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# Speeding of $\dot{V}O_2$ kinetics is not different following low-intensity blood flow restricted and high-intensity interval training

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***New Findings***

*What is the central question of this study?*

Can interval blood flow restricted cycling training, undertaken at a low intensity, promote a similar adaptation to $\dot{V}O_2$ kinetics as high-intensity interval training?

*What is the main finding and its importance?*

Speeding of pulmonary $\dot{V}O_2$ on-kinetics in healthy young subjects was not different between low-intensity interval blood flow restricted (BFR) training and traditional high intensity interval training (HIT). Since very low workloads are well tolerated during BFR cycle training and speeds $\dot{V}O_2$ on-kinetics, this training method could be used when high mechanical loads are contraindicated.

**ABSTRACT**

Low-intensity blood flow restricted (BFR) endurance training is effective to increase aerobic capacity. Whether it speeds pulmonary oxygen uptake ($\dot{V}O_{2p}$), $CO_2$ output ($\dot{V}CO_{2p}$) and ventilatory ($\dot{V}_{Ep}$) kinetics has not been examined. We hypothesized that low-intensity BFR training would reduce the phase 2 time constant ($\tau_p$) of $\dot{V}O_{2p}$, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ by a similar magnitude as traditional high-intensity interval training (HIT). Low intensity interval training with BFR served as a control. Twenty-four participants (25±6yrs; $\dot{V}O_{2max}$ 46±6ml.kg$^{-1}$.min$^{-1}$) were assigned to one of: low-intensity BFR interval training (BFR, n=8); low-intensity interval training without BFR (LOW, n=7); and high intensity interval training without BFR (HIT, n=9). Training was 12 sessions of 2 sets of 5-8 × 2-min cycling and 1 min resting intervals. LOW and BFR were conducted at 30% of peak incremental power ($P_{peak}$), and HIT was at ~103% $P_{peak}$. For BFR, cuffs were inflated on both thighs (140–200mmHg) during exercise and deflated during rest intervals. Six moderate-intensity step transitions (30% $P_{peak}$) were averaged for pulmonary on-kinetics analysis. Both BFR (pre vs post training $\tau_p$=18.3±3.2s vs 14.5±3.4s; E.S=1.14) and HIT ($\tau_p$=20.3±4.0s vs 13.1±2.9s; E.S=1.75) reduced the $\dot{V}O_{2p}$ $\tau_p$ ($p<0.05$). As expected, there was no change in LOW ($\dot{V}O_{2p}$ $\tau_p$=17.9±6.2s vs 17.7±4.3s; p=0.9). The kinetics of $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ were speeded only after HIT (38.5±10.6% $p<0.001$ and 31.2±24.7% p=0.004, respectively). Both HIT and low-intensity BFR training were effective in speeding moderate intensity $\dot{V}O_{2p}$ kinetics. These data support the findings of others that low intensity cycling training with blood flow restriction increases muscle oxidative capacity.

**Keywords:** Gas exchange; Exercise; Cycling; Endurance training.

**INTRODUCTION**

Pulmonary oxygen uptake kinetics ($\dot{V}O_{2p}$) at the onset of exercise is determined from the dynamic interactions of the pulmonary, cardiovascular and neuromuscular systems. In health, phase 2 $\dot{V}O_{2p}$ on-kinetics during moderate intensity exercise are similar to the kinetics of oxygen uptake measured across the exercising limb (Grassi et al. 1996; Koga et al. 2013), and reflect essential intramyocyte control mechanisms of muscle energetics and oxidative function (Rossiter, 2011).

For a given metabolic demand, fast $\dot{V}O_2$ kinetics mandates a smaller $O_2$ deficit, less substrate-level phosphorylation, and are associated with fatigue resistance (Cannon et al. 2011; Keir et al. 2016) and high exercise tolerance (Murgatroyd et al. 2011). As $\dot{V}O_{2p}$ kinetics determine aerobic energy provision during exercise below maximum aerobic power ($\dot{V}O_{2max}$), understanding the mechanisms by which $\dot{V}O_2$ kinetics may be speeded by physical training is relevant for both athletic populations and those with slowed $\dot{V}O_2$ kinetics, e.g. patients with chronic heart or lung disease, and the elderly (Rossiter, 2011; Poole and Jones 2012).

Low-intensity resistance or endurance exercise training, combined with blood flow restriction (BFR), is used as an alternative training method to accrue beneficial muscular training adaptations, among other benefits, especially in those where high-mechanical loads are contraindicated. In particular, endurance BFR training increases several indices of aerobic function including $\dot{V}O_{2max}$ (Park et al. 2010; Abe et al. 2010; Oliveira et al. 2016), exercise tolerance (Abe et al. 2010; Kancin & Strazar, 2012; Oliveira et al. 2016) and intramuscular adaptations supporting endurance exercise (Christiansen et al. 2018, Christiansen et al. 2019a, Christiansen et al. 2019b). The potential mechanisms responsible for increased $\dot{V}O_{2max}$ and exercise tolerance are debated, but include: increased stroke volume and cardiac output (Park et al. 2010); increased muscle capillarity and diffusive oxygen transport (Esbjörnsson et al. 1993; Evans et al. 2010, Kacin & Strazar 2011); and increased muscle oxidative enzyme activity (Kaijser et al. 1990; Esbjörnsson et al. 1993). Training-induced speeding of moderate-intensity $\dot{V}O_{2p}$ on-kinetics (Jones & Carter 2000; Laursen and Jenkins 2002; Berger et al. 2006; Gibala et al. 2006) are thought to particularly reflect adaptations in the activation and capacity for muscular oxidative phosphorylation (Korzeniewski & Rossiter, 2015). Therefore, intramuscular adaptations to mitochondrial function can be revealed in the moderate-intensity $\dot{V}O_{2p}$ on-kinetics response (Barstow et al. 1996; McKay et al. 2009; Zoladz et al. 2015) and in the associated kinetics of carbon dioxide output ($\dot{V}CO_{2p}$) and ventilation ($\dot{V}_{Ep}$) (Whipp, 2007). However, the efficacy of low-intensity endurance BFR training to speed $\dot{V}O_{2p}$ on-kinetics, and its impact on $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ kinetics, is unknown. We were therefore interested whether $\dot{V}O_{2p}$, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ kinetics were speeded following low-intensity endurance BFR training, as they are following high-intensity interval training (HIT).

