

Physical activity as a metabolic stressor¹⁻³

Edward F Coyle

ABSTRACT Both physical activity and diet stimulate processes that, over time, alter the morphologic composition and biochemical function of the body. Physical activity provides stimuli that promote very specific and varied adaptations according to the type, intensity, and duration of exercise performed. There is further interest in the extent to which diet or supplementation can enhance the positive stimuli. Prolonged walking at low intensity presents little metabolic, hormonal, or cardiovascular stress, and the greatest perturbation from rest appears to be from increased fat oxidation and plasma free fatty acid mobilization resulting from a combination of increased lipolysis and decreased reesterification. More intense jogging or running largely stimulates increased oxidation of glycogen and triacylglycerol, both of which are stored directly within the muscle fibers. Furthermore, these intramuscular stores of carbohydrate and fat appear to be the primary substrates for the enhanced oxidative and performance ability derived from endurance training-induced increases in muscle mitochondrial density. Weightlifting that produces fatigue in brief periods (ie, in 15–90 s and after 15 repetitive contractions) elicits a high degree of motor unit recruitment and muscle fiber stimulation. This is a remarkably potent stimulus for altering protein synthesis in muscle and increasing neuromuscular function. The metabolic stress of physical activity can be measured by substrate turnover and depletion, cardiovascular response, hormonal perturbation, accumulation of metabolites, or even the extent to which the synthesis and degradation of specific proteins are altered, either acutely or by chronic exercise training. *Am J Clin Nutr* 2000;72(suppl):512S–20S.

KEY WORDS Exercise, physical activity, exertion, nutrition, carbohydrate, triacylglycerol, protein synthesis, hormone, muscle

INTRODUCTION

It is becoming increasingly clear that a person's health and well-being are improved by physical activity as well as by a nutritious diet (1). Both physical activity and diet stimulate processes that, over time, alter the morphologic composition and biochemical function of the body. Physical activity and diet are interrelated in that optimal adaptation to the stress of exercise training usually requires a diet that is not lacking in various nutrients. The optimal amount of dietary nutrients for effective adaptation is a theme of this journal supplement. Physical activity should therefore be viewed as providing stimuli that stress various systems of the body to various degrees and thus promote

very specific and varied adaptations according to the type, intensity, and duration of exercise performed.

STRESS OF PHYSICAL ACTIVITY

A conceptual scheme of the stress, stimuli, and adaptation derived from physical activity in skeletal muscle is shown in **Figure 1**. Carbohydrate, fat, and protein, obtained either directly from daily meals or from endogenous stores in the body, provide the substrates that fuel the chemical reactions that in turn are catalyzed by enzymes and cofactors. In the process of these reactions, the chemical energy in substrates is converted to the type of chemical energy that cells can harness, namely ATP. ATP can be resynthesized anaerobically by dissolving glucose or glycogen (glycolysis) in the cytoplasm of cells, or it can be resynthesized aerobically by chemical reactions within the mitochondria that consume oxygen. These metabolic reactions proceed at the rates required to maintain ATP concentrations in the cells. Thus, increasing exercise intensity increases metabolic rate as reflected by increasing rates of chemical reactions, oxygen consumption, and substrate depletion. The resynthesis of ATP during exercise signals a disturbance in metabolic homeostasis and provides powerful stimuli to the cell that eventually cause it to adapt to aerobic exercise training, generally by altering the balance between select protein synthesis and protein degradation (Figure 1). Increases in mitochondrial protein within skeletal muscle as a result of aerobic endurance training are generally thought to be stimulated by some aspect of ATP resynthesis (2).

In muscle, the chemical energy released by ATP hydrolysis during contraction is converted to either heat or muscle force. Muscle force develops from the tension generated by the interaction of the actin-myosin filaments and produces a mechanical loading on the muscle fibers that also provides stimuli for muscle adaptation. In this case, however, mechanical force on muscle fibers stimulates an increase in the actin-myosin mass within the muscle fiber, again by altering the balance between synthesis and degradation of these specific proteins (3). This process describes the hypertrophy that occurs with weightlifting, as discussed below.

¹From the Human Performance Laboratory, Department of Kinesiology and Health Education and Division of Nutritional Sciences, University of Texas at Austin.

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³Address reprint requests to EF Coyle, University of Texas at Austin, Room 222, Bellmont Hall, Austin, TX 78712.

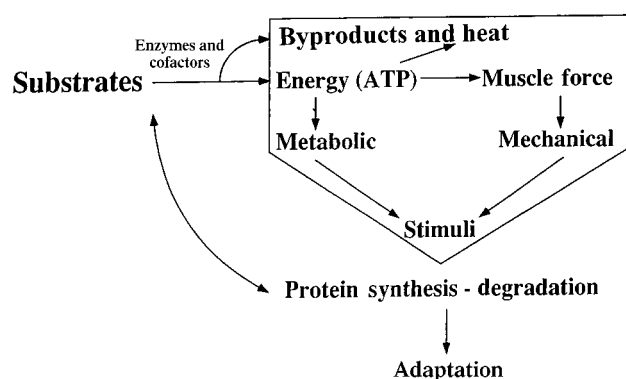


FIGURE 1. Theoretical scheme of the metabolic and mechanical stress on skeletal muscle during and after physical activity.

