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# Exercise Physiology of Normal Development, Sex Differences, and Aging

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## ABSTRACT

The scientific study of human development has evolved from studies of children to studies of the full lifespan. Many physiological changes occur throughout the lifespan and unique changes occur during normal development compared to healthy aging. An enlarging body of data supports the idea that there exist critical periods of development during which physiological perturbations to the internal milieu (e.g., disease or physical activity) can alter the overall programming of developmental processes. Although different physiological functions decline with age with widely varying rates, the aging changes accumulated throughout the physiological systems reduce the capacity to cope with the stress and maintain homeostasis. The understanding of this process of development and aging is complicated by important physiologic sex differences with regard to nearly all physiological systems. Regular physical activity can favorably modulate this developmental and aging process and can have important health benefits. However, a physically inactive lifestyle can markedly impair normal development and lead to numerous diseases. Lifelong physical activity is essential for preserving or delaying the onset of functional disability and chronic cardiovascular and metabolic diseases. © 2011 American Physiological Society. *Compr Physiol* 1:1649-1678, 2011.

## Introduction

There are a number of physiological changes that occur in humans with regard to normal growth, development, and aging. There appears to be key times during development during which physiological perturbations to the internal milieu (e.g., disease or physical activity) can alter the overall programming of developmental processes and can affect health later in life. Furthermore, exercise early in life can influence metabolism, cardiovascular structure/function, and health in adulthood. Even in fetal and early postnatal life, physical activity profoundly influences the development of bone, muscle, and fat tissue. To compound these issues, sex differences on various components of physical performance and on various physiological systems are known to exist with most physiological systems; including body composition, cardiovascular function, pulmonary function, substrate metabolism, and thermoregulation, which may have implications for exercise tolerance. Although different physiological functions decline with age with widely varying rates, the aging changes accumulated throughout the physiological systems reduce the capacity to cope with the stress and maintain homeostasis. Age-associated changes in body composition, muscle strength and power, maximal aerobic capacity are known to exist. Also, vascular disease is known to increase markedly with advancing age. The following section will examine these issues by discussing normal human physiological development, important sex differences that affect physiological function, and the aging process and how it can affect health.

## Normal Development

### Introduction

While the idea that “exercise is good for children” seems axiomatic, translating this vague notion into specific, biological mechanisms that could be used to actually influence health has proved to be difficult. Never before has the need for such research been so great. Most industrialized societies find themselves in the midst of an emerging epidemic of pediatric obesity, type 2 diabetes, and the metabolic syndrome, all, in large measure, ominous consequences of unprecedented levels of physical inactivity in children (155, 213). The parallel epidemic of childhood asthma seems equally intractable, is disproportionately affecting children in the lower socioeconomic status (288), and is itself linked to physical inactivity and obesity (172, 224, 314, 333). At the same time, therapeutic advances have created an increasing number of childhood survivors of a wide range of conditions including premature birth, congenital heart disease, lung disease (such as cystic fibrosis), pediatric arthritis, sickle cell disease, and cancer. In these children, fitness is impaired and physical activity is beneficial only if the “exercise dose” does not exacerbate

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underlying inflammatory, metabolic, or physiological abnormalities (88, 182, 326, 331, 340). Identifying optimal levels of exercise must be based on a better understanding of the mechanisms that link exercise with health and disease in the growing child. Although it would be impossible to review all of the exciting insights in this dynamic field, an attempt has been made to present information that can spur new research that can be used to benefit children. As recently noted by Ploeger and coworkers (227),

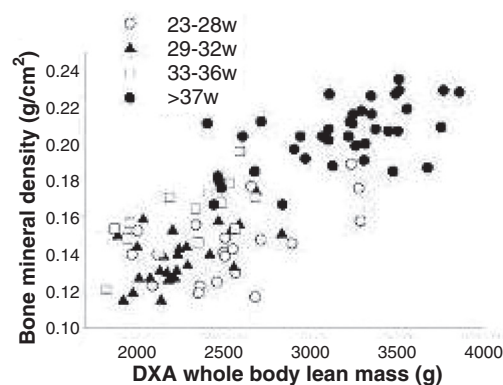
*“To optimize exercise prescriptions and recommendations for patients with a chronic inflammatory disease, more research is needed to define the nature of physical activity that confers health benefits without exacerbating underlying inflammatory stress associated with disease pathology.”*

## A current view of growth and development

### Critical periods and metabolic imprinting—role of physical activity early in human life

The normal development of exercise responses is best understood in the context of emerging concepts of growth and development. An enlarging body of data supports the idea that there exist “critical periods” of development during which physiological perturbations to the internal milieu (e.g., disease or physical activity) can alter the overall programming of developmental processes (39, 225). The long-term impact of levels of physical activity is challenging to study, but there is growing evidence that exercise early in life can influence metabolism and health in adulthood (175). Bone mineralization is one clear example of this—indeed, many clinical researchers recognize that osteoporosis in the elderly has pediatric roots (86). Children whose levels of physical activity and nutrition are substandard do not achieve sufficient bone mineral during the critical adolescent years, after which, accruing new bone mineral becomes almost impossible (45).

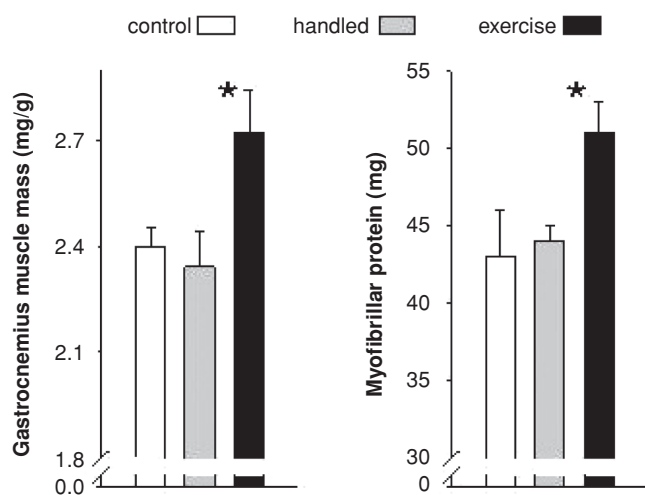
Even in fetal and early postnatal life, physical activity profoundly influences the development of bone, muscle, and fat tissue (78, 181, 255, 256, 339). For example, a number of seminal studies in animals support the idea that augmented physical activity early in life can prevent obesity from developing later in life by mechanisms related to metabolic programming through, perhaps, epigenetic phenomena. Levin and coworkers have selectively bred rats to manifest a diet-induced obesity (DIO) phenotype (175). These investigators found that only 3 weeks of exercise early in life was sufficient to prevent DIO rats from becoming obese for up to 10 weeks once the exercise was terminated and led to a persistent increase in central leptin sensitivity. Similar effects were not observed in adult DIO rats. Finally, in marked contrast to early-in-life exercise, early-in-life caloric restriction led to DIO animals that were more obese as adults once allowed to eat *ad libitum*. The authors summarized their findings as follows: “. . .early-onset exercise ameliorates, while early-onset caloric restriction accentuates, the development of obesity in genetically predisposed rats.”



**Figure 1** Bone mineral density (BMD) as a function of DXA-derived measurements of whole-body lean tissue in 102 prematurely born babies. BMD was significantly correlated to lean tissue ( $n = 102$ ,  $r = 0.80$ ,  $P < 0.001$ ). These data support the notion of a “bone-muscle” unit in which a synergistic response to factors like physical activity stimulates growth of both tissues. Data from Eliakim et al. (77).

Over the past several years, body composition has been determined in more than 150 premature babies using dual x-ray absorptiometry (DXA), bone ultrasound, muscle ultrasound, and stable isotopic dilution (77). It was found that bone mineral density and lean body mass (both measured by DXA) were highly correlated in babies born prematurely (Fig. 1). There is mounting evidence to support the concept of the functional “bone-muscle unit” in which muscle activity can stimulate bone growth through mechanoreceptors (270) and through the activity of growth hormones (GH) like insulin-like growth factor-I (IGF-I), which influence both muscle and bone (350). Indeed, absent or poor fetal movement is associated with impaired muscle development and bone mineralization (37, 255). More recently, in fetal MyoD-Myf5-deficient mice—congenitally lacking striated muscle and having no functioning “bone-muscle unit” or *in utero* mechanical loading through muscle activity—bone was profoundly abnormal and poorly mineralized (106).

