Exercise training with blood flow restriction has little effect on muscular strength and does not change IGF-1 in fit military warfighters

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Running title: aBFR in highly fit warfighters

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ABSTRACT

Objective:

Aerobic exercise with blood flow restriction (aBFR) has been proposed as an adjunctive modality in numerous populations, potentially via an enhanced growth factor response. However, the effects of aBFR on highly trained warfighters have yet to be examined. The purpose of this study was to determine if adjunctive aBFR as part of a regular physical training regimen would increase markers of aerobic fitness and muscle strength in elite warfighters. In addition, we sought to determine whether the changes in blood lactate concentration induced by aBFR would be associated with alterations in the insulin-like growth factor (IGF) axis.

Design:

Active-duty US Naval Special Warfare Operators ($n = 18$, age = 36.8 ± 2.2 years, weight = 89.1 ± 1.2 kg, height = 181.5 ± 1.4 cm) from Naval Amphibious Base Coronado were recruited to participate in 20 days of adjunctive aBFR training. Peak oxygen consumption (VO_2 peak), ventilatory threshold (VT), and 1-repetition max (1-RM) bench press and squat were assessed pre- and post-aBFR training. Blood lactate and plasma IGF-1 and IGF-binding protein-3 (IGFBP-3) were assessed pre-, 2 min post-, and 30 min post-aBFR on days 1, 9, and 20 of aBFR training.

Results:

Following aBFR training there were no changes in VO_2 peak or VT, but there was an increase in the 1-RM for the bench press and the squat (5.0 and 3.9%, respectively, $P < 0.05$). Blood lactate concentration at the 2-min post-exercise time point was 4.5–7.2-fold higher than pre-exercise levels on all days ($P < 0.001$). At the 30-min post-exercise time point, blood lactate was still 1.6–2.6-fold higher than pre-exercise levels ($P < 0.001$), but had decreased by 49–56% from the 2-min post-exercise time point ($P < 0.001$). Plasma IGF-1 concentrations did not change over the course of the study. On day 9, plasma IGFBP-3 concentration was 4–22% lower than on day 1 ($P < 0.01$) and 22% lower on day 9 than on day 20 at the 30-min post-exercise time point ($P < 0.001$).

Conclusions:

Our data suggest that aBFR training does not lead to practical strength adaptations or alterations in the IGF axis in a population of highly trained warfighters.

Keywords:

Blood flow restriction, Exercise, Insulin-like growth factor-1, IGF axis, Warfighters

Introduction

Blood flow restriction (BFR) exercise has been shown to be an effective training tool in a variety of populations [1,2] and has been proposed as an adjunctive training tool [3], particularly in athletic populations [4]. Its use as an adjunctive training tool stems from the low-intensity modality of the exercise, which minimizes exercise-induced muscle damage while eliciting a hormonal response that is similar to that observed with high-intensity exercise [5]. In theory, this mechanism of action would lead to accelerated recovery from regular training regimens due to an additional (and beneficial) hormonal response [1,6]. Data show that this holds true in sedentary individuals and some athletes [2,7]; however, it has yet to be shown as an effective training tool in highly trained and active individuals.

Data have shown that BFR resistance training (i.e., weight training) is associated with increases in growth hormone, skeletal muscle hypertrophy, and maximal strength [4,6,8]; however, little is known about BFR training in conjunction with aerobic exercise. There are some indications that low-intensity aerobic exercise with blood flow restriction (aBFR) increases maximal aerobic capacity similarly to a high-intensity endurance training program [9]; as well as, skeletal muscle cross-sectional area, and muscular strength [1,7], which is atypical of aerobic exercise alone. Furthermore, this training modality has never been assessed within an elite military population that is concurrently engaged in rigorous physical fitness regimens.

While the precise mechanisms behind favorable adaptations to BFR training have yet to be elucidated, it has been hypothesized that the increase in blood lactate concentration induced by

exercise with BFR may stimulate growth hormone secretion via a decrease in pH [5]. Indeed, it has been shown that the drop in pH induced by rhythmic handgrip exercise and vascular restriction increases sympathetic nerve activity and growth hormone secretion [10,11]. However, the link between exercise-induced lactate concentration and insulin-like growth factor (IGF)-1 concentration remains unknown.

