A Comparison of Blood Flow Restriction and Traditional Resistance Training to Investigate the Differing Adaptations and the Relative Importance of Metabolic Markers

by

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ABSTRACT

A Comparison of Blood Flow Restriction and Traditional Resistance Training to Investigate the Differing Adaptations and the Relative Importance of Metabolic Markers

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In the literature, there is inconsistency comparing blood flow restriction (BFR) to traditional resistance training (TRT) and thus, what differs between BFR and TRT is not well known. Modulators of BFR have not been looked at in detail, particularly when BFR and TRT are matched to failure. In this study, TRT was compared with suprasystolic and subsystolic levels of BFR over an 8-week training study by matching all groups to failure. Oxygenation and lactate were analyzed to determine the relationships these modulators have on the training outcomes. Similar strength, hypertrophy and endurance changes were found across all groups. TRT had lower oxygenation than the BFR groups with no difference in blood lactate between groups. Significant increases in main outcomes after training were: 1RM +24%, muscle thickness +12%, and muscular endurance +14%. Minor associations found where oxygenation negatively correlated with changes in hypertrophy and lactate positively correlated with changes in strength.
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ABBREVIATIONS

IRM: One repetition maximum
ACSM: American college of sports medicine
ASIS: Anterior superior iliac spine
au: arbitrary units
BFR: Blood flow restriction
BFR\(_{100}\): Blood flow restriction with 100\% arterial occlusion
BFR\(_{50}\): Blood flow restriction with 50\% arterial occlusion
BFR\(_{\text{pool}}\): Blood flow restriction groups data pooled together
BMC: Bone mineral content
DEXA: Dual energy X-ray absorptiometry (DEXA)
EMG: electromyography
Hb: Haemoglobin
HbO\(_2\): Oxyhaemoglobin
HHb: Deoxyhaemoglobin
HIF: Hypoxia inducible factor
IPC: Ischemic preconditioning
ITT: Interpolated twitch technique
LMM: Lean muscle mass
LOP: Least occlusive pressure, lowest occlusive pressure
MAPK: Mitogen-activated protein kinase
Mb: myoglobin
mTOR: Mammalian target of rapamycin
MVIC: Maximal voluntary isometric contraction
NIRS: near infrared spectroscopy
Post: Post-training values
Pre: Baseline values before training
P\(_t\): Peak twitch torque
RF: Rectus femoris
T\(_r\): Peak torque at rest
TRT: Traditional resistance training
T\(_p\): Peak torque plateau
TSI\(%\): Tissue saturation index
US: Ultrasound
VA: Voluntary activation
VAS: Visual analog scale
VEGF: Vascular endothelial growth factor
VL: Vastus lateralis
VM: Vastus lateralis
VO\(_2\)\text{peak}: Peak oxygen consumption
Chapter 1 - Introduction

Exercise is one of the key pillars to maintain health and avoid chronic disease. Historically, cardiovascular-based “endurance” exercise was presented as a prerequisite to a healthy lifestyle and thus encouraged by many health professionals as a key aspect to a healthy lifestyle. However, it is becoming increasingly apparent that all exercise of sufficient quantity and quality offers health benefits and resistance exercise is increasingly shown to be as important as any other mode of exercise. Specifically, resistance exercise has been shown to decrease mortality rates and improve glucose control, while simultaneously increasing performance. Due to the benefits of resistance training, there are a number of industries that benefit from implementing and maximizing resistance training, such as strength and conditioning, physiotherapy, sports performance coaching, and medicine. These industries are all trying to find ways to manipulate resistance training to optimize or enhance the desired adaptations within, commonly through prescribed weights, sets, or repetitions, using new machines for better application of forces, altering the speed of contractions or styles of lifting, such as eccentric or isometric.

Traditionally, it was thought that to maintain or increase muscle mass an intensity of at least 70% of one’s one repetition maximum (1RM) was needed and considered the minimum amount required to provide sufficient neural, contractile, and metabolic stimulus for muscle hypertrophy and increased strength gains. However, performing at this intensity is not always possible, is contraindicated to certain populations, and may not even be necessary for specific outcomes desired. Thus, working with lower intensities while also gaining similar benefits would greatly help those contraindicated to the higher intensity. Blood flow restriction (BFR) is a novel modality that manipulates resistance training to enhance or modulate its effects, particularly at lower intensities.

1.1 Literature Review Preface

BFR training is shown to have many benefits, including increased strength and hypertrophy, but understanding the underlying mechanisms still requires further research. A current issue with the understanding of BFR training is that the specific protocols used for BFR have not been standardized, thus leading to confusion in prescribing optimal training and obfuscating the
analysis between BFR studies and traditional resistance training (TRT). In addition, how (or if) BFR differs in its mechanisms between these styles of training is still unknown. There are many possible mechanistic differences: hypoxia, metabolites, cell swelling, etc; however, there is limited information on BFR and traditional training to similar levels of fatigue or failure. Training to repetition or task failure, where the participant is unable to complete another repetition, is becoming a common avenue to compare differing training programs.19

Through the process of outlining the current understanding of resistance training adaptations, reviewing the background of BFR training, and examining the current research that compares BFR to TRT, a further understanding of the possible modulators that could distinguish the mechanisms between these two styles of resistance training will be presented herein this literature review.

Chapter 2 - Literature Review

2.1 Resistance Training

Resistance exercise can be a critical component in providing long term health and wellness, as regular resistance exercise not only builds muscle strength and muscle mass, but also preserves bone density, independence, and vitality with age.4 As is well documented, the benefits go beyond just health and wellness, as resistance training is a key aspect of improving performance in a multitude of sports,9 as well as being a sport in and of itself.20 To obtain these sought after benefits, recommendations for resistance training are outcome specific, so that training for strength, for example, will more greatly benefit strength outcomes.11

Although training can be its own endeavor, generally, the purpose of resistance training is to increase one or more of the mentioned outcomes: strength, muscle size (hypertrophy), or endurance. To obtain the desired outcomes, the recommendations are classified by load (amount of weight lifted), volume (number of repetitions), rest (time between sets) and frequency (number of times trained per week). From the American College of Sports Medicine (ACSM), the recommendation for load is to lift between 70-100% of one’s 1RM for strength and hypertrophy, and 40-60% for endurance.11 Repetition ranges are related to the above factors and range from 1-12 repetitions for strength and hypertrophy, and 15+ repetitions for endurance.11
Rest between sets ranges from 3-5 min for strength and < 2 min for hypertrophy and endurance. Considering frequency, the range for all desired outcomes is between 2 and 5 days per week depending on the experience of the person performing resistance training.

Generally, the one of the most sought-after outcomes from participation in resistance training is an increase in strength. Strength, or maximal strength, is the peak force the neuromuscular system is capable of producing in a single maximal voluntary contraction. Maximal strength for a specific task is mediated by several factors, grossly broken down to neural adaptations and structural changes - with muscular hypertrophy being the main structural adaptation considered in this thesis. Neural adaptations, the adaptations of the nervous system peripheral to the muscle, are generally the first to show an effect. These are mediated through reduced inhibitory mechanisms, intramuscular coordination, and intermuscular coordination improvements. These neural adaptations are partially task and intensity specific and thus provide relatively greater increases to strength when testing on the same task than was trained; due to this “learned” factor, other modalities are typically used to investigate strength further. For example, if a typical dynamic leg extension was performed for training, a 1RM for leg extension would show greater improvements than maximal voluntary isometric contraction (MVIC) at a set angle for the leg extensors. Following these initial neural adaptations, structural adaptations, including muscular hypertrophy, is needed to continue and maximize strength gains long term.

Muscular hypertrophy, which generally results in an increase in muscle cell size, is believed to occur when muscle protein synthesis exceeds protein breakdown. Through either metabolic or mechanical stimuli, there are several primary anabolic signaling pathways that have been identified, including Akt/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), and calcium-(Ca$^{2+}$) dependent pathways. The precise mechanistic stimuli for hypertrophy is currently not well understood, as it is multifactorial and likely context-specific. There are many possible stimuli that can be organized into two distinct forms: mechanical and metabolic. Mechanical stimuli include the mechanical tension on contractile and structural proteins, and cell swelling that can cause stress to structural proteins and sarcolemma as well as damage to the cell as a whole. Metabolic stimuli include increases in known metabolites, including lactate, hydrogen, phosphate and calcium ions, as well as hypoxia. The metabolic
stimuli from resistance exercise can infer hypertrophic adaptation, but some can also stimulate other advantageous adaptations for endurance benefits.

Of the many metabolic stimuli that are produced during resistance training, hypoxia, or low oxygen in the tissues, can specifically increase factors that aid endurance performance, including hypoxia inducible factor (HIF) and vascular endothelial growth factor (VEGF), which together can increase angiogenesis and mitochondrial adaptations.\textsuperscript{28,29}

If these metabolic stimuli could be manipulated, it could be possible to enhance the effects of resistance training. One such modality that has this potential is BFR, but it is not fully known how BFR differs from TRT, and thus, a deeper understanding of BFR is needed.

\textbf{2.2 Blood Flow Restriction}

BFR is a new resistance training modality that typically involves light-load exercise while restricting blood flow of the proximal aspect of a limb using a tourniquet,\textsuperscript{30} such that if one is performing leg extensions, the quadriceps would be activated lifting the lower leg while the upper thigh is restricted. Initially gaining popularity in Japan, BFR was known as Kaatsu and invented by Yoshiaki Sato.\textsuperscript{18} Since then, it has gone by many other names: BFR,\textsuperscript{31} occlusion training,\textsuperscript{17} ischemic training\textsuperscript{32}, and the previously mentioned Kaatsu.\textsuperscript{18} As mentioned previously, resistance training was historically thought to require an intensity of 70\% of 1RM or greater\textsuperscript{11} to ensure desired strength and hypertrophy gains, but Sato showed that BFR training (or Kaatsu) could have similar benefits to traditional resistance training at 70\% 1RM while working at a much lower percentage.\textsuperscript{18} In a subsequent study, Yasuda et al., 2005 found a 7.8\% increase in muscle hypertrophy with BFR compared to 1.8\% for control where both trained at 20\% of 1RM for squats and leg curls.\textsuperscript{33} Further work revealed that while training bench press at 30\% of 1RM for only two weeks strength increased by 6\% in BFR compared to -2\% in their control group, with a 16\% increase in hypertrophy for BFR compared to 2\% in control group.\textsuperscript{34} Although these results seem extreme, it did provide proof of concept for BFR training as an innovative modality for resistance training as it was clearly different from lifting at a low percentage alone. Since then, BFR has shown promise in rehab settings for post-surgery and ACL repair,\textsuperscript{35} patellofemoral repair,\textsuperscript{36} increases in performance,\textsuperscript{31} and to help astronauts in maintaining fitness
in space. The increasing quantity of possible applications thus illustrates the growing potential of this novel training modality.

**2.2.1 BFR Training Methods**

Similar to TRT, wherein there are many possibilities for implementation, BFR training has been used in many situations and protocols since its invention. The most common protocol is to train at 20-40% of 1RM with 4 sets at a fixed repetition scheme (30-15-15-15 repetitions), i.e. the first set is performed for 30 repetitions and then three sets of 15 repetitions, with 30-60 sec rest between sets and performed for as short as a few days, up to 12 weeks or more of training. However, there has been a wide range and mix of protocols since the 30-15-15-15 repetition scheme at 20-40% had been implemented. Recently, a meta-analysis of the protocols of BFR looked into the wide-ranging protocols within BFR training. Starting with length of training, they found that protocols ranged from 6 days to 10 weeks, with most using 3 days per week training, and those that performed 2-3 days per week were between 4 and 10 weeks. This is also in line with Slysz et al., 2016, who determined using meta-analytic techniques that changes in strength and hypertrophy required over 6 and 8 weeks respectively. Loenneke et al., 2012 have also suggested that it could take up to 10 weeks to see results for strength. In opposition, Papini et al., 2015 report that for lower limb training there were greater results for BFR training compared to TRT when training for less than 2 weeks, and greater than 4 weeks resulted in minimal results. This required shorter time period to see results is counter-intuitive and in opposition to the data from other meta analyses.

