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Effectiveness of Repeated Sprint Training in Hypoxia vs. with Blood Flow Restriction

A Master Thesis in Human Movement and Sport Sciences

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Abstract

Introduction: Repeated-sprint training in hypoxia (RSH) is known to improve intermittent high-intensity performance and repeated-sprint ability (RSA), in particular by enhancing fatigue resistance. The underlying physiological changes after such short hypoxic exposure, less than 10 h for 9 sessions, are at the most interest for endurance and team sport athletes. Repeated-sprint training with blood flow restriction (RS-BFR) seems to impact performance as well by localized hypoxia and different physiological mechanisms. Therefore the purpose of this study was to assess the different effects of a three weeks of RSH vs. RS-BFR in young male adults. **Methods:** Twenty-four recreationally trained young male adults (25.8 ± 5.2 years, 77.2 ± 6.7 kg, 181 ± 7 cm) were randomly assigned to three groups experimental groups that performed nine sessions of repeated sprints (six sets of six 6-s maximal sprint with 24 s and 4 min recovery) on an electronic braked cycle ergometer either in normoxia (RSN), or RSH at a simulated altitude of 3800 m, or RS-BFR with an occlusion percentage at 45% of total arterial occlusion. Subjects were tested PRE (1 week before) and POST (1 week after) intervention. Performance tests consisted in a RSA test, a 6-min submaximal test at 1.5w.kg^{-1}, a Wingate test and a 10-km time trial (TT). The measurement of leg muscle oxygenation was assessed with near-infrared spectroscopy (NIRS). Measurement of oxygen consumption, lactate, strength, blood and biopsies were assessed at PRE and POST. **Results:** Only performance and VO_2 values are displayed in this study. RSA mean power output increased to the same extent in the three groups ($p < 0.01$) (RSN: 6.3%; RSH: 6.9%; RS-BFR: 7.3%) along with peak power output (RSN: 8.7%; RSH: 7.4%; $p < 0.01$) (RS-BFR: 8.8%; $p < 0.001$). Wingate mean power output was significantly greater in the RSH (4.2%; $p < 0.05$) and RS-BFR groups (3.4%; $p < 0.05$) but not in the RSN group. 10k TT mean power output was significantly greater post-training for every group ($p < 0.001$) (RSN: 9.9%; RSH: 10.1%; RS-BFR: 8.8%). TT cycling economy values were significantly decreased post-training for the RSH (10.2%; $p < 0.05$) and the RS-BFR groups (12.1%; $p < 0.01$) but not for in RSN group. **Conclusion:** Both RSH and RS-BFR lead to greater anaerobic (Wingate) and aerobic (economy) adaptations than the same training performed in normoxia. Repeated sprint training with BFR was as efficient as RSH with underlying physiological improvements not totally understood yet.

Résumé

Introduction: L'entraînement de répétition de sprint en hypoxie (RSH) est connu pour améliorer les performances à haute intensité, la capacité à répéter des sprints (RSA) et augmenter la résistance à la fatigue. Les changements physiologiques sous-jacents après une exposition hypoxique aussi courte, moins de 10 h en 9 séances, sont des plus intéressants pour les athlètes d'endurance et de sports d'équipe. L'entraînement de répétition de sprint avec restriction du débit sanguin (RS-BFR) semble également avoir un impact sur les performances par une hypoxie localisée avec différents mécanismes physiologiques. Par conséquent, le but de cette étude était d'évaluer les différents effets de trois semaines de RSH vs RS-BFR chez des jeunes hommes adultes. **Méthodes:** Vingt-quatre jeunes hommes adultes entraînés de manière récréative (25,8 ± 5,2 ans, 77,2 ± 6,7 kg, 181 ± 7 cm) ont été répartis au hasard dans trois groupes expérimentaux qui ont effectué neuf sessions de sprints répétés (six séries de six 6 s maximum sprint avec 24 s et 4 min de récupération) sur un ergocycle électronique soit en normoxie (RSN), soit RSH à une altitude simulée de 3800 m, ou RS-BFR avec un pourcentage d'occlusion à 45% de l'occlusion artérielle totale. Les sujets ont été testés PRE (1 semaine avant) et POST (1 semaine après) intervention. Les tests de performance ont consisté en un test RSA, un test sous-maximal de 6 minutes à 1,5 $w.kg^{-1}$, un test Wingate et un contre-la-montre (TT) de 10 km. La mesure de l'oxygénation musculaire des jambes a été évaluée par spectroscopie proche infrarouge (NIRS). La mesure de la consommation d'oxygène, du lactate, de la force, du sang et des biopsies a été évaluée au PRE et au POST. **Résultats:** Seules les valeurs de performance et de VO_2 sont affichées dans cette étude. La puissance moyenne RSA a augmenté dans la même mesure dans les trois groupes (p <0,01) (RSN: 6,3%; RSH: 6,9%; RS-BFR: 7,3%) ainsi que la puissance maximale (RSN: 8,7%; RSH: 7,4 %; p <0,01) (RS-BFR: 8,8%; p <0,001). La puissance moyenne Wingate était significativement plus élevée dans les groupes RSH (4,2%; p <0,05) et RS-BFR (3,4%; p <0,05) mais pas dans le groupe RSN. La puissance moyenne 10k TT était significativement plus élevée après l'entraînement pour chaque groupe (p <0,001) (RSN: 9,9%; RSH: 10,1%; RS-BFR: 8,8%). Les valeurs d'économie de pédalage TT ont été significativement diminuées après l'entraînement pour les groupes RSH (10,2%; p <0,05) et RS-BFR (12,1%; p <0,01) mais pas pour le groupe RSN. **Conclusion:** RSH et le RS-BFR conduisent tous deux à des adaptations anaérobies (Wingate) et aérobies (économie) plus importantes que le même entraînement effectué en normoxie. RS-BFR était aussi efficace que RSH avec des améliorations physiologiques sous-jacentes pas encore totalement comprises.

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1. Introduction

1.1 Hypoxia

Hypoxia is defined as a discrepancy between the oxygen required by the body tissues and the insufficient oxygen provided (Schumacker & Cain, 1987). It is possible to distingue two type of hypoxia: terrestrial hypoxia (hypobaric hypoxia) and artificial hypoxia (normobaric hypoxia).

1.1.1 Terrestrial hypoxia

The air of the Earth's atmosphere is composed by 20.93% of O_2, 78.08% of N_2, 0.03% of CO_2, in addition to others noble gazes, which are negligible due to microscopic volumes (i.e., less than 30 parts per million). The barometric pressure (Pb) at sea level under normal conditions (normobaric normoxia, NN) is 760 mmHg (Brimblecombe, 1996).

When the altitude increases, the Pb decreases. However, the air composition does not change. So, there will be exactly the same quantity of O_2, N_2, CO_2 whether in altitude or at sea level. According to Dalton's law (Dalton, 1802) it is known that the partial pressure of oxygen present in the air (PO_2) can be calculated with the following equation: $\mathbf{PO_2 = F_iO_2 \times Pb}$, where F_iO_2 is the fraction of inspired oxygen present in the air. A lower Pb and PO_2 will affect the amount of oxygen delivered to the cells. In fact, from the entry of the respiratory track all the way down to the mitochondria in the cells where the oxygen is utilized, a cascade occurs in order to decrease the oxygen tension to facilitate the exchange. This oxygen cascade declining PO_2 is displayed in Figure 1.

It is important to note that if the altitude is higher, 4000m for instance, the initial PO_2 is diminished up to 97 mmHg (Küpper et al., 2009). Whereas the PO_2 decrease, the Pb decreases likewise which affects the oxygen cascade by delivering a lower quantity of oxygen to the cells downstream. That is why there is a lack of oxygen for the cells to maintain their functions in altitude (see Figure 2).

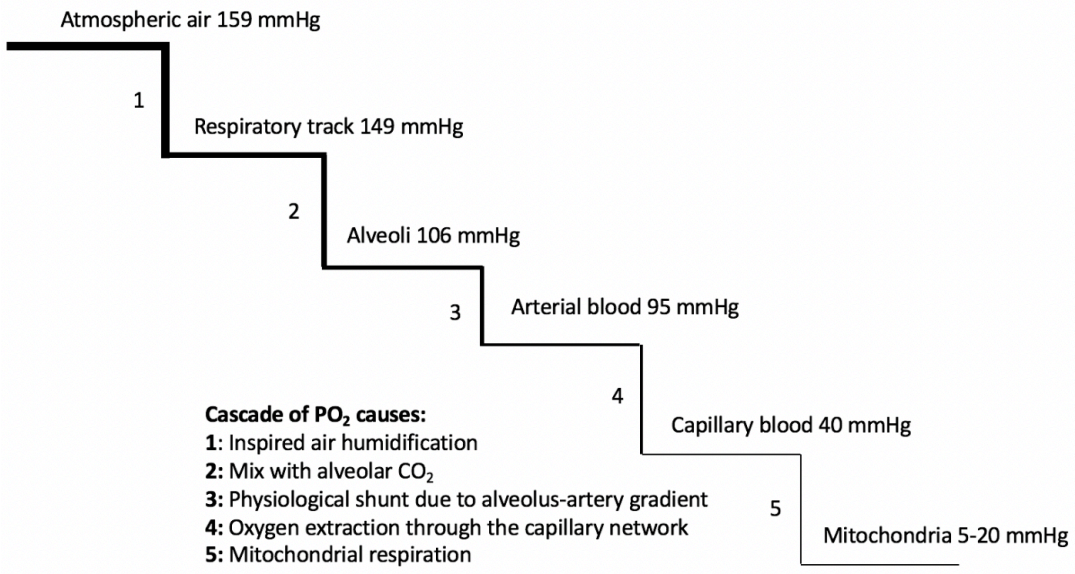

Figure 1. Oxygen cascade decrease in PO_2 from atmospheric air to the mitochondria, in normobaric normoxia, and its causes. Adapted from (Millet & Schmitt, 2011).

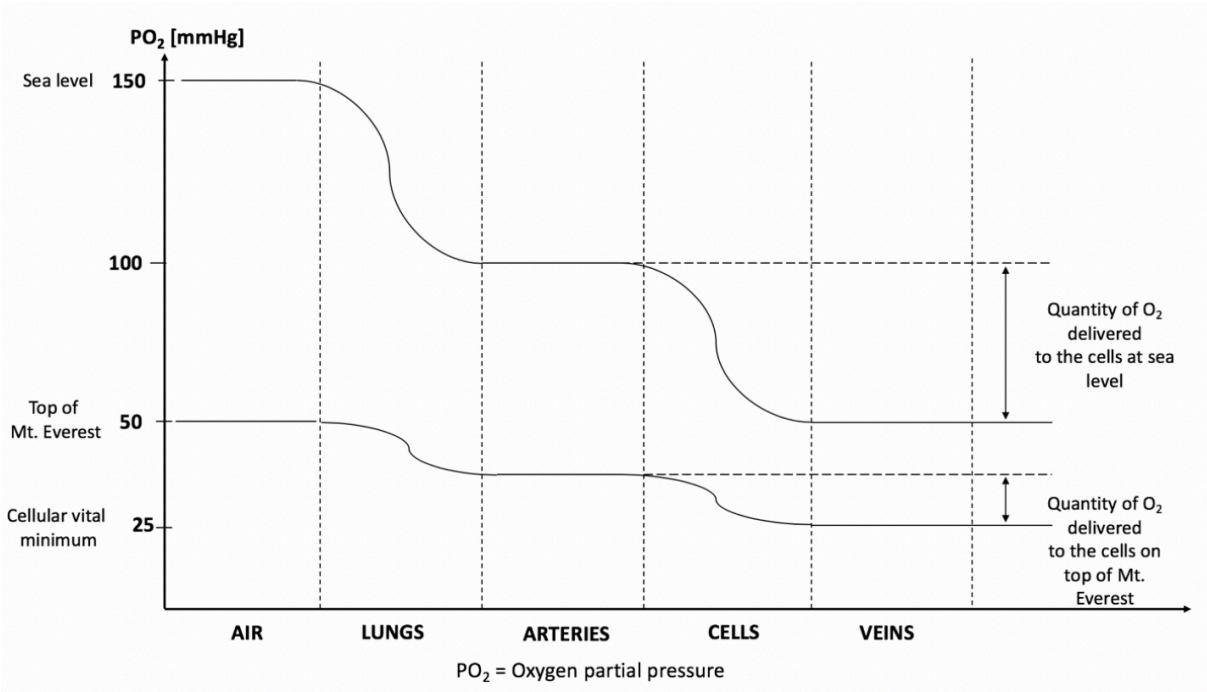

Figure 2. Effect of hypoxia on the decrease in PO_2 and its effect on the oxygen cascade. Adapted from (Millet & Schmitt, 2011).

Terrestrial hypoxia is called Hypobaric Hypoxia (HH) type. It is defined once the PO_2 attains less than 150 mmHg.

1.1.2 Artificial hypoxia

It exists different methods to induce artificial hypoxia without the need to be in real altitude. It is known that training in altitude entails some logistical difficulties such as the obligation to relocate the training center, which depending on the region may be practically difficult and very expensive. This is why there has been some interest to develop other facilities to achieve similar conditions. Whereas the Pb cannot be changed at sea level unless a hypobaric hypoxic (HH) chamber is set, the F_iO_2 has to be diminished to affect the PO_2. In order to replicate this hypoxic environment, two different techniques are utilized: Oxygen (O_2) extraction or Nitrogen (N_2) dilution. In these cases, where the Pb is not changed but the F_iO_2 and the PO_2 are, the environment is designated as normobaric hypoxia (NH). Nowadays, this technology is applied with masks (Altitrainer®), tents, rooms, chambers or even whole lodges or apartments (CNSNMM Prémanon, France) which allows athletes to train and/or sleep in a simulated altitude environment controlled and monitored by professionals.

1.2 Training in hypoxia

It all started in the early 1970's after the dominance of altitude acclimatized athletes during the Mexico Olympic games (2340 m, PB 580 mmHg). Since this event, altitude/hypoxic training has become increasingly popular among individual endurance athletes and gained the scientific interest to investigate the effectiveness of this new training method. At that time, several altitude training centers (e.g., Font-Romeu in France, Saint-Moritz in Switzerland, Colorado Spring in USA, Kunming in China) were developed for the exclusive purpose of "Live High Train High" (LHTH). This extensive exposure, three to four weeks, to hypoxic conditions at altitude is known to increase erythropoiesis, which is resulting by an augmentation of the red cells volume and thus also of the hemoglobin ([Hb]) mass. This benefits endurance athletes by enhancing the O_2 carrying capacity and their performance at sea level (Chapman et al., 1998; Levine & Stray-Gundersen, 1997). However, the major disadvantage of this training method is that the lack of oxygen affects the training intensity. In fact, the maximal aerobic capacity is diminished by ~1% every 100 m gained in altitude after 1500 m (Buskirk et al., 1967). That means that in these constant hypoxic conditions the athletes are enable to maintain their high intensities, especially during interval-training sessions (i.e., 12-15% slower at 2500 m). Since early 1970's and the popularity of LHTH, many training methods in altitude have been developed such as "Live High Train Low" (LHTL), which allows to have the hematological benefits from staying at altitude and in addition to that to ensure the high intensities of the

interval trainings (Levine & Stray-Gundersen, 1997; Levine & Stray-Gundersen, 2001). More recently several "Live Low Train High" (LLTH) methods have emerged with the development of simulated hypoxic structures updating the panorama (resumed in *Figure 3*) of means to train in hypoxia (Faiss et al., 2013; Girard, et al. 2017).

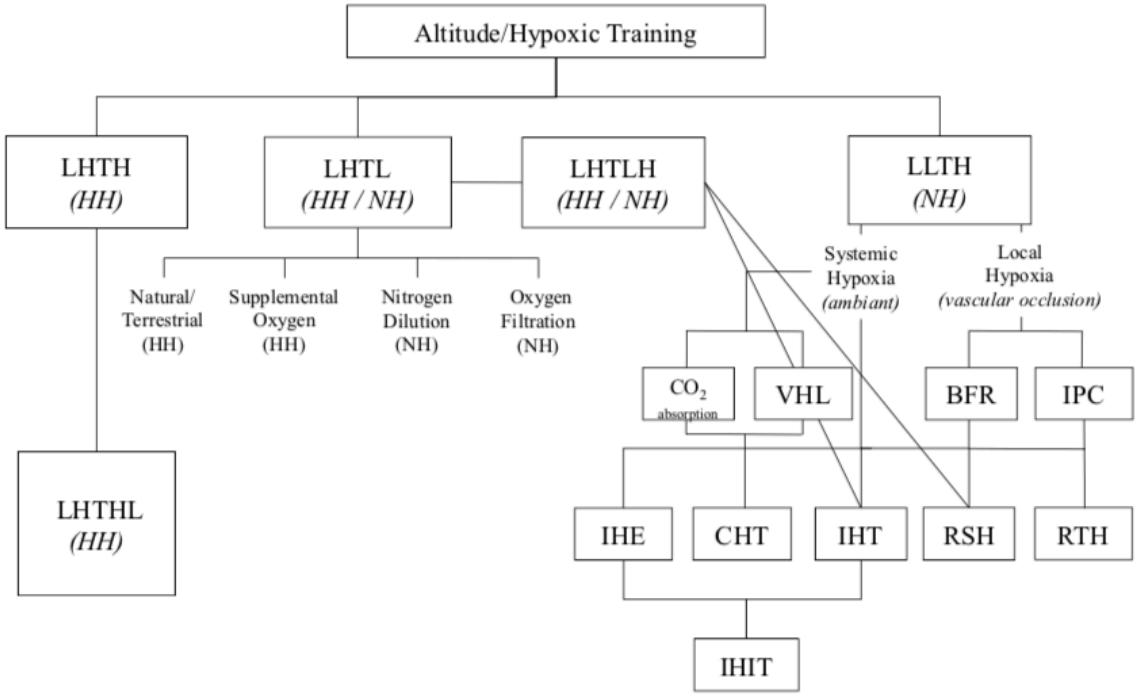

Figure 4. Current panorama of the different hypoxic training methods for a range of athletes engaged in endurance and team-sports. Adapted from (Millet et al., 2013) and (Girard et al., 2017). LHTH, live high-train high; LHTHL, live high-train high and low; LHTL live high-train low; LHTLH live high-train low and high; LLTH live low-train high; BFR blood flow restriction, CHT continuous hypoxic training; CO_2 absorption rebreathing with a mask; HH hypobaric hypoxia; IHE intermittent hypoxic exposure; IHIT IHE during interval-training; IHT interval hypoxic training; IPC ischemic preconditioning; NH normobaric hypoxia; RSH repeated-sprint training in hypoxia; RTH resistance training in hypoxia; VHL voluntary hypoventilation at low lung volume.

1.2.1 Repeated Sprint training in Hypoxia

Repeated Sprint training in Hypoxia (RSH) is defined by short duration (typically ≤30s) all-out efforts interspersed with incomplete recovery periods (≤60s) performed in a hypoxic environment (Faiss et al., 2013). The fundamental difference between Intermittent Hypoxic

Training (IHT) is the all-out sprints that demands a very high recruitment of fast-twitch fibers in the muscles. Whereas aerobic performance is impacted by altitude, sprint performance (i.e. for single maximal effort up to 60 s) is in contrary well preserved up to 3500 m or even higher (Girard et al., 2017). The benefits of IHT in comparison of the same training in normoxia has struggled to find any significant improvement for performance. Only four out of more than twenty studies at this time had shown potentially some additional benefits on performance related variables of IHT (Faiss et al., 2013). For example, the innovative training method of RSH since 2013 has demonstrated an interesting improvements on performance and a delay of fatigue when compared to the same training in normoxia (RSN) (Faiss et al., 2013). The high intensity of repeated sprint (RS) training imposes some physiological challenges. In fact, the cardiovascular system and the muscles need to make some adaptations such as: increasing skeletal muscle oxidative capacity, increasing resting glycogen content, increasing capacity for muscle lipid oxidation and enhancing peripheral vascular structure and function (Burgomaster et al., 2005; Gibala et al., 2006; Burgomaster et al., 2008; Rakobowchuk et al., 2008). Usually, exercise leads to an augmentation of blood flow in the cardiovascular system that upregulates the endothelial nitric oxide synthase, which is an enzyme increasing local NO levels that leads to smooth muscle relaxation, vasodilation and increased blood flow (Gielen et al., 2001; Tinken et al., 2009). With high intensity exercises such as RS training, these physiological responses will be larger than with low intensity exercises (Mortensen et al., 2008; Casey & Joyner, 2012). It is known that similar vascular mechanisms exist during expositions in a systemic hypoxic environment but even to a greater extent due to the lack of oxygen availability (Casey & Joyner, 2012). So, the idea of combining the metabolic stress of high-intensity interval exercise with a systemic hypoxic stress of a lower PO_2 is to induce an effective stimulus to maximize physiological responses and biological reactions. RS training performed at maximal intensity with a work to rest ratio less than 1:4 induce an early development of fatigue and a power decrement in normoxic conditions (Bishop et al., 2004). This type of training exercise when performed to exhaustion leads to a massive accumulation of metabolites in the muscles (Spriet et al., 1989) as well as an alteration of the neural drive and the muscle recruitment by the motor cortex (Ross et al., 2001). The main limiting factors at the muscular level as the sprints continue include muscle excitability due to ionic disturbances (T. Clausen et al., 1998b), energy supply from the phosphocreatine availability, as well as anaerobic glycolysis, and oxidative metabolism (Gaitanos et al., 1993). These factors are contributing to a decrement of performance limiting muscles to work efficiently and furthermore, these reactions are multiplied when they are combined with another environmental stress like hypoxia (Balsom et

al., 1994; Brosnan et al., 2000). It has been demonstrated that diminishing the oxygen availability have a detrimental impact on endurance performance as well as on the ability to repeat maximal sprints without enough recovery (Balsom et al., 1994; Smith & Billaut, 2010; Girard et al., 2011; Smith & Billaut, 2012; Billaut & Buchheit, 2013). Normally, high intensity exercise reduces tissue oxygen availability. So, in order to maintain oxygen delivery, the arteriovenous oxygen difference (oxygen extraction) is increased (Shepherd et al., 1973). The innovating RSH training method has been developed in line of these principles to maximize the stimulus applied to the body in order to enhance maximal performance and delay fatigue in comparison of the same training in normoxia (RSN) (Faiss et al., 2013). Firstly, the energy to perform repeated maximal sprints comes from anaerobic glycolysis. Secondly, as the exercise continues, the source of energy shifts towards aerobic metabolism (Gaitanos et al., 1993; Bogdanis et al., 1995). RSH training method is associated with LHTL protocols to add the hypoxic stimulus during exercise time as well. By doing so, athletes benefit from both hematological responses due to the long-time exposure to hypoxia and metabolic/peripheric adaptations after training at high intensity in hypoxia. Since 2013, RSH proved its capacity to improve performance in different sports: leg cycling (Faiss et al., 2013), cross-country skiing (Faiss et al., 2015a), running (Galvin et al., 2013), and team sports (Brocherie et al., 2015; Brocherie et al., 2018). The large majority of the studies on the subject have shown that there is a substantial benefit on the power output and the number of sprints that can be performed after such a training protocol (Millet et al., 2013).