Attempt to maximize positive stress while minimizing negative stress

The metabolic and mechanical stresses of physical activity stimulate many healthful adaptations in numerous tissues and organs in a dose-response manner (4). In this context, the stress of physical activity can elicit an overall positive outcome, reflected by a reduced risk of heart disease on the one hand and increased physical performance on the other (5). However, physical activity can also place various tissues under acute stress. An underlying question for this journal supplement is the extent to which diet or supplementation can enhance the positive stimuli of physical activity and reduce the negative stimuli so as to optimize the healthful adaptations and improvements in physical performance.

Measures of the metabolic stress of physical activity

In a general sense, the metabolic stress of physical activity can be gauged by fluxes generated within the exercising muscles in any or all of the reactions illustrated in Figure 1. It is most common to quantify ATP turnover during continuous aerobic, steady state exercise by measuring whole-body oxygen consumption. When a person lifts weights, typically for a short duration (eg, 10–30 s), ATP resynthesis is derived largely from anaerobic glycolysis, and the stress of exercise is commonly gauged from the muscle force developed. Muscle force is proportional to the amount weightlifted through a given range of motion. Other less practical and more specific ways of quantifying the various aspects of metabolic stress during physical activity include measurement of substrate turnover (ie, flux or kinetics) (6), substrate depletion (7, 8), enzymatic activity in muscle (9), heat production (10), or accumulation of metabolites (eg, lactate, hydrogen ion, ammonia, and hexose monophosphates) (11). It is even possible to use molecular techniques to probe the extent to which the synthesis and degradation of specific proteins are altered by acute physical activity or chronic exercise training (2, 3).

Increased metabolism in the active skeletal musculature must be supported, and sometimes initiated, by other systems of the body, especially the nervous, cardiovascular, endocrine, and respiratory systems (12). The metabolic stress of physical activity can also be gauged generally by the extent to which each of these systems is activated to respond. However, each of these unique systems differs somewhat in its threshold and sensitivity to the various components of metabolic stress. For example, heart rate, cardiac output, systolic blood pressure, muscle blood flow, and

plasma norepinephrine concentration all increase linearly with increasing intensity of aerobic exercise (13). Ventilation, muscle glycogenolysis, and plasma epinephrine concentration also increase with intensity of aerobic exercise but at a nonlinear rate as the metabolic stress becomes progressively more severe (13). Examples of many other types of responses could be given. The salient point is that each marker of the various systems is responding to a unique stress that its end organ is experiencing during physical activity.

Determinants of metabolic stress of physical activity

Within a given individual, the metabolic stress during physical activity is generally determined by the type and intensity of exercise, state of physical fitness, nutritional status, and environmental factors. To some extent, these determinants of metabolic stress can be controlled. Other factors that influence the metabolic stress an individual experiences during physical activity include genetic disposition, age, and sex.

Intensity and type of exercise

This paper compares the metabolic stress encountered while walking, running, and lifting heavy weights. Physical activity can be quite varied, but these 3 common activities provide good examples of the influence of increasing the intensity of prolonged aerobic exercise from walking to running and of repeatedly generating high muscle forces for short durations (ie, weightlifting). For example, presented in **Table 1** are the responses of a typical adult who engages in regular exercise and is of above-average fitness with a maximal oxygen uptake ($\dot{V}O_2\text{max}$) of $45 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ relative to body weight (ie, 3 L/min in absolute terms). Walking at 4.8 km/h (3 miles/h) would elicit $\approx 33\%$ of $\dot{V}O_2\text{max}$ in this person, which corresponds to a rate of energy expenditure of $\approx 1.25 \text{ MJ/h}$ (300 kcal/h). Healthy persons can walk for many hours at this rate. This typical person could run comfortably at 65% of $\dot{V}O_2\text{max}$ (ie, 2.5 MJ/h, or 600 kcal/h) and cover 10 km in 1 h. This would be classified as moderate- to high-intensity exercise.

Lifting heavy weights while performing actions such as leg squats, bench presses, or arm curls causes fatigue after relatively few repetitions. The intensity of weightlifting is quantified as a percentage of a person's one-repetition maximum (1RM; ie, the heaviest weight an individual can lift just one time) (14). As indicated in **Table 2**, a person can usually lift 65% of his or her 1RM for 15 repetitions and for ≈ 1 min before fatiguing. Also shown in **Table 2** is the extent to which the number of repetitions, until fatigue, declines with increases in the percentage of 1RM. For general skeletal-muscular fitness, the recommended minimum is 1 set of 8–12 repetitions of 8–10 exercises that condition the major muscle groups ≥ 2 d/wk. People can comfortably progress to completing 3 sets of each exercise 3–4 times/wk.

NEUROMUSCULAR RECRUITMENT

Movement is initiated by the central nervous system. It begins with activation of the motor cortex in the brain and depolarization of the corticospinal neurons that innervate the α motor neurons in the spine. These neurons lead to the muscle fibers that power activity. As the intensity of exercise increases, the higher muscle forces and power outputs are generated by both recruiting more motor units (ie, the motor neuron and its muscle fibers) per contraction and increasing the firing frequency with which a

TABLE 1
Aerobic metabolic stress for a typically active 30-y-old when walking and jogging¹

Activity	Percentage of $\dot{V}O_2$ max		Energy expenditure		METs
	%	L/min	MJ/h (kcal/min)		
Walking (4.8 km)	33	1.0	1.25 (300)		3–4
Jogging (9.7 km)	65	2.0	2.50 (600)		6–8