It has been previously reported that exposure of muscles in growing rats to the inflammatory factor interleukin-6 (IL-6) results in decreased muscle growth, apparently due to a state of resistance to growth factors such as IGF-I, and that running exercise could ameliorate this growth defect (29). It was further hypothesized that increased activity, for a brief period during neonatal life, would pattern the adult rat toward a less inflammatory phenotype (Fig. 2). Neonatal rats were induced to move about their cage for brief periods from day 5 to day 15 postpartum. Additional groups were undisturbed controls (CON) and handled (HAND). Subgroups of rats were sampled at 30 and 65 days of age. Relative to CON and HAND, neonatal exercise (EX) resulted in decreased circulating levels of the pro-inflammatory factors tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6, and interleukin-1 $\beta$  (IL-1 $\beta$ ) in adulthood, primarily in male rats. In addition, adult male EX rats had lower body mass and increased skeletal muscle mass, suggesting a leaner phenotype. The results of this study suggest that moderate



**Figure 2** Effect of 10 days of increased physical activity on muscle mass and myofibrillar protein at day 65 of life in male rats. These variables were increased significantly only in the rats that had been exercised early in life. Data from Bodell et al. (29).

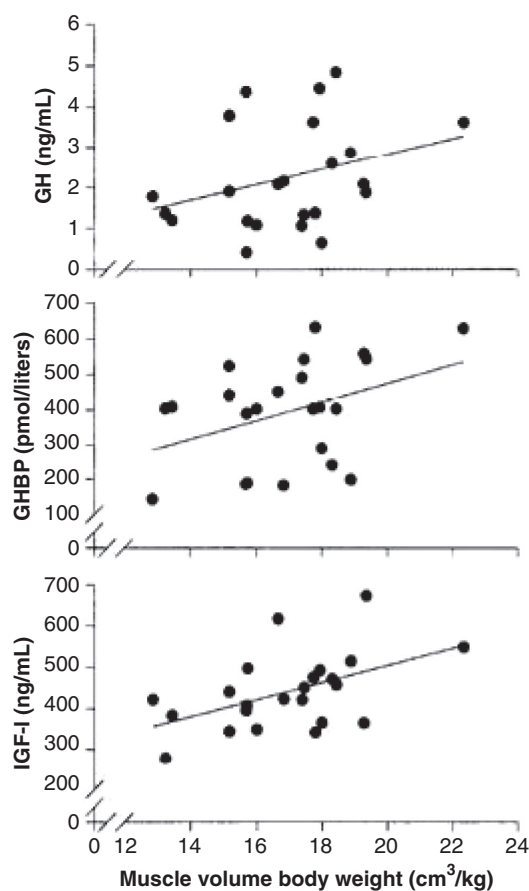
increases in physical activity early in life can influence the adult toward a healthier phenotype with regard to inflammatory mediators and relative muscle mass (31). Thus, there are promising data suggesting that programs of physical activity even in very early life may have long-term health benefits in humans.

### Growth factors and stress/inflammatory mediators—a critical balance during growth and development of children

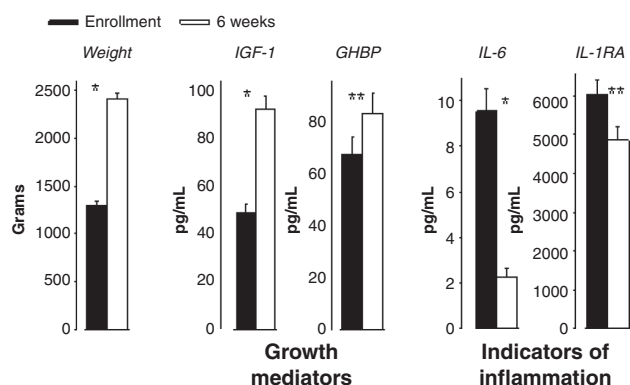
Observations show that physical activity influences body composition through the balance of growth factors [e.g., GH and IGF-I] and stress/inflammatory mediators (e.g., IL-6), which can inhibit the anabolic effects of growth mediators associated with the GH→IGF-I axis. There is growing knowledge of the effect of maturational-sensitive, exercise-related hormones and mediators on genomic, epigenetic, and functional responses to exercise in children. Prominent among these is GH, which is now known to influence a variety of physiological regulatory mechanisms even including function in neutrophils and other innate immune cells (15, 101, 325). GH increases rapidly at the onset of exercise in both adults and children (87) thus, organ systems (ranging from muscle to fat) and circulating immune cells are exposed to high concentrations of GH early in exercise. Moreover, there is intriguing and mounting data that GH is even expressed in circulating immune cells, suggesting the possibility that these cells might contribute to tissue growth in direct ways previously not thought possible (120). Finally, the upregulation of other hormones related to the hypothalamic-pituitary and the adrenal axes, like catecholamines, sex steroids, and even inflammatory cytokines like IL-6, change with growth in children, particularly around puberty (38, 100, 284).

GH pulse amplitude and frequency changes mark the onset of puberty, and the magnitude of the GH response differs significantly between boys and girls (319). GH targets one of the key growth mediators in the body, IGF-I, now known to mediate many of the growth effects associated with GH (215) as well as immune cell function (71, 173). The mechanistic link between proinflammatory cytokines and growth factors probably lies in the activity of the SOCS (suppressors of cytokine stimulating) family of proteins (218, 342). This antagonistic interaction plays a role in growth of key exercise-related tissue, like skeletal muscle, from premature babies to the elderly (1, 2, 49, 59, 76, 206, 207).

It is not surprising that physical activity alters GH and IGF-I. In adolescents, patterns of GH pulse amplitude are influenced by physical activity and muscle mass is correlated with circulating levels of IGF-I (Fig. 3) (76). Interestingly, interactions among growth factors, pro-inflammatory cytokines, and growth can be observed even in very early life. A recent study included 51 stable, growing preterm infants (2) (Fig. 4). IGF-I and GH-binding protein (GHBP) (reflecting



**Figure 3** Cross-sectional relationships between thigh muscle volume and mean overnight growth hormone concentrations ( $r = 0.35$ ;  $P < 0.05$ ; top panel), growth hormone-binding protein (GHBP) ( $r = 0.39$ ;  $P < 0.04$ ; middle panel), and circulating insulin-like growth factor-I (IGF-I) ( $r = 0.50$ ;  $P < 0.008$ ; bottom panel). Data from Eliakim et al. (76).



**Figure 4** The inverse relationship between growth mediators (IGF-I and GHBP) and indicators of inflammation (IL-6 and IL-1ra) in healthy, growing, inpatient premature babies. This study (2) shows the remarkable association between the increase in weight and IGF-I and the decrease in IL-6 over a 6-week period ( $P < 0.001$ ) in 51 prematurely born infants (all data mean  $\pm$  SEM). In addition, GHBP increased significantly ( $P < 0.05$ ) and IL-1ra decreased over the same period suggesting increased GH receptivity and reduced inflammation as the infants grew. We have also demonstrated in both premature babies and in adolescents a positive correlation between IGF-I and lean body mass.

anabolic activity and GH sensitivity) increased, while IL-6 and IL-1ra (reflecting inflammation) decreased as the babies grew.

In recent years, very exciting data have been presented linking physical activity to immune and inflammatory processes, which, as noted, can also influence the growth and development of muscle and bone. It has long been recognized in adults, and more recently in children, (223) that one of the most robust of the immune-related responses to exercise is the large increase of leukocytes (among them, neutrophils and monocytes, prototypical cells of innate immunity) in the circulating blood. This rapid immune cellular activity is an essential response to “danger” in which the immune cells are positioned to act effectively in the event of an invading pathogen, an injury or wound, or the need to signal other components of the immune system (185).

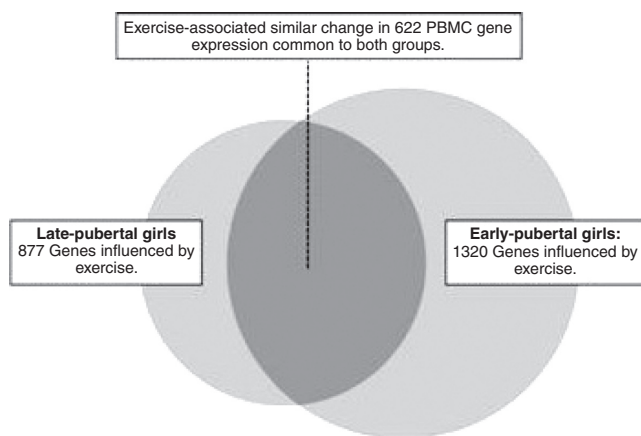
This may have been beneficial when our human progenitors were, for example, rapidly fleeing a predator or pursuing prey over rough terrain; however, any beneficial effects of immune cell activation would be lost if the pro-inflammatory response was unfettered and not balanced by equally robust compensatory mechanisms. To date, the results from this and other laboratories in peripheral blood mononuclear cells (PBMCs—monocytes, lymphocytes, and natural killer cells) in children and adults, and in neutrophils (only studied in adults), (241-244) have demonstrated that the increase in innate immune cells in the circulation is accompanied by alterations in genomic, epigenetic, and functional changes in the cells. Remarkably, the pattern of regulation is characterized by a balance among pro- and anti-inflammatory, anabolic and catabolic genes, and gene pathways (Table 1, Fig. 5).