In addition to time parameters that can be manipulated, factors specific to and within BFR can also be manipulated. Particularly, within BFR training, the amount of pressure applied by the tourniquet can be manipulated, which will alter the relative decrease in blood flow. Too light, and the pressure may not sufficiently cut off blood flow to cause an effect; too high, and it may cut off too much and limit the ability to train. There are also certain risks that could come with absolute pressures, particularly with increased perceived pain and potential damage to soft tissue. In the literature examining required pressures, the pressures varied mostly between upper and lower limbs as the muscle mass and blood flow at rest are quite different. Upper limbs ranged from 30 to 100mmHg while lower limbs ranged from 100 to 160mmHg and in
general the pressure was greater than brachial diastolic blood pressure and increased to greater
than systolic blood pressure. Similarly, Slysz et al., 2016 found pressures above 150mmHg were
most effective, but there was consensus that a single pressure across individuals would not
exhibit the same benefits. This has led to more individual-specific recommendations based on
either a percentage of lowest effective occlusive pressure (least occlusive pressure or LOP),
which is defined as the minimum pressure needed for full arterial occlusion. Alternatively,
calculations based on thigh circumference can also be used to estimate relative arterial occlusion
pressure.\textsuperscript{44,46,47} Generally, BFR recommendations range from 50-100\% of LOP or arterial
occlusion, with most recommending between 50-80\%.\textsuperscript{44,46,47} The differences in pressure do not
provide a large difference in increases in strength or hypertrophy when training at 30-60\% of
1RM, but it has been found that the higher pressures may be needed (i.e. greater than 80\% LOP),
when 20\% or less of 1RM is used.\textsuperscript{44}

Although there is a vast array of protocols for BFR training, there is general consensus of a
period of 6 to 8 weeks of training, performed 3 days per week, with intensities of 20-40\% of
1RM, and 50-100\% arterial occlusion is required to stimulate meaningful adaptation. However,
how this compares to TRT (i.e. high-loads) is still contentious, primarily due to the inherent
difficulty to match training protocols.

2.2.2 Matching BFR Training and Traditional Resistance Training

With the array of contrasting protocols for BFR training, the manner in which the efficacy of
BFR training is tested or compared for analysis of effects is also not standard. As mentioned,
most studies perform BFR at a set repetition scheme, normally 30-15-15-15 and percentage of
1RM, normally 20-40\%, and compare that to work-matched controls with no BFR.\textsuperscript{48-50}
Comparing BFR to worked-matched controls in training studies shows a multitude of benefits,
including direct increases in hypertrophy,\textsuperscript{50,51} endurance performance,\textsuperscript{50,52} and strength.\textsuperscript{49,51}
Additionally, acute studies have shown an increase in markers and factors that could lead to
further adaptations such as endurance capacity,\textsuperscript{53} hormonal markers,\textsuperscript{48,54,55} and metabolic factors
like increases in lactate and decreases in muscle oxygenation.\textsuperscript{56,57} A number of studies
specifically performed BFR to failure and then worked-matched the TRT group.\textsuperscript{56,57} These work
matched studies run under the assumption that matching to work also matches fatigue, but it does
not. Recent resistance training studies outside the domain of BFR have demonstrated that training at low and high loads to failure achieve similar increases in strength and hypertrophy, suggesting that it is the level of fatigue achieved in the muscle that is important.\textsuperscript{58,59} Thus, with BFR training to failure but TRT only work matched and generally achieving a lower level of fatigue, it is no surprise that BFR shows significant benefits as a training modality, because this design does not properly compare BFR to traditional resistance training.

Following the demonstration that BFR training adds significant training effects to a work-matched control, a more nuanced and marked design is needed to see any differing effects from traditional resistance training where it is also performed in a way that is designed to maximize adaptation (i.e., lifting to failure). With BFR making the same relative weight more difficult to lift, both in perception and the ability to move the weight, and providing similar benefits to heavier load training performed without BFR, it is difficult to compare BFR and TRT directly. The ability of resistance exercise as a whole to provide a hypertrophic effect lies, at least in part, in its ability to fatigue the muscle. Thus, having a similar time under tension (total time contracting) and having all groups performing workouts to concentric failure would be a reasonable avenue to have an analysis of different protocols. This is in agreement with Wernbom et al., 2007\textsuperscript{60} who concluded that training performed with maximum effort, such as by going to failure, and achieving the greatest recruitment of muscle fibers possible might be as important as training load. Although Davies et al., 2016\textsuperscript{61} argue that training to failure is not necessary, and that training to failure could lead to overtraining, it does seem that matching to failure is a reasonable avenue to compare modalities more directly, as suggested by Dankel et al., 2017.\textsuperscript{19}

Owing to the methodological research challenges noted above, a select number of studies have started to compare BFR to TRT using failure for both groups. Tanimoto et al., 2005\textsuperscript{62} compared BFR to multiple resistance training protocols, i.e. low load with BFR (BFR at 50% 1RM, 200mmHg), slow traditional resistance training (TRT at 30% 1RM, 6 sec cycle), isometric (isometric contraction at 50% 1RM for 56 sec/set) and high load traditional resistance training (TRT at 80% 1RM). All groups performed repetitions to failure except the isometric group which was matched to the slow group. The authors reported no difference between the groups in blood lactate measured at any time point before the onset of exercise, immediately post and 15- and 30-minutes post exercise. Similarly, plasma growth hormone did not change, except with the
isometric group, which was the only group that did not go to failure. They did, however, report that oxygenation, measured by near infrared spectroscopy (NIRS), was significantly lower in the BFR group. Additionally, Yasuda et al., 2015\(^6\) compared BFR to TRT by matching to failure and looking at muscle swelling. While training the arm flexors, they had both groups (BFR and TRT) train at 20% of 1RM to failure for 4 sets. Groups had vastly different rests between sets, with 3min for TRT and 30 sec for BFR. When training at the same percentage of 1RM, BFR is expected to require fewer repetitions to reach failure than TRT, so it is possible the different rest periods influenced these results. Despite this, by both groups training to repetition failure, there was no significant difference in any of their major outcomes, including electromyography (EMG), lactate concentration, and muscle thickness (swelling), with the only significant difference being in repetitions performed. This suggests that, in the acute time frame while training to failure, BFR and TRT are expected to cause similar effects in regard to muscle swelling. While this provides some evidence of the acute effects, longer term training could reveal differing outcomes and mechanisms underlying potential adaptations. Currently, there are only a few studies comparing BFR to TRT that perform exercises to failure in a training study; notably, many have been published during the time this thesis was being prepared, showing there is a growing desire for the more nuanced comparison. A summary of the relevant research is in Table 1 below:
### Table 1 - Summary of studies investigating the effects of BFR and TRT when controlled for failure

<table>
<thead>
<tr>
<th>Title/Author/Subjects</th>
<th>Limb/Exercise/Study design</th>
<th>% 1RM and BFR Pressures</th>
<th>Training Protocol</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscular adaptations to fatiguing exercise with and without blood flow restriction</strong> Fahs et al., 2019&lt;sup&gt;44&lt;/sup&gt; Male – 12, Female – 6</td>
<td>Leg Ext N=18, n=18/grp</td>
<td>30% 1RM both grps BFR – 0-2wks – 50% AOP 3-6wks – 80% AOP (~150, then 240mmHg)</td>
<td>6wks – 18 sessions 1min rest 0-2wks – 2sets 3-4wks – 3sets 5-6wks – 4sets All to failure</td>
<td><strong>Time effect only for:</strong> 1RM, mean power, muscular endurance, anterior thigh thickness <strong>Interaction effect for:</strong> lateral thigh thickness for BFR</td>
</tr>
<tr>
<td><strong>Blood flow restricted and traditional resistance training performed to fatigue produce equal muscle hypertrophy</strong> Farup et al., 2015&lt;sup&gt;55&lt;/sup&gt; Male – 8, Female – 2</td>
<td>Arm Flexion N=10, n=10/grp</td>
<td>40% 1RM both grps BFR – 100mmHg</td>
<td>3x/wk – 6wks 30sec rest 4 sets to failure</td>
<td><strong>Time effect only for:</strong> muscle thickness, 3RM, (no effect for MVIC) <strong>Interaction effect for:</strong> none</td>
</tr>
<tr>
<td><strong>Muscle adaptations to high-load training and very low-load training with and without blood flow restriction</strong> Jessee et al., 2018&lt;sup&gt;66&lt;/sup&gt; Male – 20, Female – 20</td>
<td>Leg Ext N=40, n=20/grp i.e., different condition per leg</td>
<td>%1RM% AOP: 70/0, 15/0, 15/40, and 15/80</td>
<td>2x/wk – 8wks 30sec for low load, 90sec for high load. 4 sets to failure (max 90reps/set)</td>
<td><strong>Time effect only for:</strong> muscle thickness, MVIC, isokinetic strength <strong>Interaction effect for:</strong> 1RM, 70/0 higher than 15/x, and endurance repetitions 15/80 higher than 70/0 and 15/0</td>
</tr>
<tr>
<td><strong>High-pressure blood flow restriction with very low load resistance training results in peripheral vascular adaptations similar to heavy resistance training</strong> Mouser et al., 2019&lt;sup&gt;67&lt;/sup&gt; Male – 20, Female – 20</td>
<td>Leg Ext and Arm Flexion N=20, n=20/grp i.e., different condition per limb</td>
<td>%1RM% AOP: 70/0, 15/0, 15/40, and 15/80</td>
<td>2x/wk – 8wks 30sec for low load, 90sec for high load. 4 sets to failure (max 90reps/set)</td>
<td><strong>Time effect only for:</strong> Venous compliance <strong>Interaction effect for:</strong> Vascular conductance - Upper body lower in 15/40 than 15/80 and 70/0, and Lower body was lower in 15/0 than 15/80 and 70/10 and 15/40 lower than 15/80 and 70/10</td>
</tr>
<tr>
<td><strong>Skeletal Muscle Mitochondrial Protein Synthesis and Respiration Increase with Low-Load Blood Flow Restricted as Well as High-Load Resistance Training</strong> Groennebaek et al., 2018&lt;sup&gt;48&lt;/sup&gt; Male – 34</td>
<td>Leg Ext and Arm Flexion N=34, n=12 BFR n=12 TRT n=10 control</td>
<td>%1RM% AOP: 70/0, 30/50, no exercise</td>
<td>3x/wk – 6 wks BFR – 30sec rest 4 sets to failure TRT – 3min rest 4 sets 10-12 (load increased if reached 12 for all sets)</td>
<td><strong>Time effect only for:</strong> Strength, mitochondria protein synthesis, and respiratory function <strong>Interaction effect for:</strong> Dynamic endurance</td>
</tr>
<tr>
<td><strong>Six Weeks of Low-Load Blood Flow Restricted and High-Load Resistance Exercise Training Produce Similar Increases in Cumulative Myofibrillar Protein Synthesis and Ribosomal Biogenesis in Healthy Males</strong> Siejacks et al., 2019&lt;sup&gt;69&lt;/sup&gt; Male – 34</td>
<td>Leg Ext N=34, n=12 BFR n=12 TRT n=10 control</td>
<td>%1RM% AOP: 70/0, 30/50, no exercise</td>
<td>3x/wk – 6 wks BFR – 30sec rest 4 sets to failure TRT – 3min rest 4 sets 10-12 (load increased if reached 12 for all sets)</td>
<td><strong>Time effect only for:</strong> RNA content, MVIC, 3RM <strong>Interaction effect for:</strong> N/A</td>
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</table>
As can be seen from Table 1 above, more work is needed to fully elucidate how the effect of training to failure affects the outcomes of TRT compared to BFR. However, the six studies above show a trend for strength: when BFR is compared to TRT with higher loads (>70% 1RM), TRT provides greater strength benefit. In the study by Jessee et al., 2019 they did not report a change in maximal voluntary isometric contractions (MVIC), which could indicate the increase in 1RM was more of a learned task improvement and represents increased intermuscular coordination at the leg extension task rather than improvements intramuscularly that would transfer to other tasks. The fact that the studies from Table 1 show no significant findings for 1RM between groups when both groups trained at the same weight suggests this as well.