¹This example applies to a person with a maximal oxygen consumption ($\dot{V}O_2$ max) of 3 L/min (ie, 45 mL·kg⁻¹·min⁻¹) and a body weight of 66 kg. METs, metabolic equivalent relative to rest (the number of times that oxygen consumption is elevated above resting metabolic rate).

given motor unit is recruited (15). A theoretical example of the pattern with which fibers in the vastus lateralis muscle are recruited during cycling and running of increasing exercise intensity is depicted in **Figure 2**. Walking or cycling at low intensity is believed to recruit mostly the type I motor units that innervate the slow-twitch muscle fibers because they have a low threshold for recruitment (15). On average among a population, approximately one-half of the fibers in the vastus lateralis are slow-twitch fibers, yet values can range from 20% to 80% (16). Running or cycling at 65% of $\dot{V}O_2$ max recruits both type I and some type IIa motor units (fast-twitch A fibers). The type IIb motor units innervating the fast-twitch B muscle fibers are not recruited to contract until the exercise intensity is high.

As indicated in Figure 2, an exercise intensity that elicits 100% of $\dot{V}O_2$ max, which can be maintained for 3–8 min before fatiguing, requires a muscular force that is only 30–60% of 1RM or maximal power. It appears that in the vastus lateralis muscle, force production >30–60% of 1RM is generated not so much by recruiting more muscle fibers but by increasing the frequency of fiber recruitment per contraction to attain the greater instantaneous actin-myosin interaction. Various muscles throughout the body differ markedly in the pattern with which they increase the number of fibers recruited compared with the frequency of recruitment to generate higher forces as acute exercise intensity increases. Thus, only one example is shown in Figure 2. This understanding also indicates that the improvement in 1RM that people typically experience after a chronic (eg, several weeks) training program of weightlifting is due partly to neurologic adaptations that are thought to increase the number and frequency of motor unit recruitment (15).

Muscle fibers that are very rarely recruited to contract are obviously under little metabolic stress and thus receive minimal stimuli. An important point of Figure 2 and the preceding discussion is that many of our skeletal muscle fibers, especially the higher-threshold, fast-twitch ones, would not be expected to be sufficiently active when a person does not engage in periodic, high-intensity, aerobic exercise or weight training. It is impressive that only 10 contractions per training session, lasting only 40 s, appear to be a powerful stimulus for some aspects of muscle adaptation (17, 18).

Substrate storage and maximal rates of utilization

The major substrates for ATP resynthesis in active muscle are fat and carbohydrate; protein plays a minor role except in extreme conditions analogous to starvation (19). Fat is stored as triacylglycerol, mostly in adipocytes throughout the body. For example, in a 66-kg person with 18% body fat, this amounts to >480 MJ

energy (100000 kcal), which is enough to fuel \approx 1600 km (1000 miles) of walking (assuming \approx 0.3 MJ/km or 100 kcal/mile). Triacylglycerol is also stored directly within individual muscle fibers [intramuscular triacylglycerol (IMTG)]. The amount of these IMTG stores is less well studied but is assumed to contain \approx 12–20 MJ energy (19). For triacylglycerol to be oxidized in skeletal muscle during exercise, it must first be hydrolyzed by the process of lipolysis to free fatty acids and transported to the metabolically active inner mitochondria (20). The fatty acids generated from adipocyte triacylglycerol are either reesterified or released from the cell for potential binding to plasma albumin, the major protein carrier in the bloodstream (20). These circulating plasma fatty acids are then available for uptake by tissue. The active skeletal muscles oxidize 80–90% of the fatty acids disappearing from the circulation (21) and the remainder are presumably reesterified. Transport of fatty acids from IMTG to the outer mitochondrial membrane is less complicated.

All fatty acids must be transported across the mitochondrial membrane for oxidation, and this may be a rate-limiting step. For example, the common long-chain fatty acid palmitate is transported via the carnitine *O*-palmitoyltransferase reaction, which is greatly inhibited by malonyl-CoA (22). This metabolite has been proposed as a fuel sensor (23) because it increases when either carbohydrate or fat is available and declines during exercise in the fasting state (24). Indeed, our laboratory observed that plasma palmitate oxidation during exercise is actively reduced when blood glucose uptake and glycolytic flux are increased (21). Furthermore, this phenomenon seems to involve reduction in mitochondrial transport, on the basis of the observation that oxidation of a medium-chain fatty acid (ie, octanoate) is neither limited nor reduced by increased glycolytic flux. It is our hypothesis that fatty acid oxidation may be limited to some extent by carbohydrate availability, which reduces fatty acid transport into mitochondria (21). This hypothesis implies that when carbohydrate and fatty acids are both readily available to muscle during exercise, carbohydrate seems to be preferred. However, people do not normally have the ability to run at 65% of $\dot{V}O_2$ max while oxidizing mostly fatty acids (ie, >70% of energy). For this reason, when carbohydrate availability is very low, such as during the muscle glycogen depletion and hypoglycemia that is typically experienced after 2–3 h of exercise, people normally are not able to exercise more intensely than 40–60% of $\dot{V}O_2$ max (25).

TABLE 2
Classification of the intensity of weightlifting for physically active people

Intensity	Percentage of 1RM ¹	Estimated number of repetitions possible ²
	%	
Very heavy	95–100	1–2
Heavy	90–95	2–6
Moderately heavy	85–90	3–8
Moderate	80–85	5–10
Moderately light	75–80	7–12
Light	70–75	10–15
Very light	65–70	15

¹1RM, one-repetition maximum (the maximal weight that can be lifted through one full range of motion).

