Aerobic Adaptations to Resistance Training: The Role of Time under Tension

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ABSTRACT

Generally, skeletal muscle adaptations to exercise are perceived through a dichotomous lens where the metabolic stress imposed by aerobic training leads to increased mitochondrial adaptations while the mechanical tension from resistance training leads to myofibrillar adaptations. However, there is emerging evidence for cross over between modalities where aerobic training stimulates traditional adaptations to resistance training (e.g., hypertrophy) and resistance training stimulates traditional adaptations to aerobic training (e.g., mitochondrial biogenesis). The latter is the focus of the current review in which we propose high-volume resistance training (i.e., high time under tension) leads to aerobic adaptations such as angiogenesis, mitochondrial biogenesis, and increased oxidative capacity. As time under tension increases, skeletal muscle energy turnover, metabolic stress, and ischemia also increase, which act as signals to activate the peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which is the master regulator of mitochondrial biogenesis. For practical application, the acute stress and chronic adaptations to three specific forms of high-time under tension are also discussed: Slow-tempo, low-intensity resistance training, and drop-set resistance training. These modalities of high-time under tension lead to hallmark adaptations to resistance training such as muscle endurance, hypertrophy, and strength, but little is known about their effect on traditional aerobic training adaptations.

Introduction: Specific Adaptations to Divergent Stressors from Exercise

According to the principle of specificity, physiological adaptations reflect the specific stress imposed on the body during various bouts of exercise [1]. Resistance training (RT) is associated with several positive adaptations [2] such as increased muscular endurance [3], muscular strength [4], power [5], sprint speed [6], and agility [7]. These tangible measures of performance stem from adaptations that occur at the nervous system and skeletal muscle. For example, common neurological adaptations to RT include increased motor unit recruitment, faster transmission of action potentials, increased rate coding, motor unit synchronization, and increased surface area of the neural muscular junction [8, 9]. At the skeletal muscle, RT increases fascicle length, pennation angle, and hypertrophy (i.e., cross-sectional area of fibers and/or muscle thickness) [10–12], which potentially contribute to increased maximal force production [9, 13]. These adaptations are caused by the manipulation of several program variables including intensity, volume, the order and exercises selected, rest intervals between sets, velocity of contraction, and frequency [2]. Studies investigating the role of the intensity and volume of RT have indicated that low-intensity, high-

volume RT and high-intensity, low-volume RT are effective to increase muscle size and strength [14, 15].

In contrast, aerobic training (AT) is associated with greater endurance capacity and improvements in maximal oxygen uptake (VO_2max), lactate threshold, ventilatory threshold, and improved exercise economy [16–18]. Improved cardiovascular performance, stimulated by AT, stems from central and peripheral adaptations. Central adaptations to AT generally include increased stroke volume, cardiac output, and myocardial efficiency, meaning that the cardiovascular system becomes more efficient at delivering oxygen to the exercising muscle [1, 19, 20]. Peripheral adaptations to AT include increased capillary density, slow-twitch muscle fiber distribution, mitochondrial density, and mitochondrial enzyme activity, meaning that the skeletal muscle becomes more efficient at extracting oxygen from the blood stream and using it in the process to synthesize adenosine triphosphate (ATP) via oxidative phosphorylation [1, 19, 20]. Research has demonstrated that high-volume, low-intensity (i.e. long slow-distance) and low-volume, high-intensity AT (i.e. high-intensity interval training or sprint interval training) are both capable of stimulating central and peripheral aerobic adaptations [20–22].

As it pertains to skeletal muscle physiology at the molecular level, adaptations to AT and RT are often viewed through a dichotomous lens in which they are not compatible [23–25]. In particular, the mechanical tension imposed by RT activates an unidentified protein kinase that upregulates the mammalian target of rapamycin (mTOR) by inhibiting the inhibitor of mTOR, tuberous sclerosis complex 2 (TSC-2) [25, 26]. This process (i.e., mechanotransduction) initiates acute protein translation which eventually leads to long-term skeletal muscle hypertrophy [25, 26]. In contrast, the metabolic stress associated with AT upregulates various protein kinases that stimulate mitochondrial biogenesis through activation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [27], that is recognized as the master regulator of mitochondrial biogenesis [28]. Although chronic adaptations depend on training status and the type of exercise performed, there is some evidence that AT can stimulate RT adaptations and vice versa [29, 30], which means there is cross-over between these signaling pathways. Specifically, some research has demonstrated that AT elicits significant skeletal muscle hypertrophy [31, 32], and others have determined that RT can stimulate increased skeletal muscle oxidative capacity [33] and markers of mitochondrial biogenesis [34]. The latter phenomenon is of particular interest in the current review because the potential RT variables (i.e., volume, intensity, and tempo) that lead to aerobic adaptations are not well understood.