It is well understood that IGF-1 is a potent anabolic peptide; however, the biological effect of IGF-1 is complicated by other IGF axis factors, such as IGF-binding proteins (BPs), which bind to IGF-1 and alter cellular interactions [12]. In humans, the primary IGFBP found in the blood is IGFBP-3. The molar ratio of IGF-1 to IGFBP-3 is of particular interest because it can provide a sense of how much free or unbound IGF-1 is in circulation. Secretion and production of IGF-1 are directly stimulated by growth hormone (via negative feedback cycle), a molar ratio that can also provide a depiction of the biological activity of growth hormone [13,14].

Therefore, the purpose of this study was to determine whether 20 days of adjunctive aBFR, as part of a regular physical training regimen, would increase markers of aerobic fitness and muscle strength in highly fit US warfighters. Furthermore, we wanted to determine whether the changes in blood lactate concentration induced by aBFR would be associated with alterations in the IGF axis.

MATERIALS AND METHODS

Experimental approach to the problem

Our study presents a novel approach in the assessment of aBFR, an increasingly popular exercise training modality. A repeated-measures design was used to assess the adjunctive effects of a 20-day aBFR training regimen in highly trained and physically fit US Naval Special Warfare (NSW) Operators concomitantly engaged in regular physical activity/training operations.

To assess any physical fitness changes due to the aBFR, the following dependent variables were measured before and after completion of the training program: peak oxygen consumption (VO_2 peak), peak heart rate (HR peak), ventilatory threshold (VT), 1-repetition maximum (1-RM) bench press, and 1-RM back squat. In addition, to assess physiological changes, blood lactate concentration and plasma IGF-1 and IGFBP-3 levels were measured during aBFR at three time points during the training sessions (pre-session, 2 min post-session, and 30 min post-session) on days 1, 9, and 20. Mean power output and HR during aBFR were also assessed on training days 1, 9, and 20.

Subjects

Participants were recruited from Naval Amphibious Base Coronado, San Diego, California. All subjects were healthy, active-duty, male NSW Operators, 23–54 years of age (Table 1). All participants were actively engaged in rigorous physical fitness training regimens that typically consisted of ≥ 6 hr/day of physical activity including 1–3 hr/day of aerobic activity ($> 50\%$ VO_2 peak), ≥ 1.5 hr/day resistance training ($> 75\%$ 1-RM), in addition to ≥ 3 hr/day of tactical training [15,16]. The participants were instructed to maintain their regularly scheduled training exercises as well as their dietary intake, and

caffeine, nicotine, and alcohol consumption during the duration of this study since the goal of this study was to assess the efficacy of regular aBFR as a supplementary training tool. The study was approved by the Institutional Review Board at Naval Health Research Center, and all participants gave their free and informed written consent.

Demographic and anthropometric assessment

During the first visit to the lab, subjects completed a basic health history questionnaire and anthropometric data were recorded. Height and weight for each subject were recorded to the nearest 0.1 cm and 0.05 kg, respectively, using a digital scale with height rod (ProMed 6129, Detecto, Webb City, MO, USA).

Pre- and post-training physiological measurements

Three days prior to the first aBFR training session (day 1), and within 3 days of completing the last aBFR training session (day 20), a modified Balke treadmill test [17] was completed to assess each subject's VO_2 peak. Subjects were instructed to warm up for 5–10 min by walking or jogging on the treadmill at a self-selected, comfortable pace. During the graded exercise test (GXT), the initial speed and grade of the treadmill were set at 3.5 mph and 0%. The speed and grade were increased by 0.5 mph and 2%, respectively, every 2 min until volitional exhaustion, at which point the GXT was terminated. During the GXT, respiratory gases were continuously collected and analyzed using the Parvo Medics TrueOne 2400 (Parvo Medics, Inc., Sandy, UT, USA) metabolic cart system, and HR was measured using a

Polar monitor (Polar Electro, Inc., Lake Success, NY, USA). Blood lactate concentrations were measured at the onset of the GXT, within the last 15 s of each 2-min stage and at 2 min post-GXT. Capillary whole blood was collected via finger stick and used immediately to assess blood lactate concentration via a handheld lactate meter (Lactate Plus, Nova Biomedical, Waltham, MA, USA). Ratings of perceived exertion (visual 15-point Borg scale) were collected upon reaching volitional exhaustion [18]. Successful achievement of VO_2 peak was based on the following objective criteria: respiratory exchange ratio (RER) ≥ 1.1 , $\text{HR} \pm 10$ bpm of age-predicted maximum, blood lactate concentration ≥ 8.0 mmol/L, and a rating of perceived exertion ≥ 18 on the Borg 15-point scale [19]. All subjects met all of the criteria during each GXT. For each subject, the VT was determined via the V-slope method as described [20].