1.2.2 Physiological adaptations of RSH training

There are fundamental different physiological adaptations between acute exercise in hypoxia and long-time exposure in this environment. Unlike the most known longer-form of hypoxic exposure or training that aim to enhance the erythropoiesis to improve oxygen (O_2) convection capacity, RSH uses an acute hypoxic exposure with short burst of exercise to maximize peripheral adaptations. In fact, it should take hundreds of hours of hypoxic exposure to be able to stimulate optimally the creation of new red cells in the blood (Levine & Stray-Gundersen, 2006) However, RSH training improves blood perfusion in the muscle, particularly in the fast twitch (FT) fibers. They become more performant thanks to a better O_2 extraction rate making them less fatigable (Faiss et al., 2013). The addition of hypoxia during this kind of very intense repeated exercise leads to a lower arterial O_2 pressure (McDonough et al., 2005) which generates a greater vasodilation in the muscles and also a higher O_2 extraction capacity of the FT fibers (Lundby et al., 2009; Casey & Joyner, 2012). In addition, RSH has been shown to

impact at a molecular level as well. In fact, Faiss et al (2013) showed that after eight sessions of RSH training on a cycling ergometer mRNAs were upregulated. Certainly, the most important mRNA is HIF-1α which is responsible for the oxygen-sensing pathways. HIF-1α mediates the changes in genes expression so that physiological mechanisms such as erythropoiesis and angiogenesis (VEGF) are regulated differently after acute or chronic exposure to hypoxia (Semenza, 2007; Hirota & Semenza, 2006). Recent research also identified other molecular adaptations concerning the downregulation of genes involved in mitochondrial biogenesis (TFAM and PGC-1α). Other mRNAs that were also studied by these authors happen to improve pH regulation capacity (CA3, MCT-1, MCT-4, NOS, prostaglandin, adenosine), to allow a shift from an aerobic to a glycolytic metabolism in the muscle which explains partly the modified behavior of the FT muscle fibers and their enhanced resistance to fatigue (Raphael Faiss et al., 2013). These physiological adaptations are likely to improve anaerobic glycolytic activity of the muscle and by doing so improving fast twitch fiber recruitment after RS training in hypoxia (McDonough et al., 2005). The performance enhancement from this kind of training is due, for the most part, to a compensatory vasodilation and an increased rate of phosphocreatine (PCr) resynthesis (Hoppeler & Vogt, 2001; Dufour et al., 2006).

1.3 Local hypoxia

1.3.1 Blood Flow Restriction

Blood flow restriction (BFR) training is another way to apply an additional stress during exercise by creating severe hypoxia locally in the muscle tissue (ischemia) (Scott et al., 2014). The use of adjustable cuffs on the proximal parts of the limbs create a total or a partial vascular occlusion when exercising. In this study, the external application of pressure allows the arterial blood inflow but blocks mostly the venous blood outflow which leads to an accumulation of blood content in the muscular tissue (Kaijser et al., 1990). The amount of BFR is calculated as a percentage of resting total vascular occlusion pressure (in this study, 45%) as Reis et al. (2019) showed that BFR training was effective for increasing deoxygenation and reducing tissue oxygenation when the relative pressure was above 40% of total occlusion. During these kinds of conditions, there is a distinct difference on a vascular/endothelial function between systemic hypoxia and BFR due to specific vascular resistance and vessel diameter adjustments, accumulation of metabolites (nitric oxide, adenosine, prostaglandins, hydrogen ions, etc.). They are both unique methods that lead to a decrease of oxygen content in the muscle tissue using different physiological mechanisms. Although, BFR training induces local hypoxia by

increasing the vascular resistance and reducing blood flow. Systemic hypoxia mechanism work through a lower FiO_2 that leads to a metabolic vasodilation response that increases blood flow for oxygen delivery.

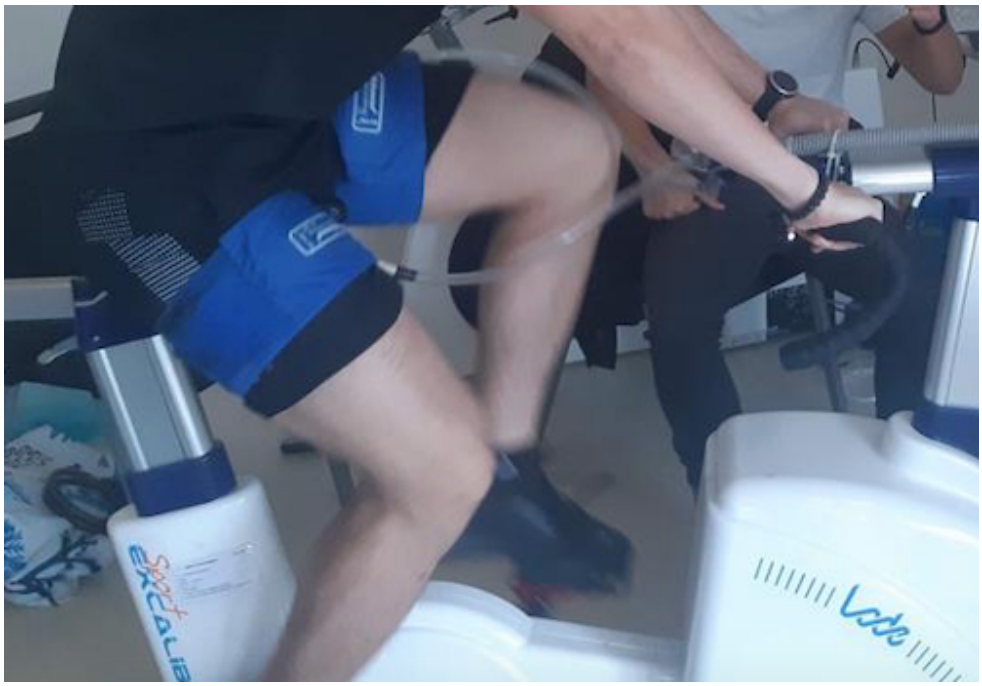

Figure 5 : Legs BFR cuffs used during repeated sprint cycling trainings.

Performing exercise with reduced blood flow into the muscle dates back to the 1960-70s with the work of Dr. Yoshiaki Sato in Japan. This technique was invented and used in combination with resistance training, where it was also known as "Kaatsu training" meaning "training with added pressure", to improve vascularization as well as rehabilitate injured limbs (Sato, 2005). In fact, this training technique has demonstrated evidences to be a viable alternative for traditional heavy-load strength training in a broad range of populations, such as the elderly and rehabilitating athletes who are unable to withstand the high mechanical stress placed upon the joints during heavy resistance training (Hughes et al., 2017). Historically, heavy exercise loads of approximately 60% to 90% of an individual's one repetition maximum (1RM) have been deemed necessary to elicit muscle hypertrophy and strength gains (Ozaki et al., 2015; « Progression Models in Resistance Training for Healthy Adults », Kraemer et al., 2002). Recent research has demonstrated that low-load training to exercise failure could stimulate muscle hypertrophy comparable in magnitude to that observed with heavy-load training after 6 (Ogasawara et al., 2013) and 8 (Schoenfeld et al., 2015) weeks of training three times per week. However, strength adaptations were maximized with heavy-load training, and cross-sectional

comparisons would suggest that hypertrophy and strength gains observed with low-load training are not as great as those achieved with heavy-load training (Schoenfeld et al., 2016). Nevertheless, from a clinical musculoskeletal rehabilitation perspective, training to muscular failure may provide one strategy to maximize hypertrophy when training using low loads in situations when using heavy loads is not feasible. Training with low loads may therefore be useful, as the early addition of muscle mass and function in rehabilitation may be beneficial for individuals who have suffered from atrophy. In recent years, research has demonstrated that augmentation of low-load resistance training with blood flow restriction (LL-BFR) to the active musculature can produce significant hypertrophy and strength gains, using loads as low as 30% of 1RM (Burgomaster et al., 2003; Takarada et al., 2004; Yasuda et al., 2011). BFR training has been found to yield hypertrophy responses comparable to that observed with heavy-load resistance training (Loenneke et al., 2012). However, studies with such findings regarding muscle hypertrophy are not common among the present literature. Since these primary researches in the field of BFR training focused on resistance training and the potential effects on the muscle mass and strength gains (Abe et al., 2006), the utilization of this method is now performed all over the world and more precisely in this study for the first time with a high intensity interval training protocol during 3 weeks (Willis et al., 2019).

1.3.2 Physiological responses of BFR training

Physiological adaptations in leg strength (Abe et al., 2010), vascular (Ozaki, Miyachi, et al., 2011) and pulmonary (Ozaki et al., 2011) components have been reported with low-load aerobic exercise and BFR. From a mechanistic standpoint, it is hypothesized that an ischemic and hypoxic muscular environment is generated during BFR to cause high levels of metabolic stress, alongside mechanical tension when BFR is used in tandem with exercise. Both metabolic stress and mechanical tension have been described as ‘primary hypertrophy factors’ (Pearson & Hussain, 2015) and theorized to activate other mechanisms for the induction of muscle growth. The main mechanisms responsible for physiological adaptations from BFR training include metabolic stress (increased lactate, PCr depletion, inorganic phosphate, decreased pH), hormonal responses (increased growth hormone, possible influence of testosterone, IGF-1, catecholamines, cortisol), intramuscular signaling (increased mTOR signaling, proliferation and differentiation of satellite cells, possible reactive oxygen species, and myostatin), intracellular swelling, muscle fiber recruitment (increased activation, greater number of fibers activated in fatigued state), and reactive hyperemia (increased blood flow to muscle when cuff is released) (Scott et al., 2014; Takarada et al., 2000).

As the artery is partially occluded while the vein is almost or completely occluded during BFR, the local blood volume and the vessel resistance is increased leading to less venous return. These changes affect the cardiovascular system by increasing the cardiac output and the active vascular bed in the muscle to match a greater oxygen demand with an elevated blood pressure during exercise (Boushel, 2010). Even if the literature is limited on the vascular responses to BFR, it is speculated that it affects the muscle fibers perfusion principle due to this increased resistance in the vessel along with the increased blood volume caused by a limited venous return (Willis et al., 2019).

BFR training results in an increased metabolic stress due to a metabolite accumulation, a higher lactate and a decreased level of pH in the muscles and the blood (Abe et al., 2006; Fujita et al., 2007; Manimmanakorn et al., 2013; Pearson & Hussain, 2015). These physiological responses lead to a shift in the contribution of the energy systems from aerobic to anaerobic which increases the production of adenosine triphosphate (ATP) without the presence of enough O_2. Whereas training in hypoxia is known to enhance hypoxia-inducible factor-1α (HIF-1α) mediated cell signaling through an increase of its mRNA expression (Maxwell, 2005), the same response with BFR training is measured but not completely understood (Taylor et al., 2016). Furthermore, BFR has been shown to up regulate the mRNA expression of the vascular endothelial growth factor and receptor (VEGF and VEGFR-2) along with endothelial nitric oxide synthase (eNOS), proposing angiogenesis due to the increased stimuli of ischemic shear stress (occurring after occlusion) during low-load resistance exercise (Scott et al., 2014; Ferguson et al., 2018). Moreover, the responses to BFR are an increased production of protein kinases (S6K1, MAPK) and of reactive oxygen species (ROS) along with a decreased production of myostatin, REDD1, MyoD and MuRF1 (Drummond et al., 2008; Wernbom et al., 2008; Larkin et al., 2012; Scott et al., 2014). It is evident that with this kind of training the muscle is exposed to a great oxidative stress that causes cell damage and impairs the NO pathway signaling, modifies the function of calcium channels, activates transcriptional factors for pro-inflammatory molecules, and protein kinases (Murphy, 2009; Genova & Lenaz, 2014; Jackson, 2015). And even if it can have detrimental effects on the cells, it leads to some interesting structural adaptations. In addition to gains in maximal muscle strength, studies have reported improved endurance capacity; i.e., increased number of repetitions to fatigue in young recreational active individuals after 4-week BFR resistance training (Kacin & Strazar, 2011), as well as improved VO_2 max (T. Abe et al., 2010) and power output during incremental all-out knee extensor testing (Christiansen et al., 2020) in untrained individuals following 6-8

weeks of BFR cycling training. Such endurance effects have been suggested to partly be attributed to increased O_2 delivery to the trained musculature after BFR training (Kacin & Strazar, 2011). The potential of BFR training to evoke adaptative gains in O_2 delivery and/or local blood flow is directly supported by reports of increased muscle filtration capacity after short-term (4 weeks) BFR training (Nielsen et al., 2020); (Hunt et al., 2013).

Recently, Willis et al. (2019) showed that in these BFR conditions of restricted vasodilation, the demand for increased blood flow could not be met with similar mechanisms as RSH. For example, a recent study with an acute repeated sprint leg cycling test to exhaustion found greater changes in tissue perfusion in blood flow restriction (BFR) conditions and thus suggested a possible stimulus for vascular regulation (Willis et al., 2018). It is important to consider globally that tissue perfusion (volume of blood per unit of time) also involves the amount of active muscle mass. This circulatory adaptation results in more active muscle vascular beds mediated by the sympathetic nervous system to regulate blood flow via the muscle metaboreflex (Clausen et al., 1998a; Boushel, 2010). Furthermore, an important consideration during intense maximal exercise (large mass of active muscle) is the rise in total vascular conductance which can take over the capacity of the body to raise cardiac output for the amount of work being performed, thus causing the active muscle to vasoconstrict in order to maintain blood pressure. These changes detected in [tHb] in the study of Willis et al. (2018) may thus create a situation for the body to overcome in order to continue exercise, and therefore, possibly a stimulus for the use of BFR training as a way to induce fluctuations in blood volume (i.e., tissue perfusion) to elicit vascular adaptation. Given the important physiological changes after BFR resistance or low intensity training, it was interesting to investigate this kind of exercise in addition to RS training and monitor the physiological responses and performance enhancements.

1.4 Aims and hypothesis

To date the existing literature reported findings either on RSH training or BFR training at low intensity and with resistance exercises. To the best author's knowledge, no previous study has been conducted on the effects of a 3-weeks RS training in hypoxia versus with BFR on recreationally trained male adults yet. In the first place, the main purpose of this study was to assess the impact of a 3 weeks RS training protocol in hypoxia (RSH), with BFR (RS-BFR) and in normoxia (RSN) on specific cycling performances (Repeated Sprint Ability; RSA), Submaximal exercise, Wingate, 10 km time trial (10kTT)). Secondly, it was to measure the

variations in the ventilation and the O_2 consumption with gas analysis to see if there is any correlation with performance data.

With regard of the previous literature on these topics, this study tested the following hypotheses:

1) Greater performance improvements for RSH compared to RSN.
2) Better economy and efficiency in cycling performances for RS-BFR compared to RSH and RSN.
3) Greater performance improvements for RS-BFR compared to RSN and RSH.

2. Methods

2.1 Subjects

Twenty-four healthy recreational cyclists volunteered to take part in this study (25.8 ± 5.2 years, 77.2 ± 6.7 kg, 180.9 ± 6.6 cm). Subjects were recruited through ads (Appendix 7.4 and 7.7) posted in every building of the University of Lausanne as well as emails sent to the local triathlon and cycling clubs.

Inclusion criterion for participants were as follow:

1. To be between 18 and 40 years old;
2. Used to high-intensity training;
3. To train at least 5 hours a week;
4. To be sane and healthy.

Exclusion criterion included:

1. Smoking;
2. Presence of any diagnosed disease;
3. To have any bones or muscle injuries within the last 3 months;
4. Any pain or other health problems that can influence the results of this study;
5. Problems with blood coagulation;
6. To consume aspirin or any anticoagulant;
7. To be allergic to xylocaine;
8. A positive answer to the PAR-Q questionnaire;
9. Lack of consent;
10. Exposure at an altitude superior of 1000 m within the last 2 weeks.

All the participants were healthy and gave their written consent (Apendix 7.5) after having been exhaustively informed about the whole experimental protocol as well as its inherent possible risks, prior to the first familiarization session where they also could have their potential questions answered. The research protocol was approved by the "Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER-VD)" on the 24th May 2019.

After meeting the requirements, the subjects were randomly assigned to three groups: a hypoxic group, an occlusion group and a normoxic group. Each experimental group underwent an identical repeated-sprint cycling training, one of which was performed in normobaric hypoxia

(RSH), at a simulated altitude of 3'800 m, whilst another one was performed with blood flow restriction (RS-BFR), at a level of maximal occlusion of 45%, and the last one was in normoxia (RSN). In order to prevent any placebo/nocebo effect, participants were not aware of the hypotheses for each training protocol on the cycling performance. Furthermore, participants from the RSH and the RSN group were not aware which group they belong to, as well as participants from the BFR group could not say if they were training in hypoxia or not.
The hypoxic group were composed of nine participants (RSH, N=9), the occlusion group, eight participants (RS-BFR, N=8) and the normoxic group (RSN, N=7). The three groups had similar characteristics, which are resumed in *Table 1*.

Table 1. Group characteristics.

Group	*Age [years]*	*Height [cm]*	*Weight [kg]*	*BMI [kg/m^2]*
RSH (N=9)	25.2 ± 5	183.1 ± 5.8	77.2 ± 7.6	23 ± 2.5
RS-BFR (N=8)	24.9 ± 3.9	180.5 ± 8.3	78.1 ± 8.4	24 ± 2.1
RSN (N=7)	27.3 ± 6.8	178.6 ± 5.7	76.1 ± 4.1	23.9 ± 2.5

All three groups were instructed to maintain their usual respective training activities but at low intensity to prevent any overload due to the heavy training protocol of the study. Furthermore, participants were not allowed to have any race or competition during the study to prevent any results bias. A 1 – 10 visual analogic scale (VAS) was used to assess the level of fatigue of the participants during the whole training protocol at each beginning of the training session.

2.2 Experimental design

This single blind study took place entirely at the University of Lausanne (UNIL) (1015 Lausanne, Suisse). The tests were conducted in the Synathlon while the training protocol were taking place in two building of the "Institut des Sciences du Sport de l'Université de Lausanne" (ISSUL), the Synathlon and the "Centre Sport et Santé" (CSS) labs. Prior to the training protocol, the groups performed 3 days of pre-tests (PRE) during a week. The first (DAY 1) and the second (DAY 2) test sessions were performed 24h apart and executed at exactly the same time from PRE to POST training period. The third (DAY 3) test session were performed randomly from 1 to 4 days after the first sessions. Afterwards, they all underwent a repeated-sprint training protocol which consisted of nine 1-h sessions spread over 3 weeks. There were about from 24 h to 72 h between each training session with at least one day of recovery. Another

set of 3 days testing were performed after the training protocol (POST) about 2 to 5 days after the last training session with the same protocol than at PRE.

The hypoxic chamber of the CSS was used during the whole training protocol of this study for the three groups. The RSH group trained with hypoxic air at a simulated altitude of 3800 m while the two other groups RS-BFR and RSN trained with normoxic air at the altitude of the Léman lake, 372 m.

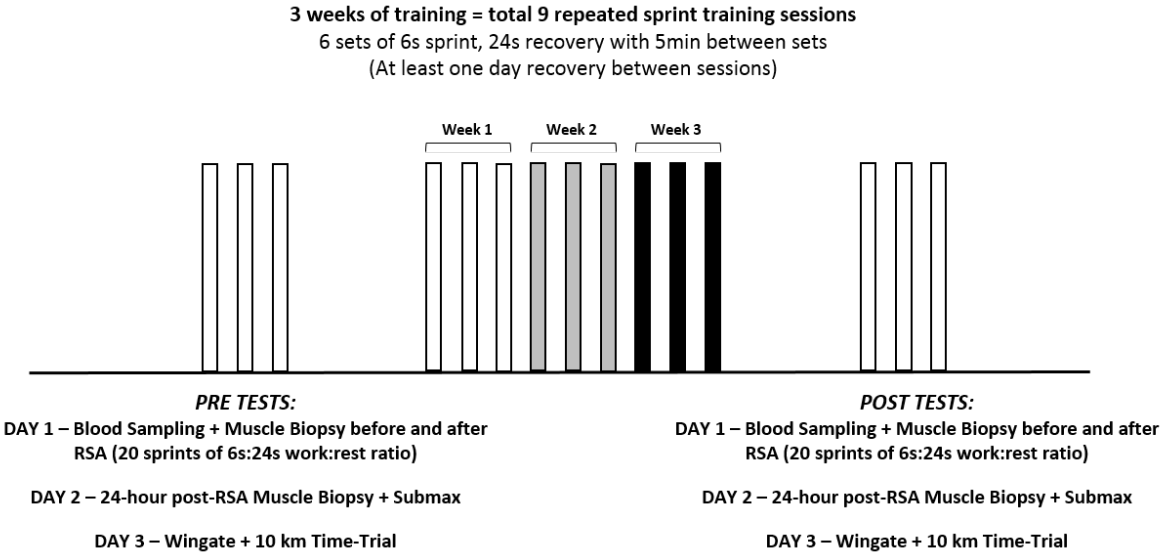

Figure 6. Study design.

2.3 Familiarization

Prior to the 3 days of pre-testing, participants were sent for a familiarization session in the Synathlon research lab where the informed consent and health questionnaire [Physical Activity Readiness Questionnaire, PAR-Q & YOU, (*Physiology CSfE, 2002*)] were collected along. Participants concerned were equipped with the BFR cuff (custom-made 4 x 70 cm cuff, 3 × 41 bladder; D.E. Hokansson Inc., Bellevue, WA, USA) for measurement of the pulse elimination pressure. Pulse elimination pressure was measured seated at rest with the leg flexed with a slight bend in the knee by gradually inflating the cuff until the point at which no more arterial blood flow was detected via Doppler ultra-sound (EchoWave II 3.4.4, Telemed Medical Systems, Telemed Ltd. Lithuania, Milano, Italy) of the femoral artery and was measured 2–3 times for accuracy in both legs, with 2 min between trials. It continued with the familiarization to the neuromuscular assessment (MVC), as well as stimulations at different frequencies (100 Hz, 10 Hz, twitch) at rest and during MVC (superimposed 100z) following the protocol described in

detail below. Participants were then seated on an electronically braked cycling ergometer (Lode Excalibur Sport Ergometer, Lode B.V., Netherlands) and dimensions were recorded and individualized for standardization during subsequent tests and training sessions. After a 5 min warm-up at 1.5 W/kg, participants performed two 6-s maximal sprints with 1 min of active recovery with no BFR or hypoxia. All sprints were performed using the "Wingate mode" form the manufacturer with an individually fixed torque factor of 0.8 Nm/kg.