²The estimated number of repetitions possible will depend on the person's strength-to-endurance ratio (14).

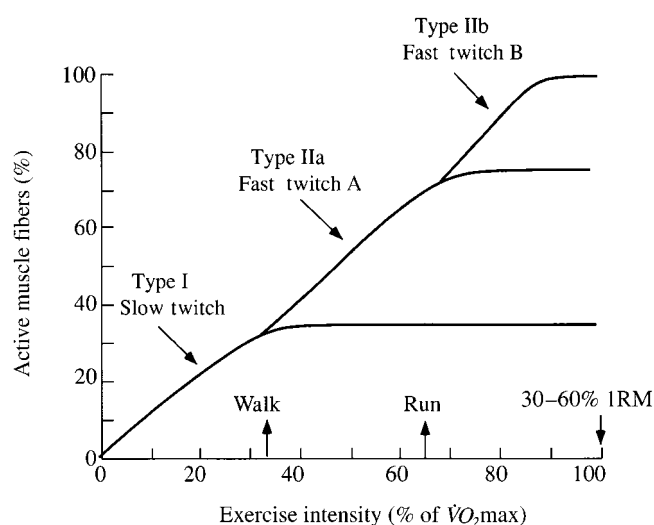


FIGURE 2. Theoretical relation between exercise intensity and the percentage of active muscle fibers in the vastus lateralis during cycling. Exercise intensity is expressed as a percentage of maximal oxygen consumption (% of $\dot{V}O_2\text{max}$) as well as a percentage of the one-repetition maximum (1RM). Note that 100% of $\dot{V}O_2\text{max}$ corresponds to $\approx 30\text{--}60\%$ of 1RM. The muscle fiber (slow and fast twitch) and motor neuron types (type I, IIa, or IIb) that are progressively recruited are indicated (15).

Other possible explanations for a limit in the rate of oxidation that can be supported solely by fatty acids during exercise may involve an anaplerotic loss of tricarboxylic acid cycle intermediates that requires replenishment from carbohydrate (26–28). Although definitive answers are lacking, it is clear that availability of carnitine for mitochondrial transport of fatty acids during exercise is not limiting and that carnitine supplementation is not beneficial in normal individuals and athletes (29, 30). Triacylglycerol in blood, another substrate, appears to be only slowly converted to fatty acids and thus is not thought to be a major substrate during exercise (31), although it is probably important for replenishment of IMTG stores after exercise.

Carbohydrate is stored in the body as glycogen, a starch comprising glucose molecules that can be readily hydrolyzed. Glycogen is stored directly in the muscle fiber and is the major source of carbohydrate during most types of exercise. The amount of glycogen stored in skeletal muscle can vary with diet and training, but it is generally in the range of 6–10 MJ (1500–2500 kcal) (19). A most important aspect of muscle glycogen hydrolysis is that it can be quickly activated to resynthesize ATP at high rates—up to 1.5–2-fold of $\dot{V}O_2\text{max}$. These high-intensity “sprints” cannot be maintained for $>30\text{--}60$ s because lactic acid accumulates in muscle and eventually inhibits excitation-contraction coupling. Glycogen stores in the liver amount to ≈ 1 MJ (240 kcal) when fed and serve primarily to maintain blood glucose concentration. As exercise intensity increases, the working muscles increase glucose uptake from blood, and to maintain blood glucose concentration, liver glucose output must increase (32). In addition to liver glycogen, blood glucose can be generated from liver glycogenolysis or from the entry of ingested glucose into the splanchnic circulation (33). Blood glucose uptake during exercise can increase to ≈ 1 g/min during prolonged exercise, which normally elicits low plasma insulin (34–37). However,

during prolonged exercise with hyperinsulinemia and hyperglycemia, blood glucose uptake can reach 2.5 g/min (38).

METABOLIC STRESS OF LOW-INTENSITY AEROBIC EXERCISE

In the fasting state

Shown in **Figure 3** is the substrate oxidation observed in well-trained cyclists at rest and after 30 min of exercise after an overnight fast (6). At rest, oxidative needs can be met by plasma fatty acids and blood glucose. During exercise at 25% of $\dot{V}O_2\text{max}$, metabolic rate is increased 3- to 4-fold above rest, a requirement met primarily by an increase in mobilization, uptake, and oxidation of plasma fatty acids (6). Blood glucose uptake increases only slightly. Low-intensity exercise markedly increases mobilization of plasma fatty acids (ie, rate of appearance of fatty acids into plasma), partly because exercise stimulates increased lipolysis and largely because the rate of reesterification of fatty acids within the adipocytes diminishes remarkably, from $\approx 80\%$ at rest to 20% during exercise (39). Lipolysis in adipose tissue is increased during exercise primarily because epinephrine stimulates β -adrenergic receptors (40) and because plasma insulin, a potent inhibitor of lipolysis, decreases (32, 41). Metabolic stress during low-intensity exercise is not great and thus responses remain relatively stable, not differing substantially after 30 min from those observed after 2–4 h (6). Blood glucose kinetics, and thus concentration, appear stable, as do plasma fatty acid kinetics and total fat oxidation (6). Accordingly, the hormonal responses that are indicative of metabolic stress are also not substantially altered. For example, plasma epinephrine and norepinephrine are only slightly increased above resting values (6). Plasma cortisol actually declines throughout prolonged low-intensity exercise, probably as a result of increased clearance (42). These responses are consistent with the observation that people can walk for many hours without much metabolic stress (43).