Following recovery from the GXT (defined as a $\text{HR} \leq 90$ bpm), muscular strength was measured using a 1-RM test for bench press and squat as described [21]. Subjects were instructed to warm up with 3-sets of incrementally increasing weights (i.e. increase each set 5–10% for bench press and 10–20% for squat) and rest periods (i.e. 1 min, 2 min, and 2–4 min) to warm-up for their testing 1-RM testing sets. Following the last warm up set, and a 2–4 min rest period, weights were increased again (5–10% for bench press and 10–20% for squat) and subjects were instructed to attempt a 1-RM; if the subjects were successful they would complete this step again until failure. Following a testing failure the weight lifted would decrease (2.5–5% for bench press and 5–10% for squat) and the subject would attempt another lift after 2–4 min of rest. All 1-RMs are defined as the maximal weight lifted successfully for a single repetition.

Training session protocol for aBFR

Each of the 20 training sessions consisted of 20 min of exercise on a modified NuStep recumbent cross trainer (NuStep Inc., Ann Arbor, MI, USA) (contralateral elbow flexion/extension and knee flexion/extension) followed by 30 min of passive recovery (no physical activity in a prone position). At the beginning of each training session, participants were fitted with liquid cooled compression cuffs, which were kept cool via circulation of a refrigerated liquid maintained at 15–18°C. In addition, a liquid cooled vest was worn and maintained at the same temperature. The cuffs were attached to each arm (2 inches distally from axilla) and thigh (4 inches proximally from patella), and the pressure of the compression cuffs was continuously maintained between 60 and 80 mmHg throughout the training session. Cuffs were applied by the same research staff member at the beginning of each training session. The foot platforms of the NuStep were fitted with a copper plate cooled via circulation of the refrigerated liquid. During aBFR, the participants placed their bare feet on the copper plates, which acted as a grounding source for the body [22].

Every exercise training session was supervised by a research staff member who ensured that the pressure of the compression cuffs was maintained and that the participants sustained the exercise intensity between the lower and upper limits of the visual power output guide provided by the NuStep program. Training sessions began with a 5-min warm-up (< 100 W). This was followed by 10 min of moderate intensity (100–150 W) exercise, and the session concluded with five 20 s sprints separated by 40 s of relaxed (< 100 W) exercise. Following the last sprint cycle, the research staff assisted in the removal of the compression cuffs and vest and moved the subject into an adjacent area, where blood samples were collected and passive recovery occurred.

Training session measurements

During each exercise session, HR and power output were recorded via Polar monitor and NuStep external readout, respectively, and averaged for the exercise bout. On days 1, 9, and 20, 8 mL blood samples were obtained before the session (pre), and 2 min and 30 min after (2 and 30 min post) the end of the training session via venipuncture at the antecubital vein using aseptic technique, with the subjects seated in an upright position. Whole blood was collected in tubes coated with the anti-coagulant ethylenediaminetetraacetic acid. The samples were centrifuged at 3000 rpm for 15 min; plasma was then aliquoted into individually labeled microcentrifuge tubes, frozen, and stored at -80°C for future analysis. All plasma samples were batch analyzed in duplicate for IGF-1 (22-IGFHU-E01 ELISA, ALPCO Diagnostics, Salem, NH, USA) and IGFBP-3 (ab190809 ELISA, Abcam Inc., Cambridge, MA, USA). The sensitivities of the assays were 0.09 ng/mL (IGF-1) and 46.4 pg/mL (IGFBP-3). Mean intra- and inter-assay variances were 4.11% and 4.58% (IGF-1), and 2.97% and 5.83% (IGFBP-3), respectively. Blood for the assessment of lactate concentration was collected via a finger stick and analyzed immediately, as described above.