We aimed to determine the effect of 4 weeks (12 sessions) of low-intensity endurance intermittent BFR training, compared with high-intensity interval training (HIT) on moderate-intensity $\dot{V}O_{2p}$, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ on-kinetics. Participants were randomly assigned to three training groups: 1) Low-intensity

cycle endurance training with blood flow restriction (BFR); 2) Traditional high-intensity cycle interval endurance training (HIT); and 3) Low-intensity training without blood flow restriction (LOW), as a BFR control. We tested the hypotheses that 4 weeks of low-intensity, endurance BFR training would be as effective at reducing the phase 2 time constant ($\tau_p$) of $\dot{V}O_{2p}$, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ on-kinetics as traditional high-intensity interval training (HIT), while low-intensity training without BFR (control) would have no effect on $\dot{V}O_{2p}$, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ on-kinetics.

## METHODS

### *Ethical approval*

This study was approved by the human subject committee Santa Catarina State University, Brazil (approval number, 140/2011.) Twenty-four young adults volunteered to participate in the study and were informed about the procedures and risks associated with the protocols. Participants provided written informed consent in accordance with the latest revision of the Declaration of Helsinki, except for registration in a database.

All participants were healthy with no known musculoskeletal or cardiorespiratory disease, and none were taking medications known to affect the cardiorespiratory system. Participants were all recreationally active, and not actively enrolled in a training program. Participants were instructed to maintain their normal diet, continue normal daily activities, and to refrain from commencing any other exercise training until the completion of the study.

### *Experimental design*

Following the completion of an initial incremental exercise test (described below), participants were assigned randomly to either HIT (n = 9*,* six males and three females), BFR (n = 8, six males and two females) or LOW (n = 7, five males and two females) intervention groups (Table 1). All exercise testing and training was completed on a cycle ergometer (Lode Excalibur Sport; Lode Medical Technology, Groningen, Netherlands). Participants came to the laboratory on three different days, both before and after 4 weeks of training to perform the following protocols (Figure 1): visit 1) a step-incremental exercise test to voluntary exhaustion, and; visits 2 and 3) Constant power exercise at moderate-intensity, at a work rate corresponding to 30% of the peak power output determined from the baseline (pre-training) incremental test. Constant power moderate-intensity exercise was repeated three times a day on two separate days, totalling 6 transitions for each participant. Participants were instructed to arrive at the laboratory fully rested and hydrated and to avoid strenuous exercise in the 48 hours preceding a test session. All test days were performed with at least 48 hours separating each visit and were conducted at the same time of day for each participant.

Procedures

During all tests and training sessions subjects were instructed to maintain cycling cadence at ~70 rpm. During all pre- and post-training exercise tests, and during the first and last training session, pulmonary gas-exchange variables were measured using a breath-by-breath system (Quark CPET, Cosmed Srl, Rome, Italy). Before each test, the $O_2$ and $CO_2$ analysers were calibrated using ambient air and a gas of known $O_2$ and $CO_2$ concentration according to the manufacturer's instructions, while the turbine flow-meter was calibrated over a range of flow rates using a 3 litre syringe. Heart rate (HR) was monitored using a Quark CPET strap (Cosmed Srl, Rome, Italy). Blood lactate concentration ([La]) was determined in earlobe capillary blood using an electrochemical method (YSI 1500 Sport, Yellow Springs Instrument, Yellow Springs, OH, EUA), which was calibrated with a 5 $mmol.l^{-1}$ lactate standard as suggested by the manufacturer.

*Incremental exercise*

The incremental exercise test began at $0.5W.kg^{-1}$ (35 ± 5.6 W), followed by a step increase of 35W for males and 25 W for females every 3 minutes until voluntary exhaustion, to provide the peak power output and $\dot{V}O_{2peak}$. $\dot{V}O_{2peak}$ was defined as the greatest 15 s average $\dot{V}O_2$ value reached during the incremental test. Peak power was determined according to the equation: peak power ($P_{peak}$) = power at last stage completed + [t / step duration x step increment], where t is the completed time of the final stage.

*Moderate-intensity constant power tests*

Subjects performed a total of 6 moderate intensity square-wave exercise tests, 3 each on two separate visit days (Fig. 1). At least 48 hours separated each visit. The exercise test began with a baseline of 3 min of rest with the participant seated on the cycle ergometer. After this, participants were instructed to begin cycling at 30% $P_{peak}$ for 6 min, while maintaining the cadence of 70 rpm. Six minutes of moderate exercise was followed by a 6 min passive recovery seated on cycle ergometer. This protocol was completed a total of 3 times in immediate succession on each visit day. The pre-training 30% $P_{peak}$ was used for all constant power tests, both pre- and post-training.

*$\dot{V}O_{2p}$, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ on-kinetics*

Each rest-work transition was time aligned to the onset of the constant power exercise (t = 0). The data were edited to remove points outside 4 standard deviations of the moving mean as previously described to represent non-Gaussian 'noise' (Lamarra et al. 1987). The individual breath-by-breath $\dot{V}O_2$ responses for the 6 transitions were interpolated on a second-by-second basis, ensemble-averaged and time-averaged to produce a standard weighted response at 10 s intervals, thereby reducing the 'noise' and increasing the confidence of the parameter estimation.

