

# Sprinting Toward Fitness

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Intense intermittent exercise, or interval training, is a powerful stimulus to induce many of the physiological adaptations typically associated with traditional, moderate-intensity continuous training. While coaches and athletes have recognized the value of interval training to enhance performance for over a century, recent scientific interest has focused on the application of this training method for health promotion. Despite renewed attention, the mechanistic basis for the physiological remodeling that occurs after interval training and the role that the stochastic nature of this type of exercise plays in mediating adaptive responses remains to be elucidated.

## Interval Training: Learning From The Past

There is renewed scientific inquiry along with widespread public interest in the potential for intense intermittent exercise to induce physiological adaptations that are similar or even superior to traditional endurance exercise in both healthy individuals and people with lifestyle-induced cardiometabolic disease (Gibala et al., 2012; Weston et al., 2014). Recent systematic reviews and meta-analyses have concluded that interval training, or alternating periods of relatively intense exercise and recovery, can be a time-efficient strategy to enhance cardiorespiratory fitness (CRF), as determined by whole-body maximal oxygen uptake ( $\text{VO}_{2\text{max}}$ ) (Batacan et al., 2017). These reports are particularly relevant because exercise capacity is a strong predictor of mortality, with a 1-metabolic equivalent (MET, 3.5 mL  $\text{O}_2/\text{kg}/\text{min}$ ) higher CRF associated with a 13% lower risk of dying from all causes and being comparable to a 5-mm Hg reduction in systolic blood pressure or 1 mmol/L lower fasting plasma glucose concentration (Kodama et al., 2009). Given that “lack of time” is a common barrier to regular physical activity, the identification of time-efficient exercise strategies that confer health benefits could favorably impact public health by reducing the economic burden associated with inactivity-related disorders.

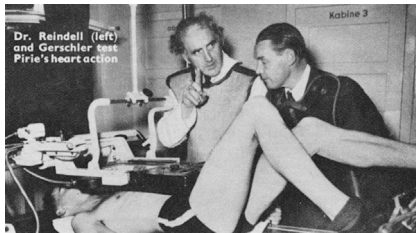
The notion that interval training is new or a groundbreaking scientific approach to physical conditioning needs to be placed in historical context. The basic practice dates back to the early 20<sup>th</sup> century and has evolved largely as a result of the trial-

and-error observations of innovative athletes and coaches. The technique was pioneered in Finland by coach Lauri Pikhala with champion runners including Hannes Kolehmainen and Paavo Nurmi. Nurmi was the most dominant distance runner in the world between 1920 and 1930, winning nine Olympic gold medals. His system of training focused on running a high number of repetitions (>20 efforts) at close to race pace with short (<60 s) rest intervals. In the 1930s, a German physician and coach, Woldemar Gerschler, along with cardiologist Herbert Reindel, devised a system of training that involved work and recovery periods based on heart rate (HR) targets. An athlete would run over a short distance fast enough to elicit a HR of  $\sim 180$  beats/min, followed by a rest period in which HR dropped to  $\sim 120$  beats/min before they commenced the next effort. Gerschler and Reindel proposed that the recovery interval was the most important aspect of their approach because it was during this phase that the heart adapted, allowing it to grow larger and stronger (Figure 1). Perhaps the most celebrated case of interval training is Sir Roger Bannister, the first person to run the mile in under four minutes. While a medical student at St Mary's Hospital, London, Bannister trained during his lunch hour using the 9 min jog to a local track to warm up, after which he promptly ran 10  $\times$  400 m in a little over  $\sim 60$  s each, with 2 min recovery. He then ran back to work, leaving 15 min to eat his lunch and (hopefully) shower. On May 6, 1954, Bannister's training culminated in a world mile record of 3 min, 59.4 s, two seconds faster than the previous record.

While coaches and athletes have appreciated the effectiveness of interval training since the early 20<sup>th</sup> century, the first scientific publications on the physiological basis of interval training for human performance did not appear until the 1960s. Over subsequent decades, the potential health-related applications of this type of training were increasingly recognized. In 1974, physiologists Edward Fox and Donald Matthews from The Ohio State University declared that “interval training is the supreme way to condition a person,” with the principles they described being applicable to “the coach, the athlete, and the person who desires to condition himself for health purposes” (Fox and Matthews, 1974). Similar to Gerschler and Reindel some 40 years earlier, Fox and Matthews (1974) emphasized the importance of the recovery period or “relief interval” for optimizing cardiovascular conditioning. Other researchers subsequently recognized the potential to apply interval training to less-healthy individuals. In the mid-1990s, Katarina Meyer conducted pioneering work on heart failure patients, deeming the method better suited for such individuals, as “interval exercise allows greater stimuli which patients probably would not have tolerated if the same intensity had been applied using a continuous method” (Meyer et al., 1996).