Calculations and statistical analyses

To assess the impact of aBFR training on physiological measures, paired *t*-tests were performed using pre- and post-aBFR training data. To adjust for changes in power output during training, lactate and IGF-1 concentrations for each subject were divided by power output for each day of training. Blood lactate and plasma IGF-1 axis data (adjusted and non-adjusted) were analyzed using a mixed-design analysis of variance (ANOVA; SPSS statistical software, version 22.0; IBM, Armonk, NY, USA) with time (pre- vs. 2 min post vs. 30 min post) and training (day 1 vs. day 9 vs. day 20) as factors. Bonferroni post

hoc follow-up analyses were conducted when appropriate. For further statistical evaluation, the subject pool was divided into tertiles based on age (lower: < 29 years, mid: 30–42 years, upper: > 42 years). These data were analyzed using a mixed-design ANOVA with time (pre- vs. 2 min post vs. 30 min post), training (day 1 vs. day 9 vs. day 20), and age as factors. Bonferroni post hoc follow-up analyses were conducted when appropriate. To examine the impact of age on physiological markers during aBFR, the subject pool was again divided into the same age tertiles (lower, mid, upper) as previously mentioned, with time and training as factors. The square of the Pearson product-moment coefficient was used to determine the significance of correlation between pre-training bench press strength and post-to-pre bench press differences, as well as the correlation between the IGF axis and lactate concentrations. Statistical significance was accepted at $P < 0.01$ when comparing age tertiles (to reduce risk of committing type 1 error) and accepted at $P < 0.05$ for all other analyses. All data are expressed as mean $\pm$ standard error of the mean.

RESULTS

Effects of aBFR training and age on physiological characteristics

Verification of exercise intensity during each exercise session was accomplished via assessment of mean power output and HR (Figs. 1A and 1B). On day 1, mean power output during aBFR was 141.3 ± 3.5 W, and by day 20, mean power output had increased by 15.8% compared with day 1 ($P < 0.05$). Mean HR during aBFR was 127.9 bpm and was not affected by 20 days of aBFR training ($P > 0.05$).

Exercise intensity, as defined by measures of mean power output and mean HR on days 1, 9, and 20, did not vary between groups ($P > 0.05$; data not shown).

The calculated VT, VO_2 , HR, lactate concentration, and RER measured at peak exercise intensity during the GXT were unchanged following aBFR training ($P > 0.05$) and were not affected by age ($P > 0.05$; Table 2). All 1-RMs were established within 3-4 testing attempts; in addition, aBFR training increased 1-RM for both the bench press and the squat (5.0% and 3.9%, respectively; $P < 0.05$). Age affected the training-induced increase in bench press strength ($P = 0.009$) but not in squat strength ($P > 0.05$). Pre-training bench press strength in the upper age tertile group was 25–34% lower compared with the lower tertile ($P = 0.001$) and mid tertile ($P = 0.002$) groups (Table 2). Post-training bench press strength was 24% lower in the upper age tertile group than in the lower age tertile group ($P = 0.006$; Table 2). The post-to-pre bench press difference was larger in the upper tertile group than in the lower tertile ($P = 0.02$) and mid tertile ($P = 0.03$) groups (Table 2). There was a negative correlation between pre-training 1-RM bench press strength and post-to-pre 1-RM bench press difference ($R^2 = 0.27$, $y = -0.2108x + 26.974$, $P < 0.03$; Fig. 4).

Effects of aBFR training and age on lactate concentration

Blood lactate concentration at the 2-min post-exercise time point was 4.5–7.2-fold higher than pre-exercise levels on days 1, 9, and 20 ($P < 0.001$; Fig. 2A). At the 30-min post-exercise time point, blood lactate was still 1.6–2.6-fold higher than pre-exercise levels ($P < 0.001$), but had decreased by 49–56% from levels observed at the 2-min post-exercise time point ($P < 0.001$). Time-dependent changes in

lactate concentrations were not affected by days of training ($P > 0.05$). To account for the changes in power output with aBFR training, lactate concentrations at the 2- and 30-min time points were also expressed as a function of power output ($\mu\text{mol}\cdot\text{mL}^{-1}\cdot\text{W}^{-1}$). When adjusted for power output, lactate concentration was 52–61% lower at the 30-min time point than at the 2-min post-exercise time point ($P < 0.001$) and this was not affected by days of training ($P > 0.05$; Fig. 3A and Table 3). An ANOVA revealed a main effect of time and a time $\times$ age interaction effect for lactate concentrations ($P < 0.001$; Table 3). Further analysis revealed that at the 30-min time point, on days 1, 9, and 20, the mid tertile group had higher (43–74%) lactate concentration compared with the lower tertile group ($P = 0.04$). At this same time point, lactate concentrations in the upper tertile group were higher (3–88%) than those in the lower tertile group, but this difference did not reach significance ($P = 0.18$). There were no differences between age tertiles for lactate normalized for power output ($P > 0.05$).