The responses were modelled as a single exponential considered beginning at the phase 1-2 transition, determined by minimizing the 95% confidence interval ($CI_{95}$) of $\tau_p$ estimation by varying the fitting field (Rossiter et al. 1999). $\dot{V}O_{2p}$, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ responses were fit to the following equation using iterative nonlinear regression procedures on Microcal Origin 6.0 (Equation 1): $Y_{(t)} = Y_{base} + A * (1 - e^{(-(t-TD)/\tau)})$.

Where Y may be $\dot{V}O_2$, $\dot{V}CO_{2p}$ or $\dot{V}_{Ep}$ at time t, $Y_{base}$ is the pre-exercise value of each variable; A is the asymptotic amplitude; TD is the time delay, and; $\tau_p$ is the time constant of the phase 2 kinetics. $Y_{base}$ was taken as the average $\dot{V}O_2$, $\dot{V}CO_{2p}$ or $\dot{V}_{Ep}$ measured during 1 min before exercise. Goodness-of-fit was determined visually from the flatness of the residuals, and by minimizing the sum squared errors. The 95% confidence interval ($CI_{95}$) for each parameter was determined by the fitting program (Microcal Origin 6.0).

*Training Protocols*

Training protocols were assigned randomly and stratified with the aim of matching sex and pre-training $\dot{V}O_{2peak}$ among the groups. The training program consisted of three exercise sessions per week on a stationary cycle ergometer for a total duration of 4 weeks.

The first week of training sessions (3 sessions) consisted of 2 sets of 5 repetitions. For the following 3 weeks (9 sessions), one repetition per set was added per week. Therefore, in the 2$^{nd}$ week the participants performed 2 sets of 6 repetitions, in the 3$^{rd}$ week 2 sets of 7 repetitions were performed, and in the 4$^{th}$ week the session consisted of 2 sets of 8 repetitions. Each repetition lasted 2 min of cycling with 1 min passive rest. The rest interval between sets was 5 min (3 min active recovery at 30% $P_{peak}$ followed by 2 min passive rest).

Each training session consisted in a warm-up of 5 min at 30% $P_{peak}$. The training power output was 30% $P_{peak}$ for LOW and BFR. In HIT, the training power output was variable, each repetition began at 110% $P_{peak}$ with a progressive 5% decrease in the power output every 30 s (i.e. 110, 105, 100 and 95% $P_{peak,}$ respectively).

The BFR group wore pressure cuff belts (18 cm wide; Missouri, Sao Paulo, Brazil) on the upper thigh of both legs during all training sessions. In the first week, cuff belts were inflated to 140 mmHg during the 2 min repetitions and deflated during the 1 min rest periods. The pressure was progressed by 20 mmHg after three completed sessions, such that in the last week the pressure applied was 200 mmHg.

Cardiorespiratory variables were measured during the first and the last training session for all groups. Ratings of perceived exertion (RPE) were reported after each repetition using the 0-10 Category Ratio Scale (Borg, 1998). Capillary blood samples (25 µl) were taken from the earlobe immediately before and after the end of the first and last training sessions for analysis of blood lactate concentration ([La]) (YSI 1500 Sport, Yellow Springs Instrument, Yellow Springs, OH, EUA).

## Statistical Analyses

Data are presented as mean ± standard deviation (SD). For each set of data, normal distribution was verified by Shapiro-Wilk test. Statistical analyses were performed by a two-way analysis of variance (ANOVA) for repeated measures (Group [HIT, BFR and LOW] × Training [pre and post]) to evaluate training effects for all dependent variables. *Post hoc* testing was performed by Fisher's least significant differences test. Statistical significance was accepted at $P < 0.05$. To make inferences about magnitude of the effect of training on $\dot{V}O_{2p}$, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ kinetics, effect sizes (ES) were calculated (Cohen, 1990) and expressed as 90% confidence limits (Batterham & Hopkins, 2006). The following formula was used to calculate the ES: ((Post mean – Pre mean) / $SD_{pooled}$); where $SD_{pooled}$= √(($SD_{pre}^2$+$SD_{post}^2$) / 2) (Cohen, 1989). ES of less than 0.2 was considered as trivial, 0.2-0.6 was small, 0.6-1.2 was moderate, 1.2-2.0 was large, and 2.0-4.0 was very large (Batterham and Hopkins, 2006).

**RESULTS**

Participant characteristics and pre-training incremental exercise responses are shown in Table 1. There were no differences in baseline characteristics among groups.

All participants completed all training sessions. A description of each exercise training group is summarized in Table 2. Power output (by design), peak lactate and peak heart rate were lower for BFR and LOW ($P < 0.05$) compared with HIT. Peak lactate and peak heart rate were also less in LOW compared with BFR ($P < 0.05$). RPE during training sessions was less in LOW ($P < 0.05$) compared to BFR and HIT, but there was no difference in training RPE between BFR and HIT.

Examples of the pre and post training $\dot{V}O_2$ kinetics during moderate intensity exercise for individual subjects within each training group are shown in Figure 2, demonstrating high goodness-of-fit. The difference in $\dot{V}O_2\,\tau_p$ for each training group is shown in Figure 3. Table 3 shows the mean parameter

values of the phase 2 $\dot{V}O_2$ kinetics. Kinetic responses were well fit with confidence intervals averaging ~5-6 s, consistent with the expected sensitivity of kinetic estimates (Benson et al. 2017). There was no mean difference in $\dot{V}O_2\,\tau_p$ following LOW, whereas $\dot{V}O_2\,\tau_p$ was reduced in BFR and HIT ($P < 0.05$) (Figure 3, Table 3). There was no difference between training-induced difference in $\dot{V}O_2\,\tau_p$ between BFR and HIT (Figure 3, Table 3). The calculated ES for $\dot{V}O_2\,\tau_p$ was moderate (ES = 1.14) for BFR and large (ES = 1.75) for HIT. The reduction in $\dot{V}O_2\,\tau_p$ with training was significantly associated with the pre-training $\dot{V}O_2\,\tau_p$, for HIT ($r = 0.78$, $P < 0.05$), and HIT and BFR combined ($r = 0.68$, $P < 0.05$) (Figure 4), but not for BFR alone ($r = 0.28$, $P > 0.05$).