## Sprint-Interval Training: Punching Above Its Weight

Interval training is infinitely variable but can be broadly classified into two categories: high-intensity interval training



**Figure 1. Early Interval Training Research**  
German physician and coach, Woldemar Gerschler, together with cardiologist Dr. Herbert Reindell, carried out “controlled training” studies in athletes based on the concept of intermittent exercise. Heart rate was monitored during all workouts with specific target zones prescribed during exercise and recovery. The investigators found a 20% increase in heart volume and improved performance after 21 days of training. The subjects included Gordon Pirie of Great Britain, who won the silver medal in the 5,000 m at the 1956 Olympics and subsequently coached one of the authors (J.A.H.).

(HIIT), which typically denotes submaximal efforts eliciting  $\geq 80\%$  of maximal heart rate, and sprint interval training (SIT), which involves “all out” efforts or an intensity corresponding to  $\geq 100\%$  of the power output or speed that is associated with an individual’s  $VO_{2max}$  (Weston et al., 2014). SIT is a particularly potent variation of interval training, as demonstrated by the classic study by Tabata et al. (1996). These workers employed a protocol comprising eight 20 s sprints on a cycle ergometer, at an intensity corresponding to 170% of  $VO_{2max}$  with 10 s of recovery. When this protocol was performed five times per week for 6 weeks,  $VO_{2max}$  was increased by a similar magnitude to a protocol involving 5 hr/week of moderate-intensity cycling. The potency of SIT to elicit adaptations comparable to traditional endurance training despite large differences in training volume and time commitment was recently demonstrated by Gillen and colleagues (2016). These workers had two groups of sedentary young men perform either SIT or moderate-intensity continuous training (MICT) three times a week for 12 weeks. The SIT workout comprised 3 × 20 s “all-out” sprints on a cycle ergometer at a power output of  $\sim 500$  W (a work-rate approximately 2- to 3-fold the power output reached by these subjects at the end of a  $VO_{2max}$  test), with 2 min of low-intensity cycling (50 W) recovery between sprints. MICT consisted of 45 min of continuous cycling at  $\sim 110$  W (moderate intensity,  $\sim 50\%$  of  $VO_{2max}$ ). Both proto-

cols involved a brief warm-up and cool-down totaling 5 min, such that SIT constituted 1 min of intense exercise within a 10 min time commitment per session, whereas MICT involved 50 min of continuous exercise per session.  $VO_{2peak}$  was increased by 19% in both groups after training, with similar training-induced improvements in insulin sensitivity, as determined by intravenous glucose tolerance tests. Skeletal muscle mitochondrial content, assessed by the maximal activity of citrate synthase, also increased to a similar extent after SIT and MICT. These results (Gillen et al., 2016) are a timely reminder of the potency of SIT to stimulate physiologically meaningful and clinically relevant improvements in health-related outcomes with minimal time commitment. The findings also highlight a fundamental question regarding the mechanisms underpinning such robust whole-body and tissue-specific adaptations after interval training in humans. Namely, how do a few hard sprints in such a short intervention period elicit such profound remodeling of physiological systems?

#### The Signal for Adaptation: Is Interval Training Different?

Exercise has traditionally been categorized as either aerobic/endurance or strength/power, with these extremes placed at opposite ends of a continuum. Concomitant with the vastly different functional and phenotypic outcomes induced by these exercise modes, the molecular pathways associated with these divergent training protocols are distinct (Hawley et al., 2014). In brief, traditional endurance training elicits changes that increase mitochondrial proteins and the respiratory capacity of the trained myofibers. These adaptations, in turn, underpin the altered patterns of substrate oxidation during submaximal exercise (from carbohydrate- to fat-based fuels) that result in less lactate production at any given submaximal power output or speed. In contrast, strength and resistance-based training stimulates the myofibrillar proteins responsible for muscle hypertrophy, culminating in increases in maximal contractile force output without substantial changes in fuel use during exercise. A paradoxical characteristic of interval training and SIT in particular is the brief, intense repeated efforts

that closely resemble resistance exercise, yet elicit adaptations associated with traditional endurance training. Training volume has been proposed to be a primary determinant of the exercise-induced increase in mitochondrial content in human skeletal muscle, but other evidence highlights the potential role of exercise intensity in mediating responses (MacInnis and Gibala, 2016).

