exercise to one minute following the final set of exercise, which aligns with our observed results.

H₂

We hypothesized that vascular conductance would increase following eight weeks of resistance training, and that it would be highest in the 15/80 and 70/00 conditions. We observed the largest increase in the high pressure group, and a large increase in the high load group. We further hypothesized that venous compliance would increase the most in the 15/80 condition, which was not observed. Venous compliance increased following eight weeks of resistance training regardless of condition.

SH₁

We hypothesized that the blood pressure response would not be statistically significantly different between the 15/80 and 70/00 conditions, and that the 15/00 condition would have the smallest increase in blood pressure. In fact, all conditions saw an increase in systolic blood pressure following exercise, and the 70/00 condition did not experience any increase in diastolic blood pressure, whereas the other three conditions did.

SH₂

We hypothesized that arterial occlusion pressure would not change across the duration of the exercise training study, and this is in fact what happened.

SH₃

We hypothesized that there would be a decrease in the perceptual response to exercise following eight weeks of resistance training. We saw at first a decrease, and then an increase, in the amount of discomfort reported by the participants. We did see a decrease in ratings of perceived exertion following the first set of exercise at the midpoint and at the end of the training study.

Significance

We have demonstrated here that forearm blood flow and vascular conductance increases both during high load training as well as during very low load training combined with high relative levels of blood flow restriction. It has been hypothesized that venous occlusion could cause a change in capillarization (Price and Skalak 1994). While that hypothesis was applied to venous occlusion in the absence of exercise, when taken with the lack of changes in capillarization seen in the moderate restriction condition, high relative levels of restriction combined with very low load resistance exercise bear it out. These same low loads in the absence of any blood flow restriction did not increase forearm blood flow. We can therefore affirm partially this hypothesis: increased pressure at the arterioles and capillaries leads to an increase in capillarization.

Future Research

Diabetic arteriopathy, a condition in which uncontrolled diabetes causes a decrease in vascular function of the extremities, most often the legs, results in peripheral neuropathy, ischemia, and in the worst cases can result in gangrene and the need for limb amputation (Huysman and Mathieu 2009). As early as the 1930s, intermittent venous occlusion was proposed as a method to treat peripheral vascular disease by increasing blood flow to the affected limb (Collens and Wilensky 1937). We have shown that very low load resistance exercise combined with high relative levels of blood flow restriction cause an increase in vascularization in the arms. Future research should

determine whether this same adaptation occurs in the legs, whether this adaptation occurs at all in patients with diabetes, and whether this would be a viable treatment option to prevent loss of function or loss of limb in at-risk patients. The most promising treatments from the present study, the 15/80 and 70/00 exercise conditions, should be examined in these populations simultaneously, as they were the two conditions that promoted the greatest increases in vascularization.

Conclusion

The blood flow response to very low load exercise, both with and without blood flow restriction, aligns with previous work performed in this laboratory. Blood flow tends to increase following the start of resistance exercise, and this increase is blunted in a pressure-dependent manner when blood flow restriction is applied during exercise. Following exercise, the amount of blood flow present is similar across all exercise conditions, suggesting that the metabolic demand is similar in each. Systolic blood pressure increased in all conditions, while diastolic did not increase significantly in the 70/00 condition. When these individual exercise conditions are performed twice a week for eight weeks, forearm blood flow increases in the high pressure and high load conditions, and it is likely that this is accomplished via different mechanisms. Both venous volume variation and venous compliance increased. Very low load resistance exercise in the upper body combined with higher blood flow restriction pressures appears to have similar effects as high load resistance exercise in the upper body with regards to vascular adaptations.

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VITA

J. Grant Mouser

MS, Exercise Physiology, University of Oklahoma	May 2015
BS, Health and Exercise Science, University of Oklahoma	May 2013
BBA, Management Information System, University of Oklahoma	May 2007
Graduate Teaching Assistant, University of Mississippi	August 2015 – May 2018
Graduate Researcher, University of Mississippi	July 2015 – May 2018
Graduate Teaching Assistant, University of Oklahoma	August 2013 – May 2015
Graduate Researcher, University of Oklahoma	August 2013 – May 2015