Effects of aBFR training and age on the IGF axis

A mixed-design ANOVA of plasma IGF-1 concentrations ($\text{ng}\cdot\text{mL}^{-1}$) uncovered a main effect of time ($P = 0.04$) but no differences between days ($P > 0.05$; Fig. 2B). Post hoc analysis revealed that plasma IGF-1 concentrations at the 2-min post-exercise time point were 3–17% higher ($P = 0.12$) than values obtained at the pre-exercise time point and 11–13% higher ($P = 0.06$) than values obtained at the 30-min post-exercise time point. When adjusted for power output, plasma IGF-1 concentration ($\text{ng}\cdot\text{mL}^{-1}\cdot\text{W}^{-1}$) was 5–18 % lower at the 30-min post-exercise time point than at the 2-min post-exercise time point ($P < 0.03$; Figure 3B) and this was not affected by days of training ($P > 0.05$).

A mixed-design ANOVA of IGFBP-3 concentrations ($\text{ng}\cdot\text{mL}^{-1}$) revealed main effects of time and day as well as a time $\times$ day interaction effect (Fig. 2C). On day 9, plasma IGFBP-3 concentration measured at each time point was 4–22% lower than the respective concentrations obtained on day 1 ($P < 0.01$; Fig. 2C). On day 9, plasma IGFBP-3 concentration at the 30-min post-exercise time point was 28–34% lower ($P < 0.001$) than at the pre-exercise time point and 12–31% lower ($P = 0.06$) than at the 2-min post-exercise time point. Furthermore, plasma IGFBP-3 concentration at the 30-min post-exercise time point was 22% lower on day 9 than on day 20 ($P < 0.001$). At each exercise time point, the IGF-1/IGFBP-3 molar ratio was higher (2–29%) on day 9 than on day 1 ($P = 0.03$; Fig. 2D). An ANOVA revealed a main effect of time for IGF-1 ($P < 0.05$) and IGFBP-3 ($P < 0.05$), a main effect of day for IGFBP-3 ($P < 0.01$) and IGF-1/IGFBP-3 molar ratio ($P < 0.05$), as well as a day $\times$ time interaction effect for IGFBP-3 ($P < 0.05$), none of which were affected by age ($P > 0.05$). There were no differences between age tertiles regarding IGF-1 normalized for power output ($P > 0.05$). There was a negative correlation between IGFBP-3 and lactate concentration at the 30-min post-exercise time point ($R^2 = 0.07$, $y = -171.25x + 7289.6$, $P < 0.05$). No other correlations between lactate and the IGF axis were found ($P > 0.05$).

DISCUSSION

In this report we show that while aBFR acutely raises blood lactate concentration by 4.5–7.2-fold immediately post exercise and 1.6–2.6-fold 30 min post exercise, the increase is not associated with changes in the IGF axis. We also show that short-term (20 days) aBFR training minimally increases maximal strength in highly active, physically fit warfighters and that the improvement in muscle strength is age dependent. In addition, 20 days of aBFR training did not increase IGF-1 or IGFBP-3 concentrations.

Taken together, our data do not provide evidence for an association between lactate, the IGF axis, and strength improvement with short-term aBFR training in this population.

Researchers have hypothesized that high lactate levels may activate the growth hormone–IGF axis and may be one of the cellular mechanisms that induces muscular adaptations when exercising with vascular restriction [5]. However, our results did not show a significant relationship between lactate and IGF-1 concentrations or the molar ratio of IGF-1 to IGFBP-3. These results are in agreement with data showing that lactate concentration does not directly correlate with growth hormone concentrations [23,24]. It is notable that the lactate concentrations exhibited by our subjects were considerably higher (4.1–14.0 mmol/L) than those observed in other studies using aBFR exercise [23,24]. Thus, while the aBFR regimen prescribed in this study elicited a large increase in lactate concentration, it failed to elicit a similar change in IGF-1 or IGFBP-3 concentrations in this population.

Furthermore, we report a novel finding in contrast to prior evidence which suggested that exercise-induced increases in lactate are directly related to the IGF-1 axis response [25]. We report here that lactate concentrations are negatively correlated with IGFBP-3 concentrations, albeit only at the 30-min post-exercise time point, when lactate concentrations were 49–56% lower than the peak at the 2-min post-exercise time point. Closer inspection of the IGFBP-3 response reveals that on days 1 and 20, IGFBP-3 concentrations remained relatively stable at each measured time point; however, on day 9, there was a significant decrease in the IGFBP-3 concentration. Studies have shown that IGFBP-3 concentrations and exercise intensity/workload are positively correlated [13,26]. In line with this notion, the reduction in IGFBP-3 concentrations from day 1 to day 9 (14%) occurred while power output

remained unchanged. Conversely, IGFBP-3 concentrations increased from day 9 to day 20 (10%) when power output was higher.