2.4 Training protocol

The training protocol was performed in a normobaric hypoxic room in the CSS premises at the university of Lausanne (UNIL) (ATS Altitude, Australie). Altitude was simulated through O_2 extraction by means of a filter and a compressor system. The hypoxic device either simulated an altitude of 3'800 m above sea level, with a F_iO_2 of ~13% for the RSH group; or simulated altitude of 372 m, with a F_iO_2 of ~20.9% for both RS-BFR and RSN group. Regardless of the altitude simulated, in both conditions the chamber was ventilated and so produced the same sound to blind the participants. Fans were used in the chamber as well to have the air within circulates. Just before the beginning of the session, participants were asked about their general capacity to perform of the day including psychological and physical fatigue with an analogic scale between 1, as the lowest, and 20, as the better form they could have.

Trainings lasted ~60 min. After a standardized 10 min warmup at 1.5 W/kg, participants performed six sets of six repetitions of 6 s sprints interspersed with 24 s of easy spinning recovery. A 5 min easy spinning recovery at 1.5 W/kg separated each set. (See *Figure 7*)

Participants were told to cycle as fast as they could for each and every sprint of the training session. They were strongly encouraged by the experimenters and were told not to pace themselves throughout the repeated sprints. All the training sessions were conducted with the cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands) where the participants were told to sprint seated. To standardize the beginning of each sprint, the cycling cadence was imposed to the participants and needed to be at ~80 rpm. This was to prevent them to be able to be more economic during the sprint without having to spend energy to accelerate the ergometer without any resistance. The saturation of the participants was measured with an infrared oximeter on the right index (wristox, Nonin) after the first, the third and the last block of repeated sprint without them knowing any values. That helped to confuse even more in which experimental conditions they were in. They completed the training with an active recovery of

easy cycling at 1.5 W/kg during the last 7 min of the session. Participants were allowed and encouraged to hydrate themselves during recovery phases of the training sessions.

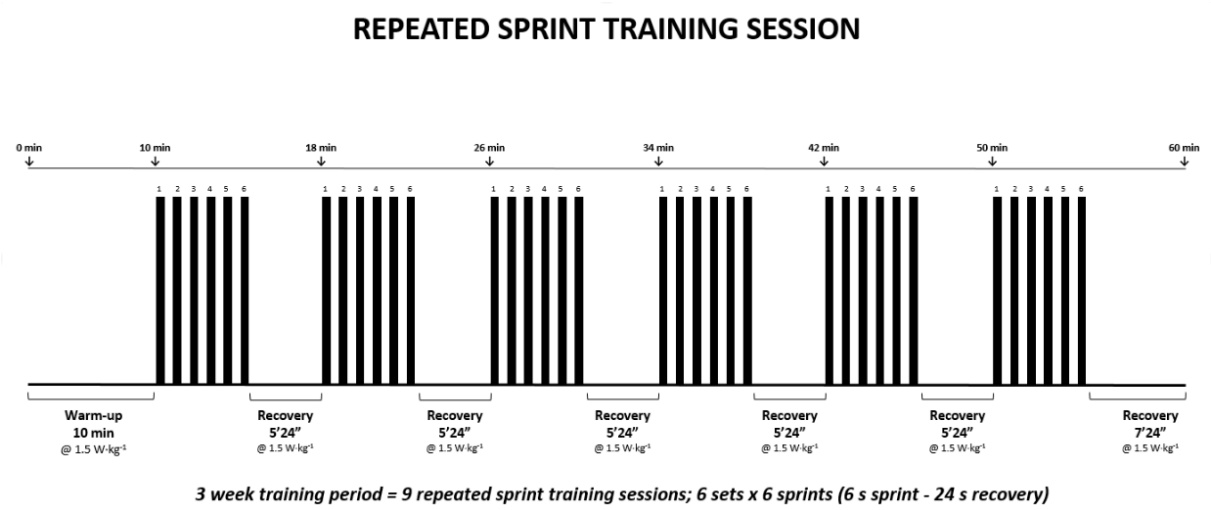

Figure 8. One training session protocol.

2.5 Testing

DAY 1:

Repeated sprint ability (RSA) test, blood sampling, muscle microbiopsies and electrostimulation before and after the RSA test.

Participants were instructed to come at a fasting state the day of the test. After the health and consent questionnaires filled and verified, participants were lied down to rest. Then they had time to complete the food questionnaire where they had to write down precisely everything they have eaten the last day before this first visit. They took the second food questionnaire at home to be able to write down what they eat the day after the first visit. After ten minutes of rest, blood samples and muscle microbiopsies were collected. Then participants were seated and prepared on an ergometer chair with an isometric leg extension setup fixed at an angle of 90° on the knee (Universal Load Cell, VPG Revere transducers, Germany) to perform two maximal voluntary contractions of 5 s in order to measure the maximal isometric force (extension) of their right leg following the protocol in *Figure 9.*

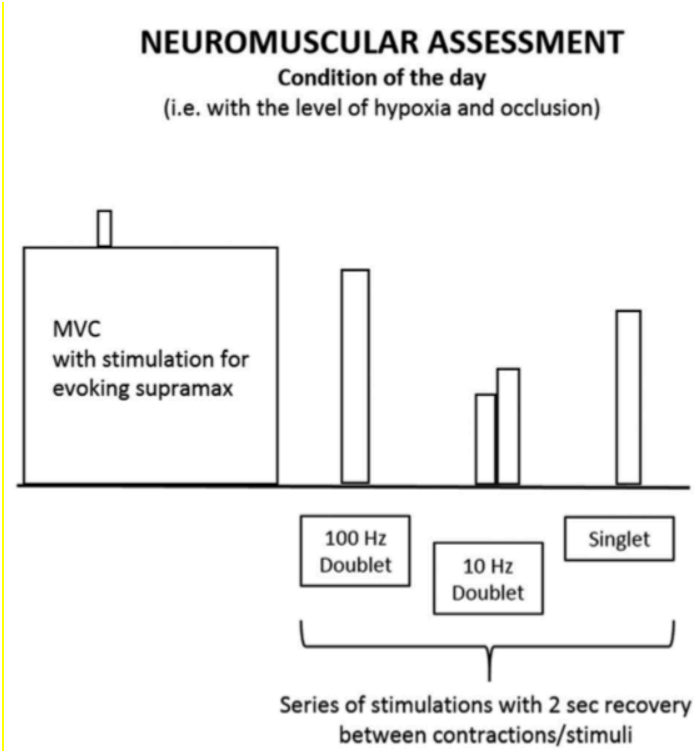

Figure 10. The electrostimulation protocol.

The electrostimulation finished, participants took place on the electronic braked cycling ergometer where their settings were measured and replicated during each subsequent training and testing session. The NIRS device was installed on the vastus lateralis of the right leg, on the third of the distance separating the knee from the hip. Tape and elastic straps were used to ensure that the system do not move during the RSA test. The calibration of the NIRS began by a 2 min rest were the participants had to stay on the seated position, hands placed on the handlebar and their foot leaned on a box to standardize the extension of their leg. Then, participants were told to cycle at 80 rpm during 1 min with a 50 W resistance and for another minute with a 100 W resistance to finish the calibration of the NIRS.

Following the protocol, participants did a warmup cycling exercise on the ergometer composed by 1 min at 1.5 W/kg followed by two 6 s sprints with 1 min of recovery. After the warmup sequence, participants performed the RSA test, made of twenty 6 s all-out sprints with 24 s of active recovery, to exhaustion or to the end of the test.

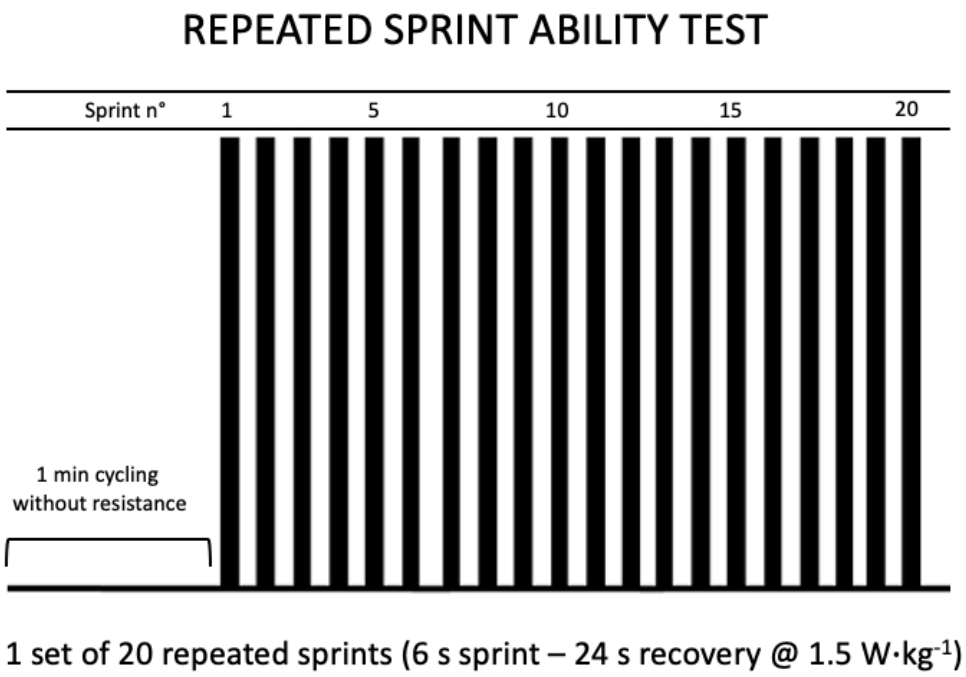

Figure 11. The repeated sprint ability test (RSA).

As soon as the RSA test was finished, participants were seated again on the electrostimulation chair to assess the neuromuscular fatigue. (Time to begin the stim: ~1 min) A Rate of Perceived Exertion (RPE) scale was used to assess the level of exertion and pain for the legs and the breathing at the end of the test. The last step of this first day of testing was the post RSA microbiopsies that were collected about 10 min after the RSA test.

DAY 2:

Microbiopsy and electrostimulation post 24 h and 6 min Submax test at 1.5 W/kg.

Firstly, participants gave their food questionnaires filled with all the food they have eaten the day before. They also needed to be at a fasting state for this DAY 2 tests. After a 10 min rest period layed down, participants did the exact same protocol as DAY 1 for the first microbiopsy and the electrostimulation. The muscle microbiopsy was performed at exactly 24 h post the RSA test of DAY 1 as the electrostimulation. Participants were then prepared on the cycling ergometer with their individual settings. The NIRS device was installed on their right leg and the same calibration protocol as DAY 1 was performed prior to the test.

In addition to that, the measurements of gas exchanges (VO_2) were recorded during the submaximal test and needed to be calibrated as well. So, after a volume and a gas calibration by the system of the gas analyzer (Medgraphics CPX, Loma Linda, CA, USA), participants put the mask on and didn't move in the same seated position as before during 1 min prior to the test. Finally, participants performed the 6 min submaximal cycling test at 1.5 W/kg and then

informed the experimenters about their perceived exertion concerning their leg and their breathing on the Borg's scale (#/20).

DAY 3:

30 s Wingate and 10 km Time Trial test (250 kJ).

Participants were allowed and welcomed to eat preferably a light meal or a collation prior to these tests. After the same NIRS and the VO_2 calibration protocols as DAY 1 and 2, participants installed on the cycling ergometer, performed firstly the 30 s all-out Wingate test. There was a 1 min free resistance cycling at 80 rpm prior to the beginning of this test. At the end of the 30 s test, the mask was kept on until their breathing was starting to cooldown to make sure to have the highest values of VO_2 possible. Between this first test and the next 10kTT, participants were instructed to get off the ergometer and be still during 15 min. Before the beginning of the time trial, participants cycled freely against the 10kTT resistance mode (Wingate mode, 0.8 $Nm.kg^{-1}$) of the ergometer during 2 min without generating any fatigue. Then the mask was put on and the participants were prepared on the cycling ergometer for this last test. The goal was to perform as fast as possible a virtual distance of 10km represented by an amount of energy to produce of 250 kJ. Participants were free to use their own tactic of pacing throughout the test as long as they gave their maximal effort. They were only told when they were at 25%, 50%, 75% and 90% of the test completion. Each participant was strongly encouraged during the whole test in order to maximize their motivation. At the end of the test, participants informed the experimenters about their perceived exertion concerning their legs and their breathing on the Borg's scale.

2.6 Statistical analysis:

Data are presented as mean ± SD or relative changes (%) unless otherwise stated. Normal distribution of the data was tested using the Shapiro–Wilk test. ANOVA two-way repeated-measures analysis of variance with 1 between factor (condition; RSN vs RSH vs RS-BFR) and 1 within factor (time; Pre vs Post) were used to compare RSA-related performance variables. Multiple comparisons were made using the Holm–Sidak post hoc test. For each analysis of variance, partial eta-squared (η2 p) was calculated as measure of effect size. According to Cohen, 16 values of 0.01, 0.06, and 0.14 were considered as small, medium, and large, respectively. All analyses were made using Sigmaplot (version 11.0 software; Systat Software, Inc, San Jose, CA). Null hypothesis was rejected at $P < 0.05$.

3. Results

The training exposure for the RSH subjects was 60 min of normobaric hypoxia (~3800 m, FIO_2, ~13%) per training session, thereby totalizing 540 min over the entire intervention. Conversely, RSN and RS-BFR spent 60 min in normoxia (~380 m, FIO2, 20.9%) per training session for a total of 540 min. The application of blood flow restriction was used 10 sec before and after each bloc of sprints accumulating 20 min per training session for a total of 180 min.
Because of the neutral training place, subjects could not discriminate if they were in hypoxia or normoxia. Furthermore, subjects couldn't tell if they were training with BFR in addition to hypoxia or not. The blinding process was successful as more than 70% of subjects did not guess their conditions correctly. There were no serious health problems reported by the subjects.

3.1 RSA results

Table 1. Physiological and metabolic results from the Repeated Sprint Ability Test (RSA)

		RSA				
		RSN		**RSH**		**RS-BFR**
HR (bpm)	Pre	180.1 ± 12.2	Pre	169.2 ± 11.9	Pre	175.4 ± 10.4
	Post	181.6 ± 14.7	Post	172 ± 7.1	Post	179.1 ± 15.7
Lactate (mmol.L^{-1})	Pre	10.3 ± 2.1	Pre	7.9 ± 0.7	Pre	10.5 ± 2.8
	Post	10.1 ± 3.7	Post	9.2 ± 3.2	Post	10.6 ± 2.5
Sdc (%)	Pre	29.1 ± 20.9	Pre	19.5 ± 14.7	Pre	21.6 ± 15.5
	Post	15.2 ± 9.5**	Post	12.1 ± 8	Post	14.4 ± 10.7
RPE legs (Borg 6-20)	Pre	17.2 ± 2.2	Pre	15.2 ± 3.1	Pre	16.1 ± 1.3
	Post	15.7 ± 1.5	Post	16.9 ± 1	Post	14.8 ± 1.9
RPE breath (Borg 6-20)	Pre	18.5 ± 2	Pre	16.9 ± 2.4	Pre	17.9 ± 1.7
	Post	15.7 ± 1.7***	Post	16.9 ± 2.1	Post	16.5 ± 2.1*

*Mean ± SD. * ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$) for significant difference with Pre.*

Values for heart rate (HR) [bpm], blood lactate concentration (Lactate) [mmol.L^{-1}], fatigue decrement score (Sdc) [%], rating of perceived exertion for legs (RPE legs) [Borg 6-20], rating of perceived exertion for breath (RPE breath) [Borg 6-20].

Physiological values along with metabolic responses are shown in *Table 2*. HR as well as the lactate values did not significantly change from Pre. The fatigue decrement score (Sdc, %)

decreased significantly from pre to post training ($p < 0.01$) (47.8%) for RSN with a non-significant improvement for RSH ($p < 0.07$) (37.9%) and RS-BFR ($p < 0.1$) (33.3%). RPE breath decreased significantly ($p < 0.001$) (15.1%) from pre to post training for RSN as well as for RS-BFR ($p < 0.05$) (7.8%).

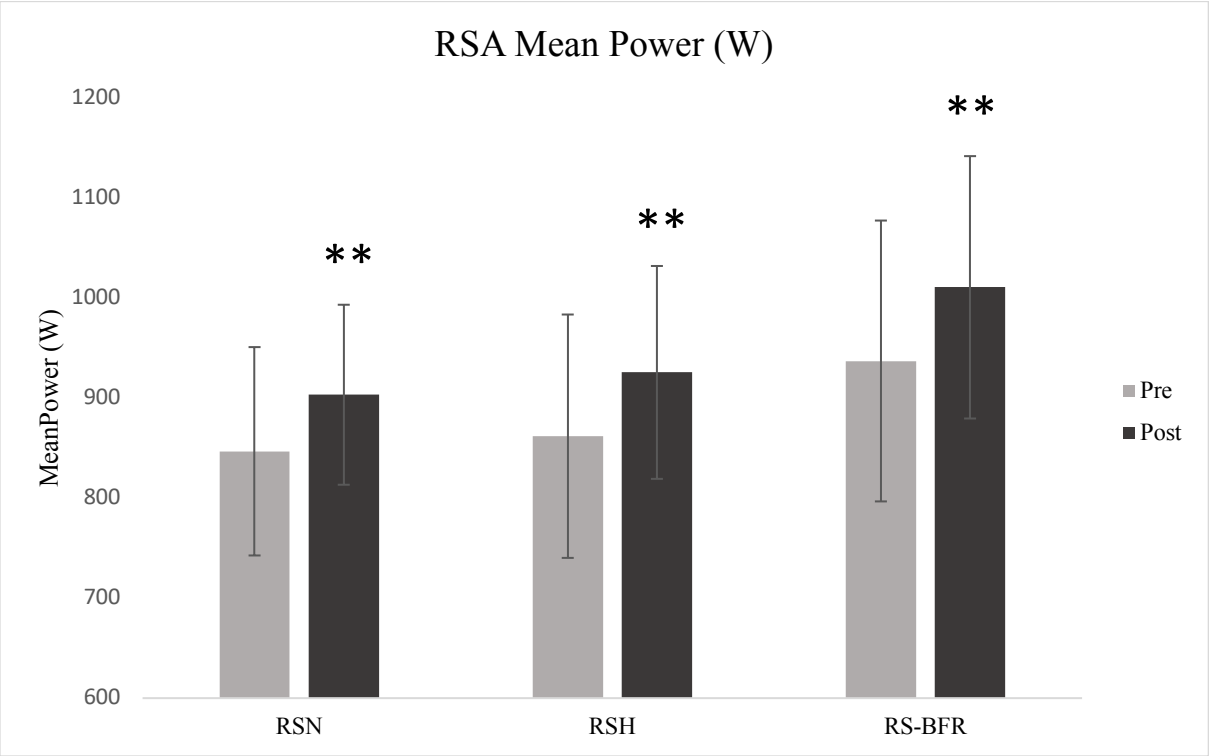

*Figure 12. Performance values of Mean Power during the Repeated Sprint Ability Test between pre- and post-training for RSN, RSH and RS-BFR. Mean ± SD. ** $p < 0.01$.*

Figure 13 highlights that mean power output was significantly greater at post in each group ($p < 0.01$) (RSN: 6.3%; RSH: 6.9%; RS-BFR: 7.3%).

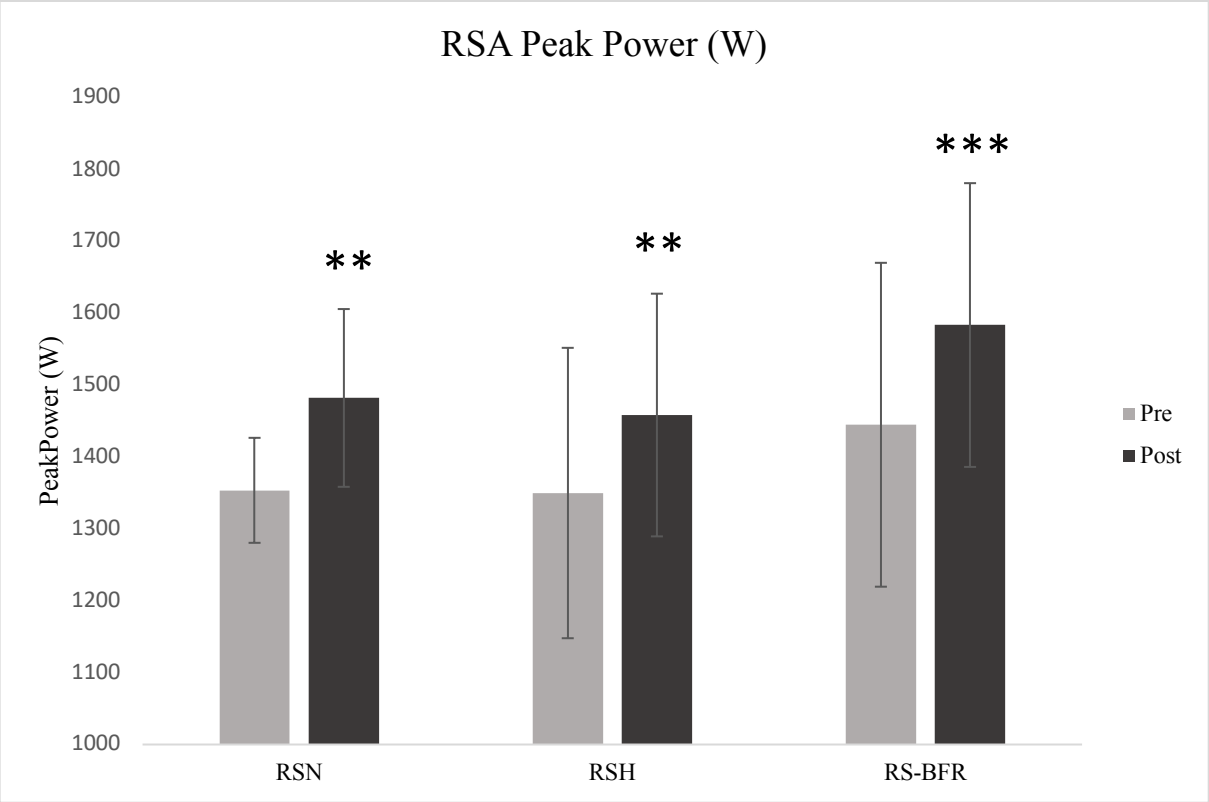

*Figure 14. Performance values of Peak Power during the Repeated Sprint Ability Test between pre- and post-training for RSN, RSH and RS-BFR. Mean ± SD. ** $p < 0.01$, *** $p < 0.001$.*

Figure 15 illustrates that peak power output was significantly greater at post in each group RSN: 8.7%; RSH: 7.4%; $p < 0.01$; RS-BFR: 8.8%; $p < 0.001$.