In addition to the 1RM effects, there also seems to be a trend for added endurance benefits for BFR. Jessee et al., 2019 found BFR at 80% LOP provided the greatest improvement in muscular endurance. Seeing an effect like this when all groups went to failure is intriguing; however, the number of repetitions per set was restricted to a maximum of 90, which may not have been to failure in some groups. This was likely not an issue for the higher pressure BFR groups or high load TRT, but it would be for the lower pressure BFR and light load TRT groups as they could have surpassed this number in a set. They did not report the repetitions in the study, but they did mention that two participants in the 15% 1RM TRT condition did 90 repetitions for every set. Therefore, it is reasonable to assume that many sets overall in both of the 15% 1RM groups, (TRT and 40% LOP BFR group) did not reach failure. Despite this, there could still be an additional endurance effect between BFR at 15% 1RM and 80% LOP and TRT at 70% 1RM (which is the more traditional resistance training intensity). Further, Groennebaek et al., 2018 showed dynamic endurance increases for BFR over TRT. Again, this could be a true benefit for BFR, but it is noteworthy that their BFR group went to failure every set and had very low set rest, whereas their TRT group only ensured failure on the last set and had 3 min set rests. This difference could change the focus of the training compared to a more traditional comparison at 1min set rest. Mouser et al., 2019 reported an interaction for vascular conductance with BFR demonstrating greater changes than TRT. Although it is outside the scope of this thesis, their finding, as they suggest, could represent additional endurance and health benefits compared to higher intensity TRT.
It could be telling that the studies by Jessee et al., 2019, Mousser et al., 2019 and Groennebaek et al., 2018, although matching to failure, did reveal some small differences between BFR and TRT. This could be due to the fact that they had a higher number of participants compared to the other failure-matched studies, allowing them to find significance amongst small effect sizes. Additionally controlling for the crossover effect by not having two limbs from the same individual concurrently participating in different groups likely aided in parsing out these smaller effects. Despite these well-designed studies, what could cause these small differences is still not known.

2.2.3 Possible Modulators of BFR Training

Within the literature, there are many possible factors or mechanisms of action that could affect BFR, or could affect BFR in a different degree than TRT. These modulators (substances that can change the degree of effect) could allow for a better understanding of muscular adaptations with BFR and TRT. The mechanisms mediating BFR muscular adaptations has been speculated in recent reviews,\textsuperscript{70,71} to be driven by a plethora of factors including, but not limited to, muscle oxygenation and metabolic stress, muscle fibre type recruitment, growth hormone, mTOR signaling, myostatin, heat shock proteins, nitric oxide synthase, cell swelling and reperfusion. Most of these mechanisms are suggested from evidence in studies in which load and repetitions were matched. For example, lactate and growth hormone were found to be significantly higher after BFR compared to control exercise after one session of training in a study by Takarada et al.\textsuperscript{48} The training was performed to failure for BFR for all sets at \textasciitilde 20\% of 1RM at \textasciitilde 215mmHg, whereas the control group (TRT) also did \textasciitilde 20\% 1RM but only repetition matched the BFR. This type of study shows how BFR differs from TRT when training at the same percentage of 1RM and how the changes brought about from BFR are manifested. However, since fatigue, or the cellular manifestations thereof, is likely the main driver for adaptations, these studies do not show what, if anything, is truly different about the mechanisms of BFR.

Similarly, cell swelling has been noted as a key modulator for BFR,\textsuperscript{72} and the “swollen” feeling one gets from performing BFR lends itself to the assumption that this is a true effect; however, this is not fully supported by the evidence. To test this exact aspect, Yasuda et al., 2015 studied two groups performing arm curls paired with BFR (30 sec rest, 20\% 1RM and 160mmHg) and...
TRT (3 min rest, 20% 1RM), all sets to failure, and blood sampling was done before the first set, after the last set, and 15, 30, 60min after the last set. They found both groups had similar swelling (muscle thickness from ultrasound) throughout and thus cell swelling is likely not a BFR specific modulator. With this previously touted modulator at best an insignificant contributor, other modulators, such as lactate and metabolites have shown promise.

Lactate, and correspondingly the buildup of metabolites, has been suggested as another key modulator for BFR training. Lactate measurements are typically taken from the finger or earlobe where a capillary blood sample is analyzed in a blood lactate analyzer. This general technique thus represents the systemic measurement of blood lactate after it has left the active muscle. Similar to other modulators, lactate, and correspondingly the buildup of metabolites, has generally been suggested with studies that are not failure-matched, such as Takarada et al., 2000 and Nitzsche et al., 2018. However, it is worth noting that, within failure-matched studies, there are further suggestions that lactate could be a differential modulator for BFR. Gentil et al., 2006 found that BFR and TRT led to increased lactate compared to a super slow speed resistance training method, which would similarly be expected to cause alterations in normal blood flow to the working muscle. Although this does not show a difference compared to TRT, it does show a difference with varying methods of resistance training with BFR.

Furthermore, lactate was taken from the earlobe and was only taken pre and 3 min post the one set of exercise. It could also be the case that with more sets, such is common in both TRT and BFR, a difference could have been detected. Yet, there are studies that show lactate responses to be the same as TRT, and even some that show TRT can be higher, thus demonstrating the inconsistencies in the literature. A possible modulator that has shown more consistency and great promise as a BFR modulator is oxygenation.

As one of its key tenants, BFR has been said to reduce blood flow and decrease oxygenation, but whether failure (or similarly matched studies) still show a difference is less known. There does seem to be a possibility that oxygenated flow plays a mechanistic role as a stimulus for adaptation, as Ganesan et al., 2015 measured hemoglobin (Hb) and oxygen saturation in the vastus medialis (VM) during a session of knee extension exercise. They reported lower oxygen saturation with BFR at 100mmHg than the TRT trial where both performed at 50% 1RM and went to failure. The main finding from this study was that tissue oxygenation was lower for BFR...
than TRT even when controlled for failure, suggesting that this could be a differing mechanism for BFR.

### 2.2.3.1 Oxygenation and TRT

Despite tissue oxygenation being one of the possible modulators of resistance training in general, and one of the few that could differentiate the mechanisms of BFR and TRT, it has not been examined extensively. This has historically been due to the fact that methods have been too invasive or expensive. However, the emergence of near infrared spectroscopy (NIRS) in more portable and inexpensive devices has led to the ability to more readily study tissue oxygenation across many forms of exercise.

NIRS is a non-invasive technique that uses the absorption of light in the 700-1,000 nm spectrum. The absorption spectrum of light remitted from a tissue sample varies mainly with oxyhaemoglobin (HbO$_2$) (720nm) and deoxyhaemoglobin (HHb) (760 nm) levels. NIRS has been used to study muscle tissue oxygenation (percentage of oxygenated to deoxygenated haemoglobin) extensively in the last few decades. In 1994, Mancini et al. confirmed the high correlation of changes in NIRS with venous saturation values, where they found an average correlation coefficient of 0.92. Thus, NIRS appears to be a valid non-invasive method of monitoring tissue oxygenation that gives further insight into the modulators and mechanisms of resistance training and specifically BFR training.

Using NIRS, the study of how oxygenation levels change with different TRT protocols and techniques is now possible. Studies that have looked at oxygenation in traditional resistance training have found that decreases of approximately 10-30% occur, and it appears that there is minimal (if any) difference between training methods when protocols use failure as an endpoint. Azuma et al., 2002 found that, at exhaustion, the change in oxygenation in the vastus lateralis (VL) and rectus femoris (RF) at 30% and 40% of 1RM were 13.3±1.9 and 9.0±1.6% for VL and RF respectively. Hoffman et al., 2003 found oxygenation levels of 72.7±18.0% and 79.9±13.4% for their light intensity, high volume (15 repetitions with 60% of 1RM), or high intensity, low volume (4 repetitions with 90% of 1RM) groups respectively. These were not controlled to failure, but some subjects did reach failure in the high-intensity group, which could explain some of the greater degree of error overall. Hoffman et al., 2003 also found that
the group that had a greater oxygenation disruption showed a correlation to a higher growth hormone response along with 58% higher lactate levels. They also measured re-oxygenation, which was delayed in their LI group. Other studies have found a connection with the level of deoxygenation and hypertrophy. Miyamoto et al., 2013\(^2\) suggested that the typically observed regional differences of hypertrophy are related to the regional differences in deoxygenation as opposed to activation, as there is a lack of difference in regional activation.

Taken together, this suggests that NIRS can provide a reliable and non-invasive method for estimating the oxygenation of working muscles under numerous training situations. Though it has not shown marked differences in traditional training techniques and more studies are needed to fully elucidate oxygenation’s role in hypertrophy, particularly with regional differences and possibly with BFR training.

### 2.2.3.2 Metabolites and TRT

In strenuous exercise, there are a number of by-products that result from cellular metabolism. Among the many by-products are lactate, hydrogen and phosphate ions. In addition, lactate production has been associated with the production of other metabolites.\(^3\) Lactate, and other correlated metabolites, have implications to muscular adaptations following training,\(^4\) as it has been shown that metabolic stress is correlated with hypertrophy,\(^5\) and it could also affect fibre recruitment.\(^6\) Lactate itself has also been associated with increasing hypertrophy through the increase in human growth hormone.\(^7,8\) Whether lactate causes a direct affect or not, lactate being the most easily tested, through minor finger or earlobe capillary blood samples and a point-of-care analyzer, has become a key determinant of metabolic production for non-invasive investigations.

### 2.2.3.3 Oxygen and Metabolites with BFR

How tissue level oxygen consumption and metabolite production together are influenced during BFR training may be a key aspect to understanding BFR and its effects, yet this has only recently been studied. One such study, Tanimoto et al., 2005,\(^6\) compared four different training methods for leg extensions: low load with BFR (BFR at 50% 1RM, 200mmHg), slow traditional training (TRT at 30% 1RM, 6 sec cycle), isometric (isometric contraction at 50% 1RM for 56 sec/set)
and high load traditional training (TRT at 80% 1RM), where all groups went to failure except for the ISO group. They found that compared to the HL (high load TRT group) the greatest decrease in oxygenation was in the LO (BFR group). They also found no significant differences between the groups (other than ISO) in lactate or growth hormone. In a more recent study, Karabulut et al., 2014 found that compared to the HL group, the greatest decrease in oxygenation was in the LO group. They also found no significant differences between the groups (other than ISO) in lactate or growth hormone. In a more recent study, Karabulut et al., 2014 used leg extensions to study the rectus femoris (RF) oxygenation with BFR with a cuff pressure at 1.44x arm systolic blood pressure for four sets with a fixed repetition scheme (30-15-15-15 repetitions). An additional aspect to the study involved manipulating the pressure of the tourniquet before the start of exercise. Correspondingly, they found that manipulating the initial pressure changed muscle oxygenation, but no pressure correlated more strongly with lactate levels. Although not compared to TRT, they did show the connection of degrees of BFR pressures and changes in oxygenation. Furthermore, Reis et al., 2019 reported that as the occlusion pressure increased, the tissue oxygenation decreased finding that 80% LOP was needed to see a significant difference from the TRT group, although all groups performed the same 20% 1RM and 30-15-15-15 repetition protocol. While these studies report on the metabolic perturbations following a single bout of high-load and BFR resistance training protocols, to our knowledge, no studies have tracked tissue oxygenation in a BFR training study over time to understand the relationship with longer-term adaptation.

In addition to how metabolites and oxygenation affect BFR, how these contribute to the differences between BFR and TRT is also a consideration. In a study looking at metabolic changes with BFR, Yanagisama et al., 2017 showed that there was a greater increase in phosphate ions, and decrease in oxygenation and hydrogen ions in the plantar flexors of for BFR compared to TRT. This demonstrates that generally, when one metabolite changes, so do the others and this is tightly linked with oxygenation. However, it may be possible to change one factor (metabolites or oxygenation) more than the other in order to understand which is primarily responsible for stimulating the muscle to adapt. As previously mentioned, Karabulut et al., 2014 found that varying the pressures for BFR before exercise changed the muscle oxygenation during exercise, but this change in pressures had no correlations with lactate. This finding suggests it could be possible to vary the degree of pressure to get a greater change in oxygenation compared to lactate. Although there are studies that show there are no differences in oxygenation and lactate when varying pressures in BFR, those studies were done with the contralateral limb as different conditions so the cross-transfer effect could confound any
findings. The cross-transfer effect is when training one limb only, the contralateral limb shows some of the same adaptations with no training, particularly with BFR. Due to this cross-transfer effect, some differing adaptions between BFR and TRT could be missed. Furthermore, a greater degree of tissue oxygenation change would be needed to assess a correlation with oxygenation and lactate, with resistance training and specifically BFR. Thus, it is unclear if manipulating the degree of occlusion, as in using a 100% occluded protocol compared to a 50% occluded protocol, resulting in decreased muscle tissue oxygenation elicits a correlating response of desired outcomes of strength, hypertrophy or endurance and at possibly different levels of metabolite buildup.