What has so dramatically changed in this field is the new understanding that the functional dynamism of innate im-

**Table 1** Individual Genes Upregulated by Exercise in PBMCs and Neutrophils—Evidence for Balanced Response of Pro- and Anti-Inflammatory Function and Growth Factor

|   |  |
|---|--|
| <b>Pro-Inflammatory</b>                     |  |
| PTGDS—prostaglandin D2 synthase 21 kDa      | Oxidative stress and inflammation                |
| CTSW—cathepsin W (lymphopain)               | NK cell protease                                 |
| CCL4—chemokine, MIP 1- $\beta$              | Involved in asthma and nephritis                 |
| HSPA1B—heat shock 70 kDa protein 1- $\beta$ | Possible endogenous “antigen”                    |
| <b>Anti-Inflammatory</b>                    |  |
| DUSP—dual specificity phosphatase 1         | Attenuates SAPK pathways                         |
| IL-1RA—interleukin-1 receptor antagonist    | Attenuates IL-1 and 6                            |
| CST7—cystatin F                             | Inhibits cathepsin                               |
| AKR1C3—aldo-keto reductase family 1         | Attenuates oxidative stress                      |
| <b>Growth Promotion</b>                     |  |
| EREG—epiregulin                             | Promotes wound healing                           |
| EGR1—early growth response-1                | Angiogenesis                                     |
| RTP801—hypoxia-inducible growth factor      | Stimulated by hypoxia $\rightarrow$ angiogenesis |
| ECGF1—endothelial growth factor             | Angiogenesis                                     |

mune cells is much broader than envisioned earlier. Until fairly recently, the idea that neutrophils were anything other than terminally differentiated cytotoxic agents (165), could be critical partners in angiogenesis, (342) or that monocytes contributed to post-exercise muscle remodeling (277, 303, 307) would have been viewed with great skepticism. Of course, the importance of the inflammatory function of these cells; indeed, leukocytes are increasingly seen to be involved in childhood diseases including asthma, (17) cystic fibrosis (111), and sickle cell anemia (130). However, the emerging view is that



**Figure 5** Comparison of the effect of exercise on peripheral blood mononuclear cell (PBMC) genes in early- and late-pubertal girls, showing the relative magnitude of the effect (circles) and the size of the overlap (shaded area). There were 622 PBMC genes that were significantly altered by exercise in both groups. Additional studies are required to determine whether or not the gene expression patterns represent true maturational differences in the exercise response.



physical activity modulates the balance among these various, seemingly antagonistic, functions of leukocytes—cells that can interact with virtually every tissue in the body. How the interaction between circulating immune cells and specific tissues affects mechanisms of exercise response in growing children, in health and disease, is an area of promising research.

## Cardiopulmonary responses to exercise in children and adolescents

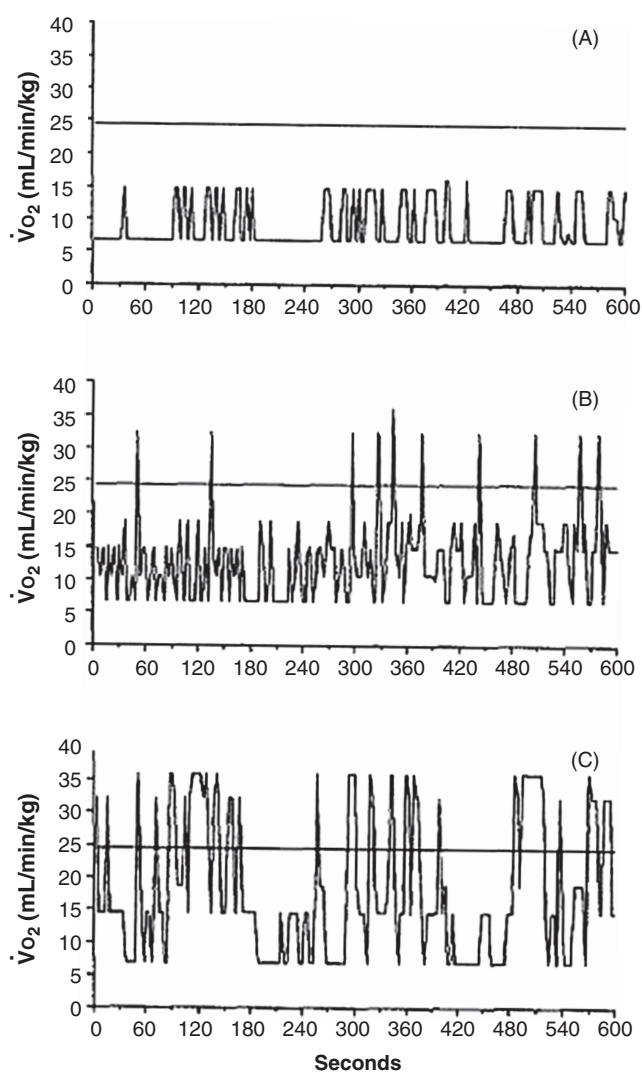
### Real patterns of physical activity in children

The bulk of studies focused on understanding the mechanisms of metabolic and gas exchange responses to exercise in children come from formal in laboratory exercise protocols. Typically, the child is tested on a cycle ergometer or treadmill and gas exchange and heart rate are measured as work increases in a progressive manner. But these studies do not reflect the patterns of physical activity typically observed in children under natural conditions (Fig. 6) (16). In this study, over a 12-h day, children spent a mean of 22.3 min in high-intensity activities, but the median duration of an intense activity event was very short—just 3 s. No bout of intense activity lasting 10 consecutive minutes was ever recorded, and 95% of intense activity events lasted less than 15 s. These results indicate that children engage in very short bursts of intense physical activity interspersed with varying intervals of activity of low and moderate intensity. This seems to be the case even during relatively active periods during the day, including sports practice, dance or swimming classes, or school recess. Other studies have corroborated the brief duration of children's intense activities (20, 203).

It is likely that cardiorespiratory, hormonal, metabolic, substrate, thermoregulatory, cardiovascular, and lipid responses vary according to different patterns of exercise in children. If the predominant tempo of exercise experienced by children under natural everyday conditions, including during organized athletics, is one of the rapid change with only very brief bursts of intense activity, then the physiological mechanisms linking tissue anabolism and ultimate growth and development operate in ways not yet understood. To uncover the biological significance of these observed patterns, new protocols will be needed to measure responses to both very brief spurts of exercise and rapidly changing levels of exercise over sustained periods. For behavioral and health scientists aiming to promote health-related fitness, recognition of this normative tempo of physical activity could guide the development of new activity promotion interventions that may be both more appealing and more effective.

### The “problem” of size

The process of growth in children is dynamic. The body increases in size and the organs develop and mature until the



**Figure 6** Profiles of estimated children's  $\dot{V}O_2$  during 10-min periods. The data were derived from direct observations of children. The solid line represents the anaerobic or lactate threshold (LAT). (A) Profile of a girl's  $\dot{V}O_2$  during a representative 10-min period of relatively low activity. (B) Profile of a girl's  $\dot{V}O_2$  during a representative 10-min period of relatively moderate activity; 5% of observations are above LAT. (C) Profile of a boy's  $\dot{V}O_2$  during a 10-min period of relatively intense activity; 26.5% of observations are above LAT.