3.2 Submaximal test

Table 3. Performance and physiological results during the submaximal test.

	Submaximal					
	RSN		**RSH**		**RS-BFR**	
Mean Power (W)	Pre	1.5 w/kg	Pre	1.5 w/kg	Pre	1.5 w/kg
	Post	1.5 w/kg	Post	1.5 w/kg	Post	1.5 w/kg
HR (bpm)	Pre	128.3 ± 14.1	Pre	118.7 ± 20	Pre	122.1 ± 14.9
	Post	126.1 ± 11.6	Post	112.9 ± 13.6*	Post	119.3 ± 16.3
VE (L.min^{-1})	Pre	49.2 ± 7.8	Pre	46 ± 7.1	Pre	47.3 ± 6.3
	Post	48.7 ± 8.3	Post	44.7 ± 4.4	Post	49.2 ± 5.9
BF (cycl.min^{-1})	Pre	21.6 ± 6	Pre	20.9 ± 5.5	Pre	22.9 ± 5.1
	Post	25.1 ± 8.2	Post	21.4 ± 5.5	Post	23.7 ± 3.8
VO_2 (mL.min^{-1})	Pre	1964.1 ± 159.1	Pre	1985.2 ± 247.7	Pre	1972.1 ± 236.5
	Post	1847.4 ± 156.2*	Post	1878.4 ± 187.8	Post	1991 ± 214.4
Lactate (mmol.L^{-1})	Pre	2.07 ± 1.02	Pre	1.63 ± 0.72	Pre	1.29 ± 0.48
	Post	1.91 ± 0.82	Post	1.29 ± 0.33**	Post	1.29 ± 0.31
RER	Pre	0.87 ± 0.05	Pre	0.87 ± 0.04	Pre	0.91 ± 0.17
	Post	0.89 ± 0.05	Post	0.85 ± 0.04	Post	0.88 ± 0.03
Efficiency (%)	Pre	21.1 ± 1.36	Pre	21.3 ± 2.07	Pre	21.6 ± 1.27
	Post	22.2 ± 1.51	Post	22 ± 1.57	Post	21 ± 1.34
Economy (mL.w^{-1}.min^{-1})	Pre	17.22 ± 0.63	Pre	17.18 ± 1.36	Pre	16.84 ± 0.7
	Post	16.19 ± 0.67*	Post	16.3 ± 1.05	Post	17 ± 0.88
RPE legs (Borg 6-20)	Pre	8.2 ± 1.8	Pre	8.8 ± 1.9	Pre	9.3 ± 1.7
	Post	8.7 ± 1.9	Post	9 ± 2.2	Post	9.6 ± 1.9
RPE breath (Borg 6-20)	Pre	8.9 ± 1.8	Pre	9.6 ± 2.6	Pre	10 ± 1.6
	Post	8.6 ± 2	Post	8.7 ± 1.8	Post	9.5 ± 1.6

*Mean ± SD. * ($p < 0.05$), ** ($p < 0.01$) for significantly difference in time from Pre.*

Values for mean power calculated for each subject as 1.5 [w/kg] (MeanPower), heartrate (HR) [bpm], total ventilation (VE) [L.min^{-1}], breath frequency (BF) [cycl.min^{-1}], maximal oxygen consumption (VO_2) [mL.min-1], blood lactate concentration (Lactate) [mmol.L^{-1}], respiratory exchange ratio (RER), cycling efficiency (Efficiency) [%], cycling economy (Economy) [mL.w^{-1}.min^{-1}], rating of perceived exertion for legs (RPE legs) [Borg 6-20], rating of perceived exertion for breath (RPE breath) [Borg 6-20].

Table 4 shows the physiological, the performance and the metabolic data measured during the submaximal test. The intensity of the submaximal test was 115.8 ± 10.2 W corresponding to 1.5 w/kg. HR was lower at Post ($p < 0.05$), (4.9%; $p < 0.05$) in the RSH group but not for RSN and RS-BFR. On the one hand, VE and BF values did not significantly change from Pre. On the other hand, VO_2 values decreased (5.9%) in the RSN group compared to RSH and RS-BFR.

The concentration of blood lactate at the end of the submaximal test decreased significantly (10.9%; $p < 0.01$) at post for the RSH group, whereas no significant change was observed for RSN and RS-BFR. RER and efficiency did not significantly change. There was a significantly decreased cycling economy in RSN (6%; $p < 0.05$) but not in RSH and RS-BFR. Finally, there were no significant changes in RPE legs and RPE breath values.

3.3 Wingate test

Table 5. Performance, physiological and metabolic data measured during the Wingate Test.

		Wingate				
		RSN		**RSH**		**RS-BFR**
Peak Power (W)	Pre	1349 ± 137.5	Pre	1315.6 ± 187.5	Pre	1517.6 ± 260
	Post	1354.6 ± 97.6	Post	1395.7 ± 211.7	Post	1523.8 ± 155
VE (L.min^{-1})	Pre	141.7 ± 8.7	Pre	149.2 ± 23.9	Pre	156.6 ± 25.8
	Post	148.5 ± 27.1	Post	148.8 ± 25	Post	162.4 ± 31
BF (cycl.min^{-1})	Pre	59.3 ± 8.3	Pre	62.8 ± 11.2	Pre	67.2 ± 6.2
	Post	57.5 ± 11.1	Post	61.6 ± 13.1	Post	59.5 ± 12.4
VO_2 (mL.min^{-1})	Pre	3457.1 ± 396.6	Pre	3741.9 ± 578.5	Pre	3674.3 ± 657
	Post	3423.9 ± 531.7	Post	3620.2 ± 446.6	Post	3591.1 ± 715.5
Lactate (mmol.L^{-1})	Pre	9 ± 2.6	Pre	7.9 ± 2.4	Pre	8.6 ± 1.8
	Post	9.5 ± 4.7	Post	7.3 ± 2.1	Post	9.5 ± 1.9
RER	Pre	1.42 ± 0.17	Pre	1.33 ± 0.12	Pre	1.44 ± 0.12
	Post	1.34 ± 0.18	Post	1.28 ± 0.15	Post	1.39 ± 0.01

*Mean ± SD. * ($p < 0.05$), for significantly difference in time from Pre.*

Values for peak power (Peak Power) [W], total ventilation (VE) [L.min^{-1}], breath frequency (BF) [cycle.min^{-1}], maximal oxygen consumption (VO_2) [mL.min^{-1}], blood lactate concentration (Lactate) [mmol.L^{-1}], respiratory exchange ratio (RER).

Table 6 displays the performance, the physiological and the metabolic data of the 30s Wingate test. There was no significant change in any parameter measured or calculated. There is only a small non-significant improvement in RER values ($p = 0.055$) (RSN: -5.6%; RSH: -3.8%; RS-BFR: -3.5%) as well as efficiency values ($p = 0.08$) (RSN: +4.7%; RSH: +10.8%; RS-BFR: +6.5%).

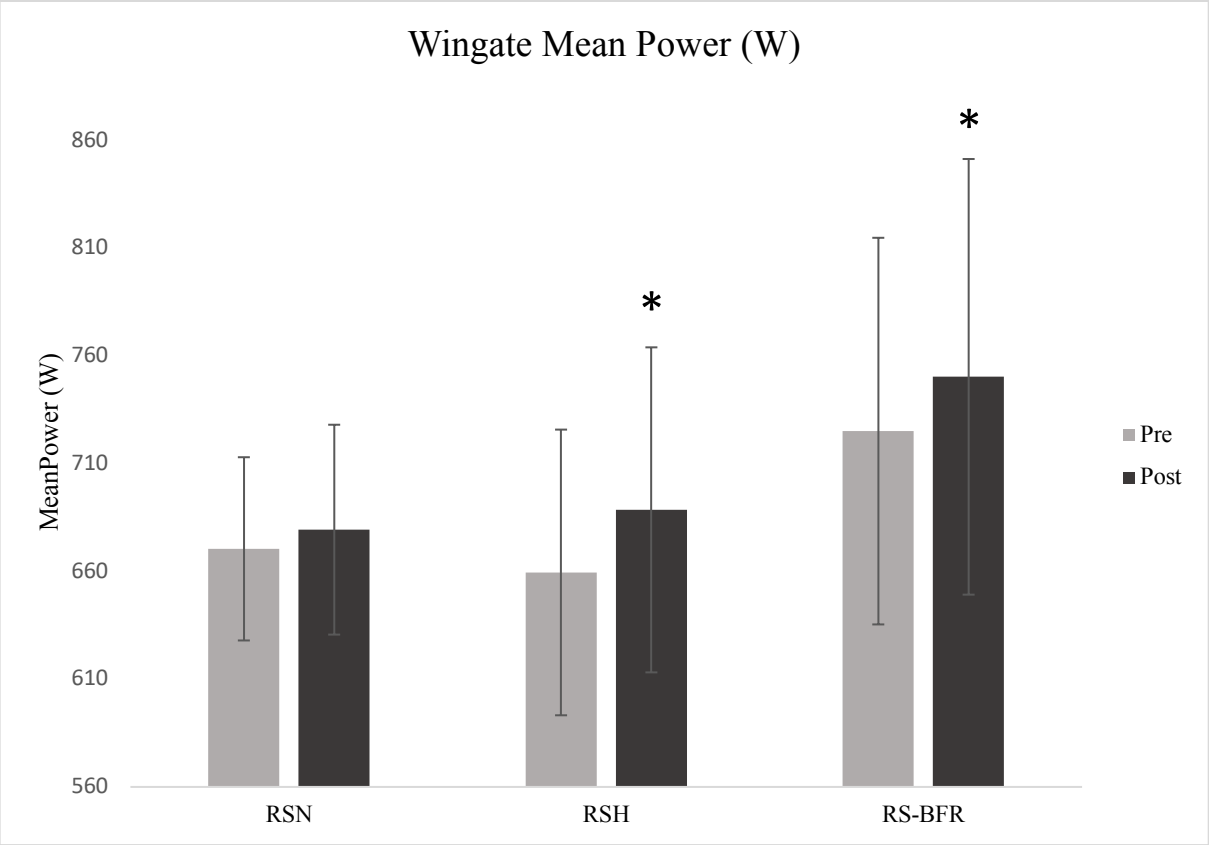

*Figure 16. Performance values of Mean Power during the 30s Wingate test at pre- and post- for RSN, RSH and RS-BFR. Mean ± SD. * ($p < 0.05$).*

Figure 17 illustrates that mean power output was significantly greater at post in RSH (4.2%; $p < 0.05$) and RS-BFR (3.4%; $p < 0.05$) but not in RSN.

3.4 10 km Time Trial

Table 7. Physiological data measured during the 10-km time trial Test (10kTT)

		10kTT				
		RSN		**RSH**		**RS-BFR**
HR (bpm)	Pre	184 ± 8.8	Pre	180.7 ± 12.6	Pre	185.1 ± 7.1
	Post	187.6 ± 7.4	Post	182.3 ± 7.9	Post	186 ± 8
VE (L.min^{-1})	Pre	114.4 ± 15.6	Pre	114.2 ± 29	Pre	114.4 ± 33.6
	Post	124 ± 8.9	Post	121.7 ± 29.9	Post	126.7 ± 28.9*
BF (cycl.min^{-1})	Pre	42.3 ± 8	Pre	40.6 ± 9.5	Pre	40.9 ± 10.4
	Post	43.7 ± 7.1	Post	43.5 ± 9.3	Post	43.4 ± 6.3
VO_2 (mL.min^{-1})	Pre	3320 ± 510.5	Pre	3467.7 ± 778.7	Pre	3508.6 ± 828.2
	Post	3516 ± 605	Post	3509 ± 738.7	Post	3621.3 ± 743.3
RER	Pre	1.03 ± 0.04	Pre	1.00 ± 0.03	Pre	1.02 ± 0.05
	Post	0.99 ± 0.04	Post	1.02 ± 0.06	Post	1.04 ± 0.05
Efficiency (%)	Pre	21.4 ± 2	Pre	21 ± 4.2	Pre	20.5 ± 2.3
	Post	22.5 ± 2.4	Post	22.6 ± 2.3	Post	23 ± 2.6*
RPE legs (Borg 6-20)	Pre	17.1 ± 2	Pre	17.4 ± 2.6	Pre	18.4 ± 1.1
	Post	18.5 ± 1.7*	Post	18.7 ± 2*	Post	18.4 ± 1.6
RPE breath (Borg 6-20)	Pre	17.1 ± 1.6	Pre	17.5 ± 2.3	Pre	18.1 ± 1.5
	Post	16.9 ± 1.7	Post	17.7 ± 2.5	Post	18 ± 2.7

*Mean ± SD. * ($p < 0.05$), for significantly difference in time from Pre.*

Values for heartrate (HR) [bpm], total ventilation (VE) [L.min^{-1}], breath frequency (BF) [cycl.min^{-1}], maximal oxygen consumption (VO_2) [mL.min^{-1}], respiratory exchange ratio (RER), cycling efficiency (Efficiency) [%], cycling economy (Economy) [mL.w^{-1}], rating of perceived exertion for legs (RPE legs) [Borg 6-20], rating of perceived exertion for breath (RPE breath) [Borg 6-20].

Table 8 illustrates the physiological data of the 10kTT test. No significant change was observed for the HR values. Besides the significant increase for RS-BFR VE values from pre- to post-training ($p < 0.05$) (10.8%), no significant change was detected for the other VE, BF, VO2 and RER values. The cycling efficiency values increased significantly for RS-BFR ($p = 0.05$) (12.2%), whereas it did not for RSN and RSH. RPE legs were significantly greater post-training for RSN ($p < 0.05$) (8.2%) and RSH ($p < 0.05$) (7.5%) whereas no significant change was observed for RS-BFR. There was no significant change for RPE breath for any group.

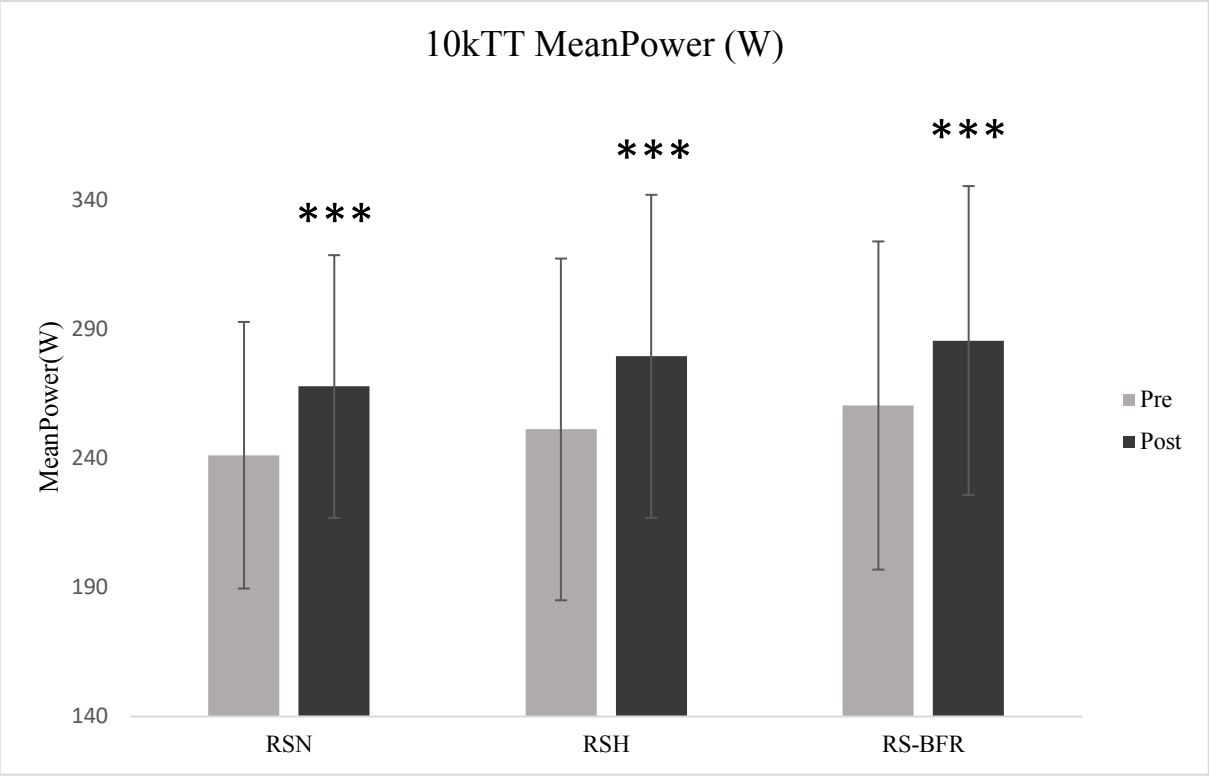

*Figure 18. Mean Power during the 10-km Time Trial Test at Pre and Post in RSN, RSH and RS-BFR. Mean ± SD. *** $p < 0.001$.*

Figure 19 shows that mean power output was significantly greater at post in every group (RSN: 9.9%; RSH: 10.1%; RS-BFR: 8.8%; $p < 0.001$).

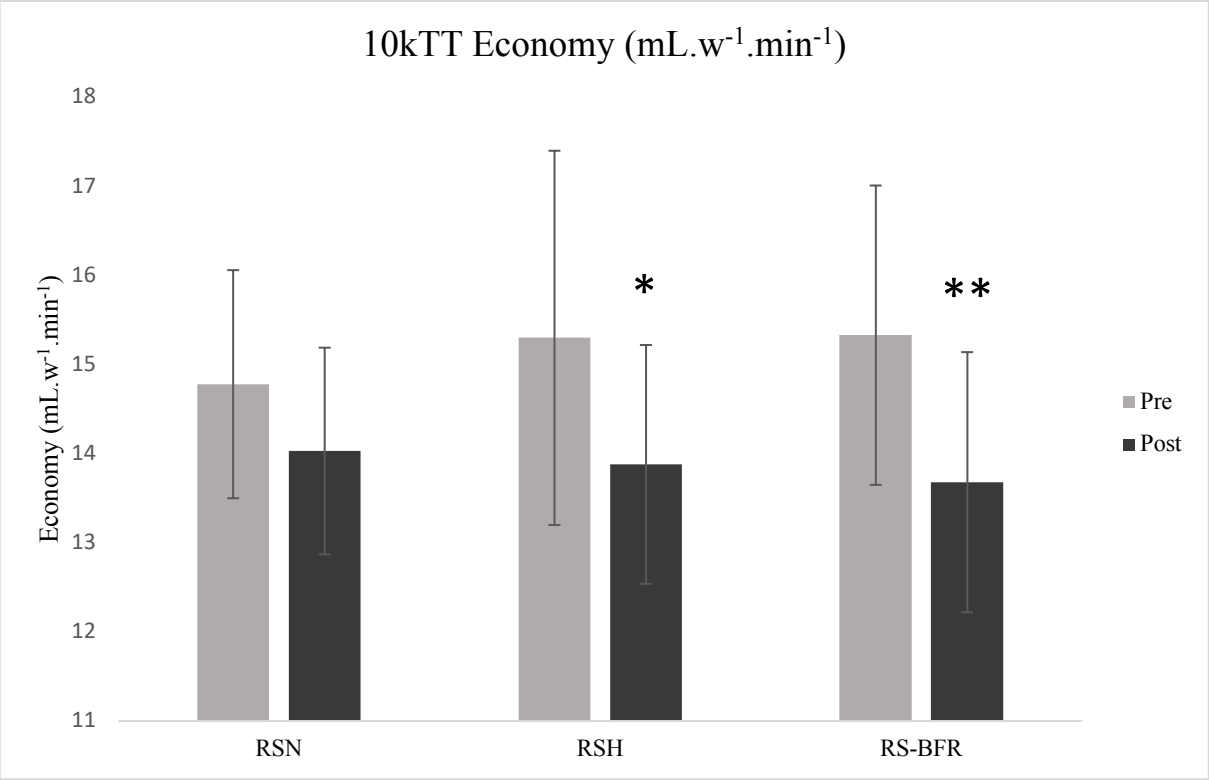

*Figure 20. Economy values during the 10km Time Trial Test at pre and post for RSN, RSH and RS-BFR. Mean ± SD. * $p < 0.05$, ** $p < 0.01$.*

Figure 21 illustrates that cycling economy was decreased at post in RSH (10.2%; $p < 0.05$) and RS-BFR (12.1%; $p < 0.01$) but not for RSN.

4. Discussion

To the best of our knowledge, this is the first study to assess the effects of a 3 weeks repeated sprint training protocol with hypoxia versus BFR on performance and physiology adaptations. The purpose of this study was to assess the effects of nine sessions of repeated-sprint training in three different conditions, in normoxia, in hypoxia and with BFR in healthy recreational young adults.

The main findings of the present study were:

1. **RSA** mean and peak power were improved in all groups.
2. **Wingate** mean power were improved only in RSH and RS-BFR.
3. **10kTT** mean power was improved in all groups but the cycling economy was improved only in RSH and RS-BFR.

4.1 RSA

The principal findings indicate that there were no additional effects on performance after either training in hypoxia or with BFR compared to the same training protocol in normoxia. By acknowledging so, our first hypothesis is rejected.

The absence of additive benefits of RSH or RS-BFR over RSN on RS performance contrasts with at least two recent studies, where the number of repeated sprints (cycling or double-poling) to exhaustion were increased by approximately 40% after 2-4 weeks (6-8 sessions and thereby less than in the present study) of RSH (3-4 sets of five 10 s all-out sprints with 20 s recovery, FiO_2 = 13.8 %) vs. RSN in moderately trained cyclists and highly trained cross-country athletes (Faiss et al., 2013; Faiss et al., 2015b). In fact, every group improved to the same extent for RSA mean power (*Figure 22*). Our results are in line with those of Montero & Lundby (2017) with a double-blind cross-over study indicating that RSH did not improve RS performance compared with RSN in endurance-trained subjects. Hamlin et al. (2017) showed as well that a 3-weeks repeated sprint training (six sessions of four sets of 5 × 5 s sprints with 25 s and 5 min of active recovery between reps and sets, respectively) in either normobaric hypoxia (n = 9; FIO_2 = 14.5%) or normobaric normoxia (n = 10; FIO_2 = 20.9%) increased YoYo performance in well-trained rugby players with unclear differences found between groups. Goods et al. (2015) used similar training and testing procedures to our study (cycling repeated sprint) and found non-significant changes between normoxic and hypoxic groups post-exposure for

repeated sprint running ability, reinforcing the principle of specificity in training and highlighting the importance of team sport athletes performing predominantly running-based training. Goods et al. (2015) showed that the preference of using running as a training mode is supported by recent suggestions that RSA enhancements following RSH training may be greater in running compared to cycling (Girard et al., 2013). Previous work from their laboratory also supported this hypothesis, given that they noted a two-fold greater drop in oxygen saturation, and a two-fold greater increase in blood lactate levels (than found previously) following a similar repeated-sprint task utilizing a running mode (Goods et al., 2014). This greater oxidative and metabolic strain may partially explain why running-based training interventions could result in greater performance outcomes, as suggested by Girard et al. (2013). It should also be considered whether the fixed number of sprints performed here in the cycling RSA test prevented any improvements being found later in an open-loop RSA task as reported by Faiss et al. (2013). These authors suggest that RSH training may not necessarily produce faster mean sprint times, but rather an improved ability to maintain these times for longer. However, this appears an unlikely outcome of our investigation, even if the RSA task was a close-loop one (i.e., with a predetermined number of sprints) since the only group that significantly improved their fatigue decrement score was the RSN group. Indeed, whereas improvement in RSA has also been reported in "close-loop" protocol (Beard et al., 2019; Fornasier-Santos et al., 2018; Gatterer et al., 2019; Kasai et al., 2015; Kasai et al., 2017; Oriishi et al., 2018; Wang et al., 2019) meaning an increased velocity or power output during a repeated sprint test, in this study only the RSN group actually succeeded to maintain significantly a better power output percentage throughout the 20 sprints of the RSA test by reducing the drop in power output from the first to the last sprint.