The pre- and post-training mean values of $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ for all three conditions are shown in Table 4. $\tau_p$ for both $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ were significantly reduced after HIT but failed to reach significance for BFR. As expected, $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ kinetics were not affected by LOW (Table 4). The ES for $\dot{V}CO_2\,\tau_p$ was moderate (ES = 0.67 for BFR and very large (ES = 2.1) for HIT. The ES for $\dot{V}_{Ep}\,\tau_p$ was moderate for both BFR (ES = 1.16) and HIT (ES = 1.13).

**DISCUSSION**

This is first study to show that low-intensity endurance interval blood flow restricted training speeds pulmonary $\dot{V}O_2$ on-kinetics (reduces $\tau_p$) in healthy young participants. The post-training $\dot{V}O_2$ kinetics responses were not different between low intensity BFR training and traditional high intensity interval training (HIT). These results support our hypothesis that BFR endurance training would result in a faster $\dot{V}O_{2p}$ on-kinetics, and therefore resulted in increased oxidative energy provision during moderate intensity exercise.

The magnitude of the training-induced response during HIT exceeded that of BFR, which may be partly due to slower pre-training $\dot{V}O_2$ kinetics in the HIT group allowing greater room for improvement (McKay et al., 2009). We also show that the control group of low-intensity interval training without blood flow restriction (LOW), but at the same power output as used in BFR, did not alter $\dot{V}O_{2p}$ on-kinetics pre- to post-training. In addition, moderate to large effect sizes were seen in speeding the kinetics of $\dot{V}CO_{2\,p}$ and $\dot{V}_{Ep}$ in both BFR and HIT, but not in LOW. These data are consistent with the notion that physiologic strain induced by low-intensity exercise with blood flow restriction, such as reduced $O_2$ delivery, increased substrate level phosphorylation, intramuscular metabolite accumulation and reperfusion, may provide a strong intramuscular stimulus for adaptation (Corvino et al. 2017; Christiansen et al. 2018).

$\dot{V}O_{2p}$ on-kinetics can be speeded using different types of training (Phillips et al. 1995; Berger et al. 2006; McKay et al. 2009; Murias et al. 2010; Williams et al. 2013 Zoladz et al. 2013; Christensen et al. 2016). The mechanisms involved in the speeding of $\dot{V}O_{2p}$ kinetics by a training program are complex, and likely involve an integration of both metabolic (mitochondrial) and cardiovascular (convective and diffusive oxygen transport) adaptations. However, moderate intensity exercise is typically

thought not to be limited by oxygen delivery, because interventions that increase convective or diffusive transport do not typically speed $\dot{V}O_{2p}$ kinetics in moderate exercise (Grassi et al. 2005; Koga et al. 2005; Richardson et al. 2015; c.f. Gurd et al. 2005). Therefore, the primary adaptation that allows faster moderate-intensity $\dot{V}O_{2p}$ kinetics response is likely to be intramuscular in the form of increased oxidative enzyme expression and/or speeded each-step activation of oxidative phosphorylation at exercise onset (Rossiter, 2011; Korzeniewski et al. 2018).

In our study, 4 weeks of HIT training speeded $\dot{V}O_2$ on-kinetics by 34 ± 18 %, in line with previous studies of short-term HIT training (McKay et al. 2009; Christensen et al. 2016). However, we also demonstrated that a similar duration of low-intensity endurance interval training, combined with BFR, speeded $\dot{V}O_{2p}$ on-kinetics by 24 ± 19 %, despite performing 3.5-times less work compared to HIT. This mode of BFR exercise reduces oxygen delivery to muscle, decreasing tissue oxygen saturation (Corvino et al. 2017) and increasing accumulation of metabolites (e.g. ADP, AMP, $NAD^+$), variables that are involved in stimulating increased oxidative enzyme activity and/or mitochondrial biogenesis by activation of AMP kinase and/or SIRT1 for PCG-1$\alpha$ dependent transcription (Hudlicka & Brown 2009; Zhao et al. 2011; Larkin et al. 2013; Taylor et al. 2016; Christiansen et al. 2018; Ferguson et al. 2018; c.f. Conceição et al. 2016). Furthermore, several studies demonstrate that reduced blood flow to the exercising limbs produces beneficial adaptive responses that are likely responsible for speeded $\dot{V}O_{2p}$ kinetics, such as increased muscle oxidative enzyme activity, capillary density in quadriceps (Esbjörnsson et al. 1993; Conceição et al. 2019) and enhanced microvascular filtration capacity in humans (as an index of capillarity) (Evans et al. 2010). Together these factors may be responsible for speeding $\dot{V}O_2$ kinetics (Rossiter. 2011) and increasing $\dot{V}O_{2peak}$ and exercise tolerance (Abe et al. 2010; Kancin & Strazar, 2011; Oliveira et al. 2016; Christiansen et al. 2019b).

Interestingly, the effect size of the speeded $\dot{V}O_{2p}$ kinetics in the BFR group was slightly less (moderate) than in the HIT group (large), while the pre-training $\dot{V}O_{2peak}$ did not differ between groups. In healthy subjects, the magnitude of training-induced speeding in $\dot{V}O_{2p}$ kinetics is correlated with the starting value (Berger et al. 2006; McKay et al. 2009) (Figure 2), i.e. the effective room for improvement (reduction in $\tau_p$) was smaller in the BFR group. The very fast at pre-training $\dot{V}O_{2p}$ kinetics (ranging from 20-17s), may therefore have limited the effect size in the BFR group compared to HIT. Both HIT and BFR resulted in post-training $\tau_p$ values of ~14 s, which is close to the smallest values reported in humans (Jones & Koppo, 2005; Korzeniewski et al. 2018). This implies training-induced speeding of $\dot{V}O_{2p}$ kinetics may have reached a limit beyond which significant further increases may not be possible (Figueira et al. 2008; Korzeniewski et al. 2018). In addition, the total training volume in HIT was ~3.5 times greater than BFR group (4,436 vs. 1,263 kJ, respectively; Table 1). Therefore, the greater effect size for $\dot{V}O_{2p}$ kinetics in HIT may reflect that the training stimulus and response in HIT exceeded that of low-intensity BFR.