Previously, Steele et al. [35] concluded that RT can stimulate several AT adaptations such as increased cardiac output and VO_2max when sets are performed to momentary muscular failure. As it pertains to skeletal muscle adaptations, the effects of RT on mitochondrial biogenesis [36] and mitochondrial volume [37] have also recently been reviewed and a similar conclusion was reached: Low-intensity, high-volume RT (e.g., high time under tension – TUT) is likely a stronger stimulus for traditionally aerobic adaptations compared to high-intensity, low-volume RT (e.g., low-TUT) [36, 37]. However, these review papers did not discuss the mechanisms by which high-TUT RT elicits such adaptations or provide a general overview of acute and chronic adaptations to high-TUT training modalities. Hence, the purpose of the current review is to detail the mechanisms of exercise-induced mitochondrial biogenesis, provide a case for why high-TUT can stimulate this pathway, and highlight what is known about three specific types of high-TUT RT: Slow repetition tempo RT, traditional low-intensity RT, and drop-set RT. Specifically, the acute physiological responses and long-term muscular adaptations will be reviewed for each style of training.

Mitochondrial Biogenesis: The Central Role of PGC-1α Activation

Mitochondrial biogenesis is the synthesis of new reticular components that increase mitochondrial volume (i.e., increased quantity) and the activity of enzymes within the mitochondria (i.e., increased quality). Although other signaling cascades contribute to mitochondrial biogenesis [38], PGC-1α is considered to be the master regulator and key influencer for aerobic adaptations and oxidative phenotypes [1, 19, 28]. In fact, PGC-1α has been implicated in the regulation of skeletal muscle mitochondrial biogenesis as muscle specific deletion of PGC-1α results in attenuated mitochondrial biogenesis in response to physical training [39]. During exercise, repeated muscular contractions lead to an increase in several contractile-induced stressors such as AMP/ATP ratio, reactive oxygen species (ROS), intracellular Ca^{2+}, lactate, ischemia, and decreased energy availability [1, 19, 22, 25, 27]. These signals activate several protein kinases such as calcium/calmodulin protein kinase II (CaMKII), p38 mitogen-activated protein kinase (p38MAPK), and AMP-activated protein kinase (AMPK), which activate downstream transcription factors and co-activators to increase the expression of mitochondrial proteins [1, 19, 22, 25, 27]. Specifically, CaMKII, p38MAPK, and AMPK directly stimulate mitochondrial biogenesis by phosphorylating PGC-1α, causing it to translocate to the nucleus [25, 27, 30]. Moreover, AMPK, lactate, and NAD^+ activate NAD^+-dependent deacetylase family of sirtuins (SIRT), which controls metabolic flux through the citric acid cycle and has been implicated in mitochondrial biogenesis by regulating PGC1- α activity through its deacetylase activity [40]. Tumor suppressor protein 53 (p53) is also activated by AMPK and p38MAPK, and it exerts regulatory effects on transcription factors and mitochondrial content [1, 19, 27]. In short, exercise-induced metabolic stress and increased skeletal muscle energy turnover activate upstream regulators of PGC-1α, which converge on and phosphorylate PGC-1α, allowing for its translocation.

When PGC-1α translocates to the nucleus, it activates several transcription factors such as nuclear respiratory factors one and two (NRF-1 and -2), which increase the transcription of PGC-1α, cytochrome c oxidase subunits, and mitochondrial transcription factor A (TFAM) [1, 19, 24, 27]. TFAM modulates mitochondrial biogenesis by affecting mitochondrial DNA transcription and replication [41]. There is also evidence that PGC-1α influences angiogenesis by upregulating the activity of vascular endothelial growth factor (VEGF) [18, 42, 43]. Thus, the repeated upregulation of PGC-1α leads to post-exercise transcription of genes involved in mitochondrial biogenesis and angiogenesis, which eventually leads

to peripheral physiological adaptations. For example, data from acute studies suggest that high-intensity interval training (HIIT) elicits significant metabolic stress and the activation of PGC-1α, which leads to increased levels of gene transcripts regulated by PGC-1α [27, 44, 45]. When training bouts are repeated, HIIT leads to increased oxygen uptake, mitochondrial volume, mitochondrial enzyme activity, and capillary density [18, 21, 22].

Some have compared HIIT to RT because they are both characterized by brief periods of high-energy turnover interspersed by periods of rest [34, 46, 47]. Considering that energy depletion (e.g., reduced ATP and CrP) and metabolic stress increase with the number of repetitions completed per set [48, 49], we speculate that sets of RT with high-TUT may stimulate the activation of upstream modulators of PGC-1α similar to HIIT, leading to greater PGC-1α mRNA response, and ultimately to enhanced mitochondrial biogenesis. For example, a set of RT performed for 5 repetitions with a 3-second tempo (e.g., 2:1 seconds) and high intensity (e.g., 90 % of 1-RM) would have a TUT of 15 seconds while a set of RT performed for 20 repetitions with the same tempo but low intensity (e.g., 50 % of 1-RM) would have a TUT of 60 seconds. Gronneback and Vissing [36] suggested in a recent review that the latter style of RT (i.e., high-TUT) would have a positive effect on mitochondrial biogenesis because it stimulates greater turnover rate of ATP, metabolic stress, and tissue deoxygenation compared to low-TUT RT. More recently, Parry et al. [37] stated that future research should be done to assess the effect of high-intensity (i.e., low-TUT) and low-intensity (i.e., high-TUT) RT on mitochondrial biogenesis, and hypothesized that the latter would have a greater effect due to greater metabolic perturbations (i.e., higher blood lactate). We submit that this hypothesis is interesting and the relationship between blood lactate and mitochondrial biogenesis is worth further discussion.