After eating a meal

Fatty acid mobilization and oxidation are markedly reduced when a meal containing carbohydrate is eaten during the hours before exercise, or even when carbohydrate is eaten during low-intensity exercise (33, 44, 45). Of course, carbohydrate ingestion at rest or during very low-intensity exercise with minimal increases in catecholamines will stimulate insulin secretion. Insulin is a potent inhibitor of lipolysis and plasma fatty acid mobilization and is a potent stimulator of muscle glucose uptake (41, 46). With both of these effects of insulin, substrate oxidation shifts from plasma fatty acids to blood glucose (21, 44, 46). The source of the increased carbohydrate oxidation appears to be largely blood glucose from the ingested carbohydrate (46). Therefore, eating before or during low-intensity exercise does not seem to present much metabolic stress because it does not appreciably increase endogenous glucose utilization. In fact, if the amount of carbohydrate in the meal is larger than the increase in carbohydrate oxidation that it stimulates, glycogen and glucose stores in the body will increase (47).

State of physical fitness

Endurance training is well known for increasing fat oxidation during exercise, partly because of increases in mitochondria, which contain the necessary oxidative enzymes (5). For example,

when walking at the same speed that elicits an absolute oxygen consumption of $20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, endurance-trained persons displayed a rate of fat oxidation that was 32% higher than that of untrained subjects (48). This speed elicited 28% of $\dot{V}O_{2\text{max}}$ in the trained subjects and 43% of $\dot{V}O_{2\text{max}}$ in the untrained subjects. Interestingly, rates of lipolysis and plasma fatty acid mobilization were not significantly different, and even the rates of plasma fatty acid disappearance from the circulation were similar in untrained and endurance-trained subjects. In untrained subjects, the rates of plasma fatty acid mobilization were in excess of total fat oxidation during exercise. Thus, the limiting factor for fat oxidation does not appear to be the availability of fatty acids. It is assumed that the muscle's intrinsic ability to oxidize fat limits its oxidation, possibly owing to suboptimal mitochondrial density (5).

During low-intensity exercise, the endurance-trained subjects, who probably had an increase in mitochondrial density of ≈ 2 -fold (5), showed a close matching between plasma fatty acid disappearance and total fat oxidation (6, 48). Thus, the major effect of endurance training for increasing fat oxidation during low-intensity exercise does not appear to be an increase in lipolysis or plasma fatty acid mobilization; rather, endurance training increases the matching between plasma fatty acid disappearance and total fatty acid oxidation, probably owing to increased mitochondrial density.

Because fat oxidation is increased in endurance-trained subjects, carbohydrate oxidation must be reduced. It is interesting that this reduction in carbohydrate oxidation is partly due to a reduction in muscle glucose uptake (49). This is despite the fact that skeletal muscle in endurance-trained subjects is more sensitive to insulin and also possesses more of the proteins (ie, protein glucose transporter measured in the total muscle) responsible for transporting glucose into the muscle (50). Thus, the disparity between the isolated biochemical properties of the muscle, which would seem to favor increased glucose uptake during exercise, and the actual observation of reduced glucose uptake during whole-body exercise indicate that other factors are involved that are not clearly understood.

METABOLIC STRESS OF MODERATE- TO HIGH-INTENSITY AEROBIC EXERCISE

In the fasting state

The sources for substrate oxidation after 30 min of moderate- to high-intensity exercise at 65% of $\dot{V}O_{2\text{max}}$ in endurance-trained subjects who fasted overnight are shown in Figure 3. The increase in oxygen consumption and thus mitochondrial respiration for increased ATP resynthesis is generated by the greater disturbance of metabolic homeostasis in the muscle fiber during more intense exercise (5). These metabolic disturbances [ie, increased ADP, AMP, and inorganic phosphate concentrations (51)] also serve to accelerate muscle glycogenolysis, thus contributing to the large increase in total oxidation in general and carbohydrate oxidation in particular. Blood glucose uptake by muscle also increases with increasing intensity of exercise. However, its contribution to total energy is not yet very high after only 30 min of exercise (Figure 3). Heavy reliance on muscle glycogen is necessary because fat, for the reasons discussed above, cannot be oxidized at sufficiently high rates during moderate- to high-intensity exercise. Interestingly, the rate of plasma

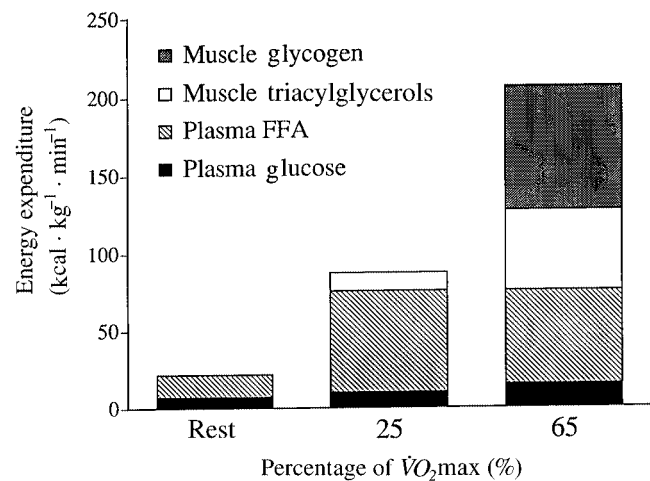


FIGURE 3. Contribution of the 4 major substrates to energy expenditure at rest and after 30 min of exercise at 25% and 65% of maximal oxygen consumption ($\dot{V}O_{2\text{max}}$) in well-trained men when fasted. FFA, free fatty acids. To convert kcal to kJ, multiply by 4.184. Adapted from Romijn et al (6).