$\dot{V}O_2$ kinetics are associated with the kinetics of $\dot{V}CO_{2p}$ and ventilation (Whipp, 2007). $\dot{V}CO_{2p}$ kinetics tends to be slightly slower than $\dot{V}O_{2p}$ kinetics at least partly due to intramuscular PCr breakdown and transient $CO_2$ storage in muscle and blood. $\dot{V}_{Ep}$ kinetics typically track very closely to those of $\dot{V}CO_{2p}$.

Our findings of moderate to large effects on $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ kinetics following HIT are consistent with the overall increase in oxidative metabolism (and reduction in substrate-level phosphorylation) during the moderate exercise transient. We were unable to detect a speeding of $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ kinetics following BFR training ($p = 0.83$ and $p = 0.88$, respectively. This resulted in an apparent dissociation between the training adaptions of $\dot{V}O_{2p}$ and $\dot{V}CO_{2p}$. While this may be due to large variability in $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ and the small sample size, it is possible that specific adaptations in BFR alter the responses of muscle $CO_2$ production, transient buffering of $CO_2$ and/or ventilatory control to a different degree than in HIT. Additional work is needed to identify whether the observed moderate effect size indicating speeded $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ kinetics (E. S = 0.66 and E. S = 1.16), is consistent with the finding of speeded $\dot{V}O_{2p}$ kinetics.

We were not able to quantify the magnitude of blood flow reduction during BFR. It is likely that the external pressure (140 - 200 mmHg) applied in our study using an 18 cm wide cuff (Wernbom et al. 2008) was enough to reduce blood flow and promote adaptations in aerobic responses to exercise (Oliveira et al. 2016). We note at least four other methodological limitations: 1) The participants initiated moderate-intensity exercise transitions from rest, which increases the phase 1 response to exercise and may reduce the data in phase 2. The use of this method might be one reason why $\dot{V}O_{2p}$ kinetics were very fast in this study. As the same methods were used for all three training conditions before and after training, we do not believe that it exerted undue influence on the findings; 2) The sample size was small and was composed by both genders. However, for the present study the data was not widely distributed (SD's of the primary variables are small). Further, for young adults there seems to be little influence of sex in baseline $\dot{V}O_2$ kinetics or in training response (Murias et al., 2010, 2011). Also, in moderate exercise Murias et al. (2010, 2011) reported similar $\dot{V}O_2$ kinetics for men and women of similar fitness levels; 3) The lactate threshold (LT) was not directly measured, however our $\dot{V}O_{2p}$ kinetics response data at 30% of $P_{peak}$ show a steady-state after 2-3 minutes consistent with the absence of a $\dot{V}O_{2p}$ slow component that is only observed above LT. This was also confirmed by low blood lactate concentration during the low condition, which was undertaken at the same power output (Table 2); 4) We were not able to make direct measurements of muscle oxidative capacity to confirm that the speeded $\dot{V}O_{2p}$ kinetics were associated with intramuscular adaptations in oxidative capacity.

In summary, four weeks (3 sessions per week) of low-intensity aerobic interval blood flow restriction training (BFR) and high intensity interval training (HIT) were effective speeding moderate intensity $\dot{V}O_{2p}$ kinetics. No significant changes in $\dot{V}O_{2p}$ kinetics were observed in the control group (LOW), which was performed at the same power output as the BFR group but without blood flow restriction. Since very low workloads are well tolerated during BFR cycle training, this training method could be used for rehabilitation in athletes recovering from injury, or in frail, elderly or disabled persons in whom high mechanical loads are contraindicated. Further research is needed to examine the mechanisms underlying the adaptations of $\dot{V}O_{2p}$ kinetics evoked by low-intensity interval BFR training.

**Conflicts of interest**

The authors declare that they have no conflicts of interest concerning this article.

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**Author Contributions**

All the work was done in the Human Performance Research Group in the Center for Health and Exercise Science, Santa Catarina State University. R.B Corvino, M.F.M. Oliveira and F. Caputo, designed the experiments, contributed data acquisition, and wrote the manuscript. H.B. Rossiter, contributed to the analysis and interpretation of the data, and critically revised the work. B.S. Denadai, designed the experiments, contributed to the interpretation of the data, and critically revised the work. All authors approved the final version of the manuscript, all persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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**Table 1**. Participant characteristics and pre-training peak incremental exercise responses.

| | **LOW** | **BFR** | **HIT** |
|---|---|---|---|
| M/F (n) | 5/2 | 6/2 | 6/3 |
| Age (yrs) | 23 ± 4 | 25 ± 5 | 25 ± 3 |
| Height (cm) | 170 ± 13 | 173 ± 9 | 174 ± 9 |
| Body mass (kg) | 68.5 ± 13.1 | 71.2 ± 12.5 | 71.5 ± 9.3 |
| Peak power (W) | 222 ± 40 | 236 ± 60 | 232 ± 34 |
| $\dot{V}O_{2peak}$ ($ml.kg^{-1}.min^{-1}$) | 44.6 ± 4.0 | 47.0 ± 7.8 | 45.4 ± 4.1 |