Upregulating PGC-1α: The Potential Role of Lactate

Mechanistic studies in cell cultures and rodents have provided strong evidence that lactate is involved in mitochondrial adaptations. Specifically, it has been demonstrated that incubation of L6 cells with lactate increased mRNA expression of PGC-1α [50], and similar results were achieved in vivo by lactate intraperitoneal administration in mice [51]. Interestingly, attenuation of the increase in lactate during exercise by administration of dichloroacetate, an activator of pyruvate dehydrogenase, reduced HIIT-induced increases in mitochondrial enzyme content in mouse skeletal muscles [52], implicating exercise-induced lactate production in mitochondrial adaptations. Moreover, Takahashi et al. [53] demonstrated that 3-week lactate intraperitoneal administration increased mitochondrial enzyme activity (e.g., citrate synthase, 3-hydroxyacyl CoA dehydrogenase, and cytochrome c oxidase), and showed that lactate administration prior to endurance exercise training enhanced training-induced mitochondrial enzyme activity in the skeletal muscle [53]. Later, the same group showed that four weeks of oral lactate administration + exercise increased cytochrome c oxidase activity in skeletal muscle more than exercise alone in mice [54]. Finally, it was reported that chronic intramuscular lactate treatment increased PGC-1α and citrate synthase protein content in the gastrocnemius of rats [55]. Altogether, these findings suggest that lactate increases mitochondrial enzymes through PGC-1α activation, and that exercise-induced mitochondrial adaptations are related to lactate production.

Although the precise pathways activated by lactate to induce PGC-1α-mediated mitochondrial adaptations are still under investigation, it has been reported that lactate injection can increase AMPK activity in the soleus muscle in mice [56]. Because AMPK is an upstream activator of PGC-1α [27], it could be involved in lactate-induced PGC-1α activation and mitochondrial adaptations. Conversely, in vitro [57] and in vivo [58] evidence shows that when ROS production is blunted, contraction-induced PGC-1α response is impaired, suggesting that ROS is an important mediator of exercise-induced PGC-1α activation. Although it has been suggested that the lactate upregulation of PGC-1α is mediated by ROS [59], there is currently no direct evidence to confirm this hypothesis. However, it was recently reported that lactate increased ROS generation in a dose-dependent manner in skeletal muscle [60]. Therefore, we speculate that lactate accumulation during exercise increases ROS production, which would lead to a ROS-mediated PGC-1α activation culminating in mitochondrial biogenesis. Finally, lactate might also affect mitochondrial biogenesis in an autocrine and/or paracrine fashion. It has been reported that a selective receptor for lactate, called G-protein-coupled receptor 81 (GPR81), exists in various tissues, including skeletal muscle [61, 62]. Interestingly, silencing of GRP81 in lactate-treated cancer cells did not increase PGC-1α mRNA expression, in contrast to the increase observed in control cells [63], suggesting that lactate induces PGC-1α gene transcription by GRP81 activation. Whether the lactate-GRP81 pathway plays a role in exercise-induced mitochondrial biogenesis requires further investigation.

These mechanistic studies suggest that lactate may be implicated as a signaling molecule that mediates mitochondrial adaptations through PGC-1α activation, but research in human subjects is equivocal. For instance, greater lactate accumulation during cycle ergometry (i.e., repeated supramaximal sprints) has been associated with higher exercise-induced phosphorylation of CaMKII and p38 MAPK, along with higher PGC-1α mRNA response [64]. Although a direct cause-and-effect relationship between lactate accumulation and PGC-1α activation cannot be established with their study design, the authors speculated that greater metabolic stress (i.e., higher blood lactate) is related to greater activation of the PGC-1α mRNA response [64]. In contrast, Moberg et al. [65] recently reported that higher levels of muscle lactate did not facilitate increased mRNA encoding of PGC-1α following RT with and without preceding lower-body cycle ergometry. However, these results should be interpreted with caution because both conditions elicited a robust muscle lactate response (10.8 vs. 13.5 mmol/L) which did not allow for a dose-response assessment between lactate and PGC-1α mRNA. In other words, 10.8 and 13.5 mmol/L elicited similar responses, but it is unknown if values of 4, 6, or 8 mmol/L would have led to an inferior mRNA response (i.e., there may exist a saturation point above which lactate does not affect PGC-1α). Ultimately, it is difficult to isolate the effect of lactate on mitochondrial biogenesis in human skeletal muscle during exercise because several stressors/signals (e.g., lactate, energy turnover,

hypoxia) converge on PGC-1α where they elicit their effects concurrently.