2.3 Research Question

To date, no training studies have investigated the effect of suprasystolic and subsystolic levels of BFR for manipulating tissue oxygenation (using NIRS) and the buildup of metabolic by-products to assess the effects of these metabolites on strength, muscular hypertrophy and endurance. Specifically, there is a lack of studies with research designs that control the exercise stimuli by matching to repetition failure, and few that account for the cross-transfer effect by allocating each individual to a single group (as opposed to one leg in each group). Thus, using an 8-week resistance training study, BFR and TRT will be compared in young, healthy, recreationally active adults to examine the effect muscle tissue oxygenation and lactate have on the effects of training with varying degrees of BFR. This will be observed through the effect on strength, hypertrophy and endurance when comparing traditional resistance training (TRT) and a high (BFR\textsubscript{100}) and a low (BFR\textsubscript{50}) blood flow restriction pressure, while employing a training protocol that had similar sets and repetitions, and controlled for the degree of fatigue by going to failure. It is postulated that BFR\textsubscript{100} could decrease oxygenation more than BFR\textsubscript{50} while lactate could stay similar between the BFR groups, while TRT would have an attenuated decrease in oxygenation and increase in lactate. Additionally, it is expected that all groups would have similar levels of hypertrophy and increases static strength. Differences in outcomes would be expected in 1RM as TRT is expected to have greater increases, and BFR\textsubscript{100} and BFR\textsubscript{50} to possibly have greater increases in endurance. This will aid in the ability to see the true differences these metabolic markers can cause in strength, hypertrophy and endurance across BFR and TRT.
2.4 Methods

In this thesis, the main equipment for training and for all dynamic muscular testing was a robotically controlled resistance device, the 1080 Quantum (1080 Motion, Lidingö, Sweden), which was uniquely attached to a standard leg extension machine (the Element Fitness Carbon Dual 9019 Leg Extension/Leg Curl; The Treadmill Factory, Mississauga, Canada) as seen in Figure 1, above. This set up was used to allow precise control of the custom-made dynamometer and easily manipulate the resistance, and it allowed testing on the same apparatus. This set up has previously been shown by our lab to correlate with the gold standard Humac Norm (CSMi Medical Solutions, Stoughton, MA) and has a high repeatability, demonstrating it is a valid testing and training apparatus.94

Lactate measurements for resistance training studies have typically been collected from the finger or ear lobe95,96 to give values for systemic blood lactate. BFR studies have similarly done this,62,75 but the issue of restricting or occluding blood from leaving the exercising limb in venous circulations is that systemic lactate values would thus not account for these tissue level changes. Due to this, a novel toe prick sampling was implemented to assess the lactate accumulation in the exercising limb (below the level of circulatory restriction) to account for the
fact that blood from that limb would not freely circulate in systemic circulation. Pilot tests were performed to assess the validity of the toe prick in comparison to a standard finger prick in multiple non BFR exercising situations, and it was found that there was high correlation of the lactate values between the toe and the finger. Since the toe was sufficiently validated as a technique, the toe technique was thus implemented for the analysis of lactate for all exercising limbs in the main study, which included BFR limbs.

NIRS was used to measure percent tissue oxygenation, or tissue saturation index (TSI%). NIRS is a noninvasive method that utilizes a 25 mm reflectance probe to measure the absorption of light photons in the 700–1000 nm spectrum. The absorption spectrum of light remitted from a tissue sample varies mainly with oxyhaemoglobin (HbO₂) and deoxyhaemoglobin (HHb) levels. The optical attenuation at 720 nm is responsive to oxyhaemoglobin, and the attenuation at 760 nm is responsive to oxyhaemoglobin and deoxyhaemoglobin. Despite the fact that haemoglobin (Hb) and myoglobin (Mb) spectrums overlap, the NIRS signal is primarily derived from the small blood vessels, because the blood vessels have large total amounts of blood and the signal is virtually complete from these vessels. From the ratio of 720 nm and 760 nm absorbance, a relative tissue saturation index (TSI%) can be obtained. The spectrometer system automatically provided an average of every 10 sec data before, during and after knee extension exercises for each dependent variable measured. TSI% measurements were taken as change from baseline. Specifically, PortaMon, Artinis Medical Systems BV, Netherlands was used for its ease of use and has been validated for use in exercise studies. The literature has shown rectus femoris (RF), vastus lateralis (VL) and vastus medialis (VM) as commonly measured muscles. For this study, RF was used as it has been used in related literature and was easily palpable and easily marked consistently by marking 50% of the distance between the top of the patella and anterior superior iliac spine (ASIS). The NIRS device was held in place using an elastic strap and with a black cloth over top to block out all external light. The main parameter investigated was TSI% and it was analyzed for each set, each break and in the following within workout contexts.
Table 2 – Additional parameters of TSI% calculated for analysis

<table>
<thead>
<tr>
<th>TSI% Parameter</th>
<th>Description of TSI% Parameter</th>
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<tr>
<td>Deoxygenation of Workout</td>
<td>Average TSI% of the entire workout including rests</td>
</tr>
<tr>
<td>Deoxygenation of Work Sets</td>
<td>Average TSI% of the entire workout not including rests</td>
</tr>
<tr>
<td>Deoxygenation of Last Set</td>
<td>Average TSI% of the last set performed in the workout</td>
</tr>
<tr>
<td>Accumulated Deoxygenation Stress of Workout</td>
<td>Average TSI% of the workout multiplied by total time of workout</td>
</tr>
<tr>
<td>Accumulated Deoxygenation Stress of Work Sets</td>
<td>Average TSI% of the work sets multiplied by total time of work sets</td>
</tr>
<tr>
<td>Accumulated Deoxygenation Stress Last Set</td>
<td>Average TSI% of the last set multiplied by total time of last set</td>
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As mentioned, when testing strength on the same apparatus in the same manner as training, there is a greater increase in strength in the specifically trained task, a learned task. Thus, to look into the adaptation of strength in greater depth, a maximal static task (MVIC) was used. Additionally, the MVIC was used to investigate the activation level of the participants. The activation level was tested as some studies have reported an increase in activation with higher load training. In addition to testing differences in training, the activation level was also used to ensure participants were sufficiently motivated and encouraged; for this, a VA % of 90% or greater was required. As mentioned in the introduction, there are multiple avenues for increasing strength, (neural and structural, etc.), and although there are likely many facets to strength and hypertrophy in a training study, this study did not test the underlying mechanisms. Two distinct tests each for changes in strength and hypertrophy were performed to support confidence in both outcomes.

For the training protocol, while pilot testing multiple standard BFR training protocols, it was found that the standard repetition scheme of 30-15-15-15 was unattainable using our setup and protocol. Participants generally could not perform more than the first set when blood flow was restricted and generally found that, if failure was reached, they were not capable of performing any further sets. Participants reported that they were completely unable to move their limb after failure was reached on the first set, until pressure was released from the cuff. Thus, the study was designed to achieve a similar volume of repetitions but to avoid failure until the fourth set for each participant, which resulted in the prescription of 3 sets of 10 repetitions and a fourth set to failure.
The following is presented in manuscript style in preparation for publication.
Chapter 3 - Manuscript

High Load Traditional Resistance Training and Two Levels of Low Load BFR
Produce Similar Levels of Hypertrophy and Increases in Strength and Endurance
with Limited Effect from Tissue Oxygenation or Lactate

3.1 Introduction

The benefits of exercise, and particularly resistance exercise, are well known and continue to evolve as our understanding of their physiologic effect grows. Resistance exercise has been shown to decrease mortality,\textsuperscript{5-7} aid in glucose control,\textsuperscript{8} and increase performance\textsuperscript{9}. Due to the multitude of benefits of resistance training, elucidating how to maximize its effects has long been a driving motivator for exercise research. A growing and novel modality to manipulate resistance training and to enhance its effects is blood flow restriction (BFR) training.\textsuperscript{16}

Resistance exercise has been shown to be effective, and has traditionally been prescribed, using loads greater than 70% of a one repetition maximum (IRM).\textsuperscript{60,98,99} This intensity was thought to be the minimum required to provide sufficient neural, contractile, and metabolic stimulus for muscle hypertrophy and increased strength gains.\textsuperscript{11} Recent studies show that training with loads much lower than traditionally prescribed result in similar hypertrophic gains, whereas gains in strength are promising, but not as robust.\textsuperscript{58,59,100} Similarly, it has been demonstrated that BFR training, with loads as low as 20% of IRM cause increases in hypertrophy and strength that are similar to traditional resistance training (TRT) with heavier loads.\textsuperscript{16} BFR training has shown potential to augment training in a variety of situations and for multiple groups requiring physical training including athletes,\textsuperscript{101} astronauts,\textsuperscript{37} and for patients undergoing rehabilitation.\textsuperscript{102,103} While BFR training has been examined and applied in a number of different ways, how its mechanisms of adaptation differ, if at all, from TRT is still unknown. Proposed mechanisms include an increase in metabolic stress through the build-up of waste products,\textsuperscript{104} increased local hypoxic stress,\textsuperscript{105} and training induced cell swelling.\textsuperscript{71}
With a lack of consensus on the mechanisms specific to BFR, tissue oxygenation stands out as a likely contributor, even though it has not been studied in detail. To date, studies have considered the acute effects of decreasing local tissue oxygenation via BFR, but not how altering this stimuli repeatedly over time might affect adaptation to longer-term training. Specifically, whether tissue oxygenation and metabolites modulate hypertrophy and strength in a dose-dependent manner has not been investigated. Along with a potentially greater drop in tissue oxygenation from BFR, there could be an increase in endurance performance, as is observed in some preliminary BFR studies and perhaps related to the effect noted following use of a similar blood flow manipulation technique, ischemic preconditioning.

In addition to variations in the possible local modulators of adaptation, the protocol for BFR training has not been standardized, particularly when comparing to traditional resistance training. Some of these protocols include set and repetition schemes at varying intensities (repetitions of 30-15-15-15 sets to task failure, and others that include varying degrees of matching to the control i.e., to failure or not, volume match by load lifted, etc.). For training with or without BFR, there is debate as to whether task failure is ideal, and also whether it is required at all. Similarly, total time under tension and volume have been discussed in TRT for many years, with a suggestion that a combination of training at a moderately high intensity and with multiple sets is likely ideal. To compounding this, a more systemic response from BFR has been shown, such that a “cross-transfer effect” may occur, which means a BFR trained limb could impart physical benefits to a non-BFR trained limb. This cross-transfer, although exists in all styles of training, has shown to be greater in BFR training as shown by Madarame et al., where BFR showed a significant cross-transfer effect in isometric strength, 1RM and cross sectional area of the thigh where traditional training only saw significant effects in 1RM. Evidence in the existing literature thus may well be confounded by this cross-transfer effect as many studies to date have allocated different limbs to different training conditions. Other possible interferences in the understanding of BFR training is an incomplete understanding of the effect different BFR pressures could have on the outcomes of training. The amount of pressure administered would change the effect of BFR, but there are limited studies on the effect of different pressures, on outcomes, and within the tissue. Karabulut et al., 2014 and Reis et al., 2019 both show that oxygenation can be changed with varying BFR pressures, but no study to date has looked at the effect of differences in oxygenation with longer term training.
Thus, with differing restriction pressures, it is possible to more clearly expose any differences
with BFR training and TRT, particularly as it pertains to the effects of oxygenation and
metabolites. This can be done by safely accruing multiple sets while going to failure on the final
set, and controlling for the crossover effect by only using one condition per subject. This could
occur by manipulating the amount of occlusion in multiple groups, thereby enhancing the
differences between oxygenation and metabolites, and between blood flow restriction and
traditional training.

The purpose of this research is to compare BFR to TRT, in young, healthy, recreationally active
adults through an 8-week resistance training study. Through this training, the differences
between three groups of training, TRT and two levels of BFR (BFR\textsubscript{50} and BF\textsubscript{100}), will be
investigated. In particular, we are seeking to understand whether oxygen and lactate levels have a
greater effect on changes in strength, hypertrophy and muscular endurance for BFR training
compared to TRT, all while employing a training protocol that had similar sets and repetitions,
and controlled for the degree of fatigue by going to failure.