A core principle of all training protocols is that any acute exercise signal needs to exceed a certain “threshold stimulus” to induce a variety of physiological adaptations that ultimately result in long-term phenotypic changes. Exercise provokes widespread changes in numerous tissues and organs that are caused by the increased metabolic activity of active skeletal muscle. To meet this challenge, multiple integrated inter-organ responses function to blunt the homeostatic threats caused by the increased muscle energy turnover and whole-body oxygen demand (Hawley et al., 2014). During MICT lasting  $\sim 1$  hr,  $O_2$  supply is plentiful and substrate demand by the active muscles is largely met by the oxidation of carbohydrate- and fat-based fuels. There is a primary reliance on type I, slow-twitch muscle fibers, and the rate of change of cellular dynamics and disturbances to whole-body homeostasis is negligible. In contrast, both HIIT and SIT evoke extensive perturbations to both local (muscle) and systemic (cardiovascular, respiratory, neural, and hormonal) homeostasis. SIT in particular requires substantially higher absolute power outputs compared to MICT, necessitating the recruitment of type II, fast-twitch fibers. This in turn requires extensive use of non-oxidative substrate metabolism to meet muscle energy demands, which are fueled exclusively by intramuscular substrates (high-energy phosphates and glycogen) with little or no contribution from fat-based fuels. The greater absolute energy demand and altered fiber recruitment drives the higher absolute oxygen flux and total fuel requirement of interval compared to low- to moderate-intensity continuous exercise. Accordingly, in contrast to MICT, the rate of change of cellular dynamics and disturbances to whole-body homeostasis induced by intermittent exercise, and SIT in particular, is extensive.

The “stop-start” nature of intermittent exercise and the associated intracellular

“spikes” in various signaling pathways is one potential mechanism to explain skeletal muscle responses to interval training, including superior adaptation after HIIT compared to MICT despite matched work, or similar adaptation elicited by SIT and MICT training despite differences in total work (Maclinnis and Gibala, 2016). This could be in turn linked to fluctuating energy demands associated with repeated rest-work cycles. For example, acute interval as compared to continuous exercise has been shown to elicit greater AMP-activated protein kinase (AMPK) phosphorylation, presumably owing to larger transient increases in [AMP] and/or increase in the [ADP/ATP] ratio. A downstream target of AMPK is the transcriptional co-factor peroxisome proliferator-activated receptor  $\delta$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), a critical regulator of mitochondrial biogenesis. SIT robustly increases the gene expression of PGC-1 $\alpha$  after several hours of recovery, and evidence of increased nuclear PGC-1 $\alpha$  protein content immediately after SIT but not MICT is consistent with the notion that intermittent exercise is a more time-efficient option to promote molecular events regulating mitochondrial biogenesis. The potential role of glycogen as an important metabolic signal could also be involved in mediating divergent exercise-induced adaptations to intermittent and continuous exercise. It is also possible that, in addition to sensing absolute changes in levels of various signals such as sarcoplasmic [Ca<sup>2+</sup>], the muscle cell responds to absolute rates of change, which are more stochastic and dramatic during intermittent as compared to continuous, submaximal exercise. Contraction-induced alterations in intracellular [Ca<sup>2+</sup>] may be linked to distinctive programs of gene expression that establish phenotypic diversity among skeletal myofibers and confer some of the whole-body adaptations after SIT protocols. Finally, the increased reactive O<sub>2</sub> species levels, acidosis, and altered redox state, including NAD/NADH, may also play roles

in fine-tuning signaling responses after SIT. Additional studies are needed, both in terms of the early time course of molecular events that occur in human muscle in response to repeated bouts of SIT and how these potentially link or translate into chronic training adaptations.

### Sprinting Forward: Where to from Here?

The precise role of exercise intensity, duration, and volume in acutely modifying various signaling cascades and coordinating specific training-induced physiological adaptations remain to be determined. Issues surrounding the optimal exercise “training impulse” need to be addressed by systematic “dose-response” studies. Deciphering the cellular mechanisms underpinning the widespread benefits of interval-based training, and how acute exercise responses are integrated over time into improved health outcomes, may offer insight into some of the critical physiological pathways to target in order to fight the battle against inactivity-related diseases. Most interval training studies to date are of relatively short duration (lasting up to a few months), and longer trials with large subject cohorts of men and women of diverse ages and health status are urgently needed to help pinpoint the time course of adaptation in different populations. Such information may be a prelude to “personalized” exercise prescriptions that will ultimately help individuals obtain the maximum benefits of regular physical activity. In the final analyses, SIT is only one option in the armory of primary care interventions that can be used to fight chronic metabolic diseases. After all, interval training is just one aspect of the multi-faceted periodized training strategies that have been used by competitive athletes for over a century.

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