The other finding of this study is that repeated sprint cycling training with BFR significantly increased RSA mean power output ($p < 0.01$, 7.3%) but there was no difference with the other groups. Whereas it was the first time, to the authors knowledge, that BFR was used with a 3 weeks repeated sprint training protocol the outcomes were unpredictable. Even if the underlying physiological changes after RS-BFR were partially known (Willis et al., 2019) the effects of a repeated sprint protocol on performance were yet to be proven. Nevertheless, the expectations were high because of the well-known increased metabolic stress and impaired oxygen availability of BFR training (Tanimoto et al., 2005; Nielsen et al., 2020; Ferguson et al., 2018) In fact, the peak power output during the RSA test was significantly improved in every group. Indeed, BFR training is known to enhance hypertrophic pathways that could affects the peak power output whereas power equals force multiplied by speed (P=F*V). Teixeira et al., (2017)

demonstrated that phosphocreatine concentration was impacted and intramuscular inorganic phosphate were accumulating when BFR was maintained during rest intervals compared to the protocol that removed BFR during this period and thus more energy was derived from the anaerobic system with a resultant increase in blood lactate. Considering that high mechanical stress was held constant (RS training) and metabolic stress was augmented by applying BFR, this strategy may offer a potential benefit for long term muscle hypertrophy (Teixeira et al., 2017). However, the results of Teixeira et al. showed that BFR did not increase muscle activation when the load was already relatively high (>70% 1RM), and, in fact, might even reduce it. As RS cycling training is a maximal effort, these explanations could be applied to our results.

All these RSA results need to be confirmed and discussed in comparison with the mRNAs analysis (blood sampling and microbiopsies) to allow a better understanding of the current underlying mechanisms.

4.2 Submaximal test.

During the 6-min cycling test at a submaximal intensity, the subjects had to perform a relative intensity of 1.5w.kg^{-1}. As expected, this test was easy for them as the RPE legs and breath values ranged from 8 to 10 out of 20 on Borg's scale (*Table 9*). Whereas no physiological parameters changed for RS-BFR, VO_2 ($p < 0.05$), (5.9%) and cycling economy ($p < 0.05$), (6%) decreased for RSN as well as HR ($p < 0.05$), (4.9%) and lactate concentration ($p < 0.01$), (10.9%) for RSH. Despite these small physiological changes, it is uncertain that the repeated sprint training protocol induced any significant changes at all for low intensity exercise.

4.3 Wingate test.

The Wingate test is considered as the gold standard for assessment of anaerobic power. In this study, significant increases in mean power were observed for RSH and RS-BFR but not in RSN (*Figure 23*). The anaerobic adaptations induced by RSH are still debated. Indeed, Faiss et al. (2013) reported no differences in the improvement in the Wingate test between RSN and RSH. However Faiss et al. (2013) demonstrated also that physiological parameters such as the amplitude of blood flow variations during sprint phases was increased, mRNA expression of factors involved in pH regulation and glycolysis as well as factors involved in mitochondrial biogenesis were increased after RSH suggesting a potential enhancement of the glycolytic (but not oxidative) activity in muscle. Takei et al. (2020) showed that one previous study reported

that performance during a single Wingate effort improved when assessed 9 days but not 2 days after the hypoxic training intervention (Hendriksen & Meeuwsen, 2003). Two other studies using trained sprinters reported that 5 to 6 consecutive days of hypoxic training (repeated maximal sprints of 15–30s) and repeated sprint training (repeated maximal 6-s sprints) failed to induce improvement in single Wingate effort 3 days after the intervention (Kasai et al., 2017; Kasai et al., 2019). Since performance was assessed in the first few days after the intervention, mid and long-term consequences of our intervention are unknown. While it cannot be ascertained that performance gains would have reached a peak at this time, our data support a view that 2-5 days would allow sufficient recovery from the intervention to measure positive effects. In the real world, most athletes would normally train hard up to 1-2 weeks prior to the actual competition, and then taper their training in the days preceding major events (Mujika & Padilla, 2003). With this in mind, our training routine seems practically relevant to be included in the busy schedule of sprinters in the lead up of competition.

These observed improvements in glycolytic parameters of the present study were similar to those reported in response to resistance training with BFR (Sundberg, 1994; Burgomaster et al., 2003) and aerobic training with BFR (Park et al., 2010). The metabolic stress with BFR training plays an important role in initiating muscle adaptations (Suga et al., 2012; Teixeira et al., 2017). Dependence on anaerobic metabolism and disturbed oxygen delivery during BFR training could result in increased muscle glycogen stores ((Sundberg, 1994; Burgomaster et al., 2003) which would improve anaerobic power especially in groups that trained with a pressure of 200mmHg or higher creating a highest metabolic stress (Amani-Shalamzari et al., 2019). It should also be noted that the current study used 45% (90.3 ± 10.3mmHg) of the pressure corresponding to total occlusion at rest as recommended by Loenneke et al., 2014 to promote muscle adaptation during resistance training and previously used on lower limb muscle during high-intensity repeated sprint exercise (Willis et al., 2018).Willis et al. (2018) showed that there were increased changes in [tHb], interpreted as changes in tissue blood volume (Ijichi et al., 2005; Van Beekvelt et al., 2001), as the sum of changes in both oxyhemoglobin and deoxyhemoglobin, in both 45% and 60% conditions, when compared with the control. With BFR, the vein is nearly completely occluded, thus increasing the local blood volume and the venous resistance due to reduced venous return. This circulatory adaptation results in more active muscle vascular beds (tissue perfusion: volume of blood per unit of time) mediated by the sympathetic nervous system to regulate blood flow via the muscle metaboreflex (Clausen, 1977; Boushel, 2010). These changes detected in [tHb] may thus create a situation for the body to overcome in order to continue exercise, and therefore, possibly a stimulus for the use of BFR

training as a way to induce fluctuations in blood volume (i.e., tissue perfusion) to elicit vascular adaptation (Willis et al., 2018).

In the present study, those physiological adaptations could potentially explain the increase of performance in mean power during the Wingate test for RSH and RS-BFR.

4.4 10kTT

In terms of aerobic capacity, the virtual 10km Time Trial test was utilized to test the ability of the subjects to perform as fast as they could a 250 kJ effort that lasted from 11 (for the best athlete) to 26 minutes (for the weakest). As expected, RPE legs and breath were both really high (17-19/20) with a small increase at spot in RPE legs for RSN and RSH. All groups increased significantly their mean power output ($p < 0.001$) meaning that the repeated-sprint training protocol, independently of the condition, enhanced aerobic performance in healthy subjects. However, cycling economy was significantly improved only after RSH and RS-BFR. This is an novel findings since Faiss et al. (2013) reported no improvement for a 3-min all out test after 8 sessions of RSH. Whereas the performance was not impaired differently by the training conditions, some physiological parameters improved after RSH and RS-BFR. The improvement of cycling economy cannot be explained by a better absolute aerobic power since there was no change in VO_2, nor in BF with only a small significant increase in VE for RS-BFR. These improvements could be explained by the physiological response of cells from the HIF-1α during exposure to an hypoxic environment (Gore et al., 2007). Gore et al. (2007) showed that HIF-1α was identified for its role in regulating the transcription of the EPO gene (G. L. Wang et al., 1995); however, HIF-1α is also induced by hypoxia in many cell lines and activates multiple genes, which in turn encode proteins that mediate adaptive responses, other than hematological ones (Sasaki et al., 2000). Parameters activated by HIF-1α include EPO and transferrin for iron metabolism and red cell production; vascular endothelial growth factor (VEGF) and others for angiogenesis/cell survival; glycolytic enzymes including phosphofructokinase (PFK), hexokinase and lactate dehydrogenase that are important for energy metabolism; glucose transporters 1 and 3, and monocarboxylate transporters 1 and 4 critical for glucose uptake and lactate metabolism by the muscles; carbonic anhydrase for pH regulation; nitric oxide synthase and heme oxygenase, which produce the vasodilators nitric oxide (NO) and carbon monoxide; and tyrosine hydroxylase that codes for a pivotal enzyme for dopamine synthesis and accelerates ventilation (Sasaki et al., 2000). The plethora of HIF-1α mediated responses to hypoxia implies that an increase in EPO concentration could be

concurrent with other physiological changes such as increased carbohydrate metabolism, increased ventilation, enhanced muscle buffering, and more efficient use of oxygen in the muscles. Furthermore, these physiological changes appeared to show greater improvements in the anaerobic threshold and time of onset blood lactate accumulation (OBLA) after sprint interval cycling training performed in hypoxia than normoxia (Puype et al., 2013).

5. Practical applications

In the present study, RSH and RS-BFR were more effective in improving both anaerobic and aerobic physiological parameters than RSN. The physiological parameters improvements such as the cycling economy found during the 10kTT after RS-BFR and RSH let us suggest that this kind of training could be promising for the future. However, from a coach's point of view, performance improvements may be considered the most important outcomes even though they not always were found to have practical relevance (Mendez-Villanueva & Buchheit, 2013).

It has to be clearly stated that the practicability of the proposed training regime in small hypoxic chambers should be compared to the BFR cuffs. If BFR training leads to the same or even better improvements in performance than with systemic hypoxia, it could be very interesting for coaches to have a more practical and easier way to train their athlete. Indeed, BFR cuffs are more likely to be used by coaches due to their lower price and their simplicity of use compared to hypoxic chambers.

This study showed that 9 repeated sprint sessions over 3 weeks led to performance improvements in young healthy male adults with a potential additional performance enhancement after RSH and RS-BFR 2 to 5 days after intervention. This kind of short training protocol could be very interesting for athletes that have a full year calendar.

6. Limitations

The small sample-size certainly is the major weakness of the study which could potentially explain the variety in physiological and performance results of RSA, submaximal, Wingate and 10kTT tests.

Many of the physiological parameters measured but not analysed yet (i.e., neuromuscular responses, molecular adaptations from the blood sampling or the biopsies,) will enable us to further investigate the underlying mechanisms.. Bishop & Girard (2013) have speculated that

an improved phosphocreatine resynthesis rate and increased mitochondrial activity are possible adaptations following RSH training. Such physiological mechanisms are likely vital to repeated sprint efforts, and as such, the influence of sprint training on these variables should be analyzed in future RSH training studies. Muscle buffer capacity has also been proposed as a positive non-hematological adaptation to hypoxic training (Gore et al., 2007) with suggestions that this may lead to improved RSA (Edge et al., 2006).

Due to the short timing of the study, the many subjects to train and the limited equipment, we had to use different BFR cuffs and hypoxic machines for training. Firstly, we mostly used the BFR cuffs (custom-made 4 x 70 cm cuff, 3 × 41 bladder; D.E. Hokansson Inc., Bellevue, WA, USA) but the BFR B-strong cuffs (B Strong LLC 2020. B Strong BFR TRAINING SYSTEMTM & B Strong BFR BandsTM) was also utilized during approximately 20% of the training time. Secondly, we mostly used the hypoxic chamber of the CSS at the University of Lausanne but for approximatively 10% of the training time, an Altitrainer connected to a mask was utilized.

7. Conclusion

The purpose of the present study was to assess the effects of a 3-weeks repeated sprint training in systemic hypoxia versus with blood flow restriction in young healthy male adults and the results showed that (1) RSA was not more improved than after RSN, (2) Wingate mean power was improved after RSH and RS-BFR but not RSN (3) the 10km time trial mean power was improved to the same extent in the three groups but there was an improved cycling economy only after RSH and RS-BFR.

In conclusion, firstly, the results of this study do not entirely support the fact that RSH have actually additional benefit for RSA performance. Secondly, it appeared that repeated sprint training with BFR tends to be as efficient as RSH with underlying physiological improvements not totally understood yet. This is why further studies should focus on physiological changes after RS-BFR and investigate the potential for performance enhancement.

8. Bibliography

1. Abe, T., Sakamaki, M., Fujita, S., Ozaki, H., Sugaya, M., Sato, Y., & Nakajima, T. (2010). Effects of Low-Intensity Walk Training With Restricted Leg Blood Flow on Muscle Strength and Aerobic Capacity in Older Adults. *Journal of geriatric physical therapy*. https://doi.org/10.1097/JPT.0b013e3181d07a73
2. Abe, Takashi, Kearns, C. F., & Sato, Y. (2006). Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *Journal of Applied Physiology*, *100*(5), 1460-1466. https://doi.org/10.1152/japplphysiol.01267.2005
3. Amani-Shalamzari, S., Rajabi, S., Rajabi, H., Gahreman, D. E., Paton, C., Bayati, M., Rosemann, T., Nikolaidis, P. T., & Knechtle, B. (2019). Effects of Blood Flow Restriction and Exercise Intensity on Aerobic, Anaerobic, and Muscle Strength Adaptations in Physically Active Collegiate Women. *Frontiers in Physiology*, *10*. https://doi.org/10.3389/fphys.2019.00810
4. Balsom, P. D., Gaitanos, G. C., Ekblom, B., & Sjödin, B. (1994). Reduced oxygen availability during high intensity intermittent exercise impairs performance. *Acta Physiologica Scandinavica*, *152*(3), 279-285. https://doi.org/10.1111/j.1748-1716.1994.tb09807.x
5. Beard, A., Ashby, J., Chambers, R., Brocherie, F., & Millet, G. P. (2019). Repeated-Sprint Training in Hypoxia in International Rugby Union Players. *International Journal of Sports Physiology and Performance*, *14*(6), 850-854. https://doi.org/10.1123/ijspp.2018-0170
6. Billaut, F., & Buchheit, M. (2013). Repeated-sprint performance and vastus lateralis oxygenation : Effect of limited O $_2$ availability: Muscle reoxygenation in hypoxia. *Scandinavian Journal of Medicine & Science in Sports*, *23*(3), e185-e193. https://doi.org/10.1111/sms.12052
7. Bishop, D., Edge, J., Davis, C., & Goodman, C. (2004). Induced Metabolic Alkalosis Affects Muscle Metabolism and Repeated-Sprint Ability: *Medicine & Science in Sports & Exercise*, 807-813. https://doi.org/10.1249/01.MSS.0000126392.20025.17
8. Bishop, D. J., & Girard, O. (2013). Determinants of team-sport performance : Implications for altitude training by team-sport athletes. *British Journal of Sports Medicine*, *47 Suppl 1*, i17-21. https://doi.org/10.1136/bjsports-2013-092950

9. Bogdanis, G. C., Nevill, M. E., Boobis, L. H., Lakomy, H. K., & Nevill, A. M. (1995). Recovery of power output and muscle metabolites following 30 s of maximal sprint cycling in man. *The Journal of Physiology*, *482*(2), 467-480. https://doi.org/10.1113/jphysiol.1995.sp020533
10. Boushel, R. (2010). Muscle metaboreflex control of the circulation during exercise. *Acta Physiologica*, *199*(4), 367-383. https://doi.org/10.1111/j.1748-1716.2010.02133.x
11. Brimblecombe, P. (1996). *Air Composition and Chemistry*. Cambridge University Press.
12. Brocherie, F., Millet, G. P., D'Hulst, G., Van Thienen, R., Deldicque, L., & Girard, O. (2018). Repeated maximal-intensity hypoxic exercise superimposed to hypoxic residence boosts skeletal muscle transcriptional responses in elite team-sport athletes. *Acta Physiologica*, *222*(1), e12851. https://doi.org/10.1111/apha.12851
13. Brocherie, Franck, Girard, O., Faiss, R., & Millet, G. P. (2015). High-Intensity Intermittent Training in Hypoxia : A Double-Blinded, Placebo-Controlled Field Study in Youth Football Players. *Journal of Strength and Conditioning Research*, *29*(1), 226-237. https://doi.org/10.1519/JSC.0000000000000590
14. Brosnan, M. J., Martin, D. T., Hahn, A. G., Gore, C. J., & Hawley, J. A. (2000). Impaired interval exercise responses in elite female cyclists at moderate simulated altitude. *Journal of Applied Physiology*, *89*(5), 1819-1824. https://doi.org/10.1152/jappl.2000.89.5.1819
15. Burgomaster, K. A., Howarth, K. R., Phillips, S. M., Rakobowchuk, M., MacDonald, M. J., McGee, S. L., & Gibala, M. J. (2008). Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans : Metabolic adaptations to sprint or endurance training in humans. *The Journal of Physiology*, *586*(1), 151-160. https://doi.org/10.1113/jphysiol.2007.142109
16. Burgomaster, K. A., Hughes, S. C., Heigenhauser, G. J. F., Bradwell, S. N., & Gibala, M. J. (2005). Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. *Journal of Applied Physiology*, *98*(6), 1985-1990. https://doi.org/10.1152/japplphysiol.01095.2004
17. Burgomaster, K. A., Moore, D. R., Schofield, L. M., Phillips, S. M., Sale, D. G., & Gibala, M. J. (2003). Resistance Training with Vascular Occlusion : Metabolic Adaptations in Human Muscle: *Medicine & Science in Sports & Exercise*, *35*(7), 1203-1208. https://doi.org/10.1249/01.MSS.0000074458.71025.71
18. Buskirk, E. R., Kollias, J., Akers, R. F., Prokop, E. K., & Reategui, E. P. (1967).

Maximal performance at altitude and on return from altitude in conditioned runners. *Journal of Applied Physiology*, *23*(2), 259-266. https://doi.org/10.1152/jappl.1967.23.2.259

19. Casey, D. P., & Joyner, M. J. (2012). Compensatory vasodilatation during hypoxic exercise : Mechanisms responsible for matching oxygen supply to demand: Hypoxic dependent vasodilatation during exercise. *The Journal of Physiology*, *590*(24), 6321-6326. https://doi.org/10.1113/jphysiol.2012.242396
20. Chapman, R. F., Stray-Gundersen, J., & Levine, B. D. (1998). Individual variation in response to altitude training. *Journal of Applied Physiology*, *85*(4), 1448-1456. https://doi.org/10.1152/jappl.1998.85.4.1448
21. Christiansen, D., Eibye, K., Hostrup, M., & Bangsbo, J. (2020). Training with blood flow restriction increases femoral artery diameter and thigh oxygen delivery during knee-extensor exercise in recreationally trained men. *The Journal of Physiology*, *598*(12), 2337-2353. https://doi.org/10.1113/JP279554
22. Clausen, J. P. (1977). Effect of physical training on cardiovascular adjustments to exercise in man. *Physiological Reviews*, *57*(4), 779-815. https://doi.org/10.1152/physrev.1977.57.4.779
23. Clausen, T., Nielsen, O. B., Harrison, A. P., Flatman, J. A., & Overgaard, K. (1998a). The Na+,K+ pump and muscle excitability. *Acta Physiologica Scandinavica*, *162*(3), 183-190. https://doi.org/10.1046/j.1365-201X.1998.0295e.x
24. Clausen, T., Nielsen, O. B., Harrison, A. P., Flatman, J. A., & Overgaard, K. (1998b). The Na^+,K^+ pump and muscle excitability : Na+,K+ pump and excitability. *Acta Physiologica Scandinavica*, *162*(3), 183-190. https://doi.org/10.1046/j.1365-201X.1998.0295e.x
25. Drummond, M. J., Fujita, S., Takashi, A., Dreyer, H. C., Volpi, E., & Rasmussen, B. B. (2008). Human Muscle Gene Expression following Resistance Exercise and Blood Flow Restriction: *Medicine & Science in Sports & Exercise*, *40*(4), 691-698. https://doi.org/10.1249/MSS.0b013e318160ff84
26. Dufour, S. P., Ponsot, E., Zoll, J., Doutreleau, S., Lonsdorfer-Wolf, E., Geny, B., Lampert, E., Flück, M., Hoppeler, H., Billat, V., Mettauer, B., Richard, R., & Lonsdorfer, J. (2006). Exercise training in normobaric hypoxia in endurance runners. I. Improvement in aerobic performance capacity. *Journal of Applied Physiology*, *100*(4), 1238-1248. https://doi.org/10.1152/japplphysiol.00742.2005

27. Edge, J., Bishop, D., & Goodman, C. (2006). Effects of chronic NaHCO3 ingestion during interval training on changes to muscle buffer capacity, metabolism, and short-term endurance performance. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *101*(3), 918-925. https://doi.org/10.1152/japplphysiol.01534.2005
28. *EIM-PAR-Q1-ada.pdf*. (s. d.). Consulté 6 janvier 2021, à l'adresse https://www.fgcu.edu/mariebcollege/rehabilitationsciences/exercisescience/files/EIM-PAR-Q1-ada.pdf
29. Faiss, Raphaël, Girard, O., & Millet, G. P. (2013). Advancing hypoxic training in team sports : From intermittent hypoxic training to repeated sprint training in hypoxia: Table 1. *British Journal of Sports Medicine*, *47*(Suppl 1), i45-i50. https://doi.org/10.1136/bjsports-2013-092741
30. Faiss, Raphael, Léger, B., Vesin, J.-M., Fournier, P.-E., Eggel, Y., Dériaz, O., & Millet, G. P. (2013). Significant Molecular and Systemic Adaptations after Repeated Sprint Training in Hypoxia. *PLoS ONE*, *8*(2), e56522. https://doi.org/10.1371/journal.pone.0056522
31. Faiss, Raphael, Willis, S., Born, D.-P., Sperlich, B., Vesin, J.-M., Holmberg, H.-C., & Millet, G. P. (2015a). Repeated Double-Poling Sprint Training in Hypoxia by Competitive Cross-country Skiers: *Medicine & Science in Sports & Exercise*, *47*(4), 809-817. https://doi.org/10.1249/MSS.0000000000000464
32. Faiss, Raphael, Willis, S., Born, D.-P., Sperlich, B., Vesin, J.-M., Holmberg, H.-C., & Millet, G. P. (2015b). Repeated Double-Poling Sprint Training in Hypoxia by Competitive Cross-country Skiers: *Medicine & Science in Sports & Exercise*, *47*(4), 809-817. https://doi.org/10.1249/MSS.0000000000000464
33. Ferguson, R. A., Hunt, J. E. A., Lewis, M. P., Martin, N. R. W., Player, D. J., Stangier, C., Taylor, C. W., & Turner, M. C. (2018). The acute angiogenic signalling response to low-load resistance exercise with blood flow restriction. *European Journal of Sport Science*, *18*(3), 397-406. https://doi.org/10.1080/17461391.2017.1422281
34. Fornasier-Santos, C., Millet, G. P., & Woorons, X. (2018). Repeated-sprint training in hypoxia induced by voluntary hypoventilation improves running repeated-sprint ability in rugby players. *European Journal of Sport Science*, *18*(4), 504-512. https://doi.org/10.1080/17461391.2018.1431312
35. *French_UIAA_MedCom_No15_Travail_en_conditions_hypoxiques_2012_V2-14.pdf*. (s. d.).
36. Fujita, S., Abe, T., Drummond, M. J., Cadenas, J. G., Dreyer, H. C., Sato, Y., Volpi, E.,