### 3.2 Methods

#### 3.2.1 Subjects

Thirty adult participants (15 men and 15 women) were recruited. Eligible participants were
between the ages of 18 and 45, free from any current or ongoing musculoskeletal injuries or
neuromuscular disorders involving the hips, knees, or ankles, renal or kidney disease or a family
history of renal or kidney disease, and could not have completed any formal lower body
resistance training for at least 6 months prior to the start of the study. This study was approved
by and carried out in accordance with the recommendations of the University of Guelph’s
Research Ethics Board (REB#17-08-010). Prior to any data collection, all participants signed an
informed consent form.

#### 3.2.2 Experimental Design

A randomized, between-group, parallel design training study was employed, with participants
randomly assigned to one of three groups: BFR at maximum arterial occlusion (BFR\textsubscript{100}), BFR at
50% of maximum arterial occlusion (BFR\textsubscript{50}), or traditional resistance training (TRT). Both BFR groups trained at 20% of their 1RM (maximal amount that could be lifted once) while the TRT grouped trained at 70% of their 1RM. Maximal strength (1RM) and training weights were assessed at baseline, and then reassessed after 4 weeks. Measurements were collected at baseline (pre), and after 4 (mid) and 8 (post) weeks of training. The aim of using these particular exercise intensities was to induce similar fatigue across all groups by having participants perform approximately the same number of repetitions. Participants completed leg extension resistance training 3 times per week for 8 weeks, for a total of 24 sessions, separated by a minimum of 24 hours. Both legs were trained independently throughout the course of training, and single leg tests were performed at each testing point, with one leg randomly assigned as the testing leg at the onset of the study. Testing was separated by 48-72 hours and was as close to the same time of day as possible. Before each testing session the participants were asked to refrain from any strenuous exercise for 24 hours, and caffeine and alcohol for 12 hours. Intra-workout testing investigated discomfort levels, lactate, and tissue oxygenation using a NIRS device, through a typical training session and was performed on the third training visit.

All participants performed resistance training on a standard leg extension machine connected to a custom-built 1080 Quantum dynamometer. Training included 4 sets of single-leg knee extensions with a 1-minute break between each set. The first 3 sets were 10 repetitions, while the fourth set was to failure. To account for differing acclimation to the training, if a subject performed more than 20 repetitions on their last set for two sessions in a row, moving forward the first three sets were increased to sets of 12 instead of 10. Volume was recorded as the average number of repetitions per workout, while load was recorded as the number of repetitions multiplied by the average weight.

Each participant completed 5 testing visits and one separate intra-workout test day that occurred on the third training day. Test day 1 included: height and weight for participant characteristics, thigh length and circumference for BFR and NIRS set up, ultrasound of rectus femoris thickness, isometric muscle function (MVIC, VA%), dynamic muscle function (1RM, and endurance kicking task). Test day 2 included DEXA for thigh mass, and VO\textsubscript{2}peak for total body endurance. Test days 1 and 2 were completed at baseline and after 8 weeks of training, whereas test day 1 was also completed after 4 weeks of training. The overall design is shown in Figure 2.
Figure 2 – A schematic representation of the study design.
Isometric contractile properties of the knee extensors were quantified using a Humac Norm multi-joint dynamometer (CSMi Medical Solutions, Stoughton, MA). Subjects were seated with their hip angle at 110°, with a four-point seat belt immobilizing participants’ shoulders, and inelastic straps restraining their hips and thigh to limit movement to the knee extension. The experimental knee angle was set at 90° and was aligned with the dynamometer’s axis of rotation, and the dynamometer’s arm was fastened with a padded strap superior to the malleoli.

Torque and stimulus trigger data were sampled at 1,000 Hz using a 12-bit analog-to-digital converter (PowerLab System 16/35, AD Instruments, Bella Vista, Australia). All data was analyzed with Labchart (AD Labchart, Pro Modules 2014, version 8) software. The stimulation used in this experiment was a single pulse stimulus (square wave 1,000 µs pulse at 400 V) delivered to the femoral nerve using a Digitimer DS7AH constant current stimulator (Digitimer Ltd., Welwyn Garden City, UK). The anode (Cleartrace 1700-030 ECG Electrode, ConMed, Utica, New York, USA) was placed over the inguinal triangle and the cathode, a custom-made aluminum electrode pad (dimensions: 6-8 cm width and 8-10 cm length) wrapped in a damp paper towel covered in conductive gel was placed over the inferior gluteal fold. Peak twitch torque (Pt) was determined by increasing the single pulse stimulation current by 10-25 mA (per stimulation) until Pt plateaued, and current further increased by ~15% to ensure activation of the entire motor neuron pool.

All contractions were isometric knee extensions. The following protocol was completed during each of the three testing sessions. Once orientated in the dynamometer, the participants’ Pt was determined. The participant then completed 2-3 maximal voluntary isometric contractions, 3-5 sec in duration, at 90° of knee extension (referenced to a straight leg = 0°), separated by 3 min of rest. During these MVICs, visual feedback was provided via a real-time torque tracing on a computer monitor and participants were verbally encouraged during the contractions. VA during MVICs was assessed using the interpolated twitch technique (ITT). Briefly, using the current determined for Pt, single pulse electrically-evoked twitches were delivered manually during each MVC ~2 sec prior the contraction, during peak torque plateau (Ts), and 2 sec following at rest.
Participants’ data were only included if they achieved a minimum VA level of 90% or greater. VA% was calculated as: $\text{VA} \% = (1 - (T_s/T_r)) \times 100$.

### 3.2.4 Dynamic Muscle Function

Prior to training, participants visited the lab to have their 1RM measured on the custom-built 1080 Quantum dynamometer, which differed from the Humac Norm dynamometer used for MVICs. The setup has been previously validated as a reliable testing apparatus, but was not used for direct comparison with the Humac Norm Dynamometer as the robotically controlled resistance was provided using cable linear speed monitoring, and included a leg-extension specific cam on the resistance cable. Following a short warmup, participants performed a 1RM test whereby the weight was set to ~80% of 1RM and after each successful lift the intensity was increased by ~5%. The weight was increased until participants could not complete a lift through the entire range of motion and 2-3 min of rest was allotted between each attempt. Each contraction was only considered successful when the participants completed a full extension, from knee angle of 90° to 0°, in a controlled manner without assistance. If a participant could do the maximum the machine resisted (55 kg) more than once, a calculated maximum was used using this equation:

$$1\text{RM} = \frac{3\text{RM}}{1.0278 - (3 \times 0.0278)}$$

and repeated for both legs.

Following the 1RM test, a 10-minute break was provided prior to a unilateral test of dynamic knee extension to volitional failure at 20% of 1RM using the same dynamometer (1080 Quantum). The test was performed at a constant pace of 3 sec per lift cycle (1.5 sec concentric, 1.5 sec eccentric) with the pace set using an electronic metronome (Metronome Beats – Stonekick v4.4.1). If the initially prescribed range of motion (90°) deteriorated more than one 1/3 of the prescribed range of motion, the test was terminated by an examiner before volitional failure.

### 3.2.5 Muscle Thickness – Ultrasound

Muscle thickness was assessed via ultrasound (US) prior to any exercise testing. Transverse ultrasound images of the participant’s experimental leg’s RF was obtained using a portable brightness mode (B-mode) ultrasound-imaging device (Sonosite M-Turbo, Markham, On,
Images were obtained (figure 3) while the participants were seated, with their hip and knee angles adjusted to 90° with muscles relaxed. Minimal and consistent pressure was applied with the probe to limit compression of the muscle and a generous amount of water-soluble transmission gel was applied to the skin. Non-uniform hypertrophy was accounted for by taking measurements at three spots along the RF at 30, 50, and 70% of thigh length. Thigh length was measured using a standard anthropometric tape measure at 30, 50, and 70% of the distance from the ASIS to the medial, superior border of the patella for the rectus femoris (RF). All ultrasound image analyses were performed using Image-J Software (National Institutes of Health, USA, version 1.8.0_112) by a single, experienced investigator. Prior to all analyses, each image was scaled from pixels to cm using the straight-line function in Image-J. The muscle thickness of the RF was measured as the distance (cm) from the adipose tissue-muscle interface to the muscle-muscle interface. Muscle thickness was determined using the straight-line function in the Image-J software. Two measurements were taken at each site and the average was used as the final measurement.

Figure 3 - Representative Ultrasound image with measurement. Green line represents centre of image and yellow line the measured distance taken as RF thickness.
3.2.6 Thigh lean mass – Dual X-ray Absorptiometry (DEXA)

Hypertrophy of the thigh was measured as thigh mass for all but two subjects (due to scheduling issues) by DEXA, using the fan-beam technology (model QDR 4500A, Hologic, Waltham, MA). After completion of the scans, results were calculated using the system’s most recent software release (2019). Lean muscle mass (LMM) was calculated by subtracting bone mineral content (BMC) from Lean+BMC. For the thigh, a region was defined by placing a horizontal line at the lowest point of the ischial tuberosity as the upper margin for the legs and a horizontal line at the centre of the knee joint, as shown in Figure 3.

Figure 4 - DEXA Region for Thigh Mass

3.2.7 Aerobic Fitness – Maximal aerobic capacity (VO2peak)

To determine VO2peak, participants performed a step ramp protocol on a cycle ergometer (Velotron, Racermate Inc., Seattle, U.S.A.). The protocol consisted of 2-minute stages that started at 50% of the participant’s weight in kg converted to Watts (i.e., if the participant weighed 80 kg, the first stage was 40 W). Each 2-minute stage thereafter increased by the starting stage (i.e., for an 80 kg participant, stages would be 40 W, 80 W, 120 W, etc.). Breath-by-breath measures of pulmonary gas exchange, heart rate, and ventilation were accomplished using a metabolic cart (Quark CPET, COSMED, Rome), which was calibrated using a precision 3L syringe and gases of known concentration. The test was terminated at volitional failure or if a consistent plateau in VO2 was observed. VO2peak was the maximal VO2 observed when data was corrected using 30 second rolling average filtering. The stage at which oxygen consumption corresponded to 50 and 70% (VO2 @ 50%, VO2 @ 70%) of VO2peak was recorded and oxygen consumption before and after training for the specific stage was used for analysis. VO2peak was also used as a comparative data point.

3.2.8 Intra-Workout Testing

Each participant was tested during a training session to investigate acute changes to tissue oxygenation, as percent tissue saturation (TSI%), discomfort using a visual analog scale (VAS), and blood lactate using a toe prick on the exercising leg and a lactate analyzer. The Intra-
workout session was performed on session 5 or the third training session. The intra-workout timeline is outlined in Figure 4, below.

![Intra-workout Testing Timeline](image)

Muscle blood oxygenation was assessed using a portable, spatially resolved, dual wavelength NIRS apparatus (PortaMon, Artinis Medical Systems BV, Netherlands). The portable device was placed at 50% of the distance between the ASIS (Anterior Superior Iliac Spine) and the superior part of the patella on the quadriceps muscle to investigate rectus femoris oxygenation levels. The device was secured using Velcro straps and a thick black cloth was placed on top to ensure no external light. Tissue oxygenation was recorded before the cuff was inflated for the baseline values. After participants were seated, the cuff was strapped on, and tissue oxygenation was continuously monitored before, during and 5 minutes after exercise with (or without) the BFR cuff. The spectrometer system automatically provided an average of every 10 sec data before, during and after knee extension exercises for each dependent variable measured. TSI% measurements were taken as change from baseline. Additional parameters of TSI% are shown in table 3 below.

<table>
<thead>
<tr>
<th>TSI% Parameter (abbr for table)</th>
<th>Description of TSI% Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deoxygenation of Workout (Workout)</td>
<td>Average TSI% of the entire workout including rests</td>
</tr>
<tr>
<td>Deoxygenation of Work Sets (Work Sets)</td>
<td>Average TSI% of the entire workout not including rests</td>
</tr>
<tr>
<td>Deoxygenation of Last Set (Last Set)</td>
<td>Average TSI% of the last set performed in the workout</td>
</tr>
<tr>
<td>Accumulated Deoxygenation Stress of Workout (Acc Stress Workout)</td>
<td>Average TSI% of the workout multiplied by total time of workout</td>
</tr>
<tr>
<td>Accumulated Deoxygenation Stress of Work Sets (Acc Stress Work Sets)</td>
<td>Average TSI% of the work sets multiplied by total time of work sets</td>
</tr>
<tr>
<td>Accumulated Deoxygenation Stress Last Set (Acc Stress Last Set)</td>
<td>Average TSI% of the last set multiplied by total time of last set</td>
</tr>
</tbody>
</table>
Lactate measurements were taken from the toes of the exercising leg using a lactate analyzer (Lactate Plus, Nova Biomedical, Waltham, MA). Samples were taken at baseline immediately after each of the 4 sets, and 5 minutes after the last set finished. Isopropyl alcohol wipes were used to clean the puncture site before collecting blood. A 2.4 mm lancet was used to prick the subject’s toe and collect a drop of blood into the lactate analyzer strip at each time point and recorded.