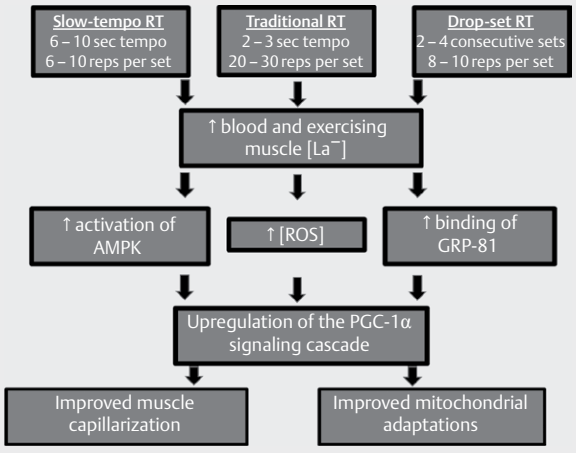
Regardless of the exact mechanisms (▶ **Fig. 1**), there is evidence that lactate accumulation is associated with the activation of mitochondrial biogenesis [50–55; 61–63] and that blood lactate has a positive, linear relationship with TUT during sets of RT [66–71]. Moreover, Burd et al. [72] reported that higher-TUT RT (i.e., 30 % 1-RM) resulted in greater sarcoplasmic protein synthesis (e.g., which includes mitochondrial proteins) compared to lower-TUT RT (i.e., 90 % 1-RM). Later, the same researchers measured greater mitochondrial protein synthesis following a bout of RT with high-TUT [73]. Thus, it is clear that high-TUT RT leads to greater metabolic stress (i.e., greater lactate accumulation) than low-TUT RT, but whether these styles of RT lead to divergent peripheral aerobic adaptations deserves further discussion.

Low vs. High-intensity RT: Effect on Peripheral Aerobic Adaptations

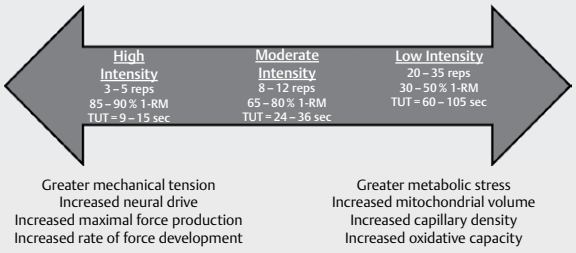
Many studies that have compared low vs. high-intensity RT are comprised of blood flow restriction (BFR) interventions. The effect of such training on angiogenesis and mitochondrial biogenesis has recently been reviewed [18]. Because BFR training evokes high levels of ischemia, metabolic stress, and hypoxia, its effect on muscle capillary density and oxidative metabolism are particularly interesting. In fact, research on acute bouts of RT have demonstrated that the addition of BFR to low-intensity RT decreased muscle oxygenation [42], increased gene expression for proteins involved in angiogenesis [42], and increased markers of mitochondrial biogenesis [43]. Thus, it is logical that low-intensity BFR training has stimulated increased capillarization [74] and muscular endurance [75] when repeated for 3–8 weeks. As it pertains to mitochondrial adaptations, one study has compared the effects of high-intensity RT vs. low-intensity RT with BFR [76]. After six weeks of training, data revealed that both BFR (4 sets, 30 % of 1-RM) and high-load RT (4 sets, 70 % of 1-RM) had positive effects on mitochondrial protein fractional synthetic rate and mitochondrial respiration with no differences between groups. Citrate synthase increased only in the BFR group, but the difference did not achieve statistical significance [76]. As it pertains to aerobic adaptations, more research is needed to determine if low-intensity RT with BFR is superior to traditional forms of high-intensity RT.

Regarding traditional RT (i.e., no BFR), only two studies have assessed the effect of low vs. high-intensity RT (i.e., without BFR) on capillarization, cellular respiration, and markers of mitochondrial biogenesis and mitophagy. Holloway et al. [77] compared the effect of low-repetition (8–12 reps; 75–90 % of 1-RM) vs. high-repetition (20–25 reps; 30–50 % of 1-RM) RT in resistance-trained men. Data revealed that both programs had a positive effect on capillarization and protein markers of vasodilation, implying that positive adaptations to the microvasculature occurred irrespective of intensity and TUT [77]. Other findings were reported by Lim et al. [34] who compared the effect of three RT programs in untrained males: 30 % of 1-RM to failure, 80 % of 1-RM to failure, or 30 % of 1-RM with work matched to the 80 % of 1-RM group. Results indicated that protein markers for mitochondrial biogenesis, mitochondrial capacity, and mitophagy increased only in the group that trained with 30 % of 1-RM to failure [34]. In their discussion, the authors speculated that when sets of RT are performed with high-volume (i.e., high-TUT), the metabolic stress incurred during the session leads to aerobic/oxidative adaptations [34]. In short, the hypothesis that low-intensity, high-TUT training would have a positive effect on peripheral aerobic adaptations is logical, but the limited research done in this area remains inconclusive. Future research should be done to assess this hypothesis and determine if training status influences the effect of different intensities on such adaptations.

As displayed in ▶ **Fig. 2** it is now known that hypertrophy occurs along a wide spectrum of intensities (30–90 % of 1-RM) and corresponding rep-ranges (3–35 reps per set) [3, 14, 15, 78, 79]. Assuming a traditional 2:1 second repetition tempo, this effective repetition range corresponds with 9–105 seconds of TUT per set. Because the effective range of TUT for hypertrophy is wide, it behooves us to explore unique adaptations that occur at extreme ends of the spectrum. For example, it is generally accepted that RT with low-TUT (i.e., 80–95 % of 1-RM) is superior for increasing maximal strength [80, 81] while RT with high-TUT (i.e., 30–50 % of 1-RM) is superior for muscular endurance [3, 78]. The latter is the focus of the current review, and the following section will summarize research on acute and chronic RT for three specific techniques that use high-TUT: Slow-tempo, high-volume low-intensity, and drop-set training.