& Rasmussen, B. B. (2007). Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *103*(3), 903-910. https://doi.org/10.1152/japplphysiol.00195.2007

37. Gaitanos, G. C., Williams, C., Boobis, L. H., & Brooks, S. (1993). Human muscle metabolism during intermittent maximal exercise. *Journal of Applied Physiology*, *75*(2), 712-719. https://doi.org/10.1152/jappl.1993.75.2.712
38. Galvin, H. M., Cooke, K., Sumners, D. P., Mileva, K. N., & Bowtell, J. L. (2013). Repeated sprint training in normobaric hypoxia. *British Journal of Sports Medicine*, *47*(Suppl 1), i74-i79. https://doi.org/10.1136/bjsports-2013-092826
39. Gatterer, H., Menz, V., Untersteiner, C., Klarod, K., & Burtscher, M. (2019). Physiological Factors Associated With Declining Repeated Sprint Performance in Hypoxia. *Journal of Strength and Conditioning Research*, *33*(1), 211-216. https://doi.org/10.1519/JSC.0000000000001891
40. Genova, M. L., & Lenaz, G. (2014). Functional role of mitochondrial respiratory supercomplexes. *Biochimica Et Biophysica Acta*, *1837*(4), 427-443. https://doi.org/10.1016/j.bbabio.2013.11.002
41. Gibala, M. J., Little, J. P., Van Essen, M., Wilkin, G. P., Burgomaster, K. A., Safdar, A., Raha, S., & Tarnopolsky, M. A. (2006). Short-term sprint interval *versus* traditional endurance training : Similar initial adaptations in human skeletal muscle and exercise performance: Rapid adaptations to sprint or endurance training in humans. *The Journal of Physiology*, *575*(3), 901-911. https://doi.org/10.1113/jphysiol.2006.112094
42. Gielen, S., Schuler, G., & Hambrecht, R. (2001). Exercise Training in Coronary Artery Disease and Coronary Vasomotion. *Circulation*, *103*(1). https://doi.org/10.1161/01.CIR.103.1.e1
43. Girard, O., Brocherie, F., & Millet, G. P. (2013). On the use of mobile inflatable hypoxic marquees for sport-specific altitude training in team sports. *British Journal of Sports Medicine*, *47*(Suppl 1), i121-i123. https://doi.org/10.1136/bjsports-2013-092794
44. Girard, O., Brocherie, F., & Millet, G. P. (2017). Effects of Altitude/Hypoxia on Single- and Multiple-Sprint Performance : A Comprehensive Review. *Sports Medicine*, *47*(10), 1931-1949. https://doi.org/10.1007/s40279-017-0733-z
45. Girard, O., Mendez-Villanueva, A., & Bishop, D. (2011). Repeated-Sprint Ability – Part I : Factors Contributing to Fatigue. *Sports Medicine*, *41*(8), 673-694.

https://doi.org/10.2165/11590550-000000000-00000

46. Goods, P. S. R., Dawson, B., Landers, G. J., Gore, C. J., & Peeling, P. (2015). No Additional Benefit of Repeat-Sprint Training in Hypoxia than in Normoxia on Sea-Level Repeat-Sprint Ability. *Journal of Sports Science & Medicine*, *14*(3), 681-688.
47. Goods, P. S. R., Dawson, B. T., Landers, G. J., Gore, C. J., & Peeling, P. (2014). Effect of Different Simulated Altitudes on Repeat-Sprint Performance in Team-Sport Athletes. *International Journal of Sports Physiology and Performance*, *9*(5), 857-862. https://doi.org/10.1123/ijspp.2013-0423
48. Gore, C., Clark, S., & Saunders, P. (2007). Nonhematological Mechanisms of Improved Sea-Level Performance after Hypoxic Exposure. *Medicine and science in sports and exercise*, *39*, 1600-1609. https://doi.org/10.1249/mss.0b013e3180de49d3
49. Hamlin, M. J., Olsen, P. D., Marshall, H. C., Lizamore, C. A., & Elliot, C. A. (2017). Hypoxic Repeat Sprint Training Improves Rugby Player's Repeated Sprint but Not Endurance Performance. *Frontiers in Physiology*, *8*. https://doi.org/10.3389/fphys.2017.00024
50. Hendriksen, I., & Meeuwsen, T. (2003). The effect of intermittent training in hypobaric hypoxia on sea-level exercise : A cross-over study in humans. *European journal of applied physiology*, *88*, 396-403. https://doi.org/10.1007/s00421-002-0708-z
51. Hirota, K., & Semenza, G. L. (2006). Regulation of angiogenesis by hypoxia-inducible factor 1. *Critical Reviews in Oncology/Hematology*, *59*(1), 15-26. https://doi.org/10.1016/j.critrevonc.2005.12.003
52. Hoppeler, H., & Vogt, M. (s. d.). *Muscle tissue adaptations to hypoxia*. 8.
53. Hughes, L., Paton, B., Rosenblatt, B., Gissane, C., & Patterson, S. D. (2017). Blood flow restriction training in clinical musculoskeletal rehabilitation : A systematic review and meta-analysis. *British Journal of Sports Medicine*, *51*(13), 1003-1011. https://doi.org/10.1136/bjsports-2016-097071
54. Hunt, J. E. A., Galea, D., Tufft, G., Bunce, D., & Ferguson, R. A. (2013). Time course of regional vascular adaptations to low load resistance training with blood flow restriction. *Journal of Applied Physiology*, *115*(3), 403-411. https://doi.org/10.1152/japplphysiol.00040.2013
55. Ijichi, S., Kusaka, T., Isobe, K., Okubo, K., Kawada, K., Namba, M., Okada, H., Nishida, T., Imai, T., & Itoh, S. (2005). Developmental Changes of Optical Properties in Neonates Determined by Near-Infrared Time-Resolved Spectroscopy. *Pediatric Research*, *58*(3), 568-573. https://doi.org/10.1203/01.PDR.0000175638.98041.0E

56. Jackson, M. J. (2015). Redox regulation of muscle adaptations to contractile activity and aging. *Journal of Applied Physiology*, *119*(3), 163-171. https://doi.org/10.1152/japplphysiol.00760.2014
57. Kacin, A., & Strazar, K. (2011). Frequent low-load ischemic resistance exercise to failure enhances muscle oxygen delivery and endurance capacity : Ischemic training and muscle endurance. *Scandinavian Journal of Medicine & Science in Sports*, *21*(6), e231-e241. https://doi.org/10.1111/j.1600-0838.2010.01260.x
58. Kaijser, L., Sundberg, C. J., Eiken, O., Nygren, A., Esbjornsson, M., Sylven, C., & Jansson, E. (1990). Muscle oxidative capacity and work performance after training under local leg ischemia. *Journal of Applied Physiology*, *69*(2), 785-787. https://doi.org/10.1152/jappl.1990.69.2.785
59. Kasai, N., Mizuno, S., Ishimoto, S., Sakamoto, E., Maruta, M., & Goto, K. (2015). Effect of training in hypoxia on repeated sprint performance in female athletes. *SpringerPlus*, *4*, 310. https://doi.org/10.1186/s40064-015-1041-4
60. Kasai, N., Mizuno, S., Ishimoto, S., Sakamoto, E., Maruta, M., Kurihara, T., Kurosawa, Y., & Goto, K. (2017). Impact of Six Consecutive Days of Sprint Training in Hypoxia on Performance in Competitive Sprint Runners. *Journal of Strength and Conditioning Research*, *33*, 1. https://doi.org/10.1519/JSC.0000000000001954
61. Kasai, N., Mizuno, S., Ishimoto, S., Sakamoto, E., Maruta, M., Kurihara, T., Kurosawa, Y., & Goto, K. (2019). Impact of Six Consecutive Days of Sprint Training in Hypoxia on Performance in Competitive Sprint Runners. *Journal of Strength and Conditioning Research*, *33*(1), 36-43. https://doi.org/10.1519/JSC.0000000000001954
62. Larkin, K. A., Macneil, R. G., Dirain, M., Sandesara, B., Manini, T. M., & Buford, T. W. (2012). Blood flow restriction enhances post-resistance exercise angiogenic gene expression. *Medicine and Science in Sports and Exercise*, *44*(11), 2077-2083. https://doi.org/10.1249/MSS.0b013e3182625928
63. Levine, B. D., & Stray-Gundersen, J. (1997). "Living high-training low" : Effect of moderate-altitude acclimatization with low-altitude training on performance. *Journal of Applied Physiology*, *83*(1), 102-112. https://doi.org/10.1152/jappl.1997.83.1.102
64. Levine, B. D., & Stray-Gundersen, J. (2001). The effects of altitude training are mediated primarily by acclimatization, rather than by hypoxic exercise. In R. C. Roach, P. D. Wagner, & P. H. Hackett (Éds.), *Hypoxia* (Vol. 502, p. 75-88). Springer US. https://doi.org/10.1007/978-1-4757-3401-0_7
65. Levine, B. D., & Stray-Gundersen, J. (2006). Dose-Response of Altitude Training :

How Much Altitude is Enough? In R. C. Roach, P. D. Wagner, & P. H. Hackett (Éds.), *Hypoxia and Exercise* (Vol. 588, p. 233-247). Springer US. https://doi.org/10.1007/978-0-387-34817-9_20

66. Loenneke, J. P., Thiebaud, R. S., Abe, T., & Bemben, M. G. (2014). Blood flow restriction pressure recommendations : The hormesis hypothesis. *Medical Hypotheses*, *82*(5), 623-626. https://doi.org/10.1016/j.mehy.2014.02.023
67. Loenneke, Jeremy P., Thiebaud, R. S., Fahs, C. A., & Rossow, L. M. (2012). Blood flow-restricted resistance exercise : Rapidly affecting the myofibre and the myonuclei. *The Journal of Physiology*, *590*(21), 5271-5271. https://doi.org/10.1113/jphysiol.2012.242859
68. Lundby, C., Calbet, J. A. L., & Robach, P. (2009). The response of human skeletal muscle tissue to hypoxia. *Cellular and Molecular Life Sciences*, *66*(22), 3615-3623. https://doi.org/10.1007/s00018-009-0146-8
69. Manimmanakorn, A., Hamlin, M. J., Ross, J. J., Taylor, R., & Manimmanakorn, N. (2013). Effects of low-load resistance training combined with blood flow restriction or hypoxia on muscle function and performance in netball athletes. *Journal of Science and Medicine in Sport*, *16*(4), 337-342. https://doi.org/10.1016/j.jsams.2012.08.009
70. Maxwell, P. H. (2005). Hypoxia-inducible factor as a physiological regulator : Hypoxia-inducible factor. *Experimental Physiology*, *90*(6), 791-797. https://doi.org/10.1113/expphysiol.2005.030924
71. McDonough, P., Behnke, B. J., Padilla, D. J., Musch, T. I., & Poole, D. C. (2005). Control of microvascular oxygen pressures in rat muscles comprised of different fibre types : Microvascular oxygen pressures and fibre type. *The Journal of Physiology*, *563*(3), 903-913. https://doi.org/10.1113/jphysiol.2004.079533
72. Mendez-Villanueva, A., & Buchheit, M. (2013). Football-specific fitness testing : Adding value or confirming the evidence? *Journal of Sports Sciences*, *31*(13), 1503-1508. https://doi.org/10.1080/02640414.2013.823231
73. Millet, G., Girard, O., Beard, A., & Brocherie, F. (2019). Repeated Sprint Training in Hypoxia – An innovative method. *Deutsche Zeitschrift für Sportmedizin*, *2019*. https://doi.org/10.5960/dzsm.2019.374
74. Millet, G. P., Faiss, R., Brocherie, F., & Girard, O. (2013). Hypoxic training and team sports : A challenge to traditional methods? *British Journal of Sports Medicine*, *47*(Suppl 1), i6-i7. https://doi.org/10.1136/bjsports-2013-092793

75. Millet, G. P., Faiss, R., & Pialoux, V. (2013). Evidence for Differences Between Hypobaric and Normobaric Hypoxia Is Conclusive: *Exercise and Sport Sciences Reviews*, *41*(2), 133. https://doi.org/10.1097/JES.0b013e318271a5e1
76. Millet, G. P., & Girard, O. (2017). Editorial : High-Intensity Exercise in Hypoxia: Beneficial Aspects and Potential Drawbacks. *Frontiers in Physiology*, *8*, 1017. https://doi.org/10.3389/fphys.2017.01017
77. Millet, M. G., & Schmitt, M. L. (2011). *S'entraîner en altitude : Mécanismes, méthodes, exemples, conseils pratiques*. De Boeck Supérieur.
78. Montero, D., & Lundby, C. (2017). No Improved Performance With Repeated-Sprint Training in Hypoxia Versus Normoxia : A Double-Blind and Crossover Study. *International Journal of Sports Physiology and Performance*, *12*(2), 161-167. https://doi.org/10.1123/ijspp.2015-0691
79. Mortensen, S. P., Damsgaard, R., Dawson, E. A., Secher, N. H., & González-Alonso, J. (2008). Restrictions in systemic and locomotor skeletal muscle perfusion, oxygen supply and V_{O2} during high-intensity whole-body exercise in humans : Metabolic demand and muscle perfusion. *The Journal of Physiology*, *586*(10), 2621-2635. https://doi.org/10.1113/jphysiol.2007.149401
80. Mujika, I., & Padilla, S. (2003). Scientific bases for precompetition tapering strategies. *Medicine and Science in Sports and Exercise*, *35*(7), 1182-1187. https://doi.org/10.1249/01.MSS.0000074448.73931.11
81. Murphy, M. P. (2009). How mitochondria produce reactive oxygen species. *Biochemical Journal*, *417*(1), 1-13. https://doi.org/10.1042/BJ20081386
82. Nielsen, J. L., Frandsen, U., Jensen, K. Y., Prokhorova, T. A., Dalgaard, L. B., Bech, R. D., Nygaard, T., Suetta, C., & Aagaard, P. (2020). Skeletal Muscle Microvascular Changes in Response to Short-Term Blood Flow Restricted Training—Exercise-Induced Adaptations and Signs of Perivascular Stress. *Frontiers in Physiology*, *11*. https://doi.org/10.3389/fphys.2020.00556
83. Ogasawara, R., Loenneke, J. P., Thiebaud, R. S., & Abe, T. (2013). Low-Load Bench Press Training to Fatigue Results in Muscle Hypertrophy Similar to High-Load Bench Press Training. *International Journal of Clinical Medicine*, *04*(02), 114. https://doi.org/10.4236/ijcm.2013.42022
84. Oriishi, M., Matsubayashi, T., Kawahara, T., & Suzuki, Y. (2018). Short-Term Hypoxic Exposure and Training Improve Maximal Anaerobic Running Test Performance. *The Journal of Strength & Conditioning Research*, *32*(1), 181-188.

https://doi.org/10.1519/JSC.0000000000001791

85. Ozaki, H., Abe, T., Mikesky, A. E., Sakamoto, A., Machida, S., & Naito, H. (2015). Physiological stimuli necessary for muscle hypertrophy. *The Journal of Physical Fitness and Sports Medicine*, *4*(1), 43-51. https://doi.org/10.7600/jpfsm.4.43
86. Ozaki, H., Miyachi, M., Nakajima, T., & Abe, T. (2011). Effects of 10 Weeks Walk Training With Leg Blood Flow Reduction on Carotid Arterial Compliance and Muscle Size in the Elderly Adults. *Angiology*, *62*(1), 81-86. https://doi.org/10.1177/0003319710375942
87. Ozaki, H., Sakamaki, M., Yasuda, T., Fujita, S., Ogasawara, R., Sugaya, M., Nakajima, T., & Abe, T. (2011). Increases in thigh muscle volume and strength by walk training with leg blood flow reduction in older participants. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *66*(3), 257-263. https://doi.org/10.1093/gerona/glq182
88. Park, S., Kim, J. K., Choi, H. M., Kim, H. G., Beekley, M. D., & Nho, H. (2010). Increase in maximal oxygen uptake following 2-week walk training with blood flow occlusion in athletes. *European Journal of Applied Physiology*, *109*(4), 591-600. https://doi.org/10.1007/s00421-010-1377-y
89. Pearson, S. J., & Hussain, S. R. (2015). A Review on the Mechanisms of Blood-Flow Restriction Resistance Training-Induced Muscle Hypertrophy. *Sports Medicine*, *45*(2), 187-200. https://doi.org/10.1007/s40279-014-0264-9
90. Progression Models in Resistance Training for Healthy Adults: (2002). *Medicine and Science in Sports and Exercise*, *34*(2), 364-380. https://doi.org/10.1097/00005768-200202000-00027
91. Puype, J., Van Proeyen, K., Raymackers, J.-M., Deldicque, L., & Hespel, P. (2013). Sprint Interval Training in Hypoxia Stimulates Glycolytic Enzyme Activity: *Medicine & Science in Sports & Exercise*, *45*(11), 2166-2174. https://doi.org/10.1249/MSS.0b013e31829734ae
92. Rakobowchuk, M., Tanguay, S., Burgomaster, K. A., Howarth, K. R., Gibala, M. J., & MacDonald, M. J. (2008). Sprint interval and traditional endurance training induce similar improvements in peripheral arterial stiffness and flow-mediated dilation in healthy humans. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *295*(1), R236-R242. https://doi.org/10.1152/ajpregu.00069.2008
93. Reis, J. F., Fatela, P., Mendonca, G. V., Vaz, J. R., Valamatos, M. J., Infante, J., Mil-

Homens, P., & Alves, F. B. (2019). Tissue Oxygenation in Response to Different Relative Levels of Blood-Flow Restricted Exercise. *Frontiers in Physiology*, *10*, 407. https://doi.org/10.3389/fphys.2019.00407

94. Ross, A., Leveritt, M., & Riek, S. (2001). Neural Influences on Sprint Running : Training Adaptations and Acute Responses. *Sports Medicine*, *31*(6), 409-425. https://doi.org/10.2165/00007256-200131060-00002
95. Sasaki, R., Masuda, S., & Nagao, M. (2000). Erythropoietin : Multiple physiological functions and regulation of biosynthesis. *Bioscience, Biotechnology, and Biochemistry*, *64*(9), 1775-1793. https://doi.org/10.1271/bbb.64.1775
96. Sato, Y. (2005). The history and future of KAATSU Training. *International Journal of KAATSU Training Research*, *1*(1), 1-5. https://doi.org/10.3806/ijktr.1.1
97. Schoenfeld, B. J., Ogborn, D., & Krieger, J. W. (2016). Effects of Resistance Training Frequency on Measures of Muscle Hypertrophy : A Systematic Review and Meta-Analysis. *Sports Medicine*, *46*(11), 1689-1697. https://doi.org/10.1007/s40279-016-0543-8
98. Schoenfeld, B. J., Peterson, M. D., Ogborn, D., Contreras, B., & Sonmez, G. T. (2015). Effects of Low- vs. High-Load Resistance Training on Muscle Strength and Hypertrophy in Well-Trained Men: *Journal of Strength and Conditioning Research*, *29*(10), 2954-2963. https://doi.org/10.1519/JSC.0000000000000958
99. Schumacker, P. T., & Cain, S. M. (1987). The concept of a critical oxygen delivery. *Intensive Care Medicine*, *13*(4), 223-229. https://doi.org/10.1007/BF00265110
100. Scott, B. R., Slattery, K. M., Sculley, D. V., & Dascombe, B. J. (2014). Hypoxia and Resistance Exercise : A Comparison of Localized and Systemic Methods. *Sports Medicine*, *44*(8), 1037-1054. https://doi.org/10.1007/s40279-014-0177-7
101. Semenza, G. L. (2007). Hypoxia-Inducible Factor 1 (HIF-1) Pathway. *Science's STKE*, *2007*(407), cm8-cm8. https://doi.org/10.1126/stke.4072007cm8
102. Shepherd, A., Granger, H., Smith, E., & Guyton, A. (1973). Local control of tissue oxygen delivery and its contribution to the regulation of cardiac output. *American Journal of Physiology-Legacy Content*, *225*(3), 747-755. https://doi.org/10.1152/ajplegacy.1973.225.3.747
103. Smith, K. J., & Billaut, F. (2010). Influence of cerebral and muscle oxygenation on repeated-sprint ability. *European Journal of Applied Physiology*, *109*(5), 989-999. https://doi.org/10.1007/s00421-010-1444-4

104. Smith, K. J., & Billaut, F. (2012). Tissue Oxygenation in Men and Women During Repeated-Sprint Exercise. *International Journal of Sports Physiology and Performance*, *7*(1), 59-67. https://doi.org/10.1123/ijspp.7.1.59

105. Smyth, A. L. (2019). *John Dalton, 1766–1844 : A Bibliography of Works By and About Him*. Routledge.

106. Spriet, L. L., Lindinger, M. I., McKelvie, R. S., Heigenhauser, G. J., & Jones, N. L. (1989). Muscle glycogenolysis and H+ concentration during maximal intermittent cycling. *Journal of Applied Physiology*, *66*(1), 8-13. https://doi.org/10.1152/jappl.1989.66.1.8

107. Suga, T., Okita, K., Takada, S., Omokawa, M., Kadoguchi, T., Yokota, T., Hirabayashi, K., Takahashi, M., Morita, N., Horiuchi, M., Kinugawa, S., & Tsutsui, H. (2012). Effect of multiple set on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *European Journal of Applied Physiology*, *112*(11), 3915-3920. https://doi.org/10.1007/s00421-012-2377-x

108. Sundberg, C. J. (1994). Exercise and training during graded leg ischaemia in healthy man with special reference to effects on skeletal muscle. *Acta Physiologica Scandinavica. Supplementum*, *615*, 1-50.