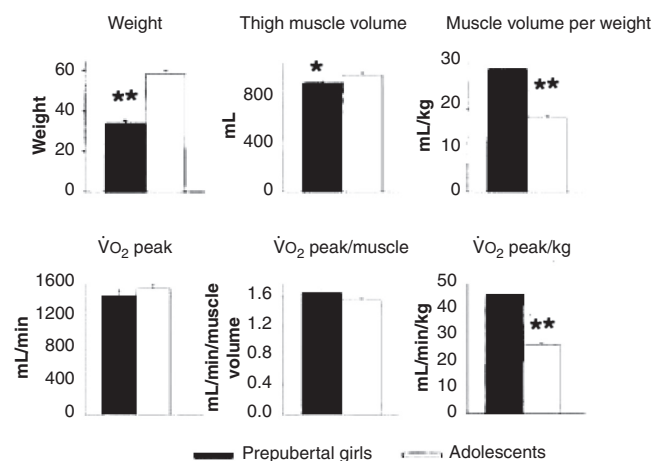
organism's structure and function are “optimized” for the human being's particular ecological niche. During this period, the gas exchange system must adapt to increasing metabolic demands. The idea, noted above, that there exist critical periods of growth and development has energized efforts to accurately characterize allometric (defined loosely as the study of the relationship among size, shape, and metabolic function) descriptions of exercise responses in children. In previous work with children, cardiorespiratory growth has been characterized by identifying aspects of gas exchange responses to exercise, which appear to remain constant despite changes in body size and age (50, 51). In this way the determination of those aspects of cardiorespiratory function that appear

to be controlled throughout the growth period can be better identified.

A problem central to understanding the growth and development of exercise responses in children and adolescents is how to account for rapid changes in body mass. Traditional exercise responses, such as  $\dot{V}O_{2\max}$ , are determined in no small measure by muscle mass. Is a healthy 6-year-old boy unfit because his peak  $\dot{V}O_2$  of 1.1 liter/min falls far short of the 4.1 liter/min peak observed in an 18 years old? The question is not as moot as one might initially suppose—indeed, one would exclude even a healthy 6 years old from strenuous tasks (e.g., preparing for the military) not because they were unfit as a 6 years old, but because they lack the capability of performing the required work, the latter conclusion easily and correctly drawn from comparing the peak  $\dot{V}O_2$  of the child and the young adult.

How then does one compare exercise responses in a 6-year-old child with an 18-year-old young adult? The issue of proper normalization of metabolic responses in the context of changing body mass remains controversial (46, 309). Ratios (e.g., peak  $\dot{V}O_2$  to body mass) are a convenient and simple way of comparing physiological variables in organisms of different size. However, simplistic interpretations of ratios (similar to gauging fitness in 6 years old using normative data from young adults) must be avoided. Nowhere is this conundrum more evident than in attempting to determine fitness in growing children when, particularly during adolescence, body composition, and the ratio of lean-to-fat tissue, changes so dramatically (Fig. 7) (79).

The science of allometric scaling has been applied to exercise responses in adult humans, animals, and children with,



**Figure 7** Comparison of weight, thigh muscle volume, and  $\dot{V}O_2$  peak in prepubertal and late-adolescent girls. Although thigh muscle volume was significantly greater in the adolescent girls, the increase was not nearly as great as the increase in weight. Consequently, thigh muscle volume per weight was much lower in the adolescent girls. Neither  $\dot{V}O_{2\text{peak}}$  nor  $\dot{V}O_{2\text{peak}}$  normalized to muscle was significantly different between the two groups. Consequently,  $\dot{V}O_{2\text{peak}}$  per kilogram body mass was significantly smaller in the adolescent girls. Significant difference, prepubertal versus adolescent girls, \* $P < 0.0001$ , \*\* $P < 0.05$ . Data from Eliakim et al. (79).

perhaps surprisingly, a great deal of controversy (9, 10, 26, 50, 127, 190, 191, 305). The noted comparative biologist, A. A. Heusner, set out a potentially useful paradigm for scaling biological systems with relevance to exercise in children. He wrote (126),

*“From a thermodynamic point of view a physical quantity describes either an extensive or an intensive property of a thermodynamic system. An extensive property is one whose magnitude depends on the size of a system (mass, surface area, volume, energy, heat capacity, etc.); an intensive property is one whose magnitude is size-independent (density, pressure, temperature, etc.). If two systems are geometrically, mechanically, and chemically similar, the magnitudes of their respective intensive properties are the same. The constancy of intensive properties is a necessary condition for similarity. Animals that are similar must also meet this requirement.”*

This approach is useful in determining which exercise-associated physiological variables intrinsically change during the process of growth. The use of simple scaling equations such as:

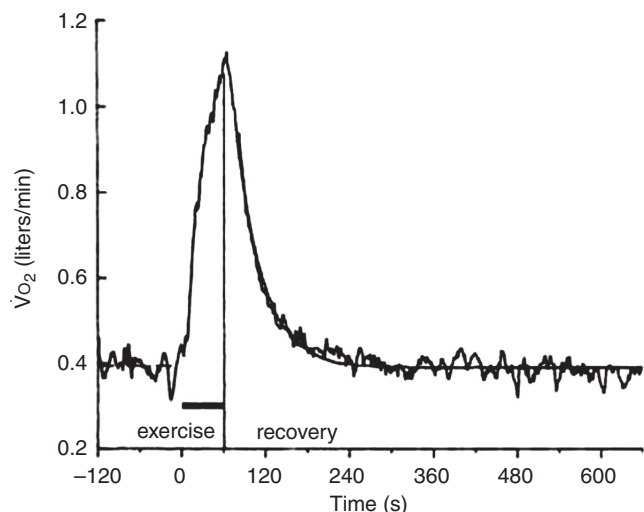
$$P \propto M^b$$

where  $P$  is a metabolic variable, and  $b$  is the scaling factor. In extensive exercise metabolic variables,  $b$  is close to 1 suggesting a dependence on body size itself. As expected, obvious size-dependent aerobic parameters of exercise include peak  $\dot{V}O_2$ , a variable dependent in large measure on the mass of muscle, the tissue ultimately responsible during exercise for oxygen uptake and carbon dioxide production. Among mature animals of different sizes, the scaling factor for peak  $\dot{V}O_2$  is typically found to be 0.75, and there is much discussion and debate regarding the potential determinants of this value (58). During growth in children, the scaling factor for peak  $\dot{V}O_2$  differs by gender and is close to 1 in boys and was 0.83 in girls (8, 50). The allometric analysis of exercise variables is useful because it helps form hypothesis about fundamental mechanisms of growth and development. For example, the gender differences in the scaling factors for  $\dot{V}O_{2\max}$  in children and adolescents suggest that factors other than size alone must contribute to peak oxygen uptake during the process of maturation (313). What these factors are remains to be determined.

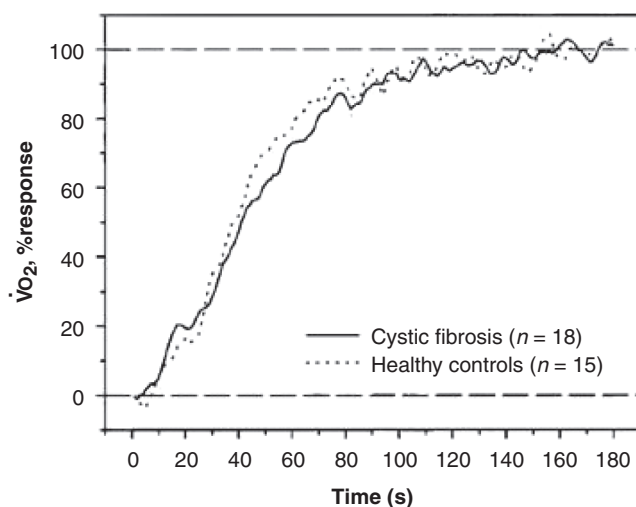
Intensive properties are characterized by scaling factors that approach 0. Thermodynamic work efficiency, for example, identified in a classic paper by Whipp et al. (329) as one of the four key aerobic properties of exercise, is derived from the ratio of the work actually performed by the exercising subject to the total energy expended. Since both maximal work performed and energy expenditure depends on muscle mass, one would expect the body mass determinant to appear in both elements of the work efficiency ratio, canceling each other out (as it were) and rendering work efficiency an intensive property. Indeed, work efficiency in growing children changes very little with age (50).

The utility of this analysis becomes clear when examining children with disease or disability. For example, the relationship between  $\dot{V}O_2$  and work rate is distinctly abnormal in children who had undergone the Fontan procedure for a variety of congenital heart diseases (312). In these affected children, thermodynamic work efficiency, a property of ATP kinetics at the level of the muscle, was probably not altered; rather, the presence of impaired oxygen delivery to the working muscle confounded the use of surrogate variables (e.g., total body oxygen uptake as a surrogate for total energy expenditure) in the calculation of work efficiency, but led to new insights into the mechanisms that impair exercise performance in children with congenital heart disease.