fatty acid mobilization and uptake during exercise does not increase as the intensity increases from 25% to 65% of $\dot{V}O_{2\text{max}}$, despite large increases in plasma catecholamines. It seems that plasma fatty acid mobilization during exercise is quite responsive to the low amount of hormonal activation typical of low-intensity exercise. However, total fat oxidation is markedly higher during exercise at 65% of $\dot{V}O_{2\text{max}}$ than at 25% of $\dot{V}O_{2\text{max}}$, apparently because of the marked oxidation of fatty acid from IMTG. Although little is known about the factors that stimulate lipolysis of IMTG (52), it is suspected to be responsive to some of the same factors that activate muscle glycogenolysis, at least during moderate- to high-intensity exercise (20).

There is practical interest in identifying the exercise intensity that oxidizes (ie, burns) the most body fat. As indicated in Figure 3, during exercise at 25% of $\dot{V}O_{2\text{max}}$, a high percentage (≈ 60 –85% of $\dot{V}O_{2\text{max}}$) of energy is derived from fat, whereas during exercise at 65% of $\dot{V}O_{2\text{max}}$, ≈ 50 % of the energy is derived from fat. However, because the total energy expenditure is 2- to 3-fold higher at 65% of $\dot{V}O_{2\text{max}}$ than at 25% of $\dot{V}O_{2\text{max}}$, the actual absolute rate of fat oxidation ($\text{MJ} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ or $\text{kcal} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) is much higher at the higher intensity, largely owing to oxidation of IMTG. In terms of using exercise that can be performed for only a limited amount of time (eg, 1 h/d) to lower body fat stores, it seems that exercise at 65% of $\dot{V}O_{2\text{max}}$ would be more effective than exercising at 25% of $\dot{V}O_{2\text{max}}$, because absolute fat loss from the body would be higher.

Prolonged exercise

Shown in Figure 4 are the alterations in substrate mix that occurred throughout several hours of exercise at 65–75% of $\dot{V}O_{2\text{max}}$ in endurance-trained men after an overnight fast (6, 19, 53). The relative contribution of fat and carbohydrate changes only slightly: fat oxidation increases and carbohydrate oxidation declines slightly. The most dramatic shift in substrate oxidation occurs in the source of carbohydrate energy. With increasing

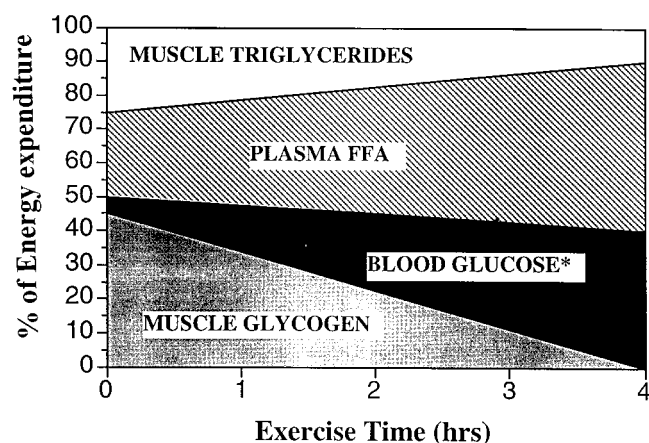


FIGURE 4. Percentage of energy derived from the 4 major substrates during prolonged exercise at 65–75% of maximal oxygen uptake. Initially, approximately one-half of the energy is derived each from carbohydrate and fat. As muscle glycogen concentration declines, blood glucose becomes an increasingly important source of carbohydrate energy for muscle. *After 2 h of exercise, carbohydrate ingestion is needed to maintain blood glucose concentration and carbohydrate oxidation. FFA, free fatty acids. Reproduced from reference 19 with permission. Copyright American Society for Clinical Nutrition.

duration of exercise, the contribution of muscle glycogen declines as its stores are lowered, and the contribution of blood glucose increases to remarkably high amounts. This shift from muscle glycogen to blood glucose is necessary to maintain the total carbohydrate oxidation that is required of exercise at this intensity because of the limitations in fat oxidation. This progressive and heavy reliance on blood glucose oxidation forms the basis for carbohydrate ingestion during prolonged exercise (53). After 1–2 h of exercise at these intensities, blood glucose concentration begins to decline because of an imbalance, whereby glucose disappearance from blood becomes greater than glucose appearance into blood (36, 53). Reductions in liver glycogen stores contribute to the inability to maintain blood glucose concentration. As a result, people exercising in the fasted state usually become hypoglycemic (ie, blood glucose <3 mmol) during the third hour and then become fatigued (25, 53). Fatigue is preceded by a decline in carbohydrate oxidation and is related to the depletion of muscle glycogen with concomitant hypoglycemia. The metabolic stress of substrate depletion in the exercising muscles at the point of fatigue suggests an energy production imbalance (eg, ATP flux), as reflected by increased ammonia concentrations (28). Carbohydrate ingestion throughout exercise maintains blood glucose concentration and carbohydrate oxidation, which delays fatigue (54).