▶ **Fig. 1** An overview of the proposed mechanism for how resistance training (RT) with high time under tension (TUT) stimulates peripheral aerobic adaptations by upregulating the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) signaling cascade. Slow-tempo, traditional, and drop-set are three applications of RT with high-TUT that lead to high muscle and blood lactate concentrations. Mechanistic studies in cells and rodents have demonstrated that lactate increases activation of adenosine monophosphate activated protein kinase (AMPK) and concentration of reactive oxygen species (ROS) which directly upregulate the PGC-1α signaling cascade. Additionally, lactate may stimulate PGC-1α by directly binding to its G-protein-coupled receptor 81 (GPR81). Because high-TUT leads to greater lactate concentration than low-TUT, and lactate has been implicated as a potential signaling molecule in the PGC-1α signaling cascade, it is logical to suggest that RT with high-TUT may facilitate aerobic adaptations through PGC-1α.



▶ **Fig. 2** A summary of the effective repetition range for hypertrophy (3–35 reps) that emphasizes potential unique adaptations to resistance training (RT) with low and high time under tension (TUT). Assuming that a traditional repetition tempo is used (e.g., 2:1 seconds), this repetition range also corresponds with a TUT of 9–105 seconds per set. Here, we submit that high-intensity RT is associated with greater mechanical tension and increased strength while low-intensity RT is associated with greater metabolic stress and aerobic adaptations such as increased capillary density, mitochondrial volume, and skeletal muscle oxidative capacity.

Applications of RT with High-TUT

Slow Tempo Resistance Training

Repetition tempo, which is sometimes referred to as repetition duration, equals the length of time that comprises the eccentric, isometric, and concentric phases during one repetition of exercise [82]. For example, a repetition with a three-second concentric phase, one-second isometric pause, and three-second eccentric phase would be a seven-second tempo and would be denoted as 3:1:3 sec [66, 83]. As it pertains to muscular strength, in a recent meta-analysis of 15 studies, Davies et al. [84] concluded that fast (e.g., eccentric phase = 1–3 seconds; concentric phase = < 1 second) and moderate-slow (e.g., eccentric phase = 1.7–3 seconds; concentric phase = 1.7–3 seconds) repetition tempos significantly improve muscular strength. When considering skeletal muscle hypertrophy, in another recent meta-analysis of 8 studies, Schoenfeld et al. [85] concluded that similar muscle growth occurred along a wide repetition tempo spectrum (0.5–8 seconds) when sets were performed to momentary muscle failure. Clearly, there is a wide range of effective repetition tempos.

To the best of our knowledge, not much evidence is available regarding the effect of repetition duration on muscular endurance and aerobic fitness. However, the prospect of lengthening repetition duration to stimulate cardiovascular adaptations is a noteworthy topic, because this will have a direct effect on the TUT during sets of RT [86]. For example, a set of 12 repetitions with a 12-second duration (6:6 sec) would have a TUT of 144 seconds, while a set of 12 repetitions with a 2-second duration (1:1 sec) would have a TUT of 24 seconds [73]. Although speculative, it is possible that sets of RT with slower repetition tempos, and thereby longer TUT, have a positive effect on peripheral aerobic adaptations because some research suggests that metabolic stress (e.g., blood lactate) increases linearly with TUT [66–71]. Others have shown that as TUT increases, muscle oxygenation decreases [66, 83] while mitochondrial protein synthesis increases [73]. Thus, the notion that slow-repetition, high-TUT RT can potentially stimulate aerobic peripheral adaptations is a logical speculation.

Acute effect of repetition tempo on metabolic stress

There are several variations of repetition tempos that may influence metabolic stress incurred during a bout of RT. Gentil et al. [89] compared the effect of four types of RT: 10-RM (2:2 second tempo), functional isometrics (2:5:2 second tempo), vascular occlusion (20-second isometric followed by repetitions with a 2:2 second tempo), and one super-slow repetition (30:30 second tempo). The greatest blood lactate response occurred in the functional isometric (4.5 mmol/L) and vascular occlusion (4.2 mmol/L) conditions, and the authors suggested that performing isometric pauses (5 or 20 seconds) had a more profound effect on metabolic stress than overall TUT [89]. If their assertion is true, a 2:5:2 second tempo (i.e., 5 second isometric phase) would increase blood lactate by more than a 6:3 second tempo (i.e., no isometric phase) even though the repetition duration is the same (e.g., 9 seconds). To date, this hypothesis has not been tested. In other research, Mazzetti et al. [90] had ten resistance-trained men perform lower-body RT under three conditions: Slow (2:2 sec, 4 × 8 reps, 60 % 1-RM), fast (2:1 sec, 4 × 8 reps, 60 % 1-RM), and heavy-fast (2:1 sec, 6 × 4 reps, 80 % 1-RM). Data indicated that blood lactate increased linearly with TUT as slow (TUT = 32 sec) was greater than fast (TUT = 24 sec), which was greater than heavy-fast (TUT = 12 sec). However, it is difficult to provide definitive conclusions from this study because subjective effort and proximity to failure were not reported and the difference between tempos was narrow (3 vs. 4 sec).