Values are mean ± SD; M/F, male/female; $\dot{V}O_{2peak}$, peak oxygen uptake

**Table 2**. Description of training

| Parameters | LOW | BFR | HIT |
|---|---|---|---|
| **Exercise protocol** | 2 sets [120s × 5-8 reps] | | |
| | 1 min rest between repetitions / 5 min rest between sets | | |
| **Prescribed intensity** | 30% $P_{peak}$ | 30% $P_{peak}$ | 100% $P_{peak}$ |
| **Actual training power (W)** | 66 ± 12 * | 68 ± 13 * | 237 ± 35 |
| **Rating of perceived exertion** | 1.3 ± 0.5 * # | 7.3 ± 1.4 | 7.6 ± 1.4 |
| **Peak [La] (mM)** | 1.6 ± 0.4* # | 5.3 ± 1.7* | 10.1 ± 2.0 |
| **Peak HR (%$HR_{MAX}$)** | 60 ± 5.1* # | 70 ± 9.2* | 96 ± 2.9 |
| **Total session time (min)** | | | |
| **Range 1st – 12th session** | | (33 – 51 minutes) | |
| **Session volume (kJ)** | 103 ± 34 * | 105 ± 34 * | 370 ± 120 |
| **Range 1st - 12th session** | (79 – 127) | (81 – 130) | (284 – 455) |
| **Total training volume (kJ) Range 1st - 4th week** | 1235 ± 61 * | 1264 ± 63 * | 4436 ± 220 |
| | (237 – 380) | (243 – 388) | (853 – 1365) |

Values are mean ± SD (range). Rating of perceived exertion, Peak HR and [La] represent the mean of the average values obtained during the 1st and 12th training session. Rating of perceived exertion measured by 0 to 10 scale. * significantly different from HIT; # significantly different from BFR ($P < 0.05$).

**Table 3**. Moderate-intensity $\dot{V}O_{2p}$ kinetics before and after LOW, BFR or HIT training.

| Parameter | Condition | Group | | |
|---|---|---|---|---|
| | | **LOW** | **BFR** | **HIT** |
| **Power output (W)** | PRE / POST | 66 ± 12 | 68 ± 13 | 69 ± 9 |
| **$\dot{V}O_{2base}$ (l.min$^{-1}$)** | PRE | 0.49 ± 0.11 | 0.44 ± 0.10 $^{\$}$ | 0.47 ± 0.06 |
| | POST | 0.48 ± 0.10 | 0.45 ± 0.07 | 0.48 ± 0.10 |
| **A (l.min$^{-1}$)** | PRE | 0.90 ± 0.16 | 0.83 ± 0.13$^{\#}$ | 0.92 ± 0.21 |
| | POST | 0.93 ± 0.27 | 0.86 ± 0.19 | 0.88 ± 0.19 |
| **$\tau_p$ (s)** | PRE | 17.9 ± 6.2 | 18.3 ± 3.2 | 20.3 ± 4.0 |
| | POST | 17.7 ± 4.3 | 14.5 ± 3.4*$^{\$}$ | 13.1 ± 2.9*$^{\$}$ |
| **$CI_{95}\tau_p$ (s)** | PRE | 5.6 ± 1.2 | 5.4 ± 2.9 | 5.7 ± 2.0 |
| | POST | 4.7 ± 1.3 | 5.0 ± 2.3 | 4.7 ± 1.3 |
| **$\dot{V}O_{2EE}$ (l.min$^{-1}$)** | PRE | 1.37 ± 0.27 | 1.27 ± 0.18$^{+}$ | 1.40 ± 0.25 |
| | POST | 1.38 ± 0.33 | 1.31 ± 0.23 $^{\$}$ | 1.36 ± 0.26 |

Values are mean ± SD. $\dot{V}O_{2base}$, baseline $\dot{V}O_2$; A, asymptotic amplitude; $\tau_p$, time constant of $\dot{V}O_2$ on-kinetics; $CI_{95}\tau_p$, 95% confidence interval for $\tau_p$; $\dot{V}O_{2EE}$, end-exercise $\dot{V}O_2$. $^{\#}$ significantly different from HIT at the same time point; $^{+}$ P < 0.05 from LOW and HIT at the time point; * P < 0.05 from pre-training; $^{\$}$P < 0.05 from LOW at the same time point.

**Table 4.** Moderate-intensity $\dot{V}CO_{2p}$ and $\dot{V}_{Ep}$ kinetics before and after LOW, BFR or HIT training.

| | LOW | | BFR | | HIT | |
|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| $\dot{V}CO_{2BASE}$ **(l.min$^{-1}$)** | 0.41 ± 0.09 | 0.42 ± 0.11 | 0.36 ± 0.08 | 0.39 ± 0.11 | 0.41 ± 0.10 | 0.42 ± 0.09 |
| **A (l.min$^{-1}$)** | 0.79 ± 0.17 | 0.78 ± 0.22 | 0.76 ± 0.17 | 0.77 ± 0.12 | 0.82 ± 0.20 | 0.75 ± 0.17 |
| $\tau_p$ $\dot{V}CO_2$ **(s)** | 48.4 ± 22 | 45.7 ± 13.0 | 44.7 ± 15.0 | 35.2 ± 12.0 | 56.8 ± 12.4 | 34.4 ± 7.6* |
| $\dot{V}_{EBASE}$ **(l.min$^{-1}$)** | 15.0 ± 2.7 | 16.0 ± 5.0 | 13.8 ± 2.9 | 14.2 ± 2.8 | 14.7 ± 3.3 | 15.4 ± 3.5 |
| **A (l.min$^{-1}$)** | 21.6 ± 4.3 | 20.6 ± 6.2 | 17.7 ± 3.5 | 18.4 ± 2 | 21 ± 5.5 | 18.8 ± 4.7 |
| $\tau_p$ $\dot{V}_E$ **(s)** | 55.3 ± 18.0 | 50.5 ± 9.3 | 46.7 ± 8.2 | 35.4 ± 11.0 | 63.1 ± 16.0 | 42.7 ± 18.0* |

Values are mean ± SD. $\dot{V}CO_{2base}$, baseline $\dot{V}CO_2$; A, asymptotic amplitude; $\tau_p$, time constant of $\dot{V}CO_2$ on-kinetics; $\dot{V}E_{base}$, baseline $\dot{V}_{Ep}$; A, asymptotic amplitude; $\tau_p$, time constant of $\dot{V}_{Ep}$ on-kinetics. * P < 0.05 from pre-training at same condition group.