The stress of moderate- to high-intensity exercise is reflected in hormonal responses, which, among other functions, serve to regulate substrate utilization and cardiovascular responses. After 30 min of exercise at 65% of $\dot{V}O_2\max$, plasma epinephrine and norepinephrine are elevated \approx 4- to 6-fold above resting values (6, 55). Hypoglycemia markedly stimulates epinephrine release, probably in an attempt to attenuate reductions in blood glucose concentration by increasing liver glucose output and/or reducing glucose uptake (56, 57). The fatigue experienced from hypoglycemia and muscle glycogen depletion is also associated with marked elevations in plasma cortisol, indicating activation of the

hypothalamic-pituitary-adrenal axis (58). These hormonal markers of metabolic stress influence numerous physiologic systems, and some of the responses do not appear to be productive. For example, elevation of cortisol is believed to acutely reduce immune function (59). This is thought to be a possible cause of the observation that chronically stressed individuals, especially those who are performing exhaustive exercise on a daily basis, appear to be more susceptible to upper respiratory tract infections (59, 60).

After eating a meal

Total fat oxidation during the first 100 min of exercise is markedly suppressed and carbohydrate oxidation is obviously increased when carbohydrate is ingested during the 6 h before moderate- to high-intensity exercise (44, 61). The observation that fat oxidation increases as exercise duration increases is largely due to the reversal of this suppression of fat oxidation resulting from the last meal. This effect is related to the insulin effect of the meal, which appears to persist long after plasma insulin has returned to fasting values (44, 61). This observation is supported by the finding that increases in plasma glycerol concentration during exercise, an index of lipolysis, were blunted for \leq 12 h after ingestion of carbohydrate (44). Preexercise carbohydrate ingestion reduced oxidation of both plasma fatty acid and IMTG (21). There is much practical interest as to whether preexercise carbohydrate feedings that raise insulin sufficiently, as do almost all carbohydrate feedings, should be avoided. These feedings also produce a phenomenon in which blood glucose concentration declines during the first 30 min of exercise (44, 62), most likely because of increased blood glucose uptake by muscle (46). It seems that the determinant of whether metabolic stress is increased depends on whether the reduction in fat oxidation is met by a sufficient increase in blood glucose oxidation. If not, muscle glycogen oxidation might be increased (62), an effect that could be interpreted as increased metabolic stress. With the idea that preexercise carbohydrate feedings should be sufficiently large to stimulate a sufficiently high muscle glucose uptake to offset reduced fat oxidation, persons are practically advised to ingest \geq 1 g carbohydrate, rather than smaller amounts, per kilogram body weight before exercise (19).

State of physical fitness

The increased fat oxidation during moderate-intensity exercise that is characteristic of endurance training appears to be due solely to increased oxidation of IMTG. In a 2-study series, exercise metabolism was measured before and after training at the same absolute intensity that elicited 64% of pretraining $\dot{V}O_2\max$ (63, 64). Of interest was the observation that total fat oxidation increased during exercise despite a significant reduction in plasma fatty acid mobilization and oxidation (64). Direct measures of IMTG use in muscle confirmed that its use increased dramatically with endurance training, and calculations suggested that it could account for the entire increase in fat oxidation (63). Conversely, muscle glycogen use was reduced (63), and blood glucose uptake was also found to be reduced (49). It appears that the increase in both mitochondrial density and IMTG use are functionally related, which is interesting because these IMTG droplets are often in physical contact with the mitochondria (65). The mitochondria provide the cellular organelles for oxidation with less disturbance of homeostasis, and thus less glycogenolysis, and the IMTG provides the substrate for the shift from carbohydrate to fat oxidation.

CARDIOVASCULAR STRESS OF AEROBIC PHYSICAL ACTIVITY

The cardiovascular system supports physical activity primarily by ensuring adequate delivery of blood carrying oxygen, substrates, and hormones to the exercising muscles. The removal of metabolic waste products from muscle, as well as the dissipation of heat from the body, are other important cardiovascular functions during physical activity. The most functional cardiovascular responses involve generation of the appropriate arterial blood pressure and blood flow to various organs (14, 66, 67). The central nervous system responds immediately to physical activity by increasing the efferent activity of the sympathetic nervous system to the heart and blood vessels while withdrawing parasympathetic activity (60, 67).

Sensory (ie, afferent) nerves monitor the metabolic status of exercising muscles, as well as blood pressure and other factors (eg, oxygen content, pH, and temperature) in several areas of the circulation, thus providing feedback to the central nervous system regarding the adequacy of cardiovascular responses (66). Aerobic exercise stimulates a metabolite-induced local vasodilatation in the arterioles of the contracting muscles, thus dramatically increasing blood flow, provided that blood pressure is maintained or increased. The nervous system responds to this challenge by increasing activity in the sympathetic nerves that release norepinephrine in the heart, thereby increasing the heart rate. Norepinephrine released in the kidneys, liver, and resting muscle increases vascular resistance to these organs (67). Therefore, the basic pattern of response is an increase in heart rate and cardiac output with increased exercise intensity and an even more dramatic increase in muscle blood flow as an increasingly greater percentage of cardiac output is directed to the exercising muscles (67).