With TUT matched at 36 seconds per set, Lacerda et al. [91] demonstrated that faster tempo repetitions (3 seconds) increased blood lactate more than slower tempo repetitions (6 seconds). Similar results were achieved by Vargas-Molina et al. [92] when TUT was matched at 60 seconds per set. This study improved upon the methods of Lacerda et al. [91] because effort was matched between conditions as every set was performed to momentary muscular failure. Thus, there is agreement in the current literature that metabolic stress increases with TUT [66–71]. Moreover, when TUT is matched, metabolic stress is greater under conditions where more repetitions are performed per set (e.g., 20 vs. 10 reps) and faster/traditional tempos (e.g., 3 vs. 6 sec) are used (91, 92). In the future, researchers should emulate the design of Vargas-Molina et al. [92] by matching TUT and assessing the effect of several tempo schemes on a variety of exercises (i.e., single vs. multiple joint, upper vs. lower body). Furthermore, it would be beneficial to measure muscle oxygenation during these exercises [66, 83], and to include advanced biochemical analysis (e.g., western blotting and immunohistochemistry) to measure markers of mitochondrial biogenesis and angiogenesis.

Effect of tempo and TUT on long-term adaptations

Several recent systematic reviews and meta-analyses have conclusions positing that significant hypertrophy and strength occur along a spectrum of fast, traditional, slow, and super slow repetition tempos (e.g., 0.5–10 seconds) [82, 84, 85]. Moreover, Tanimoto et al. [66] reported that low-intensity RT with slow contractions (50 % of 1-RM, 3:1:3 second tempo) and high-intensity RT with normal contractions (80 % of 1-RM, 1:1:1 second tempo) similarly in-

creased hypertrophy and muscular strength after training with the knee-extension exercise. Years later, the same researchers reached similar conclusions when applying these training styles to total body lifting with five exercises [83]. Similar results were found when these training styles were applied to elderly lifters [93], even when lower RT intensity was used (30 % of 1-RM) [94]. Together, these studies demonstrate that the low-intensity, slow-tempo style of RT (i.e., 7 seconds per repetition) can stimulate positive neuromuscular adaptations when used in concert with low external loads corresponding to 30–60 % of 1-RM.

Unfortunately, the researchers did not measure or report longitudinal outcomes for muscular endurance or aerobic fitness in these studies [66, 83, 93, 94]. However, in their discussions, the authors made a case that the slow-tempo style of lifting causes strong metabolic perturbation because the muscles slowly/constantly occlude blood vessels, which causes deoxygenation in a manner similar to BFR. This speculation warrants further investigation, and the assessment of whether low-intensity slow-tempo training stimulates increases in muscular endurance and aerobic fitness should be done. Moreover, it will be important for future researchers to match the TUT between conditions as the majority of the papers summarized in this section compared very different TUT (i.e. 56 vs 24 seconds) conditions, making it difficult to determine the effect of repetition tempos.

Traditional High-volume, Low-intensity RT

Resistance training adaptations (e.g., endurance, strength, and power) tend to be specific to the combination of training variables used during a program. The specificity of RT was best exemplified by Campos et al. [95] who reported that improvements in muscular endurance were greatest in the high-repetition group (2 sets; 20–28 reps), increases in muscular strength were greatest in the low-repetition group (4 sets; 3–5 reps), and hypertrophy only occurred in the low and intermediate-repetition groups (3 sets; 9–11 reps) [95]. Although their conclusions suggested that RT adaptations were largely specific to intensity, more recent evidence suggests that improvements for hypertrophy, strength, and power occur along a spectrum of 20–80 % of 1-RM [78, 79]. Moreover, Schoenfeld (14), in a recent meta-analysis concluded that low (< 60 % 1-RM) and high (> 65 % 1-RM) intensity RT have similar and positive effects on muscular strength (9 studies, n = 251) and hypertrophy (8 studies, n = 191). Thus, because high-volume, low-intensity RT stimulates hypertrophy and strength, it is intriguing to see if this style elicits unique benefits such as increased muscular endurance and aerobic fitness.

Acute metabolic effects of high-volume, low-intensity RT

Lactate, an anaerobic by-product that is formed when pyruvate binds to two hydrogen ions after glycolysis [92, 96], is often used as a proxy measure of metabolic stress during various styles of RT [89, 90]. Rogatzki et al. [67] demonstrated that endurance-style RT (2 sets, 20 reps, 50 % of 1-RM) elicited greater blood lactate response than hypertrophy (3 sets, 10 reps, 70 % of 1-RM) and strength (5 sets, 5 reps, 85 % of 1-RM) RT during back squat exercise. Similarly, da Silva et al. [68] showed a dose-response relationship between TUT and blood lactate concentration during 8, 10, and 12 RM training on the bench press. In addition to lactate, transient increases in the "anabolic hormones", such as growth hormone (GH), insulin growth factor 1 (IGF-1), and testosterone [97], have been indicated as proxy markers of metabolic stress during RT [98]. Fink et al. [87] demonstrated that training with 40 % of 1-RM significantly increased IGF-1 and GH after training with bench press and back squat. Compared to training with 8 RM, the same researchers reported that GH concentration was only elevated after training with 20 RM [88].