**Figure Legends**

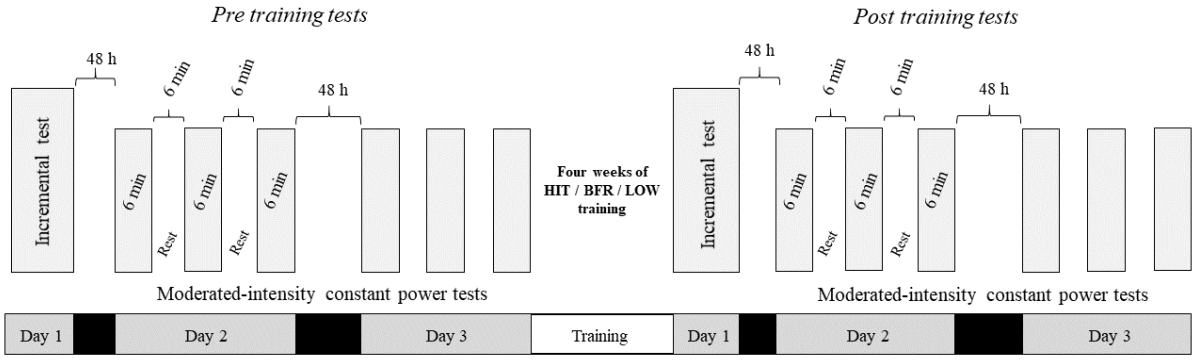


**Figure 1.** Experimental design.

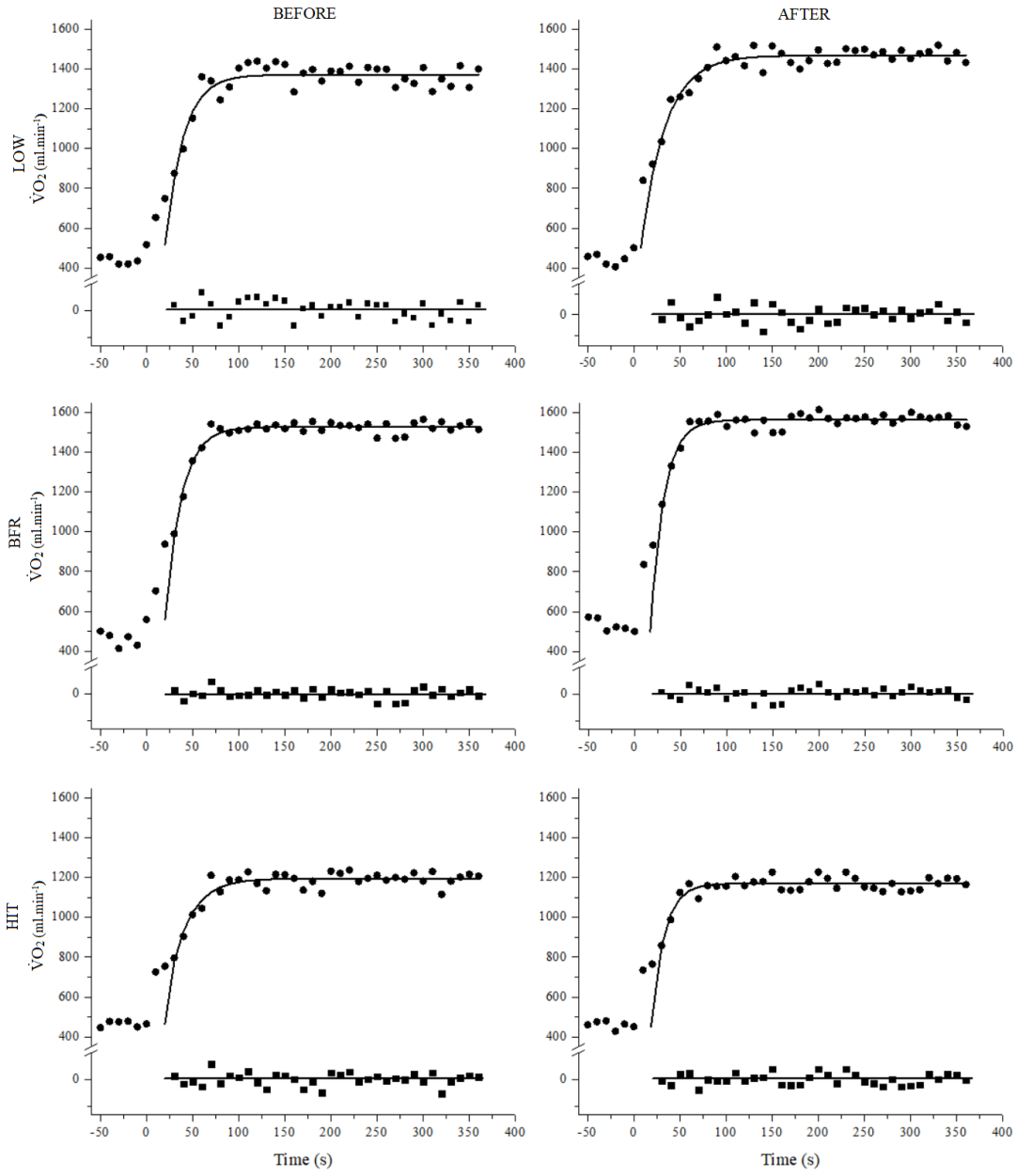


**Figure 2.** Example $\dot{V}O_{2p}$ kinetics responses to moderate intensity exercise in representative subjects (n = 1 per group) before (left panels) and after (right panels) LOW (upper panels), BFR (middle panels) and HIT (bottom panels) training regimes. Data are 10s average values. Fitted curves are mono-exponential fits to the phase 2 $\dot{V}O_{2p}$ response. The fit residuals are shown within each panel.