In this population of warfighters, low-intensity aBFR involving both arms and legs did not increase VO_2 max. Previous evidence has shown that 2–8 weeks of walk or cycle training with BFR increases VO_2 max in fit young men [7,9]. The lack of improvement in VO_2 max in our study is not surprising given that our subjects were initially highly fit and had maintained this level of fitness for at least 5 years and, in some cases, for nearly 2 decades. In addition, there was no evidence of a change in the VT of our subjects. While our results are in contrast to prior reports which suggest that aBFR may increase aerobic capacity [7,9], our findings may reflect the pre-training fitness level of our study population.

It has been suggested that aBFR be used as a potential adjunctive exercise modality to increase muscular strength and hypertrophy [3]. Evidence supports an increase in muscular cross-sectional area and strength following walk and cycle training with BFR in young men and athletes [1,7]. Similar to others, we found that there was a small strength increase (4–5%) in 1-RM for both the bench press and squat [1,2,7]. However, when the data were split by age tertiles, only the oldest age group (> 42 years) showed an improvement in 1-RM bench press (14%). It is also important to note that the older subjects presented with the lowest pre-training bench press values. Our data are in line with those of others showing that improvements in strength are highly dependent on pre-training strength levels [27]. Therefore, we conclude that the strength gains we observed with aBFR training are not age dependent; rather, our data indicate that strength gains may occur when pre-training measures of strength are low.

In addition, while these changes in strength are statistically significant, they are not likely to be practically relevant to the warfighter.

There are some limitations to this study. The primary limitation is that this population of individuals is highly trained and their mechanisms for compensation in high-intensity exercise are likely well developed. Further, these individuals routinely train at high intensity, thus the protocol might not have been sufficient to elevate endogenous IGF production. In addition, emerging data indicates that local muscular factors may be more influential in exercise mediated muscular adaptations than systemic factors [28]. Nevertheless, this study points to the fact that when evaluating this type of training, the targeted population is critical. Future efforts should focus on individuals who are recovering from a musculoskeletal injury and would like to maintain an elevated degree of exercise intensity without the impact of striking the ground.

In summary, among NSW Operators, our data indicate 20 days of low-intensity aBFR training as an adjunctive exercise modality does not alter the IGF axis and does not practically increase muscular strength. Thus, for a highly fit population, this type of exercise is not beneficial. Future efforts should perhaps focus on the use of this type of exercise from a rehabilitation standpoint to help minimize fitness loss.

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FIGURE LEGENDS

Fig. 1. Power output and heart rate during aerobic exercise with blood flow restriction (aBFR). Power output (A) and heart rate (B) were measured continuously and averaged over the exercise period. Data for days 1 (open bar), 9 (hatched bar), and 20 (black bar) of aBFR training are reported. Values are means $\pm$ SE for $n = 18$. [#] $P < 0.05$ vs. day 1.

Fig. 2. Effect of aerobic exercise with blood flow restriction (aBFR) training on lactate, IGF-1, and IGFBP-3 concentrations and IGF-1/IGFBP-3 molar ratio before, and 2 min and 30 min after aBFR. Blood lactate concentration (A) was measured via finger stick and plasma IGF-1 (B) and IGFBP-3 (C) concentrations were measured via ELISA before (open bar), and 2 min (hatched bar) and 30 min (black bar) after aBFR on days 1, 9, and 20 of aBFR training. (D) IGF-1/IGFBP-3 molar ratio was calculated for each subject at each respective time point. Values are means $\pm$ SE for $n = 18$. ^{*} $P < 0.05$ vs. pre-exercise time point; [†] $P < 0.05$ vs. 2-min post-exercise time point; [‡] $P < 0.05$ vs. respective value on day 9; [#] $P < 0.05$ vs. day 1.

Fig. 3. Effect of aerobic exercise with blood flow restriction (aBFR) training on lactate and IGF-1 concentration, adjusted for changes in power output. Blood lactate concentration (A) was measured via finger stick, and plasma IGF-1 concentration (B) was measured via ELISA. For each subject, lactate and IGF-1 concentrations obtained at the 2 min (hatched bar) and 30 min (black bar) post-exercise time points were divided by power output obtained on days 1, 9, and 20. Values are means $\pm$ SE for $n = 18$.