It has been reasoned that age- or size-independent variables of cardiorespiratory function might be found by examining the dynamics of  $O_2$  uptake ( $\dot{V}O_2$ ) in response to exercise. During transitions from rest to exercise, or from one level of energy requirement to another, the response of the organism is structured to maintain homeostasis at the cellular level (162); thus the supply of environmental  $O_2$  is determined by the needs of the cells. Since the stores of  $O_2$  in the body are very small relative to metabolic demand, dynamics of  $\dot{V}O_2$ , measured at the mouth during exercise transitions are closely coupled in time to cellular events (Fig. 8). Using Heusner's construct of intensive and extensive properties, the rough geometric similarity between children and adults would suggest that  $\dot{V}O_2$  kinetics would change little with growth in children. In fact, while not approaching the size dependence of extensive variables such as  $\dot{V}O_{2max}$ , some kinetic gas exchange and heart rate variables associated with exercise change signifi-



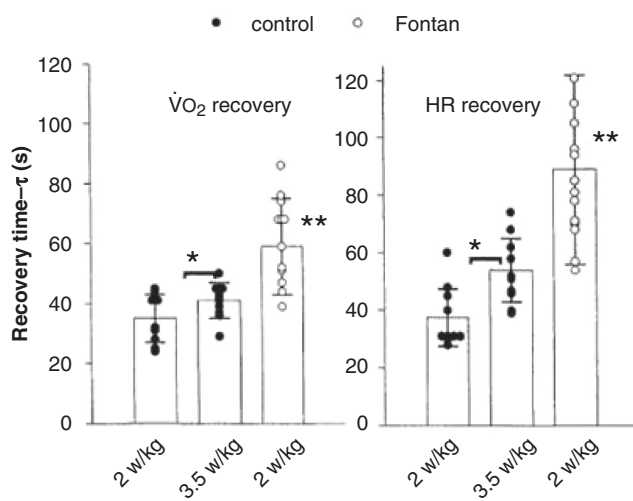
**Figure 8**  $O_2$  uptake response to 1-min of high-intensity exercise (125% of the maximal work rate) in an 8-year-old girl. Shown also is best-fit single exponential as described in text. Vertical line indicates end of 60-s exercise. Area under  $\dot{V}O_2$  curve from time 0 to end of 10-min recovery period [mean baseline values (- -) were subtracted] is used to calculate cumulative  $O_2$  cost of exercise. Area to right of vertical line to end of recovery (again, mean baseline values were subtracted) represents  $O_2$  cost for recovery period.



**Figure 9** Average  $\dot{V}O_2$  response to an increase in work rate at time 0 s in healthy controls and patients with cystic fibrosis. There was a significant difference in the time course of  $\dot{V}O_2$  between the groups.

cantly with growth itself, revealing underlying maturational mechanisms not readily explained by size alone (47, 138).

Moreover, there is a growing body of data showing that these kinetic responses are influenced by disease, and may be useful in following the impact of chronic disease on exercise responses as children grow and develop. For example, in cystic fibrosis, a disease that initially impacts primarily the lung, oxygen uptake kinetics are impaired even in relatively healthy subjects (Fig. 9) (123). In children with Fontan repair of congenital heart lesions, the recovery from just 1-min exercise is markedly prolonged (see Fig. 10) (312).



**Figure 10** HR and  $\dot{V}O_2$  recovery times for control and Fontan group subjects. In control subjects, recovery times were longer after the higher work rate protocols ( $*P < 0.05$ ). In Fontan group subjects, recovery times were prolonged compared with the same absolute (2 W/kg) and relative (3.5 W/kg) protocols in control subjects ( $**P < 0.001$ ).





**Figure 11** Lactate production from 10, 2-min bouts of high-intensity exercise in early and late pubertal boys. Consistent with previous studies, lactate production is lower in younger children.

### Lactate, buffering, and the regulation of $CO_2$ during exercise in children

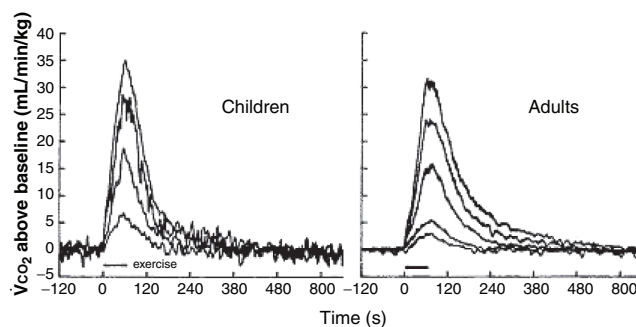
Nowhere are maturational differences in the exercise response as apparent as in the control of breathing during exercise. With physical activity, a major challenge to cellular homeostasis is the production of lactic acid in working muscles. The excess production of hydrogen ion is countered by a robust system to maintain pH within a very narrow range. Buffering consists predominantly of the  $CO_2$ - $HCO_3^-$  and hemoglobin mechanisms. Regulation of pH during exercise is tied to ventilation because  $P_{aCO_2}$  is tightly controlled despite the excess  $CO_2$  produced by the buffering process (324). The challenge to homeostasis is even greater because oxidative phosphorylation in the working muscle leads to large increases in  $CO_2$  as the work increases.

There are clear differences in lactate responses to exercise between adults and children. For example, in Figure 11, lactate and other variables are presented from a recent study comparing brief exercise in early and late pubertal boys (242). Although lactate increased significantly in both groups, the magnitude of the increase was substantially larger in the older participants. As noted, this is a well-known maturational difference (24) related, most likely, to lower levels of muscle lactate dehydrogenase (154) and/or a greater dependence on aerobic rather than anaerobic metabolism in the performance of muscular work (346) in the younger participants.

There is also a growing body of literature indicating differences in the coupling of ventilation ( $\dot{V}_E$ ) and  $\dot{V}CO_2$  during exercise between children and adults. During progressive exercise, for example, the slope of the  $\dot{V}_E$ - $\dot{V}CO_2$  relationship is higher in children compared with adults (48, 304). This can be explained (by review of the alveolar gas equation) by some combination of a lower  $P_{aCO_2}$  set point in children or greater dead space ventilation. Surprisingly, the differences in ventilatory control are even more marked with studies focused on the  $CO_2$  and ventilatory recovery from brief, 1-min bouts of exercise (Figs. 12 and 13) (7).

### Maturation of substrate utilization

Often ignored in translational research is the growing understanding that children are not just miniature adults. The



**Figure 12**  $\dot{V}CO_2$  responses (above baseline 0-W pedaling) to a 1-min burst exercise in children and adults. The data are normalized to body weight and can be distinguished in order of work intensity because as the work intensity increases, the  $\dot{V}CO_2$  response is progressively larger [i.e., 50% AT, 80% AT, 50% $\Delta$  (the difference between the work rate at the anaerobic or lactate threshold and max), 100% max, 125% max (in children the 50% AT exercise was excluded from the study)]. Note the generally faster recovery in children. Similar results, not shown, were observed for  $\dot{V}_E$  responses. Data from Armon et al. (7).

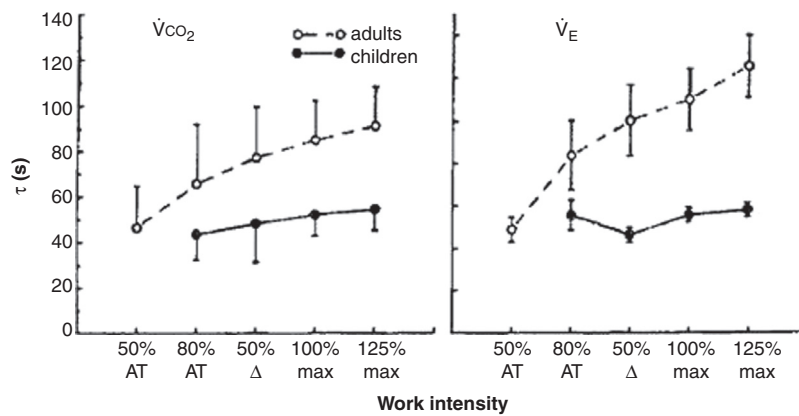
notion that one can simply scale down physiologic, genomic, and therapeutic advances derived from adult studies and fit them to the pediatric population is increasingly recognized as untrue. Indeed, as is prominently displayed on the current NHLBI website, “Children have often had to accept medicines and treatments based on what is known to work in adults. As a society, we should not agree to this ‘hand-me-down’ approach.”