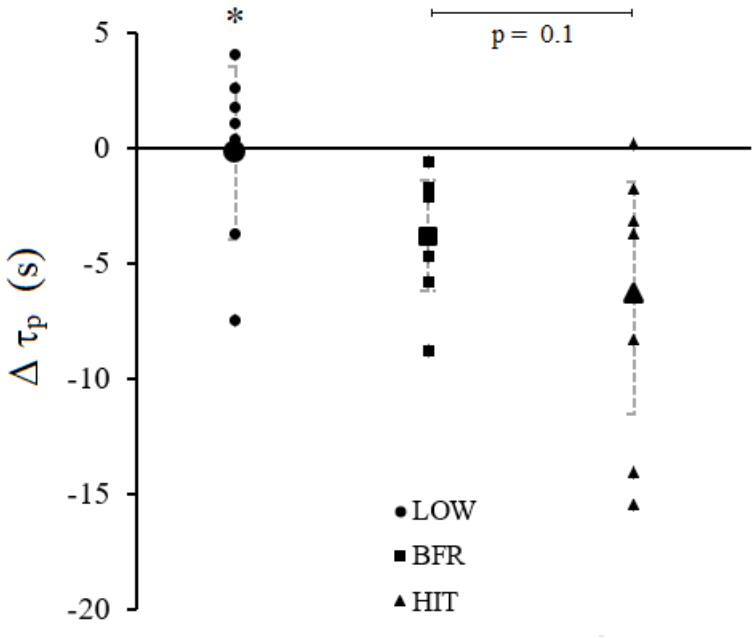


**Figure 3.** Individual change (Δ) in $\dot{V}O_{2p}$ $\tau_p$ from pre- to post-training for LOW (solid circles, n = 7), BFR (solid squares, n = 8) and HIT (solid triangles, n = 9). Dashed horizontal lines represent mean ± SD. * significantly different from BFR and HIT.

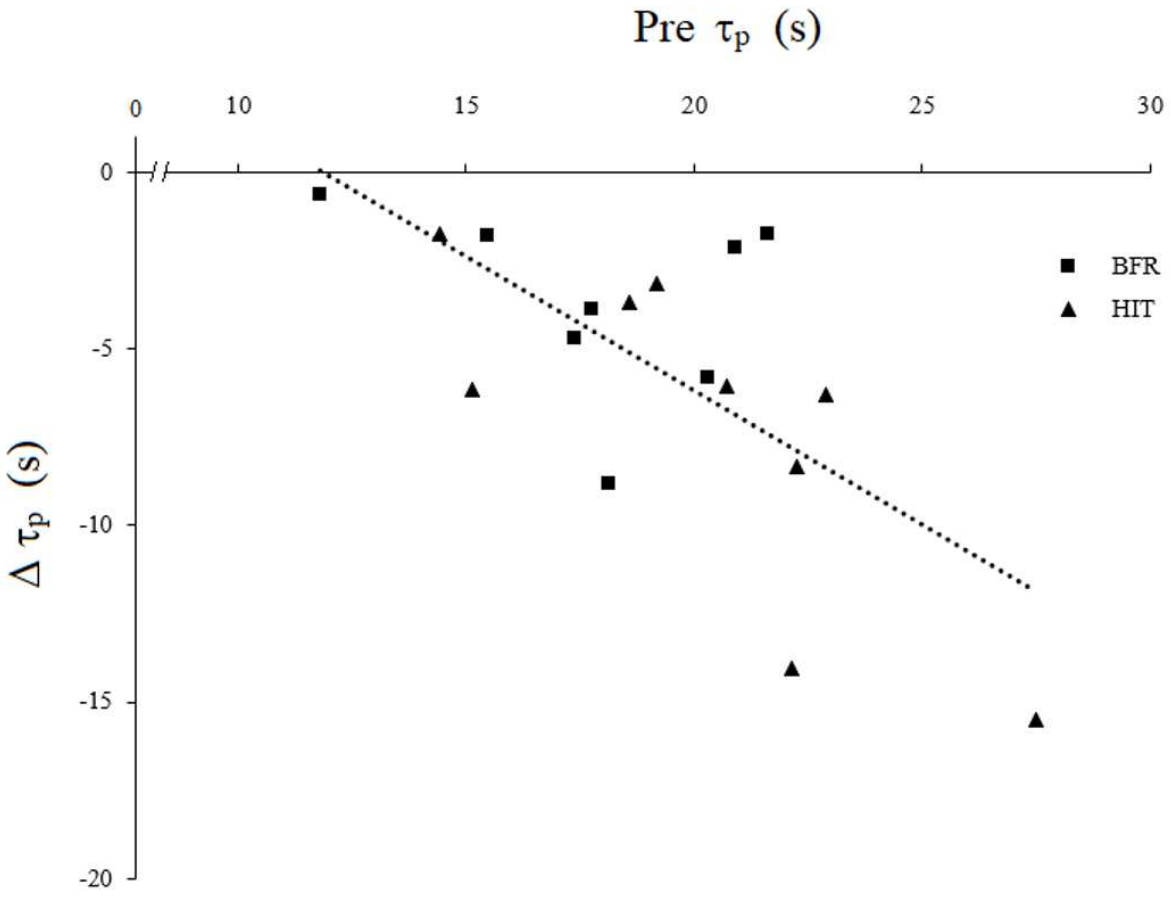


**Figure 4**. Relationship between the change (Δ) in $\dot{V}O_{2p}$ $\tau_p$ from pre- to post-training as a function of pre-$\tau_p$. Data from both HIT (closed triangle, n = 9) and BFR (close square, n = 8) are plotted and all data are fit to a linear regression.