A 100-point visual analog scale (VAS) was used to measure discomfort at all points lactate was measured - baseline, after each set and 5 minutes after the last set. Participants were instructed to rate the level of discomfort of the workout by clicking on a linear scale rated 0 to 100.

### 3.2.9 Blood Flow Restriction

BFR was applied 15 seconds before the first set started and continued through all sets and between-set rests until the last repetition to volitional failure on the last set. Automated tourniquets (PTSii Delfi Medical Innovations Inc., Vancouver) were used. The tourniquet was placed directly inferior to the gluteal fold and were fastened tightly around the thigh using Velcro straps. BFR pressures were controlled by the automated device. BFR\textsubscript{100} pressure was set to the individualized lowest effective limb occlusion pressure (LOP) that was measured by the device. On the other hand, BFR\textsubscript{50} used pressures that corresponded to 50% occlusion and was based on thigh circumference, as shown in Table 4.\textsuperscript{92} The 50% occlusion was based on previous literature that allowed an appropriate relative occlusion that was approximately 50% of arterial occlusion. Leg circumference was measured at 33% of the distance from the inguinal crease to the top of the patella.\textsuperscript{46}
### Table 4 - BFR Pressures and corresponding thigh circumference for desired LOP%

<table>
<thead>
<tr>
<th>Thigh circumference</th>
<th>40% LOP Pressure Used</th>
<th>50% LOP Pressure Used</th>
<th>60% LOP Pressure Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45-50.9cm</td>
<td>80mmHg</td>
<td>100mmHg</td>
<td>120mmHg</td>
</tr>
<tr>
<td>51-55.9cm</td>
<td>100mmHg</td>
<td>130mmHg</td>
<td>150mmHg</td>
</tr>
<tr>
<td>56-59.9cm</td>
<td>120mmHg</td>
<td>150mmHg</td>
<td>180mmHg</td>
</tr>
<tr>
<td>≥60.0cm</td>
<td>140mmHg</td>
<td>180mmHg</td>
<td>210mmHg</td>
</tr>
</tbody>
</table>

#### 3.2.10 Statistical Analysis

Baseline participant characteristics were compared between TRT, BFR$_{100}$ and BFR$_{50}$ using one-way ANOVA. Training outcomes (1RM, MVIC, US, DEXA, Endurance Kicking, VO$_{2\text{peak}}$) between BFR$_{100}$, BFR$_{50}$, and TRT were examined using 3(group)x3(time point) repeated-measures ANOVA. Intra-workout testing outcomes (TSI%, VAS, Lactate) between BFR$_{100}$, BFR$_{50}$, and TRT were examined using 3(group)x2(time point) repeated-measures ANOVA. Post-hoc testing was performed to follow-up on significant ANOVA results using a Bonferonni test to correct for multiple comparisons. All data were assessed for normality and corrected for lack of normality using the Greenhouse-Geisser test if necessary. Change scores used for correlation analysis were performed by subtracting baseline values (PRE) from post-training values (POST). Correlation analysis without adjustment was used to examine relationships between all outcome measures stated above. Data are reported as mean ± SD with significance set a priori at p<0.05. Statistical analysis was performed using SPSS (Version 24; IBM, Chicago, IL).

#### 3.3 Results

##### 3.3.1 Subjects

Of the 30 participants recruited, four men and six women did not complete the study. Seven participants dropped out after the orientation session due to interference of current training or due to time commitments, and three subjects dropped out during the first three weeks of training.
due to concerns about the total time commitment. Therefore, the data from 20 subjects, 9 women and 11 men (22 ± 2 years; height = 171.2 ± 10.7 cm; weight = 68.7± 14.0 kg) was analyzed and reported. General characteristics of each group are presented in Table 4 below.

Table 5 – Subject Characteristics

<table>
<thead>
<tr>
<th>Anthropometric Measure</th>
<th>BFR\textsubscript{100}</th>
<th>BFR\textsubscript{50}</th>
<th>TRT</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (m/f)</td>
<td>7 (4/3)</td>
<td>6 (4/2)</td>
<td>7 (4/3)</td>
<td>20 (11/9)</td>
<td>--</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>23.7 ± 3.5</td>
<td>21.2 ± 1.6</td>
<td>21.4 ± 1.5</td>
<td>22.2 ± 2.6</td>
<td>0.14</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.72 ±0.07</td>
<td>1.74 ±0.10</td>
<td>1.68 ±0.13</td>
<td>1.71 ±0.10</td>
<td>0.62</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.5 ± 13</td>
<td>70 ± 13</td>
<td>62.6 ± 15</td>
<td>68.7 ± 14</td>
<td>0.34</td>
</tr>
</tbody>
</table>

3.3.2 Oxygenation

For the intra-workout training session, there were no group and time interaction effects as no group had a change in tissue oxygenation (TSI\%) more than any other (p=0.25), but there was an effect of time across all groups (p<0.001) and a group effect (p=0.049). The accumulated stress of tissue deoxygenation (TSI\% multiplied by time) was also considered. For the accumulated stress of deoxygenation, the last set performed by the participants as well the total workout had group differences where BFR\textsubscript{50} had greater decreases in accumulated deoxygenation stress compared to BFR\textsubscript{100} and TRT. The decrease in TSI\% from baseline throughout the intra-workout testing is shown in figure 5 where TRT was shown to have the smallest decrease compared to the two BFR conditions.
Figure 6 - TSI% from Baseline across the intra-workout training session for BFR100, BFR50 and TRT. Error represented as SEM. Sig values set at p<0.05. * = TRT significantly different than BFR100 and BFR50.

When BFR100 and BFR50 were pooled together (BFRpool) to analyze BFR with TRT irrespective of pressure, the drop in oxygenation, as well as the accumulated deoxygenation stress (drop in TSI% multiplied by time), was shown to be greater for BFRpool across the whole workout.
### Table 6 – Tissue oxygenation values shown through tissue saturation index (TSI%) from NIRS across the intra-workout testing session. TSI% - % change from baseline. Accumulated Stress – arbitrary units (au).

<table>
<thead>
<tr>
<th>Variable</th>
<th>BFR&lt;sub&gt;100&lt;/sub&gt;</th>
<th>BFR&lt;sub&gt;50&lt;/sub&gt;</th>
<th>TRT</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=7</td>
<td>n=6</td>
<td>n=7</td>
<td>n=20</td>
<td></td>
</tr>
<tr>
<td><strong>TSI% All Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work sets (%Δ)</td>
<td>-13.9± 6.2</td>
<td>-18.7± 9.7</td>
<td>-11.3± 7.3</td>
<td>-14.4± 8.0</td>
<td>0.251</td>
</tr>
<tr>
<td>Workout (%Δ)</td>
<td>-13.9± 6.0</td>
<td>-17.6± 9.1</td>
<td>-8.4± 5.3</td>
<td>-13.1± 7.6</td>
<td>0.078</td>
</tr>
<tr>
<td>Acc Stress – work sets (au)</td>
<td>-1515± 754&lt;sup&gt;®&lt;/sup&gt;</td>
<td>-3332± 1636&lt;sup&gt;®$&lt;/sup&gt;</td>
<td>-1777± 925&lt;sup&gt;®&lt;/sup&gt;</td>
<td>-2171± 1346&lt;sup&gt;®&lt;/sup&gt;</td>
<td>0.027&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acc Stress – workout (au)</td>
<td>-3939± 1835&lt;sup&gt;®&lt;/sup&gt;</td>
<td>-6352± 3081&lt;sup&gt;®$&lt;/sup&gt;</td>
<td>-2532± 1349&lt;sup&gt;®&lt;/sup&gt;</td>
<td>-4170± 2578&lt;sup&gt;®&lt;/sup&gt;</td>
<td>0.018&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Last set (%Δ)</td>
<td>-11.60± 6.7</td>
<td>-19.77± 8.9</td>
<td>-13.4± 7.1</td>
<td>-14.7± 7.9</td>
<td>0.157</td>
</tr>
<tr>
<td>Acc Stress – last set (au)</td>
<td>-246.7± 152.6&lt;sup&gt;®&lt;/sup&gt;</td>
<td>-1586± 973.0&lt;sup&gt;®$&lt;/sup&gt;</td>
<td>-532.4± 285.3&lt;sup&gt;®&lt;/sup&gt;</td>
<td>-748.6± 783.4&lt;sup&gt;®&lt;/sup&gt;</td>
<td>0.001&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>TSI% BFR Pooled</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work sets (%Δ)</td>
<td>-16.1± 8.0</td>
<td>-11.3± 7.3</td>
<td>-14.4± 8.0</td>
<td>0.204</td>
<td></td>
</tr>
<tr>
<td>Workout (%Δ)</td>
<td>-15.6± 7.5</td>
<td>-8.4± 5.3</td>
<td>-13.1± 7.6</td>
<td>0.038&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Acc Stress – Work sets (au)</td>
<td>-2353± 1513</td>
<td>-1777± 925&lt;sup&gt;®&lt;/sup&gt;</td>
<td>-2171± 1356&lt;sup&gt;®&lt;/sup&gt;</td>
<td>0.405</td>
<td></td>
</tr>
<tr>
<td>Acc Stress – Workout (au)</td>
<td>-5052± 2685</td>
<td>-2532± 1349</td>
<td>-4170± 2579</td>
<td>0.033&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Sig values set at p<0.05. * = ANOVA significant p<0.05. For post hoc testing: @ = different than BFR<sub>100</sub>, # = different than BFR<sub>50</sub> and $ = different than TRT.

### 3.3.3 Lactate

All groups increased lactate values throughout the intra-workout testing session (p<0.001), but no group increased more than any other (p=0.82). Lactate rose 32% from 2.3± 1.4mmol/L at baseline to 3.0± 1.2mmol/L after set 4 and rose to its highest level after the 5 min break to 4.0± 1.3mmol/L. Lactate changes through the intra-workout testing session across all groups can been seen in Figure 6, where, notably, post 5-minute lactate was significantly higher than all other time points (p≤0.002)
3.3.4 Discomfort using a Visual Analogue Scale (VAS)

Across all groups, the participants discomfort level throughout the intra-workout testing session started from a low at baseline, increased through set 4, and returned to near baseline levels 5 minutes after the final. Additionally, there was a group and time interaction effect (p<0.001) where BFR100 had increased discomfort more than BFR50 and TRT (p<0.001) through the workout, but no differences were found between BFR50 and TRT. Changes in discomfort through the intra-workout testing session for all groups can been seen in Figure 7.
**3.3.5 Training Volume and Work**

The average number of repetitions completed (volume) per session was 40±9 overall. There were group differences in volume (p=0.001) where the 100% occlusion group, BFR100, completed 33±4 repetition, which was significantly lower than BFR50’s (p<0.001) 51±8 repetitions. TRT completed 40.8±3 repetitions and showed no significant differences between groups.

Work completed, represented as average number of repetitions x weight lifted in arbitrary units (au) per session, also showed a group effect (p<0.001) where, unexpectedly, TRT performed the most work with 1524±553 au (p<0.001), who trained at 70% of 1RM. The two BFR groups were not different in work completed with 415±88 au and 665±218 au for BFR100 and BFR50 respectively.
3.3.6 Strength

3.3.6.1 Dynamic and Isometric Strength

All groups increased in dynamic strength (1RM) over time, but there were no significantly greater improvements by any group when data was expressed by group mean, or as a change score from baseline (See Figure 9) (group mean p=0.15, change from baseline p=0.21). Across groups the overall average at baseline was 56.9±16.5 kg, which rose 14% to the midpoint (p=0.001) and 23.7% to post-training with 70.4±27.5 kg (p=0.004). Following training in all groups, MVIC presented no change over time (Pre: 155±51.9Nm, Mid:162.9±54.9Nm, and Post:162.5±47.8Nm, p=0.3). Voluntary activation across all groups stayed close to maximally activated with 94.8±3.5% at baseline and 96.5±3.1% at the conclusion of training (p=0.093) but were were no group and time interaction effects (p=0.25).