Michael Riddell recently published a comprehensive review of the endocrine and substrate utilization responses to exercise in children and adolescents (see Fig. 14) (248). He noted,

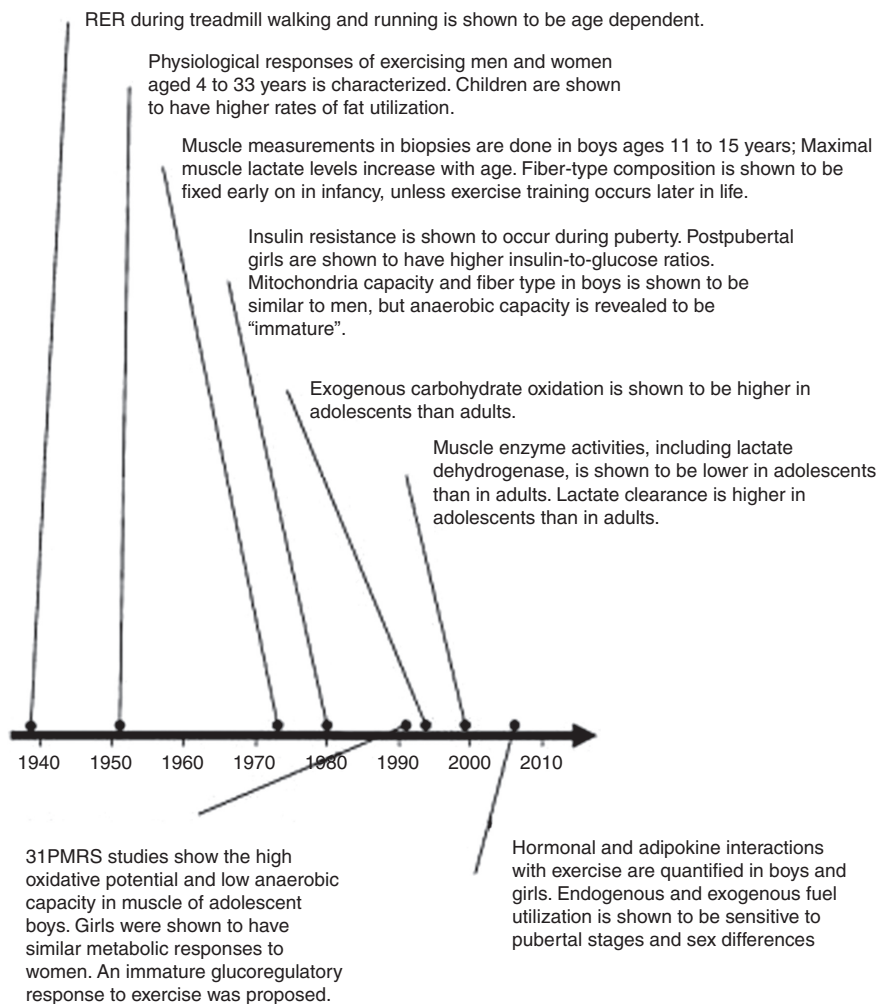
*“Prepubertal adolescents may have an immature glucose regulatory system that influences glycemic regulation at the onset of moderate exercise. During heavy exercise, muscle and blood lactate levels are lower in children than in adults and there is a greater reliance on fat as fuel. The exercise intensity that causes maximal fat oxidation rate and the relative rate of fat oxidation decreases as adolescents develop through puberty. The mechanism for the attenuated lipid utilization with the advancement of puberty, and the impact that this may have on body composition, are unknown. Surprisingly, prepubertal adolescents have relatively high rates of exogenous glucose oxidation, perhaps because of their smaller endogenous carbohydrate reserves.”*

### Muscle ATP dynamics of exercise in children and adults

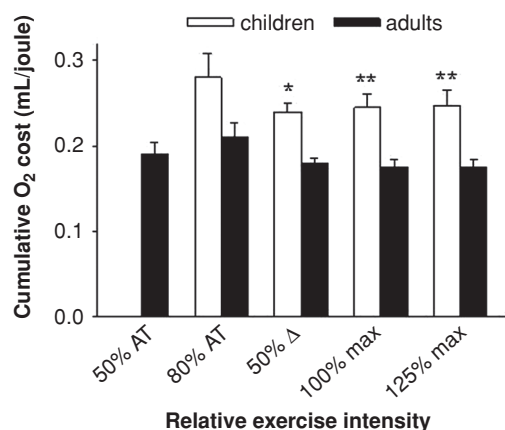
The apparent differences between children and adults in gas exchange and other metabolic responses to exercise suggested hypotheses focused on ATP and energy metabolism differences at the level of the exercising muscle itself. There is increasing evidence suggesting maturation of energy metabolism during growth. The oxygen cost of high-intensity exercise, normalized to the actual work done ( $O_2$ /joule), is higher in children, suggesting less dependence on anaerobic metabolism (Fig. 15) (347). As noted, after vigorous exercise,



**Figure 13** Recovery time constants ( $\tau$ ) for  $\dot{V}CO_2$  (left panel) and  $\dot{V}E$  (right panel). Data are presented as mean  $\pm$  SD. The recovery times were significantly shorter in children compared with adults. In adults,  $\tau\dot{V}CO_2$  increased with increasing work intensity from 50% AT to 80% AT ( $P < 0.01$ ) and from 80% AT to 50%  $\Delta$ . ( $P < 0.05$ ), and for above-AT exercise the  $\dot{V}CO_2$  time constant at 50%  $\Delta$  was significantly lower than 125% max. Note significantly shorter  $\tau\dot{V}CO_2$  than  $\tau\dot{V}E$  in the high-intensity range for adults ( $P < 0.001$ ). In children, no significant differences were found between  $\tau\dot{V}CO_2$  and  $\tau\dot{V}E$ . Data from Armon et al. (7).



**Figure 14** An overview of key discoveries in maturational determinants of substrate utilization during exercise in children. Figure from Riddell (248).

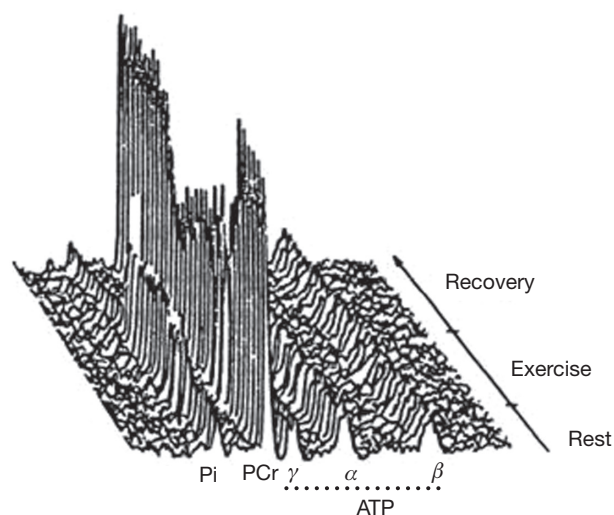


**Figure 15** Cumulative O<sub>2</sub> cost per joule at different work intensities in adults and children determined from 1 min of constant work rate cycle ergometer exercise. Values are means  $\pm$  SEM. Cumulative O<sub>2</sub> cost was not affected by increasing work intensity in children and adults. However, cost was significantly higher in children than in adults at 50% $\Delta$  (i.e., 50% of the difference between the anaerobic threshold and peak  $\dot{V}O_2$ ) ( $^*P < 0.001$ ), 100% max, and 125% max ( $^{**}P < 0.01$ ) was used for the statistical analysis of work. Data from Zanconato et al. (347).

blood and muscle lactate concentrations are lower and serum pH higher in children than in adults (220). Finally, the increase (slope) in  $\dot{V}O_2$  during constant work rate high-intensity exercise is smaller in children than in adults (6). Because the slope of  $\dot{V}O_2$  during high-intensity exercise is correlated with serum lactate levels (260), the smaller slopes in children further support the idea that lactate levels in response to high-intensity exercise are truly smaller in children. No definitive mechanism has been established for the growth-related differences in the adaptive response to high-intensity exercise. One problem has been the lack of noninvasive methods to study muscle metabolism.

The use of  $^{31}\text{P}$ -nuclear magnetic resonance spectroscopy ( $^{31}\text{P}$ -MRS) now provides a safe and noninvasive way of monitoring intracellular Pi, phosphocreatine (PCr), and pH (35) that is acceptable for studies in children. These variables, in turn, allow the assessment of muscle oxidative metabolism and intramuscular glycolytic activity. It was hypothesized that the growth-related changes in whole body  $\dot{V}O_2$  and O<sub>2</sub> cost of exercise observed during high-intensity exercise depend on a lower ATP supply by anaerobic metabolism in children. This could result either from changes in the mechanism of glycolysis in muscles or from a different pattern of fiber-type recruitment. A maturation of the kinetics of high-energy phosphate metabolites in muscle tissue during exercise was expected. This hypothesis was tested by examining Pi, PCr, P-ATP, and pH kinetics in calf muscles during progressive incremental exercise. Results obtained from children were compared with those from adults.