Blood flow to muscle during several minutes of dynamic exercise with a small muscle mass (eg, using just the knee extensors) can increase blood flow per kilogram of active muscle to values as high as $3 \text{ L} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (68). These concentrations could be considered to be hyperperfusion, owing to the relatively high content of oxygen in venous blood (67). This innate muscle capacity for high blood flow can present a severe challenge to the cardiovascular system during exercise that recruits a large muscle mass (eg, running or cycling), because the ability of this large mass to accept blood flow can easily exceed maximal cardiac output (12, 68). Therefore, during intense aerobic exercise with a large muscle mass, blood flow per kilogram muscle is typically reduced to 1–2 L/min by increased sympathetic nerve activity that superimposes vasoconstriction on metabolite-induced vasodilatation. This balanced response maintains the appropriate arterial blood pressure and minimizes overperfusion of the exercising muscle (68).

Heart rate provides a generally reasonable and practical measure of the degree of cardiovascular stress during physical activity. Thus, intensity is typically rated as a percentage of maximal heart rate (4). However, the highest heart rate a person can achieve during exercise is proportional to the amount of muscle mass activated (69). For example, during exercise with just the arms, a person may not be able to elevate the heart rate above 130 beats/min, even if the exercise is performed to the point of extreme fatigue. However, during intense running that involves large leg muscles, a typical 30-y-old can raise the heart rate to 180–190 beats/min.

The metabolic stress encountered in exercising muscles influences the cardiovascular responses of heart rate and blood pressure. The most important cardiovascular adaptation to

endurance training is an increased stroke volume during exercise (67). This allows cardiac output and muscle blood flow to be achieved with a reduced heart rate during submaximal exercise at a given absolute intensity. Furthermore, the biochemical adaptations in muscle that reduce disturbance of metabolic homeostasis also seem to be important for reducing the heart rate's response to exercise by causing less stimulation of afferent nerves in muscle (66).

Typically, the fatigue experienced in exercising muscles limits a person's tolerance for aerobic exercise and thus the cardiovascular system generally does not display signs of dysfunction, at least in persons free of ischemic heart disease or other diseases. However, the extent of cardiovascular stress during aerobic exercise can be greatly increased by hyperthermia and dehydration. Dehydration and hyperthermia can each individually reduce stroke volume during exercise (70). Furthermore, when these 2 phenomena occur together, as is typical of dehydration-induced hyperthermia, the reductions in stroke volume are more than additive, and as a result, cardiac output also declines significantly (70–72). Other indications of compromised cardiovascular function include reduced blood pressure and skin blood flow. Furthermore, the plasma norepinephrine response to dehydration-induced hyperthermia is very large and is indicative of stress (73).


METABOLIC, CARDIOVASCULAR, AND NEUROLOGIC STRESS OF WEIGHTLIFTING

When persons lift weights corresponding to 65–75% of their 1RM, they generally can perform 10–15 repetitions before becoming fatigued and unable to perform another full repetition (Table 2). The first few repetitions of such a set are not sensed as being difficult, but thereafter each repetition of the given weight becomes progressively more difficult as the neuromuscular system becomes fatigued. The motor unit activation seems to parallel the perceived effort, and the last repetition seems to elicit maximal recruitment of motor unit number and frequency, at least under those specific conditions (15). For this reason, lifting weights to the point of fatigue and failure to complete another contraction is believed to be a powerful stimulus to neurologic recruitment, especially of the high-threshold type II motor units that may not be frequently stimulated in inactive people.

The fatigue experienced with repetitive weightlifting could result from impairment of any number of factors, including recruitment, excitation-contraction coupling, ATP production, and cross-bridge cycling (74). Repetitive contractions lasting 30–90 s promote rapid muscle glycogenolysis and accumulation in muscle of hexose monophosphates and lactate, with a concomitant lowering of creatine phosphate (11). Muscle blood flow is impeded during intense contraction, which in combination with high rates of energy expenditure, makes the exercising muscles hypoxic (74). During recovery from contraction, the muscle experiences a postcontraction hyperemia and fluid shifts into the interstitial and intracellular compartments (12). The metabolic stress in the muscle contributes to the contraction-induced elevation of heart rate and arterial blood pressure, and interestingly, blood pressure remains elevated if blood flow to the fatigued muscle is occluded, thus preventing metabolic recovery (66). Weightlifting elicits a sympathoadrenal-medullary response, as indicated by elevations in plasma catecholamines postcontraction (75, 76). Furthermore, weightlifting seems to influence various anabolic hormonal and growth factor responses (74, 77).



SUMMARY

Physical activity should be viewed as providing stimuli that promote specific and varied adaptations depending on the type, intensity, and duration of exercise performed. It is clear that chronic adaptations to the acute stress of physical activity promote health (78). Prolonged walking at low intensity presents little metabolic, hormonal, or cardiovascular stress, and the greatest perturbation from rest appears to be that fat oxidation and plasma fatty acid mobilization are increased by a combination of increased lipolysis and decreased reesterification, at least when subjects are fasted. More intense jogging or running largely stimulates increased oxidation of glycogen and triacylglycerol, both of which are stored directly within the muscle fibers. Furthermore, these intramuscular stores of carbohydrate and fat appear to be the primary substrates for enhanced oxidative and performance ability derived from endurance training-induced increases in muscle mitochondrial density. Weightlifting that produces fatigue in brief periods (ie, in 15–90 s and after <15 repetitive contractions) elicits a high degree of motor unit recruitment and muscle fiber stimulation. This is a remarkably potent stimulus for altering protein synthesis in muscle and increasing neuromuscular function. 

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