Although there were no apparent relationships with changes in 1RM and lactate in the early sets of the workout, there was a relationship found with changes in 1RM and lactate levels in set 4 (r = 0.50, p = 0.02) across all groups. When only looking within the BFR groups, the only relationship found was for MVIC and set 3 lactate levels with a moderate correlation of r = 0.62, p = 0.02, but not when examined across all groups.
Figure 9 - Strength Outcomes from 8 Weeks of Training. A – One repetition maximum (1RM) (kg) values by group. Sig values set at p<0.05. For post hoc testing: * = different than Pre, # = different than Mid, @ = different than Post – B – 1RM Delta Scores (kg) by group. – C – Maximal Voluntary Isometric Contraction (MVIC) Torque (N·m) by group.

3.3.7 Hypertrophy

3.3.7.1 Muscle Thickness - Ultrasound

Irrespective of group allocation, all groups demonstrated a hypertrophic response to training over time (p<0.05) with increases observed at all points measured along the muscle (proximal through distal). No group increased rectus femoris (RF) muscle thickness to a greater extent than the others, as no group or group×time interactions were found (p=0.79). Across groups, the pooled average at baseline was 2.02± 0.32 cm, which rose 11% to the midpoint with 2.25± 0.43 cm (p=0.001), and increased 12% at post-training with 2.26± 0.44 cm (p=0.004).

Although muscle thickness was not correlated with many other metrics, the change in RF thickness across all groups was found to have a moderate correlation (r = -0.45, p = 0.046) with
the decrease in oxygenation (TSI%) within the intra-workout training session, not including rests (work sets).

### 3.3.7.2 Thigh Lean Muscle Mass - DEXA

The lean muscle mass of the participants’ thighs, measured using DEXA, increased over the 8 weeks of training across all groups (p=0.02), with a trend for a change over time between the groups (p=0.07) wherein BFR50 increased the least.

Thigh lean mass changes did not have any clear associations, except when looking exclusively at the BFR groups. Within BFR only, the change in thigh mass at the end of the 8 weeks of training was found to be correlated with the discomfort level of the third set of the intra-workout training session (r = 0.70, p ≤ 0.015).

**Figure 10** - Hypertrophy Outcomes from 8 Weeks of Training. A – Rectus Femoris (RF) Thickness (cm) measured by ultrasound by group. Sig values set at p<0.05. For post hoc testing: * = different than Pre, # = different than Mid, # = different than Post – B – RF Delta Scores (cm) by group. – C – Thigh Lean Muscle Mass (LMM) (kg) measured by DEXA pre and post for each group.
3.3.8 Endurance

3.3.8.1 Dynamic Muscular Endurance Kicking Task

Dynamic muscular endurance increased for all groups through the 8 weeks of training, whether represented as repetitions completed or as the repetitions completed multiplied by the weight lifted (work) (task, p=0.02 and work p=0.001) and no group improved more than the others over time (p=0.32). The relative changes from baseline (delta scores), although not significant, are worth noting as the TRT group performed 14% more reps after training, whereas the BFR groups approximately doubled as BFR100 performed 126% and BFR50 87% more reps. Dynamic kicking work delta scores had similar trends of 55%, 144% and 93% more for TRT, BFR100, BFR50 respectively. However, no significant changes between the groups were found.

3.3.8.2 Aerobic Fitness - VO₂peak

There were no statistical differences in alterations of VO₂peak across groups in the participants’ ability to complete submaximal or maximal stationary cycling with whole-body oxygen consumption. Across all groups, the change in oxygen consumption at the stage representing 50% of maximal (VO₂ @ 50%), was found not to be significant, but trended for a decrease of 5.3% (p=0.125), suggesting an improvement in efficiency. Similarly, VO₂peak showed a non-significant trend across all groups with an increase of 3.2% (p=0.096). When BFR was pooled, to increase statistical power across these groups, a significant effect was found for VO₂peak (p=0.04) and VO₂ @ 50% (p=0.05) increasing with time across the two groups.

3.4 Discussion

This is the first study to investigate the specific effects of an amplified difference in tissue oxygenation and lactate on training, by intentionally varying the degree of BFR. Importantly, all training had lifting protocols standardized with similar number of repetitions and training until task failure. Overall, it was found that training to task failure led to similar increases in strength, hypertrophy and endurance across two levels of BFR and TRT. Similarly, oxygenation and lactate showed minor significant relationships with strength, hypertrophy and endurance changes.
3.4.1 Strength

All groups adapted to the training protocol and demonstrated increased strength and muscle size, as expected for an 8-week resistance training protocol. The literature is divided, and thus unclear, as to the magnitude of effects between TRT and BFR in regard to strength. There are studies that suggest strength will increase more, some suggest less, while others suggest similar increases for TRT vs BFR training. The wide variety of workout matching, or the way each group within a study is compared to each other, and the lack of matching to similar levels of fatigue, are possible reasons for the vast inconsistencies in the literature. By prescribing workouts to failure in all groups, we expected to find less profound differences after training and be more accurate to true modality differences.

Irrespective of training group, all groups increased 1RM strength. Although there was high variability, which may mask some of the possible differences in strength between the groups, this shows that when recreationally active participants train to failure all will similarly gain strength regardless of the method of training (maximizing hypoxia, or metabolic build-up) and consequent load. With each group training to task failure, it is expected that, according to the Hennemen size principal, they would all maximally recruit motor units upon reaching failure and, thus, all groups would obtain similar strength training adaptations.

Although a key functional maximal strength test, one issue with using 1RM for testing strength is that it is an active task and, thus, has a skill component to it. In this study, 1RM was tested using the same exercise and apparatus used for training, which allowed all groups to become experienced with the training and test. It could be that the TRT group more appropriately trained the skill of performing a 1RM as they trained at 70% of 1RM, while the BFR groups trained at 20%. The learned ability to perform a 1RM has been known for decades, as Moritani's review in 1993 suggests that increases in strength tests were a result of the acquisition of skill, and more recently Mangine et al., 2015 show both of their groups that trained at 70% and 90% of their 1RM improved their 1RM in back squat, however, the 90% group improved to a significantly greater extent, 13.8% vs 6.1% for the 70% 1RM group.

Although a greater increase in 1RM from training at 70% with TRT compared to 20% with BFR was not specifically observed, the delta scores could suggest a trend toward TRT having greater
IRM increase (see Figure 9 B), and it is possible that the low number of participants per group and high variability between and within participants prevented this from reaching statistical significance. That said, it is likely that any trend of greater increase in 1RM for TRT is explained by the trained skill aspect and not structural changes, as other studies have shown no difference with high and low loads when training to failure. There is further evidence that shows occasionally adding higher resistance training to low load BFR could mitigate the differences between protocols, which further suggests that the difference in adaptation is the learned skilled component, and could also suggest an avenue to mitigate these differences. Furthermore, the increases in 1RM for TRT over BFR in this study and others could be due to a learning effect from the 1RM test itself as we did not perform a familiarization trial and little or no familiarization trials is common in the literature.

To further understand the route of strength adaptations, a more controlled dynamometer was used. This was done to delve deeper into how the strength adaptations may have manifested and, thus, the skill component of 1RM testing was nullified using an isometric test such that no group had trained using this contraction pattern. As expected, irrespective of group, there was no significant increase in this isometric (MVIC) through the 8 weeks of training. However, the MVIC did seem to increase over time, with an increase of ~5% overall, but there was also large interindividual variability and it would have taken a greater than realistic increase to see a significant difference as the SD was approximately 30% of the MVICs torque. The very large group variations are likely explained, at least partially, by between subject differences and the large range of baseline torque values. This was accentuated by the mix of male and female participants who differed greatly in baseline strength, although even after investigating delta scores for all groups to eliminate baseline effects, there was still no significance in torque. This test, however, does show that taking out the learned component resulted in no difference between groups over time and demonstrates its possibility to investigate the more nuanced differences of BFR and TRT when training to failure and thus having smaller effect sizes.

One of the main aspects of the study design was to investigate the cause and associations related to the main outcomes. There were no associations found between changes in any strength test with any other metric in the early phase of the workout. Lactate levels were the only possible modulator found to have a correlation with strength changes. For dynamic strength, the changes
in 1RM were correlated with the lactate levels in set 4. Similarly, in the later stages of the
workout, static strength saw the changes in MVIC were correlated with lactate levels in set 3, but
this was only when looking within the BFR groups. The fact that 1RM and MVIC only have a
single significant correlation each, as well as them being relatively weak relationships, suggests
that while they are likely players in the adaptations from resistance training, lactate and
metabolites do not seem to be the sole drivers of change, nor a differentiator of BFR to TRT, at
least for dynamic strength (1RM). With static strength (MVIC) having correlations with lactate
within the BFR groups only could suggest that there is greater importance of metabolites for
static strength. The difference could be due to a greater reliance of 1RM on learning the leg
extension task compared to the MVIC, which was not done in training, and could be a greater
indication of structural changes. The fact that 1RM was potentially more based on learning the
task compared to adaptations from potential metabolic stimuli could explain why there was only
one weak association for 1RM.

Particularly in tests that have not be affected by learning the task, a possible reason higher load
training results in greater strength adaptations compared to lower load training is due to a greater
neural drive, or percent activation, after training. This, however, counters a more recent study
by Cook et al., 2018 who reported no difference in activation between low or high load
testing. To ensure full engagement for the MVIC tests from the participants, as well as to test
if there was an increase in neural drive, percent activation was measured using evoked twitches.
In line with Cook et al., no difference was found between groups or over time. This shows that
if proper protocol and encouragement is done for all testing, the activation levels do not change
regardless of intensity trained. This is a key finding, as it confirms that the general differences
normally reported in dynamic strength changes is due to task learning and could be mitigated by
occasionally adding higher percent training and that static strength is unaffected by training
intensity.

3.4.2 Hypertrophy

Hypertrophic adaptations resulting from BFR compared to TRT have typically been more robust
than strength adaptations, with hypertrophy generally reported to be the same or better than
TRT. Accordingly, we found that for all groups, there was significant hypertrophy through the 8
weeks of training; however, no differential changes between groups were found over time. Although there was a trend for differential changes between groups over time for thigh mass, it should be noted that the BFR\textsubscript{50} and BFR\textsubscript{100} groups each had one participant unable to do the DEXA tests, which, although a seemingly small difference, accounted for a 15% drop in participant numbers in those groups. With a relatively small sample size already, this drop in participants could have affected the ability to see a significant change. The change in RF thickness was similarly found to be the same across groups, further suggesting that training to task failure was the key determinant for hypertrophic outcomes.

For aspects that were causing or associated with the hypertrophic changes, the only correlation found was with oxygenation throughout the workout, not including breaks, and the change in RF thickness. Having TRT and two levels of BFR allowed investigation into a possible wider range of oxygenation. With the oxygenation correlation being across all groups, and BFR generally having a greater decrease in oxygenation, it could suggest that BFR could attenuate the hypertrophic response that is related to a decrease in oxygenation. However, there was no difference found between any of the groups when examining RF thickness. It is also possible that a certain level of hypoxia is a required stimulus for all styles of workouts as TSI\% of the workout not including rest breaks, was not different between groups in this study. TSI\% had no relationship to any outcome metric when looking just within BFR, which may suggest that there was not enough of a difference in oxygenation levels between the members of the two BFR groups, and that differences in tissue oxygenation were not sufficiently different to cause any changes. Multiple reviews\textsuperscript{117–119} and some primary studies\textsuperscript{56,120} suggest hypoxia to be a specific mechanism for BFR, but it seems likely that it is a mechanism for resistance training as a whole rather than a differentiator for BFR in regards to hypertrophic changes. It is possible that there is a threshold of hypoxia needed and that going beyond this by reducing TSI\% even further does not augment any changes.

Although not a biological modulator, the level of discomfort a subject felt was associated with hypertrophic changes. Specifically, thigh mass was associated with discomfort, particularly in set 3 and 4. The noted relationship of increased training discomfort and increases in thigh mass could suggest that BFR requires a participant to push through a certain amount of discomfort in order to reach failure and cause adaptation, to an extent that exceeds that required for traditional
training, as there were no correlations between discomfort and any hypertrophy metric. Although allowing an avenue to investigate possibilities, correlational findings should be an avenue for future research and specific claims left for such research.

Together, this suggests that with training to task failure, the stimuli, or the downstream results of the stimuli resulted in effects that were similar for all groups. The similar effects across groups could be mediated through the associated modulators, such as oxygenation for hypertrophy and lactate for strength, but these were not robust enough nor across all metrics. Thus, the mechanisms for BFR, if at all different than TRT, are still yet to be elucidated.