109. Takarada, Y., Takazawa, H., Sato, Y., Takebayashi, S., Tanaka, Y., & Ishii, N. (2000). Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *Journal of Applied Physiology*, *88*(6), 2097-2106. https://doi.org/10.1152/jappl.2000.88.6.2097

110. Takarada, Y., Tsuruta, T., & Ishii, N. (2004). Cooperative Effects of Exercise and Occlusive Stimuli on Muscular Function in Low-Intensity Resistance Exercise with Moderate Vascular Occlusion. *The Japanese Journal of Physiology*, *54*(6), 585-592. https://doi.org/10.2170/jjphysiol.54.585

111. Takei, N., Kakinoki, K., Girard, O., & Hatta, H. (2020). Short-Term Repeated Wingate Training in Hypoxia and Normoxia in Sprinters. *Frontiers in Sports and Active Living*, *2*. https://doi.org/10.3389/fspor.2020.00043

112. Tanimoto, M., Madarame, H., & Ishii, N. (2005). Muscle oxygenation and plasma growth hormone concentration during and after resistance exercise : Comparison between "KAATSU" and other types of regimen. *International Journal of KAATSU Training Research*, *1*(2), 51-56. https://doi.org/10.3806/ijktr.1.51

113. Taylor, C. T., Doherty, G., Fallon, P. G., & Cummins, E. P. (2016). Hypoxia-dependent regulation of inflammatory pathways in immune cells. *The Journal of*

Clinical Investigation, *126*(10), 3716-3724. https://doi.org/10.1172/JCI84433

114. Teixeira, E., Barroso, R., Silva-Batista, C., Laurentino, G., Loenneke, J., Roschel, H., Ugrinowitsch, C., & Tricoli, V. (2017). Blood Flow Restriction Increases Metabolic Stress But Decreases Muscle Activation During High-Load Resistance Exercise : Blood flow restriction training. *Muscle & Nerve*, *57*. https://doi.org/10.1002/mus.25616

115. Tinken, T. M., Thijssen, D. H. J., Hopkins, N., Black, M. A., Dawson, E. A., Minson, C. T., Newcomer, S. C., Laughlin, M. H., Cable, N. T., & Green, D. J. (2009). Impact of Shear Rate Modulation on Vascular Function in Humans. *Hypertension*, *54*(2), 278-285. https://doi.org/10.1161/HYPERTENSIONAHA.109.134361

116. Van Beekvelt, M. C., Colier, W. N., Wevers, R. A., & Van Engelen, B. G. (2001). Performance of near-infrared spectroscopy in measuring local O(2) consumption and blood flow in skeletal muscle. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *90*(2), 511-519. https://doi.org/10.1152/jappl.2001.90.2.511

117. Wang, G. L., Jiang, B. H., Rue, E. A., & Semenza, G. L. (1995). Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. *Proceedings of the National Academy of Sciences of the United States of America*, *92*(12), 5510-5514.

118. Wang, R., Fukuda, D. H., Hoffman, J. R., La Monica, M. B., Starling, T. M., Stout, J. R., Kang, J., & Hu, Y. (2019). Distinct Effects of Repeated-Sprint Training in Normobaric Hypoxia and β-Alanine Supplementation. *Journal of the American College of Nutrition*, *38*(2), 149-161. https://doi.org/10.1080/07315724.2018.1475269

119. Wernbom, M., Augustsson, J., & Raastad, T. (2008). Ischemic strength training : A low-load alternative to heavy resistance exercise?: Ischemic strength training. *Scandinavian Journal of Medicine & Science in Sports*, *18*(4), 401-416. https://doi.org/10.1111/j.1600-0838.2008.00788.x

120. Willis, S. J., Alvarez, L., Borrani, F., & Millet, G. P. (2018). Oxygenation time course and neuromuscular fatigue during repeated cycling sprints with bilateral blood flow restriction. *Physiological Reports*, *6*(19), e13872. https://doi.org/10.14814/phy2.13872

121. Willis, S. J., Peyrard, A., Rupp, T., Borrani, F., & Millet, G. P. (2019). Vascular and oxygenation responses of local ischemia and systemic hypoxia during arm cycling repeated sprints. *Journal of Science and Medicine in Sport*, *22*(10), 1151-1156. https://doi.org/10.1016/j.jsams.2019.05.001

122. Yasuda, T., Ogasawara, R., Sakamaki, M., Ozaki, H., Sato, Y., & Abe, T. (2011). Combined effects of low-intensity blood flow restriction training and high-intensity resistance training on muscle strength and size. *European Journal of Applied Physiology*, *111*(10), 2525-2533. https://doi.org/10.1007/s00421-011-1873-8

7. Appendix

7.1 Food questionnaire

Questionnaire alimentaire :

ID : _____

Date : _____

Veuillez compléter le type de nourriture / boisson, le style de préparation et la quantité spécifique.

Qu'avez-vous mangé dans les 24 heures (1 jour) *précédant la première visite de test* (échantillon de sang et microbiopsies musculaires avec sprints répétés) ?

	Quelle nourriture /boisson ?	Quelle quantité ? Soyez précis s'il vous plait (poids, nombre, etc.)	Préparation spécifique (bouillir, frire, cuire / huile, épices, etc.)
Petit déjeuner			
Déjeuner			
Dîner			
Encas / Goûters			

Qu'avez-vous mangé après cette visite (1 jour) et avant la prochaine réunion (2 jour - 24 heures après la biopsie) ?

	Quelle nourriture /boisson ?	Quelle quantité ? Soyez précis s'il vous plait (poids, nombre, etc.)	Préparation spécifique (bouillir, frire, cuire / huile, épices, etc.)
Petit déjeuner			
Déjeuner			

Dîner			
Encas / Goûters			

7.2 PAR-Q questionnaire

Physical Activity Readiness
Questionnaire - PAR-Q
(revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT _____ WITNESS _____
or GUARDIAN (for participants under the age of majority)

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

CSEP | SCPE THE GOLD STANDARD IN EXERCISE SCIENCE AND PERSONAL TRAINING

7.3 Information for participants

Recrutement de volontaires pour la prochaine étude de recherche

UNIVERSITÉ DE LAUSANNE

Faculté de biologie et de médecine
Institut des Sciences du Sport (ISSUL)

Titre:
Adaptation à l'entraînement de sprints répétés avec hypoxie systémique (altitude) et / ou hypoxie localisée (ischémie)

Investigateurs: Professeurs Grégoire Millet et Bengt Kayser, Dr Fabio Borrani, Doctorante : Sarah Willis - Université de Lausanne

Participants recherchés pour étude scientifique

Pour cette étude de recherche scientifique, nous cherchons à recruter des hommes en bonne santé et de 18 à 40 ans. Les participants doivent s'entraîner au moins trois fois par semaine dans des activités d'endurance sollicitant les jambes (cyclisme, course à pied, aviron, ski, patinage, etc.) avec des exercices à intensité maximale. En outre, ils n'ont eu aucune blessure squelettique ou musculaire au cours des 3 derniers mois, douleur ou autre problème de santé pouvant influer sur les résultats de l'étude. Plus précisément, pas de problèmes de coagulation sanguine, pas de consommation d'aspirine ni d'anticoagulants, ni d'allergie à la xylocaïne. Les participants doivent pouvoir se rendre au laboratoire 15 fois en 60 mois environ, au cours d'une période d'environ 2 mois.

Le but de l'étude: L'objectif est d'évaluer les adaptations physiologiques et biologiques à un entraînement de sprints répétés de 3 semaines avec restriction du flux sanguin et / ou hypoxie systémique: 1) adaptation musculaire (voies d'expression et de signalisation des gènes), 2) performances aérobies, 3) performances anaérobies (sprints répétés).

Programme et durée de l'étude: Cette étude comportera 15 visites (3 pré-tests, 9 entraînements, 3 post-tests) au laboratoire sur une période d'environ 2 mois au Centre Sport et Santé (CSS) de l'Université de Lausanne. Chaque session durera environ 60 minutes. Par conséquent, l'engagement de temps total sera d'environ 15 heures. Les 3 essais pré et post-tests incluront (Visite 1-2, microbiopsies du muscles et prise de sang et test de performance; Visite 3, tests de performance). Les tests de performance incluront des mesures de consommation d'oxygène, d'oxygénation, de débit sanguin et de lactate sanguin. Les visites d'entraînement incluront une exposition à une occlusion partielle et / ou à des conditions hypoxiques. Les risques pour les participants sont mineurs, bien que cette étude inclut des mesures de microbiopsies musculaires et des prélèvements sanguins effectués par une infirmière et un médecin. Les complications des microbiopsies musculaires (principalement l'hématome et le risque d'infection) sont limitées par la technique utilisée. De plus, les participants auront des micro-prélèvements de sang capillaire au lobe de l'oreille pour mesurer la concentration sanguine en lactate.

Remuneration (frais de déplacement compris): 300 CHF pour la participation à l'étude d'entraînement incluant les microbiopsies musculaires.

Toutes les données seront traitées **confidentiellement**. Les participants **ne doivent s'attendre à aucun avantage médical.**

Si vous **souhaitez participer** à l'étude et pensez remplir les critères ci-dessus, veuillez **contacter** Sarah Willis, Université de Lausanne, sarah.willis@unil.ch, tel no. +41 (0) 78 875 60 15. Pour plus d'informations, vous pouvez également contacter gregoire.millet@unil.ch.

Veuillez noter que **vos coordonnées seront enregistrées** si vous parlez à Sarah Willis au téléphone et par courrier électronique. Si vous décidez que vous ne souhaitez pas participer à l'étude, vos coordonnées seront immédiatement supprimées.

7.4 Detailed study informations for participants

Répétition de sprints avec hypoxie systémique vs. localisée (ischémie)

Ce projet est organisé par : Prof Grégoire Millet, Prof Bengt Kayser, Dr Fabio Borrani, et Sarah Willis, Institut des Sciences du Sport de l'Université de Lausanne (ISSUL)

Madame, Monsieur,

Nous vous proposons de participer à notre projet de recherche. Cette feuille d'information décrit le projet de recherche,

Information détaillée

1. Objectifs du projet de recherche

L'objectif principal de cette recherche est d'évaluer les adaptations moléculaires correspondant à l'effet hypertrophique (ischémie) par rapport aux réponses vasodilatatrices (altitude simulée) en effectuant des analyses transcriptionnelles et en évaluant les réponses hémodynamiques avec oxygénation musculaire par spectroscopie et flux sanguin local par ultrason Doppler. En outre, évaluer les effets de ces méthodes d'entraînement sur l'hypoxie locale (ischémie) et systémique (altitude) sur la performance fonctionnelle.

2. Sélection des personnes pouvant participer au projet

Nous recruterons entre 33 et 36 hommes en bonne santé (actifs de manière récréative) et bien entraînés (âgés de 18 à 40 ans) qui pratiquent régulièrement des exercices de haute intensité, idéalement avec un entraînement général de plus de 5 heures par semaine, donc habitués au type de travail requis.
Les participants pourront se rendre au laboratoire pour 15 visites, chacune d'une heure environ, sur une période d'environ 2 mois. Seuls les participants en bonne santé physique et mentale seront inclus. Aucune présence de maladie ou de fumeurs, etc. ne sera autorisée. Les participants n'auront subi aucune blessure au niveau du squelette ou des muscles au cours des 3 derniers mois, ni douleur ni autre problème de santé pouvant influer sur les résultats de l'étude. Plus précisément, pas de problèmes de coagulation sanguine, pas de consommation d'aspirine ni d'anticoagulants, ni d'allergie à la xylocaïne. Les participants seront en mesure de communiquer avec les expérimentateurs et auront la possibilité de donner leur consentement.

3. Informations générales sur le projet

Cette étude en simple aveugle se déroulera en 15 visites, chacune d'environ 60 minutes, sur une période d'environ 2 mois. Il y aura 3 sessions de pré-test, suivies de 3 semaines d'entrainement (3 séances par semaine), et à nouveau de 3 sessions de post-test une fois le cycle d'entrainement terminé (voir Figure 1 ci-dessous). Les séances d'entraînement de sprints répétés cyclistes sur les jambes comprendront un échauffement de 10 minutes, suivi de 6 séries de sprints de 6 secondes et d'une récupération de 24 secondes. Chaque sprint sera effectué au maximum, aussi vite et fort que possible avec une récupération active très facile (20 W). Entre chaque série de 6 sprints, il y aura environ 5 minutes de récupération avec une résistance plus faible (1,5 W/kg). Après la dernière série, il y aura une récupération active (voir Figure 2 ci-dessous).
Les participants seront jumelés (en fonction des caractéristiques physiques et des performances des pré-tests) avec l'un des 3 groupes suivants.
GROUPES
- RSN, entraînement de sprints répétés en normoxie, contrôle (n = 11-12 +)
- RSO, entraînement de sprints répétés avec 45% d'occlusion en normoxie (n = 11-12 +)

- RSH, entraînement de sprints répétés sans occlusion dans une altitude simulée de 3800 m (n = 11-12 +)

Tous les tests et toutes les formations seront effectués dans les laboratoires de recherche de l'ISSUL, du Centre Sport et Santé et Synathlon de l'Université de Lausanne. Nous effectuons ce projet dans le respect des prescriptions de la législation suisse. La commission cantonale d'éthique compétente a contrôlé et autorisé le projet.

4. Déroulement pour les participants

Le projet se déroulera sur une période d'environ 9 semaines. Le recrutement commencera dès que le projet aura été approuvé. Chaque participant viendra au laboratoire pour un total de 15 sessions d'environ 60 min +/-.

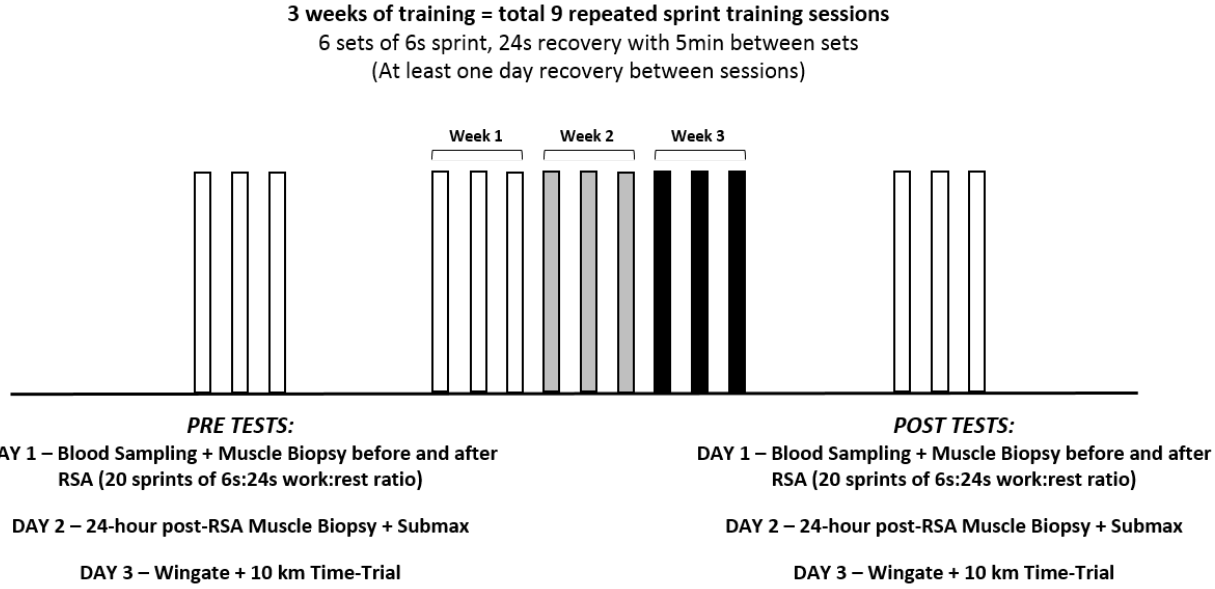

Figure 1. Protocole général d'étude d'entraînement avec trois jours de pré-test et de post-test et une période d'entraînement de trois semaines avec trois séances d'entraînement de sprint répétées chaque semaine.

Les sujets éviteront une altitude supérieure à 1000 m au cours des deux semaines précédant l'expérience, ainsi que toute activité physique intense au cours des 24 heures précédant les tests. Les participants seront invités à prendre un repas léger au moins 2 heures avant le début des tests (jours 1 et 2 du test préalable) et à rester à jeun le jour 3. Seule de l'eau est consommée dans les 2 heures précédant le test et pendant le test. En outre, un questionnaire alimentaire sera utilisé pour vérifier le régime le jour précédant chaque test, puis les sujets reproduiront leur régime au cours du post-test. Les sujets ne réaliseront pas plus de deux sessions de test par semaine. Les sujets effectueront des tests avec au moins 72 heures pour la récupération. Pour la phase de formation de 3 semaines, les sujets doivent avoir au moins 48 heures entre les sessions de formation pour permettre une récupération adéquate (par exemple, les sessions de formation doivent avoir un jour entre les sessions, par exemple, lundi-mercredi- vendredi). Il sera demandé aux sujets de ne pas effectuer d'entraînement intense en dehors de cette expérience. Tous les tests et toutes les formations seront effectués dans les laboratoires de recherche de l'ISSUL, du Centre Sport et Santé et Synathlon de l'Université de Lausanne.

Procédures de pré-test

- Jour 1 - Capacité de sprints répétés (RSA) avec prélèvement de sang et microbiopsies musculaires avant et après la RSA

Après avoir rempli et vérifié les questionnaires de consentement et de santé, les sujets s'allongeront sur un lit. Les sujets se verront remettre le questionnaire alimentaire pendant la première journée et disposeront du temps nécessaire pour compléter le premier questionnaire "Qu'avez-vous mangé dans les 24 heures (1 jour) précédé de la première visite de test (échantillon de sang et microbiopsies musculaires avec sprints répétés)?". Ils emporteront le deuxième questionnaire chez eux pour le compléter et le renvoyer le deuxième jour " Qu'avez-vous mangé après cette visite (1 jour) et avant la prochaine réunion (2 jour - 24 heures après la biopsie)?". Après 10 minutes de repos, un échantillon de sang sera prélevé puis une série de microbiopsies (voir la procédure ci-dessous). Les sujets passeront ensuite à un ergomètre de chaise sur mesure doté d'une retenue de la jambe avec un angle de 90 ° fixé pour le genou afin d'effectuer 2 contractions volontaires maximales de 5 secondes afin de déterminer la force isométrique (extenseur) du genou. Après cela, les sujets effectueront une contraction maximale unique de 5 secondes avec une seule stimulation du nerf fémoral (1 ms) pendant et immédiatement après (simple et double stimulation, 1 ms chacun) de la contraction. L'intensité de la stimulation sera déterminée par une progression progressive avant les contractions. Les participants prendront ensuite position sur un ergomètre à cycle de freinage électronique où les dimensions seront enregistrées et répliquées lors de sessions ultérieures. Les sujets commenceront à effectuer un stade sous-maximal de 6 minutes à 1,5 W / kg sans occlusion avec une évaluation du flux sanguin au cours de l'exercice, et après une récupération de 5 minutes, un autre stade sous-maximal de 6 minutes identique cette fois avec 45% de la pression d'élimination des impulsions les membres proximaux avec mesurer le flux sanguin pendant l'exercice. Après une récupération supplémentaire de 5 minutes et des sprints d'échauffement de 2 x 6 secondes pour se familiariser et s'échauffer, les sujets effectueront un test de capacité de sprint répété (RSA) de sprint de 20 x 6 s, de récupération de 24 s ou jusqu'à épuisement ou échec de la tâche (cadence <70 rpm).

- Jour 2 - Biopsie 24 heures après RSA et exercice submaximal

Les sujets commenceront comme au jour 1 avec 10 minutes de repos. Ensuite, un ensemble de microbiopsies similaires au jour 1 aura lieu pour collecter un échantillon 24 heures après le RSA (procédures ci-dessous). Environ 10 minutes plus tard, la pression maximale d'occlusion sera mesurée pendant le repos assis en gonflant progressivement le brassard jusqu'à ce que le flux sanguin artériel ne soit plus détecté par échographie Doppler de l'artère fémorale et soit mesuré deux ou trois fois avec précision, en environ deux minutes. entre essais (21).

- Jour 3 Wingate + test TT ~10 km

La masse corporelle et le pourcentage de graisse corporelle, à l'aide d'une évaluation du pli cutané sur sept sites, conformément aux directives ACSM de 2010 (20). Les sujets effectueront un seul test Wingate (WT) sur un ergomètre pour cycliste de jambe. Pour le WT, l'ergomètre sera réglé sur un mode isocinétique avec une cadence fixe. Avant le début de la semaine de travail, un échauffement de 5 minutes sera effectué à 1,5 W / kg de poids corporel.

La récupération passive de 30 minutes sera normalisée entre le WT et le 10 km TT. Après un réchauffement similaire de 5 minutes, les sujets effectueront aussi rapidement que possible un TT de 10 km. Les sujets peuvent choisir leur cadence pour les tests et la même cadence sera utilisée pendant le "contre-la-montre" dans les pré-tests et les post-tests. Pendant les tests WT et TT, les mesures de puissance, de cadence, de consommation d'oxygène, de spectroscopie dans le proche infrarouge, de saturation en oxygène, de fréquence cardiaque, d'évaluation de l'effort perçu (RPE) tous les 1 km et de 1 minute de lactate sanguin post-test sont obtenues.

Séance d'entrainement (voir la figure 2 ci-dessous)

Les séances d'entraînement des sprints répétés cyclistes sur les jambes comprendront un échauffement de 10 minutes, suivi de 6 séries de sprints de 6 secondes et d'une récupération de 24 secondes. Chaque sprint sera effectué au maximum, aussi vite et fort que possible avec une récupération active très facile (20 W). Entre chaque série de 6 sprints, il y aura environ 5 minutes de récupération du cycle actif avec une résistance plus faible (1,5 W/kg). Après le dernier set, une période de retour au calme permettra une récupération adéquate. Toutes les séances d'entraînement seront contrôlées et surveillées par les expérimentateurs avec enregistrement de la fréquence cardiaque, de la saturation en oxygène, de la puissance et de la perception de l'échelle de récupération (RPE). En outre, une session par semaine sera surveillée en ce qui concerne la puissance mécanique, le NIRS, la saturation en oxygène du pouls et la fréquence cardiaque de chaque sujet.