The preponderance of research summarized above suggests that metabolic stress increases as TUT and repetition number increase, especially when it is measured via blood lactate. However, there is a paucity of research that has compared the acute effect of different repetition ranges (e.g., 10-RM vs. 20-RM) and TUT (e.g., 30 vs. 60 seconds) on markers of metabolic stress, muscle oxygenation, and mitochondrial biogenesis during RT. Future researchers could design studies to match proximity to failure and repetition tempo (e.g., 2:1 sec), and have participants perform a lower-body exercise (e.g., belt squat) with external loads of 10-RM, 20-RM, and 30-RM with corresponding TUT of 30, 60, and 90 seconds. As suggested before, the researchers could measure muscle oxygenation, blood lactate, and markers of mitochondrial biogenesis for all conditions.

Chronic effects of high-volume, low-intensity RT

Several studies have compared the effect of low vs. high intensity RT to delineate if adaptations to RT are determined by the external load used. For instance, Leger et al. [99] recruited 25 healthy, untrained males and randomly assigned them to low (4 sets, 3–5 repetitions) or high (2 sets, 20–28 repetitions per set) volume RT. Their results showed that both training programs stimulated increased muscular hypertrophy, endurance, and strength with no differences between groups [85]. In a unilateral, within-subject research design, Mitchell et al. [78] recruited 18 healthy, untrained males, and randomly assigned their legs to one of three RT conditions: 3 sets with 30 % 1-RM, 1 set with 80 % 1-RM, and 3 sets with 80 % 1-RM. Data indicated that all groups significantly increased hypertrophy and strength. Interestingly, for muscular endurance tasks, the 30 % 1-RM condition, participants increased the number of repetitions that they could perform with 30 % and 80 % of their 1-RM. By contrast, neither 80 % 1-RM condition increased participants' repetition performance with 30 % of 1-RM [78].

Extending these research designs to trained subjects, Schoenfeld et al. [3] reported that low-load (25–35 reps, 30–50 % of 1-RM) and high-load (8–12 reps, 70–80 % of 1-RM) significantly increased hypertrophy and strength. Of note, muscular endurance (i.e., repetitions to failure with 50 % of 1-RM on bench press) only increased in the low-load group [3]. Moreover, when compared to a group of lifters who performed the same intensity for every training session (8–10 RM), those who performed a daily undulating periodization plan (2–4 RM, 8–10 RM, 25–35 RM) significantly increased repetition performance with 50 % of 1-RM on bench press [100]. This means that one weekly session of low-intensity RT was enough to improve muscular endurance. Collectively, the literature demonstrates that low-intensity, high-volume RT delivers several adaptations to RT (e.g., endurance, hypertrophy, and strength), and future research should be done to determine if such RT leads to increased oxidative capacity (i.e., at the skeletal muscle) and

improved aerobic performance. In particular, it would be interesting to determine if there are sex differences for such adaptations, as some research has demonstrated that females tolerate metabolic stress better [101] and can perform more repetitions at relative intensities compared to males [102].

Drop-set Resistance Training

A brief research review by Schoenfeld and Grgic [103] identified drop-set RT as an effective way to accrue high levels of training volume and to stimulate significant muscular adaptations in a short amount of time. To perform a drop-set, the initial set of RT with a fixed external load (e.g., 80 % 1-RM) is performed to muscular failure. From there, the load is immediately reduced by 20–25 % (i.e., no rest) and the lifter performs a subsequent set to muscular failure [103]. Although it is not strictly defined, the authors suggest that two to three drops are performed during one drop-set, and that the rest interval between drops should be kept to a minimum (i.e., just long enough to adjust the load and ensure that the lifter is in a proper starting position) [103]. When following these guidelines, it is likely that a lifter will perform 20–30 consecutive repetitions at intensities that correspond to 40–80 % 1-RM in just one set of exercise. Assuming a traditional 2:1 second eccentric to concentric repetition tempo (i.e., three second contractions), this translates to an approximate TUT of 60–90 seconds, which leads to significant metabolic stress, ischemia, and hypoxia [103]. Although the authors presented drop-set training as a means to evoke skeletal muscle hypertrophy [103], we submit that this style of RT could be used to stimulate peripheral adaptations that are typically associated with AT.

Acute metabolic effects of drop-set RT

Few studies have quantified the metabolic stress incurred during sessions of drop-set RT. For example, Goto et al. [104] demonstrated that the addition of one drop with 20, 30, or 50 % of 1-RM after finishing a standard session of RT (5 sets, 90 % of 1-RM) significantly increased GH and blood lactate. Years later, the same research team concluded that drop-set training stimulated significant decreases in muscle oxygenation, especially in trained lifters who have greater muscle thickness than their untrained counterparts [105]. Compared to straight-set training (i.e., no drop sets), Fink et al. [106] reported that drop-set RT elicited greater muscular swelling while increases in blood lactate were similar. Considering that volume (reps x % of 1-RM) was similar between groups (38.3 vs. 38.9 arbitrary units) the results from this study suggest that both training styles elicited significant metabolic stress but drop-set training did so in a more time-efficient manner (145 vs. 315 sec).

By examining the acute RT data summarized above, it is clear that drop-set training delivers a strong metabolic load to the skeletal muscle as indicated by increased blood lactate and decreased oxygenation during exercise. As previously theorized, metabolic stress and ischemia may be key factors that lead to peripheral adaptations that are intrinsic in AT such as increased vascularization, blood flow, and mitochondrial biogenesis. Future research should be done to evaluate the effect of drop-set RT on protein markers of these adaptations while measuring lactate and muscle oxygenation to help determine a cause-effect relationship between such training and peripheral aerobic adaptations.