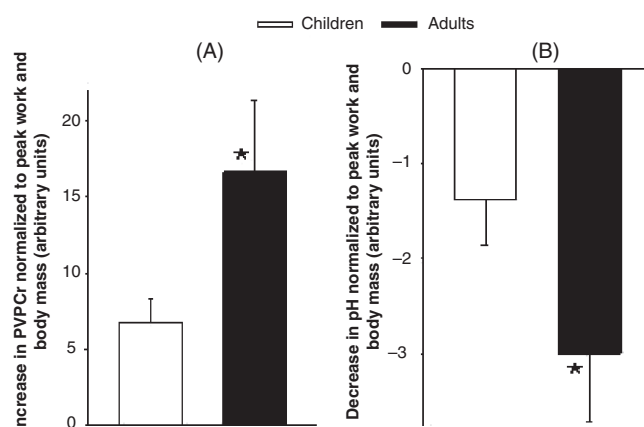
As shown in Figures 16 and 17, there were marked differences in Pi/PCr and pH between the children studied. Ours was a small sample size study consisting of 10 prepubertal children (8 boys) whose mean age 9.3 years old. The ex-



**Figure 16**  $^{31}\text{P}$ -MRS spectra from right calf of an 8-year-old boy at rest, during incremental exercise, and recovery. Data from Zanconato et al. (339).

pense and availability for research of MR facilities has limited progress in this field. There have been a handful of more recent investigations into potential maturational changes in ATP dynamics in response to exercise in children. Ratel et al. (246) for example, studied 7 boys [mean age 11.7 years old, Tanner approximately 1.5 (early pubertal)] and noted, that the rate constant of PCr recovery and the maximum rate of aerobic ATP production were about 2-fold higher in young boys than in men. They concluded that their results

*“... illustrated a greater mitochondrial oxidative capacity in the forearm flexor muscles of young children. This larger ATP regeneration capacity through aerobic mechanisms in children could be one of the factors accounting for their greater resistance to fatigue during high-intensity intermittent exercise.”*



**Figure 17** Effect of exercise on intramuscular increase in Pi/PCr (Panel A) and decrease in pH (Panel B) in children and adults. Exercise leads to significantly ( $^*P < 0.05$ ) smaller changes in ATP-related kinetics, consistent with lower lactates observed during heavy exercise in children. Data adapted from Zanconato et al. (346).

Interestingly, Willcocks et al. (332) used MRS to study quadriceps exercise in 5 girls and 6 boys who were  $13 \pm 1$  years old (clearly at more advanced pubertal status than our study or that of Ratel et al. (246)). Willcocks et al. (332) concluded that,

*“The time constant for the PCr response was not significantly different in boys, girls, men, or women. [However] the mean response time for muscle tissue deoxygenation was significantly faster in children than adults. The results of this study show that the control of oxidative metabolism at the onset of high-intensity exercise is adult-like in 13-year-olds, but that matching of oxygen delivery to extraction is more precise in adults.”*

Clearly, this is an area of fundamental developmental physiology in need of further work. As noted compellingly in a recent review by Ratel and coworkers (245),

*“Although it has been stated that children experience a larger increase in peak anaerobic power than in peak oxygen uptake during growth, experimental data derived from in vitro and in vivo muscle measurements, blood samplings and oxygen uptake dynamics do not provide a consensus regarding the corresponding metabolic profile. Time-dependent changes in muscle oxidative capacity and anaerobic metabolism with respect to growth and maturation still remain a matter of debate. More specifically, it still remains unclear whether a metabolic specificity exists before puberty i.e. whether a larger contribution of aerobic or anaerobic processes to energy production is present before puberty . . . Comparative analyses between children and adults must be performed under carefully standardized conditions. Accurate quantitative investigations of rates of aerobic and anaerobic ATP production should eventually allow us to determine whether prepubertal children have fully efficient or immature glycolytic activity and whether any adaptive oxidative changes occur during maturation.”*

### Future directions

Physical activity is essential for the healthy growth and development of children. Moreover, exercise is increasingly seen as an adjunct to therapy in the common, current pediatric epidemics of obesity and asthma, as well as in benefitting children with chronic rare diseases. For the first time, epigenetic mechanisms could begin to explain how environmental factors like levels of physical activity in infancy and childhood could alter health throughout the lifespan, and, perhaps, influence the health of subsequent generations (124, 137, 308). As outlined in this chapter, many fundamental issues regarding the growth and development of the cardiopulmonary response to exercise remain unresolved. It is our challenge to link the real life experience of physical activity in children with the underlying biological mechanisms that, ultimately, could improve child health and health throughout the lifespan.

## Sex Differences

### Introduction

Research investigating sex differences on various components of physical performance and on various physiological systems

is still evolving. It is known that important sex differences exist with regard to body composition, cardiovascular function, pulmonary function, substrate metabolism, and thermoregulation, which may have implications for exercise tolerance.

### Body composition

There are several sex differences in anthropometric measurements that exist at maturity. For example, women have narrower shoulders, broader hips, smaller chest diameters, and tend to have more fat in the hips and lower body; whereas men tend to carry more fat in the abdomen and upper body (335). The average difference in body fat between young women and men ages 18 to 24 is about 6% to 10% (20-25% for women vs. 13-16% for men) (234). This difference is thought to reflect sex-specific differences in fat deposit (namely, the breasts, hips, and thighs). Women generally gain much less fat-free mass than men (94). Both women and men tend to accumulate fat and lose fat-free body mass over time. Studies suggest that fat-free mass tends to decrease by approximately 0.1 to 0.3 kg per year (94). This loss is associated with lower levels of physical activity and of testosterone (159). With the exception of fat-free mass, the magnitude of the change in body composition (including increases in body fat) appears to be related more to the total energy expenditure than to the participant's sex (335). In general, trained athletes have lower percentages of fat than average individuals, although trained women still possess significantly more body fat than their male counterparts (335). Female athletes can be exceptionally lean, well below the relative fat value for the average young woman and even below that for the average young man (231). Such low values could result from a genetic predisposition toward leanness and/or the high weekly training distances (231). Significantly more fat-free mass is gained in response to strength training than with endurance training, and the magnitude of these responses is much less in women, primarily because of hormonal differences.

Bone and connective tissue are affected with exercise training, but these changes are not well understood. In general, animal studies and limited human studies have found an increase in the density of the weight bearing long bones (70). This adaptation appears to be independent of sex, at least in young- and middle-aged populations. Connective tissue appears to be strengthened with endurance training, and sex-specific differences in this response have not been identified (335).

### Cardiopulmonary endurance

#### Cardiovascular

While maximal heart rate is similar in both sexes at any given age, women generally have a higher heart rate response than men for any absolute level of submaximal exercise (194). When power output is controlled to provide the same relative level of exercise, usually as a percentage of  $\dot{V}O_{2\max}$ , women's heart rates are still slightly elevated compared with



men's, and their stroke volumes are markedly lower (194). Adult women exercise at a level of submaximal oxygen consumption with a 5% to 10% larger cardiac output than males (19, 275), although this difference is not consistent (236). Any apparent gender difference in submaximal cardiac output most likely results from the 10% lower hemoglobin concentration in women than in men. This sex difference helps to explain the lower aerobic capacity of women relative to men, even when considering differences in body mass and body fat (57). Additionally, lower hemoglobin content leads to women having less potential for increasing their arterial venous oxygen difference (337). The reason for higher hemoglobin concentrations in men relates to the stimulating effects on red blood cell production of testosterone (170). A proportionate increase in submaximal cardiac output compensates for this small decrease in the blood's oxygen carrying capacity. These differences also are seen at maximal levels of exercise with the exception of maximal heart rate. Because of this, the higher heart rate response in women compensates for a lower stroke volume, which results primarily from at least three factors: (i) women have smaller hearts and therefore smaller left ventricles because of their smaller body size and possibly lower testosterone concentrations; (ii) women have a smaller blood volume, which also is related to their size; (iii) the average woman may be less aerobically active and therefore less aerobically conditioned (194).

It is also important to understand that a woman's lower cardiac output at maximal rates of work is a limitation to achieving a high  $\dot{V}O_2$ max value (see previous). A woman's smaller heart size and lower plasma volume greatly limit their maximal stroke volume capacity. In fact, the studies have suggested that women have limited ability to increase their maximal stroke volume capacity with high-intensity endurance training (195). However, more recent studies have shown that young, premenopausal women were able to increase their stroke volume with training identically to men (337). Furthermore, in the untrained state after artificially increasing their plasma volume with a plasma volume expander and after  $\beta$ -blockade, women were able to increase their stroke volume to the same extent as untrained men during an acute bout of exercise (194, 195). Major cardiovascular and respiratory adaptations result from cardiorespiratory endurance training, and these adaptations do not appear to be sex specific.