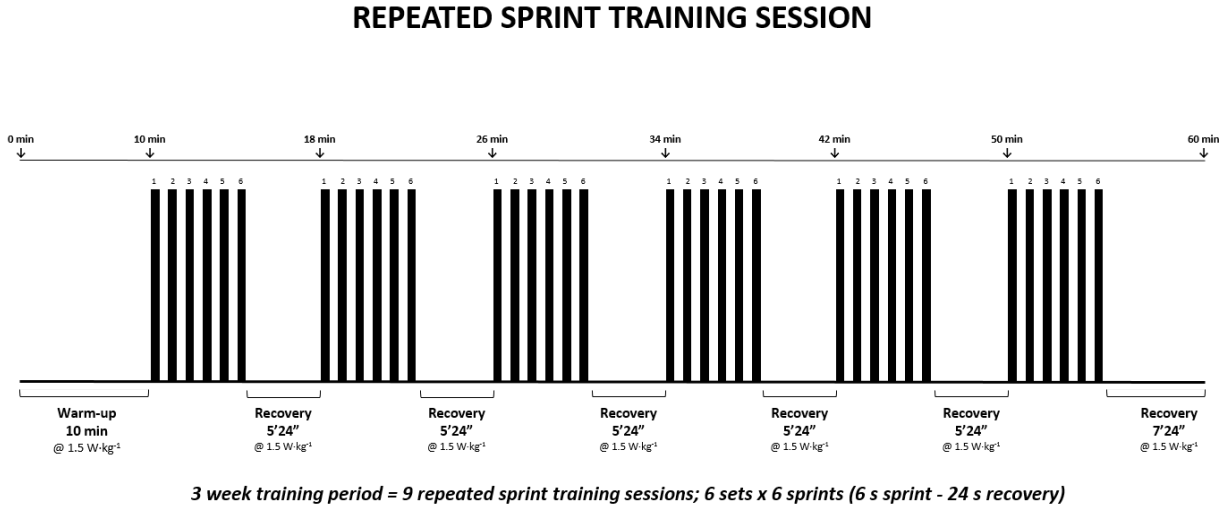

Figure 2. Séance d'entraînement au sprint répété illustrant le protocole avec échauffement suivi de 6 séries de sprints maximaux de 6 x 6 s, avec récupération active au bout de 24 s et 5 minutes de récupération entre les séries. La durée totale est de 60 minutes par session.

Procédures post-test
Les procédures seront les mêmes que pour les tests préalables, sauf que l'ordre du jour des tests est modifié. Le post-test commencera 72 heures après la dernière séance d'entraînement.
Le jour 1 comprend des prélèvements sanguins et des microbiopsies musculaires avant et après le test RSA, le jour 2 la seconde microbiopsie musculaire 24 heures après la RSA et le test d'effort submaximal et le jour 3 les tests WT et TT.

5. Bénéfices pour les participants

Le participant n'a pas de bénéfice direct de cette étude. Vous aurez aussi accès à vos données concernant les paramètres physiologiques mesurés lors de votre performance et un document synthétisant vos résultats obtenus vous sera remis à la fin de l'étude.

6. Droits des participants

Vous êtes libre d'accepter ou de refuser de participer au projet. Nous éviterons tout conflit d'intérêts potentiel concernant les méthodes de recrutement. Si vous choisissez de ne pas participer ou si vous choisissez de participer et revenez sur votre décision pendant le déroulement du projet, vous n'aurez pas à vous justifier. Vous pouvez à tout moment poser toutes les questions nécessaires au sujet de l'étude. Veuillez-vous adresser pour ce faire à la personne indiquée à la fin de la présente feuille d'information.

7. Obligations des participants

En tant que participant à cette étude, vous êtes tenu :

- De suivre les instructions de l'investigateur et de vous conformer au plan de l'étude ;
- D'informer précisément l'investigateur de la survenue d'éventuels effets indésirables ;
- D'informer l'investigateur de la prise des médicaments ; font également partie des médicaments toutes les préparations que vous avez achetées vous-même, qui sont disponibles sans ordonnance et/ou rattachées à une médecine alternative car la prise de médicament peut avoir une incidence sur les résultats de l'étude.

8. Risques

La participation à cette étude ne présente a priori pas de risques majeurs pour la santé. Bien qu'encore rare, la recherche sur la restriction de la circulation sanguine est prometteuse en ce qui concerne les conditions de sécurité. Les individus réagissent de la même façon à l'entraînement de restriction du flux sanguin et à l'exercice régulier (Loenneke et al., 2011). Une seconde étude (Clark et al., 2011) s'est intéressée aux risques potentiels liés à l'occlusion, cette dernière a mis en évidence qu'aucun effet indésirable n'a lieu lorsqu'un sujet fait face à des épisodes d'occlusion aigus ou chroniques.

Neurostimulation

La stimulation percutanée du nerf ne sera utilisée que pour des stimulations simples (secousse musculaire) ou doubles (doublets, fréquence 100 Hz) avec une largeur d'impulsion de 1 ms seulement pour limiter l'éventuel inconfort lié à la stimulation. De plus, l'intensité de stimulation sera déterminée après une augmentation très progressive de l'intensité. De plus, le type d'effort n'est pas dangereux et les méthodes de mesures utilisées (tests de force, stimulations électriques et magnétiques) sont non-invasives.

Prise de sang

La prise de sang est une mesure de routine dans notre laboratoire de physiologie de l'exercice et sera effectuée par du personnel qualifié et habitué aux prises d'échantillons sanguins. Les prises de sang ne présentent aucun risque. Seul inconvénient potentiel, l'apparition d'un léger hématome, qui se résorbe en quelques jours.

Microbiopsie musculaire

Les complications de la biopsie musculaire à l'aiguille sont limitées; sur 234 biopsies réalisées lors d'une précédente étude, aucune séquelle n'est apparue, à part 2 hématomes qui se sont résolus sans séquelles, et une perte de connaissance par réaction vagale (Magistris et al. 1998). Immédiatement après le prélèvement, quelques mouvements de flexion-extension du genou seront réalisés pour refermer les plans musculaires. Après la dernière biopsie de la session expérimentale, un pansement stérile est appliqué au site des prélèvements et le sujet reste allongé environ 30 min au repos avec une poche de glace placée sur le pansement (ce dernier est conservé pendant 24 heures). Cette technique a été utilisée récemment dans notre laboratoire, par le même médecin (Prof Bengt Kayser) qui sera sur place, et aucune complication n'avait été notée.

Les risques de blessures sont minimisés. Tous les exercices vous seront démontrés et expliqués par une personne expérimentée. Ces exercices seront effectués par vous afin d'instaurer une technique d'exécution correcte des mouvements, et minimiser ainsi les risques possibles.

9. Découvertes pendant le projet

La direction du projet vous avisera pendant l'étude de toute nouvelle découverte susceptible d'influer sur les bénéfices de l'étude ou votre sécurité, et donc sur votre consentement à y participer. Si vous ne souhaitez pas être informé, merci de l'indiquer à la direction du projet.

10. Confidentialité des données

Pour les besoins de l'étude, nous enregistrerons vos données personnelles et médicales. Seul un nombre limité de personnes peut consulter vos données sous une forme non codée, et exclusivement afin de pouvoir accomplir des tâches nécessaires au déroulement du projet. Dans le cas d'une publication, les données agrégées ne vous sont donc pas imputables en tant que personne. Votre nom n'apparaîtra jamais sur Internet ou dans une publication. Parfois, les journaux scientifiques exigent la transmission de données individuelles (données brutes). Si des données individuelles doivent être transmises, elles sont toujours codées et ne permettent donc pas de vous identifier en tant que personne. Toutes les personnes impliquées dans l'étude de quelque manière que ce soit sont tenues au secret professionnel. Toutes les directives relatives à la protection des données sont respectées et vous avez à tout moment le droit de consulter vos données.

Durant son déroulement, le projet peut faire l'objet d'inspections. Celles-ci peuvent être effectuées par la commission d'éthique qui s'est chargée de son contrôle initial et l'a autorisé, mais aussi être mandatées par l'organisme qui l'a initié. Il se peut que la direction du projet doive communiquer vos données personnelles pour les besoins de ces inspections. Toutes les personnes impliquées sont tenues au secret professionnel. Nous garantissons le respect de toutes les directives de la protection des données et ne ferons apparaître votre nom dans aucun rapport ou publication, imprimé ou en ligne.

11. Retrait du projet

Vous pouvez à tout moment vous retirer de l'étude si vous le souhaitez. Les données et le matériel biologique (échantillons de sang, tissus, etc.) recueillis jusque-là seront tout de même analysés, ceci afin de ne pas compromettre la valeur de l'étude dans son ensemble. Dans ce cas, il est impossible de rendre vos données et votre matériel biologique anonymes, c.-à-d. que vos données et votre matériel biologique resteront codées. Vous devez donc être d'accord avec cela avant de donner votre consentement. En cas de retrait d'un participant, les données ne seront incluses pour les résultats que si elles sont complètes pour les variables. Si les données sont incomplètes, l'analyse se poursuivra avec un participant de moins. Si les données sont manquantes, l'analyse visera à remplacer les valeurs par une valeur attendue basée sur l'ensemble de données. Si les données et les échantillons sont utilisés dans l'étude, ils seront anonymisés après analyse.

Rémunération des participants

Les sujets participant à cette étude bénéficient d'un dédommagement (incl. frais de voyage) de Fr 300.- ; par ailleurs ils profitent de plusieurs tests de capacité et de conseils d'entraînement personnalisés gratuits. Votre participation n'aura aucune conséquence financière pour vous ou votre assurance maladie.

12 Réparation des dommages subis

Les dommages de santé que vous pourriez subir du fait de cette étude relèvent de la responsabilité de l'Université de Lausanne qui l'a initiée et est en charge de sa réalisation. Les conditions et la procédure sont fixées par la loi. Si vous avez subi un dommage, veuillez-vous adresser à la direction du projet (Grégoire Millet et Sarah Willis).

13 Financement du projet

Aucun fond n'a été demandé pour cette étude. Le professeur Millet dispose des fonds suffisants pour cette étude et sera responsable du paiement des coûts associés à cette expérience.

14 Interlocuteur(s)

En cas de doute, de craintes ou d'urgences pendant ou après l'étude, vous pouvez vous adresser à tout moment à l'un des interlocuteurs suivants :

Grégoire Millet (PhD)
(Professeur associé)
Institut des Sciences du Sport de l'Université de Lausanne (ISSUL)
Université de Lausanne
Bâtiment Synathlon – Bureau 3114
CH – 1015 Lausanne
Tél. : +41 (0) 21 692 32 94
E-Mail : gregoire.millet@unil.ch

Sarah Willis (MSc)
(Assistante diplômée)
Institut des Sciences du Sport de l'Université de Lausanne (ISSUL)
Université de Lausanne
Bâtiment Synathlon – Bureau 2406
CH – 1015 Lausanne
Tél. : +41 (0) 78 875 60 15
E-Mail: sarah.willis@unil.ch

7.5 Consent form for participants

Déclaration de consentement

Déclaration de consentement écrite pour la participation à un projet de recherche

- Veuillez lire attentivement ce formulaire.
- N'hésitez pas à poser des questions lorsque vous ne comprenez pas quelque chose ou que vous souhaitez avoir des précisions.

Numéro BASEC du projet : (après soumission à la commission d'éthique compétente) :	
Titre de l'étude : (titre scientifique et titre usuel)	Adaptation à l'entraînement sprint répété avec hypoxie systémique (hypoxie) et / ou localisée (ischémie)
Institution responsable : (adresse complète) :	Institut des Sciences du Sport de l'Université de Lausanne (ISSUL) Université de Lausanne
Lieu de réalisation du projet :	Laboratoire de l'Université de Lausanne (ISSUL)
Directeur / directrice du projet sur le site : (nom et prénom en caractères d'imprimerie) :	GRÉGOIRE MILLET
Participant / participante : (nom et prénom en caractères d'imprimerie) : Date de naissance :	

- Je déclare avoir été informé, par l'investigateur, oralement et par écrit, des objectifs et du déroulement du projet ainsi que des effets présumés, des avantages, des inconvénients possibles et des risques éventuels.
- Je prends part à cette étude de façon volontaire et j'accepte le contenu de la feuille d'information qui m'a été remise sur le projet précité. J'ai eu suffisamment de temps pour prendre ma décision.
- J'ai reçu des réponses satisfaisantes aux questions que j'ai posées en relation avec ma participation au projet. Je conserve la feuille d'information et reçois une copie de ma déclaration de consentement écrite.
- J'accepte que les spécialistes compétents de l'institution, du mandataire du projet, de la Commission d'éthique compétente pour cette étude, puissent consulter mes données brutes afin de procéder à des contrôles, à condition toutefois que la confidentialité de ces données soit strictement assurée.
- Je serai informé des découvertes (fortuites) ayant une incidence directe sur ma santé. Si je ne souhaite pas obtenir ces informations, j'en aviserai l'investigateur.
- Je sais que mes données personnelles (et échantillons biologiques) peuvent être transmises / transmis à des fins de recherche **dans le cadre de ce projet uniquement** et sous une forme codée.

- Je peux, à tout moment et sans avoir à me justifier, révoquer mon consentement à participer à l'étude. Je sais que les données et le matériel biologique (échantillons de sang, tissus, etc.) qui nt été recueillis jusque-là seront cependant analysés.
- Je suis informé qu'une assurance a été souscrite pour couvrir les dommages imputables au projet que je pourrais subir. C'est la responsabilité civile de l'Université de Lausanne qui couvre un éventuel dommage imputable au projet.
- Je suis conscient que les obligations mentionnées dans la feuille d'information destinée aux participants doivent être respectées pendant toute la durée de l'étude. La direction de l'étude peut m'en exclure à tout moment dans l'intérêt de ma santé.

Lieu, date	Signature du participant / de la participante

Attestation de l'investigateur /de la personne assurant l'information : Par la présente, j'atteste avoir expliqué au participant / à la participante la nature, l'importance et la portée du projet. Je déclare satisfaire à toutes les obligations en relation avec ce projet conformément au droit en vigueur. Si je devais prendre connaissance, à quelque moment que ce soit durant la réalisation du projet, d'éléments susceptibles d'influer sur le consentement du participant / de la participante à prendre part au projet, je m'engage à l'en informer immédiatement.

Lieu, date	Nom et prénom de l'investigateur / de la personne assurant l'information aux participants en caractères d'imprimerie. Signature de l'investigateur / de la personne assurant l'information

7.6 Borg's scale

Rating	Perceived Exertion
6	No exertion
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

7.7 Recruitment flyer

UNIL | Université de Lausanne
Institut des sciences du sport de l'Université de Lausanne

Institut des sciences du sport de l'Université de Lausanne (ISSUL)

Cherchons VOLONTAIRES en bonne santé
qui s'entraînent au minimum 4h/semaine
hommes de 18 à 40 ans pour une étude
sur l'hypoxie lors de sprints répétés
(15 visites sur ~ fin octobre à mi-decembre)

Intéressé(e)? Contactez *Sarah Willis* pour inscription ou questions
(sarah.willis@unil.ch ou (0) 78 875 60 15)

Etude hypoxie sarah.willis@unil.ch ou 0788756015

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7.8 Ethical autorisation

canton de vaud

COMMISSION CANTONALE
D'ÉTHIQUE DE LA RECHERCHE
SUR L'ÊTRE HUMAIN

CER-VD

Av. de Chailly 23
1012 Lausanne

Prof. Grégoire Millet
UNIL - ISSUL
Quartier UNIL-Centre
Bâtiment Synathlon
Bureau 3114
1015 Lausanne

Lausanne, le 14 mai 2019
Réf. WP/cc

Décision de la Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER-VD)

No de projet	2018-02298
Titre du projet	Répétition de sprints avec hypoxie systémique vs. localisée (ischémie)
Travail de thèse de	Willis, Sarah
Investigateur principal	Prof. Grégorie Millet
Promoteur	Prof. Grégorie Millet
Centre	Prof. Grégorie Millet, Université de Lausanne, ISSUL, Lausanne, Suisse

Procédure de décision

☐ Procédure ordinaire ☐ Procédure simplifiée ☒ Procédure présidentielle

Décision

Prof. Grégorie Millet, Université de Lausanne, ISSUL, Lausanne, Suisse

☒ Autorisation accordée
☐ Autorisation avec charges
☐ En l'état, l'autorisation ne peut pas être accordée
☐ Autorisation non accordée
☐ Non entrée en matière

P:\CER\PROTOCOLES 2019\Décisions\2018-02298_prot_pos_190514.docx

Classification

☒ Projet de recherche au sens de l'ORH Catégorie : B

- ☒ recherche sur des personnes
- ☐ réutilisation du matériel biologique ou des données personnelles liées à la santé
- ☐ sur des personnes décédées
- ☐ sur des embryons et des fœtus
- ☐ avec rayonnements ionisants
- ☐ changement de catégorie selon l'Art. 48, alinéa 2 de l'ORH

Taxes et émoluments

Déjà facturé.

Voies de recours

La présente décision peut faire l'objet d'un recours au Tribunal cantonal, Cour de droit administratif et public. L'acte de recours doit être déposé auprès du Tribunal cantonal dans les **30 jours** suivant la communication de la décision attaquée ; il doit être signé et indiquer les conclusions et motifs du recours. La décision attaquée est jointe au recours. Le cas échéant, ce dernier est accompagné de la procuration du mandataire.

Copie pour information à :

☐ OFSP

☒ Autre(s) Sarah Willis, sarah.willis@unil.ch
Bengt Kayser, bengt.kayser@unil.ch

Signature

Prof. William Pralong
Vice-président

Annexes: -Obligations du requérant / Signification des décisions possibles
-Liste des documents soumis le 13.12.2018, 11.02.2019, 24.04.2019

Annexes

Obligations du requérant (promoteur ou investigateur) :

Soumission de documents : les documents modifiés et les nouveaux documents relatifs à l'étude/au projet de recherche sont soumis via le dossier de l'étude déjà existant dans le portail de soumission BASEC. Les documents qui ne sont plus valides sont effacés et remplacés par les nouveaux. Les documents révisés doivent être soumis une fois en mode « suivi des modifications » et une fois en mode « modifications acceptées » (« track changes » et « clean »). Les documents d'information et de consentement ainsi que le protocole doivent être transmis dans un format permettant la recherche (PDF navigable) ou scannés avec une fonction OCR (Optical Character Recognition). La lettre d'accompagnement, datée et signée, comprend les réponses aux questions posées. Le cas échéant, les documents révisés sont également mis à disposition des autorités compétentes pour approbation.

Remarque: La commission d'éthique compétente examine, dans le cadre du processus d'autorisation, les feuilles d'information et déclarations de consentement dans une des langues officielles suisses: allemand, français ou italien. La commission d'éthique ne fait qu'accuser réception des feuilles d'information et déclarations de consentement écrites dans d'autres langues. Le promoteur ou la direction du projet est responsable de la traduction correcte des documents.

Obligations d'annonce : Les obligations d'annonce (p.ex d'évènements indésirables, d'interruption d'étude) et de soumission pour autorisation des modifications essentielles obligatoires s'appliquent (Ordonnances). Le rapport final est à remettre à la commission d'éthique compétente dans un délai d'une année à compter de la fin ou de l'arrêt de l'étude.

Devoir d'enregistrement : Le promoteur d'un essai clinique doit procéder à l'enregistrement dans un registre primaire reconnu par l'OMS ou dans le registre de la bibliothèque médicale nationale des Etats-Unis d'Amérique (clinicaltrials.gov) puis indiquer le numéro de l'étude sur le portail BASEC. Le transfert des données vers le Swiss National Clinical Trials Portal (SNCTP) est effectué automatiquement suite à l'autorisation de l'étude par la commission d'éthique, sous réserve de l'accord du requérant. Les données relatives à l'essai clinique figurant sur les deux registres sont accessibles au public. Swissethics publie également sur son site des informations (titre et type d'étude, commission compétente) sur chaque étude ayant reçu une autorisation, à l'exception des études de phase I.

La Commission certifie se conformer aux principes ICH GCP.

Remarque : Des instructions détaillées sur la soumission sur le portail BASEC sont disponibles sur le portail lui-même.

Signification des décisions possibles

Autorisation accordée : L'étude peut commencer selon le plan de recherche accepté. Elle doit être menée dans le cadre des dispositions légales en vigueur. D'autres obligations d'autorisation (Swissmedic/OFSP) doivent être respectées.

Autorisation avec charges : L'étude peut commencer selon le plan de recherche accepté. Elle doit être menée dans le cadre des dispositions légales en vigueur. Les charges doivent être remplies dans un délai de 30 jours. Les documents modifiés seront réévalués en procédure présidentielle. D'autres obligations d'autorisation (Swissmedic/ OFSP) doivent être respectées

En l'état, l'autorisation ne peut pas être accordée : L'étude ne peut pas commencer. Prière de répondre point par point aux conditions de la commission d'éthique et de nous faire parvenir les documents révisés avec les modifications apparentes et la mention de la date de la nouvelle version.

Autorisation non accordée: L'étude ne peut pas commencer. Une nouvelle soumission reste possible.

Non entrée en matière : La commission d'éthique n'est pas juridiquement compétente pour accorder une autorisation. Un autre organe administratif peut entrer en matière ou l'étude ne nécessite pas d'autorisation.

Liste des documents soumis pour le centre principal

Prof. Grégorie Millet, Université de Lausanne, ISSUL, Lausanne, Suisse

nom du fichier	date du fichier	version
1. Cover Letter		
CoverLetter_WillisS_Training_Revision2-signed.pdf	24/04/2019	
2. Synopsis of the study plan		
see doc/cat: **4**, page/ref: **6-14**		
3. Participant information sheet and informed consent (ICF)		
StudyInformation_2_WillisS_Training_Revision2_TrackChanges-final.docx	24/04/2019	3
StudyInformation_2_WillisS_Training_Revision2_Clean-final.docx	24/04/2019	3
4. Study plan (protocol), signed and dated		
HRO_Research_Plan_WillisS_Training_Revision2_TrackChanges-final.docx	24/04/2019	3
HRO_Research_Plan_WillisS_Training_Revision2_Clean-final-signed.pdf	24/04/2019	3
6. Investigator's CV, dated		
Cv Millet English 101218-short.pdf	10/12/2018	
10. Insurance		
see doc/cat: **4**, page/ref: **15**		
11. Other documents handed over to study participants		
Recruitment Advertisement_LegTraining_English-revision-clean-final.docx	24/04/2019	3
Recruitment Advertisement_LegTraining_français-revision-clean-final.docx	24/04/2019	2
Questionnaire alimentaire_revised-clean-final.docx	24/04/2019	2
q-aap et vous IN FRENCH (PAR-Q English).pdf	13/12/2018	1
12. Details on nature and scope/value of compensation for participants		
The Patient Information Form (Document no. 3) contains details on compensation		
14. Information on secure handling of biological material and personal data, and in particular on the storage thereof		
see doc/cat: **4**, page/ref: **16-17**		
39. Miscellaneous / Varia		
Response to CER-VD_revision2_24.04.2019.docx	24/04/2019	2