Chronic effects of drop-set RT

In a longitudinal design, Goto et al. [107] concluded that strength training (5 sets, 90 % of 1-RM) and strength training with the addition of one drop set (25–35 repetitions with 40–50 % of 1-RM) both led to significant increases in endurance, strength, and rate of force development. However, the drop-set group had significantly greater increases in 1-RM for leg press, maximal isokinetic strength at a fast velocity (e.g., 300 degrees/second), and muscular endurance, which was quantified as total work performed (load x repetitions) during one set of knee-extension to failure with 30 % of maximal voluntary contraction [107]. Because total training volume was not matched, it is difficult to conclude if the differences between groups occurred strictly because of the metabolic stress imposed by the drop-set condition. Others reported that drop-set and traditional RT had similar effects on neuromuscular performance, especially muscular endurance [108]. Ozaki et al. [109] revealed that high-intensity RT (80 % of 1-RM) and drop-set RT (1 set with 80 % of 1-RM, 4 drop sets at 65, 50, 40, and 30 % of 1-RM) elicited similar increases in hypertrophy and strength while the drop-set condition led to better endurance. It is important to note that the drop-set training delivered significant adaptations despite the performance of ~1/3 of the training volume (5,308 vs. 15,365 kg) with sessions that required ~1/5 of the training time (2.1 vs. 11.6 minutes) compared to the low-load group [109].

Taken together, these studies support that drop-set RT is a time-efficient strategy to promote meaningful neuromuscular adaptations, especially muscular endurance. Indeed, when training volume is similar, it seems that drop-sets do not confer additional adaptations when compared to traditional forms of RT, but the concept of delivering such adaptations with shorter gym sessions is important considering that time is reported to be a barrier to exercise [103, 110]. Future research should be done to determine if drop-set RT leads to AT-like peripheral adaptations and if these adaptations lead to improved aerobic exercise performance.

Conclusions and Directions for Future Research

Traditionally, the physiological adaptations to AT and RT have been viewed through a dichotomous lens where AT stimulates the synthesis of mitochondrial proteins and RT stimulates the synthesis of myofibrillar proteins. Recent research suggests cross-over between these seemingly divergent training modalities as AT can cause RT adaptations and vice versa. As it pertains to RT, we submit that low-intensity, high-volume RT with high-TUT is an effective stimulus for peripheral aerobic adaptations such as increased capillary density, mitochondrial volume, and oxidative metabolism. This logical conjecture stems from the fact that RT with high-TUT leads to significant metabolic perturbation, ischemia, and skeletal muscle hypoxia, which upregulate signaling cascades for angiogenesis and mitochondrial biogenesis. More research is needed to identify the exact mechanism, but the results from several cell and rodent studies suggest that lactate may facilitate mitochondrial adaptations through the PGC-1α signaling cascade. In other words, the stress imposed by high-TUT RT reflects traditional forms of AT (i.e., HIIT), and the specific adaptations to this stress may be similar between

modalities. Research shows that slow-tempo, traditional, and drop-set training are all effective variations of high-TUT RT that increase skeletal muscle endurance, hypertrophy, and strength. Based on acute data, these training modalities also evoke significant metabolic stress and skeletal muscle hypoxia during exercise, and future research can determine if this stress leads to aerobic adaptations. Thus, there are several opportunities for future studies. Specifically, researchers should better quantify the acute metabolic stress of high-TUT RT by measuring muscle oxygenation, blood lactate, and upregulation of protein markers involved in angiogenesis and mitochondrial biogenesis. Moreover, it would be interesting to measure the chronic effect of high-TUT RT on aerobic capacity (e.g., VO_2max) and aerobic performance (e.g., 5-km time trial). The influence of training status is another possible area for research [30]. For example, it is likely that compared to trained lifters, untrained counterparts would incur more metabolic stress during high-TUT RT, which could potentially lead to superior long-term aerobic adaptations. It would be interesting to apply this logic to resistance trained participants who typically perform high-intensity, low-TUT RT. In other words, researchers can determine if performing sets of RT with 60–90 seconds of TUT provides a novel, aerobic stimulus for well-trained lifters who typically perform their RT sets with 10–30 seconds of TUT, and are, therefore, relatively untrained in high-TUT RT [111]. Finally, in a recent review by Schoenfeld et al. [112] it was concluded that the repetition range for hypertrophy and strength is very wide and that unique adaptations occur at either end of this spectrum (▶ **Fig. 2**). At the low intensity end of the spectrum, it would be interesting to follow the design of Lacerda et al. [91] and Vargas-Molina et al. [92] by matching TUT (e.g., 60 seconds) and proximity to failure (e.g., RPE of 8–9 out of 10) while varying repetition tempo within the matched TUT (e.g., 20 reps at 2:1 vs. 10 reps at 4:2 vs. 6 reps at 6:4) to evaluate the true effect of repetition tempo on aerobic (e.g., mitochondrial biogenesis) and resistance (e.g., strength) adaptations. Similar study designs can be applied to higher-intensity RT with shorter TUT (e.g., 30 seconds).

Ethical Standards

The authors confirm that the current review meets the ethical standards of the International Journal of Sports Medicine as outlined by Harriss et al. [113].

Conflict of Interest

The authors declare that they have no conflict of interest.

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