Fig. 4. Correlation between Pre-1RM Bench Press and the difference between Pre- to Post-1RM Bench Press following aerobic exercise with blood flow restriction (aBFR) training split by age tertiles. Lower age tertile (< 29 years, $n = 6$, black diamond), middle-age tertile (30–42 years, $n = 6$, grey square), and upper (> 42 years, $n = 6$, white triangle). Values are pre-1RM bench press values and the difference between pre- to post-1RM bench press.

Table 1.

Subject Characteristics.

	Pre-Training	Range
Age (yr)	36.8 ± 2.2	23–54
Height (cm)	181.5 ± 1.4	170.2–193.0
Weight (kg)	89.1 ± 1.2	80.9–102.3
BMI (kg/m ²)	27.1 ± 0.4	24.2–31.4

BMI, body mass index.

Values presented as means ± SE.

Table 2.

Effects of aerobic exercise with blood flow restriction training and age on physiological characteristics.

	Pre-Training			Post-Training		
	Lower tertile	Mid tertile	Upper tertile	Lower tertile	Mid tertile	Upper tertile
Oxygen uptake (mL·kg ⁻¹ ·min ⁻¹)	55.0 ± 2.2	49.3 ± 1.4	45.6 ± 3.2	53.5 ± 1.5	50.4 ± 1.1	48.0 ± 3.5
Heart rate (bpm)	187.3 ± 2.8	182.8 ± 3.0	172.5 ± 2.5	186.3 ± 1.4	186.7 ± 3.7	173.5 ± 3.5
Lactate concentration (mmol·L ⁻¹)	13.9 ± 1.8	12.2 ± 1.2	11.0 ± 2.7	12.8 ± 1.1	12.3 ± 0.4	9.8 ± 1.2
Respiratory exchange ratio	1.17 ± 0.02	1.15 ± 0.01	1.05 ± 0.06	1.13 ± 0.02	1.21 ± 0.06	1.11 ± 0.04
Ventilatory threshold (mL·kg ⁻¹ ·min ⁻¹)	28.7 ± 1.5	28.2 ± 1.5	30.9 ± 1.5	28.8 ± 1.2	28.4 ± 1.9	31.0 ± 0.6
1-RM Bench press ^{a,b,c} (kg)	128.1 ± 3.6	112.0 ± 3.2	84.5 ± 6.1 ^{*,†}	127.1 ± 1.8	113.1 ± 2.4	96.7 ± 9.1 [*]
1-RM Squat ^{a,b} (kg)	148.5 ± 8.2	122.0 ± 11.6	85.2 ± 9.3	155.7 ± 5.8	127.6 ± 13.0	87.1 ± 9.4

1-RM, one-repetition maximum. Values presented as means ± SE. Age tertiles: lower: < 29 years; mid:

30–42 years; upper: > 42 years.. Oxygen uptake, heart rate, lactate concentration, and respiratory

exchange ratio are peak values obtained during graded exercise test (see Methods). Ventilatory

threshold was calculated as described in Methods.

^aMain effect of training for 1-RM bench press ($P < 0.02$) and for 1-RM squat ($P < 0.05$).

^bMain effect of age ($P < 0.01$).

^cTraining × age interaction effect for 1-RM bench press. ($P < 0.01$).

* $P < 0.01$ vs. lower tertile. † $P < 0.05$ vs. mid tertile.

Table 3.

Effects of aerobic exercise with blood flow restriction and age on lactate, IGF-1, and IGFBP-3 concentrations.