### 3.4.3 Endurance

Increases in endurance capacity have been shown in many circumstances with BFR\textsuperscript{50,52} and the similar blood flow manipulation technique, ischemic preconditioning (IPC)\textsuperscript{121,122}. The current study was designed to compare two resistance training modalities, and while resistance training is not normally considered a particularly effective avenue for endurance benefits, the multitude of benefits and possible mechanisms touted by BFR proponents suggested a need for the investigation of multiple endurance metrics. As expected, dynamic muscular endurance improved over time, but contrary to suggested literature, no group had a significant increase more than any other. However, the dynamic kicking task, although not significant, showed surprising variation from pre to post training between the groups where increases of 126\% and 87\% for BFR\textsubscript{100} and BFR\textsubscript{50} dwarf the modest 14\% for TRT in the number of repetitions performed. The lack of significance is possibly due to the extremely high variability, which masked the likelihood of seeing an effect. This variability was probably caused by the makeup of each group being of mixed gender, and also the vast differences in repetitions (some participants only achieved 22 repetitions pre and 31 post while others got up 235 repetitions post). With such large variability a much larger and unrealistic difference or a much larger sample size would have been needed to see an effect. Comparatively, Kacin et al., 2011\textsuperscript{50} did a similar test in which they performed maximum repetitions with 15\% of MVIC. Pre-training, 44± 11 repetitions was achieved for their BFR group and 45± 13 repetitions for their control group. After 4 weeks of training they found increases of 63\% and 36\% respectively reaching 71± 17 reps and 60± 18 reps for their BFR and control groups. The current study matches Kacin et al., 2011 as after 4 weeks,
this studies BFR groups increased their reps by 55 and 65%, and our TRT group also increased by only 25%. However, Kacin et al., 2011\textsuperscript{50} used pre-training MVIC for pre and post task weight, while the current study used their current 1RM at the time of testing. This was done as the testing was performed on the same equipment as the training and a certain aspect of the strength and endurance improvement would be the improved strength from learning the task. Hence, when the relative endurance, the kicking task work, was used instead to measure the difference, changes of 61, 70, and 58% for BFR\textsubscript{100}, BFR\textsubscript{50} and TRT were found. A possible reason a group difference was not seen, where Kacin et al., 2011 did, was that the current study matched groups to failure whereas only Kacin’s BFR group went to failure. Their control group, however, only matched the absolute weight and repetitions of their BFR group and did not go to failure, thus it could be expected that the BFR group would get a larger training effect.

Although the lack of matching to failure in studies such as Kacin et al could artificially show a greater endurance increase for BFR, there still exists a possibility that there may be a difference between BFR and TRT. The previous BFR studies saw marked improvements in endurance from BFR training with relatively low sample sizes, likely due to them not matching to failure or similar levels of fatigue. Thus, if training to failure or similar levels of fatigue, the possible added benefits of BFR would have to be teased out better with higher sample sizes and/or more controlled training situations in order to see the likely much smaller differences.

While previous studies have reported increases in VO\textsubscript{2max}\textsuperscript{52,123} and mitochondria function\textsuperscript{124} no change at submax intensities or peak intensities were found in this study. However, it was found that when BFR groups were pooled to strengthen statistical power, there was a time effect for VO\textsubscript{2} @ 50% and VO\textsubscript{peak} across the two groups (BFR\textsubscript{pool} and TRT). It is likely that, although there was a slight change over time, the leg extensions as a training protocol was not specific enough to affect cycling ability enough to see differences between groups. This is particularly possible after noticing the smaller effects between the groups for all parameters when all groups train to failure and could be exacerbated with the lower specificity of leg extensions and cycling compared to other tests.

Overall, modulators that affect the outcomes in strength training do not seem to be different for BFR vs TRT when training to failure. Additionally, when training to failure, BFR and TRT have
similar changes in strength, hypertrophy and endurance. BFR does stand out as reaching a certain level of discomfort does seem to be needed to achieve desired hypertrophic and endurance changes, with mechanisms unknown at this point. Future research should ensure studies are designed to investigate the smaller effect sizes expected when training protocols match to failure. Finally, testing protocols should be such that a more detailed and accurate analysis of oxygenation levels are ensured.

Chapter 4 - Further Discussion – Limitations and Future Directions

While this thesis reports on important training adaptations that were primarily equal across training modalities over time, there were limitations to the study that hindered the possibility of more in-depth findings. Firstly, there was a relatively sample size and with our training design being implemented to see any true differences, the group differences were quite small, particularly compared to the large variations seen. Thus, a much larger sample size would have been needed to see these smaller differences. However, 60 subjects performing testing and 8 weeks of training through multiple labs would not have been feasible in the time frame available. As mentioned, other studies have found significant findings with a similar number of subjects per group, but most were not matched for failure, and thus more likely to see differences due to them having much greater differences in fatigue or effort. The one study that did match to failure, similarly saw limited differences between groups. In their study, Fahs et al., 2015 found a hypertrophy benefit for BFR relative to TRT. However, they had capped the repetitions at 90 reps and mentioned some of the participants in the TRT group could have reached that number, which could have led to the observed hypertrophic effect of BFR. Additionally, Jesse et al., 2018 had more participants per group and a good distribution of groups where they all reached failure and only saw interaction for 1RM, which could be expected, as mentioned, due to a learned task effect. With a goal of 10 subjects per group, we had hoped to have enough to see the smaller differences. However, it seems more participants were needed, particularly for NIRS data as visually there were large differences in oxygenation between groups, but these were not significant. The low sample size could have also allowed group differences to play a role as although subjects were randomly assigned to groups there was still noticeable (but not significant) differences in aspects of the groups, including subjects weight. Future research should ensure a sample size to allow for finer analysis of all parameters,
and to allow the ability to see any sex differences between training modalities. We had also planned on analyzing sex differences; the initial plan was to have 5 of each sex in each group which would have more likely allowed the analysis of any major changes. However, after multiple drop outs and increasing study length, we only managed three females in two of the groups and two in the other. Previous research has suggested that females could respond less to BFR and are more fatigue resistant, but there are too few studies that involve females currently to analysis accurately. A future study with 20 subjects per group, 10 of each sex, would likely be able to elucidate more complete findings.

In this study, we used a novel technique of analyzing blood lactate from the exercising leg, included while blood flow was restricted. Despite this novel technique to measure lactate during blood flow restriction by measuring it from the toe of the restricted leg, we only saw a difference over time from all groups together and no differences between the groups. This is contrary to studies that found a difference in lactate with BFR, but these studies did not match to failure and thus with different levels of fatigue, we could expect different levels of lactate. Our findings are in agreement with and are corroborated by the majority of recent studies in the literature, as they found no difference in lactate. We had hoped to highlight any potential differences that may have existed in lactate build up between BFR and TRT, as taking the measurement from the restricted exercising leg had not previously been performed. The lack of differences in lactate in the leg could be from the poorly circulating blood in the restricted legs, which potentially limited the amount of lactate to reach the extremity of the limb. Another explanation to the null findings could be that the greatest amount of lactate produced was in the last set, making it difficult to notice a difference immediately after, since peak lactate readings generally take 3-8 min post-exercise. The post-5 min break reading was the highest in all groups, which further corroborates this theory. However, as previous studies have noted, it is most likely that there is little to no difference in lactate buildup between BFR and TRT, which is further demonstrated by our findings while examining the restricted leg.

In addition, looking into higher trained individuals could be an avenue as the changes in strength, hypertrophy, and endurance seen in this group of active but not highly trained could have been too big to tease out any differences in the modalities that could have been smaller but meaningful in groups that have nearly maxed out their current training. A possible use for BFR over TRT
could be on more highly trained individuals who would possibly need to either: gain more
benefits from similar work (ie. the possible additional endurance benefits), achieve a greater
level of fatigue than they are used to, or for a change in stimulus; where it is likely moderately
trained individuals would not see the additional benefits from these conditions.
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### Chapter 6 - Appendix

#### 6.1 A – Table 7 - Strength, Hypertrophy and Endurance Data

#### Table 7 - Strength, Hypertrophy and Endurance Outcome Metrics

<table>
<thead>
<tr>
<th>Variable</th>
<th>BFR&lt;sub&gt;100&lt;/sub&gt; n=7</th>
<th>BFR&lt;sub&gt;50&lt;/sub&gt; n=6</th>
<th>TRIT n=7</th>
<th>Total n=20</th>
<th>Grp eff p-value</th>
<th>Time eff p-value</th>
<th>GrpXTime p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength</strong></td>
<td></td>
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<td></td>
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<tr>
<td>IRM (kg)</td>
<td>Pre 60± 11.1</td>
<td>Mid 63± 15.2</td>
<td>Post 65± 12.0</td>
<td>56.9± 16.5</td>
<td>0.754</td>
<td>0.003*</td>
<td>0.235</td>
</tr>
<tr>
<td></td>
<td>62.3± 18.7</td>
<td>70.6± 25.4</td>
<td>71.2± 35.7</td>
<td>64.9± 22.1</td>
<td>70.4± 27.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVIC (N-m)</td>
<td>Pre 158± 46.0</td>
<td>Mid 161± 58.8</td>
<td>Post 170± 48.4</td>
<td>162± 51.0</td>
<td>144± 63.7</td>
<td>155± 51.9</td>
<td>0.751</td>
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<tr>
<td></td>
<td>173± 52.6</td>
<td>154± 59.8</td>
<td>146± 47.8</td>
<td>162± 54.9</td>
<td>162.5± 47.8</td>
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<tr>
<td><strong>Hypertrophy</strong></td>
<td></td>
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<tr>
<td>Thigh Mass - DEXA (g)</td>
<td>Pre 5438.6± 1058.4</td>
<td>Mid 5634.2± 1073.9</td>
<td>Post 6184.7± 1849.6</td>
<td>6143.5± 1841.9</td>
<td>4939.5± 1379.5</td>
<td>5451.8± 1439.5</td>
<td>5578.4± 1471.2</td>
</tr>
<tr>
<td>RF Thickness - US avg (cm)</td>
<td>Pre 2.1± 0.30</td>
<td>Mid 2.3± 0.33</td>
<td>Post 2.3± 0.34</td>
<td>2.1± 0.39</td>
<td>1.79± 0.34</td>
<td>2.02± 0.32</td>
<td>0.237</td>
</tr>
<tr>
<td>RF Thickness - US 30% (cm)</td>
<td>Pre 2.2± 0.42</td>
<td>Mid 2.3± 0.42</td>
<td>Post 2.4± 0.26</td>
<td>2.16± 0.19</td>
<td>2.02± 0.31</td>
<td>2.14± 0.32</td>
<td>0.360</td>
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<td><strong>Endurance</strong></td>
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<td></td>
</tr>
<tr>
<td>Dynamic Kicking Task (reps)</td>
<td>Pre 36.8± 14.47</td>
<td>Mid 57.1± 47.37</td>
<td>Post 83.5± 73.5</td>
<td>61.0± 25.4</td>
<td>51.57± 18.52</td>
<td>60.95± 37.89</td>
<td>69.05± 56.56</td>
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<tr>
<td>Time to Fatigue (sec)</td>
<td>Pre 195± 86.0</td>
<td>Mid 229± 91.0</td>
<td>Post 235± 124.3</td>
<td>204.6± 52.8</td>
<td>183.7± 29.8</td>
<td>174.0± 45.8</td>
<td>198.5± 81.1</td>
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<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; 50% (L)</td>
<td>Pre 2.0± 0.37</td>
<td>Mid 1.9± 0.34</td>
<td>Post 1.8± 0.43</td>
<td>1.82± 0.35</td>
<td>1.82± 0.57</td>
<td>1.90± 0.43</td>
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<td>VO&lt;sub&gt;2&lt;/sub&gt; 70% (L)</td>
<td>Pre 2.5± 0.59</td>
<td>Mid 2.5± 0.53</td>
<td>Post 2.5± 0.63</td>
<td>2.61± 0.56</td>
<td>2.62± 0.63</td>
<td>2.64± 0.65</td>
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<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; peak (L)</td>
<td>Pre 3.4± 0.65</td>
<td>Mid 3.4± 0.65</td>
<td>Post 3.3± 0.73</td>
<td>3.27± 0.73</td>
<td>2.93± 1.05</td>
<td>3.23± 0.82</td>
<td>0.372</td>
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