		Day 1			Day 9			Day 20		
	Tertile	Pre	2 min post	30 min post	Pre	2 min post	30 min post	Pre	2 min post	30 min post
IGF-1 ^b (ng·mL ⁻¹)	Lower	221.7 ± 23.4	255.7 ± 26.9	232.3 ± 40.1	238.1 ± 22.4	242.7 ± 24.6	234.0 ± 28.3	196.0 ± 21.6	246.9 ± 37.6	202.2 ± 29.0
	Mid	197.4 ± 32.0	190.4 ± 17.7	180.4 ± 23.4	184.6 ± 14.7	180.1 ± 18.5	164.8 ± 14.5	174.5 ± 17.6	179.9 ± 17.5	179.6 ± 11.9
	Upper	226.2 ± 34.7	218.1 ± 25.0	173.8 ± 20.2	197.1 ± 40.4	229.9 ± 30.5	190.6 ± 23.2	199.5 ± 30.4	239.7 ± 38.1	218.4 ± 39.2
IGFBP-3 ^{a,b,c} (ng·mL ⁻¹)	Lower	7269.2 ± 392.4	8405.4 ± 731.3	6831.9 ± 365.0	7194.7 ± 722.4	7484.4 ± 1757.4	5148.0 ± 352.7	7827.6 ± 323.9	7404.6 ± 551.0	7233.4 ± 467.1
	Mid	7462.6 ± 784.7	8395.6 ± 1113.4	7078.3 ± 359.6	7377.6 ± 830.6	6948.4 ± 1011.7	6141.5 ± 310.2	7301.5 ± 398.6	7843.1 ± 749.3	7831.9 ± 911.8
	Upper	8622.9 ± 819.3	7480.3 ± 230.1	7375.2 ± 942.0	7910.4 ± 453.4	6411.1 ± 738.4	5240.5 ± 184.3	7198.2 ± 361.7	7474.3 ± 471.4	6209.9 ± 339.4
IGF-1/IGFBP-3 ^a (molar ratio)	Lower	0.11 ± 0.01	0.11 ± 0.02	0.12 ± 0.02	0.13 ± 0.02	0.14 ± 0.02	0.17 ± 0.02	0.09 ± 0.01	0.12 ± 0.02	0.10 ± 0.02
	Mid	0.11 ± 0.03	0.09 ± 0.01	0.10 ± 0.02	0.10 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01
	Upper	0.10 ± 0.02	0.11 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.10 ± 0.02	0.11 ± 0.02	0.13 ± 0.03
Lactate concentration ^{b,d} (mmol·L ⁻¹)	Lower	1.1 ± 0.3	7.9 ± 1.3	3.1 ± 0.6	1.8 ± 1.0	9.0 ± 1.2	3.2 ± 0.5	2.0 ± 0.8	7.2 ± 0.8	3.0 ± 0.6
	Mid	0.8 ± 0.1	10.9 ± 0.7	5.4 ± 0.9	1.5 ± 0.4	9.5 ± 1.3	5.5 ± 1.0	1.6 ± 0.8	9.3 ± 0.8	4.3 ± 0.6
	Upper	1.3 ± 0.2	7.7 ± 1.4	3.2 ± 0.7	2.0 ± 0.6	10.0 ± 0.08	6.0 ± 1.8	0.9 ± 0.2	9.6 ± 0.2	4.5 ± 1.0
IGF-1/power output (ng·mL ⁻¹ ·W ⁻¹)	Lower		1.9 ± 0.2	1.8 ± 0.3		1.7 ± 0.1	1.7 ± 0.1		1.7 ± 0.3	1.4 ± 0.2
	Mid		1.3 ± 0.1	1.2 ± 0.2		1.1 ± 0.1	1.0 ± 0.1		1.1 ± 0.1	1.2 ± 0.1
	Upper		1.6 ± 0.2	1.3 ± 0.2		1.6 ± 0.2	1.3 ± 0.2		1.3 ± 0.2	1.3 ± 0.3
Lactate/power output (μmol·mL ⁻¹ ·W ⁻¹)	Lower		59.3 ± 6.8	23.1 ± 4.8		65.0 ± 8.5	22.6 ± 2.9		49.4 ± 6.8	20.4 ± 3.7
	Mid		71.6 ± 2.0	35.2 ± 5.5		56.5 ± 4.7	32.2 ± 4.5		58.8 ± 4.4	27.2 ± 5.0
	Upper		56.0 ± 3.7	23.0 ± 5.2		67.6 ± 6.2	41.5 ± 14.5		54.7 ± 7.3	26.2 ± 5.7

IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor-binding protein 3.

Values represented as means $\pm$ SE. Age tertiles: lower < 29 years ($n = 6$), mid 30-42 years ($n = 6$), upper > 42 years ($n = 6$).

^aMain effect of day for IGFBP-3 ($P < 0.01$) and IGF-1/IGFBP-3 molar ratio ($P < 0.05$).

^bMain effect of time for IGF-1 ($P < 0.05$), IGFBP-3 ($P < 0.05$), and lactate concentration ($P < 0.001$).

^cDay $\times$ time interaction effect for IGFBP-3 ($P < 0.05$).

^dTime $\times$ age interaction effect for lactate concentration ($P < 0.05$).

A **B**

A

2 min post

30 min post

Main effect of time ($P < 0.001$) **B**

2 min post

30 min post

Main effect of time ($P = 0.03$)

Figure 3.