In addition to cardiac structure and functional sex differences, vascular sex differences also exist. Increasing evidence suggests that limb vasodilator responsiveness is sex specific. For example, young women exhibit augmented brachial artery flow-mediated dilation (174, 267) and  $\beta$ -adrenergic-mediated forearm vasodilation (164) relative to young men. Moreover, the forearm vasodilatory response to acetylcholine (64) as well as peak calf reactive hyperemia (238, 249) tend to be higher in women. Collectively, this suggests that women exhibit augmented dilatory responsiveness in the limbs. Furthermore, younger women tend to have a lower maximal cardiac output than would be predicted from their peak femoral blood flow and conductance relative to younger men (250), suggest-

ing that aerobic capacity is associated with peripheral vascular reserve in men but not women. The mechanisms contributing to the sex-specific differences in the association between aerobic capacity and local vascular reserve are unknown.

## Pulmonary

### Introduction

Important sex differences exist in resting pulmonary function that might have an effect on the ventilatory response, respiratory muscle work, and on gas exchange during exercise, which may in turn affect exercise capacity. The basis for sex differences in pulmonary function and exercise tolerance is primarily from two sources; hormones, and in structural/morphological differences.

### Hormones

The menstrual cycle can affect pulmonary function during exercise primarily through changes in circulating levels of progesterone and estrogen. Effects of progesterone on the pulmonary system include hyperventilation (200), a partially compensated respiratory alkalosis (80), and an increase in both the resting hypercapnic ventilatory response (HCVR) and the hypoxic ventilatory response (HVR) (200, 270). However, no studies have been able to correlate actual progesterone levels with the alterations in ventilatory responsiveness. An augmented ventilatory drive associated with increased progesterone levels coupled with a reduced airway diameter in women (see below) may contribute to an increased prevalence of expiratory flow limitation during exercise (188).

Increased estrogen levels tend to increase fluid retention and therefore increase blood volume (33), which could potentially affect pulmonary gas exchange. Sansores et al. (266) demonstrated that resting diffusing capacity (DLCO) is reduced during the early follicular phase of the menstrual cycle when progesterone and estrogen levels are low, compared to the late follicular and mid luteal phases. The authors speculate that this difference is likely attributed to changes in pulmonary blood volume. These effects during exercise have not been directly investigated. In addition, progesterone and estrogen receptors have recently been identified in mast cells in human airways (348). This discovery may help explain and account for some of the effects of sex hormones in airway function and differences in ventilation.

### Morphology

Under normal circumstances, for the standard young healthy normally fit adult male, it is clear that structural and functional capacity of the pulmonary system, including the lung and chest wall and the supporting neural control system, exceeds the demands placed on them for flow rate, volume, and  $O_2$  and  $CO_2$  exchange (61). Women, however, may be an exception as morphological differences in lung structure between sexes have been documented. Specifically,

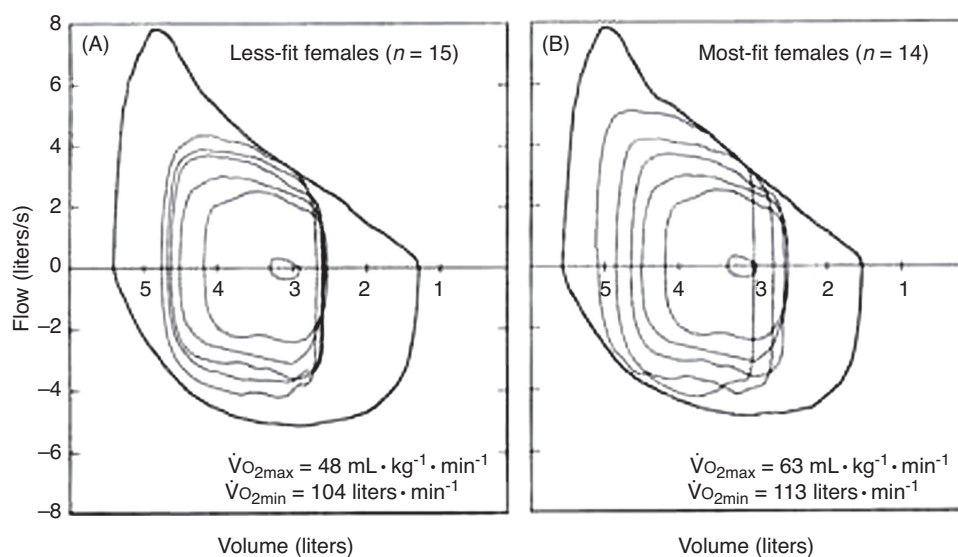
height-matched men have larger airway diameters (192) and larger lung volumes and diffusion surfaces (273, 306) compared with postpubertal women. Sex differences in lung diffusing capacity can be explained by fewer total number of alveoli (smaller surface area) and smaller airway diameter relative to lung size in women (lower maximum flow rates), and these differences probably become significant relatively late in the growth period of the lung (192, 306). Also, adult women consistently have smaller lung volumes and lower maximal expiratory flow rates even when corrected for sitting height relative to men (56). There does not, however, appear to be a sex difference in the elastic properties of the lungs and chest wall or pulmonary compliance (147). Therefore, given these pulmonary structural differences that exist between men and women, and recognizing that physical training sufficient to increase maximal aerobic capacity has no measurable effect on lung function or structure, women may be more susceptible to pulmonary limitations during exercise compared to men given similar metabolic demands.

### Hyperventilation of exercise

The hyperventilation of heavy exercise leads to significant increases in both inspiratory and expiratory muscle work and in both the resistive and elastic work of breathing. Nevertheless, a substantial reserve exists for increases in ventilation in the young- to middle-aged normal, healthy untrained man, even at maximal exercise (62). However, with a high ventilatory demand experienced by some elite men, they begin to approach the mechanical limits for inspiratory and expiratory pressure and flow development (expiratory flow limitation; EFL) (148).

Thus, as the tidal loop begins to intersect the maximal flow volume loop (MFVL), end-expiratory lung volume begins to increase to permit further increases in flow rate within the MFVL. This relative hyperinflation results in further increases in the elastic work of breathing, and inspiratory muscle work approaches 85% to 95% of capacity of the inspiratory muscles to produce pressure (148). Expiratory flow limitation in turn causes reflex inhibition of the hyperventilatory response (147), constrains ventilation, and increases the work associated with breathing. A greater work of breathing likely leads to more rapid respiratory muscle fatigue (14). Thus, the effects of mechanical constraints of the lung on volumes and maximal expiratory flow rates become very important to the control of breathing during high-intensity exercise.

Because women tend to show reduced airway diameter compared to men (see above), women are more likely to show greater mechanical limits to expiratory flow creating a smaller maximal flow: volume envelope compared to men (188). Figure 18 shows ensemble averaged tidal flow: volume loops for rest through maximal exercise in highly fit and less fit women. This figure demonstrates that the combination of increased ventilatory demand with airways vulnerable to closure in women likely leads to significant expiratory flow limitation sooner [i.e., at a lower  $\dot{V}_E$  (70-100 liters/min) and at a much lower  $\dot{V}O_2$ ] than their male contemporaries. As a result, women would probably show increased hyperinflation, marked increases in both the elastic and flow resistive work of breathing, and dyspnea at a given  $\dot{V}_E$  compared to the average man. Also, it would be expected that women would experience a lack of substantial hyperventilation at a  $\dot{V}O_2$  (and  $\dot{V}CO_2$ ) that men would typically would not.



**Figure 18** Response to progressive exercise, showing group mean tidal flow-volume loops for less-fit ( $n = 15$ ; A) and highly fit women ( $n = 14$ ; B) at rest and during light (55%  $\dot{V}O_{2max}$ ), moderate (74%  $\dot{V}O_{2max}$ ), heavy [90%  $\dot{V}O_{2max}$ , near-maximal (96%  $\dot{V}O_{2max}$ )], and maximal exercise plotted relative to group mean maximal voluntary flow volume loop.  $\dot{V}_{Emax}$ , maximal ventilation. Flow limitation is present when expiratory tidal flow-volume loop intersects boundary of volitional maximal flow-volume loop. Data are from McClaran et al. (188).

As a consequence of greater EFL, the active healthy female may be especially vulnerable to high fatiguing levels of the work of breathing during heavy exercise. During exercise at intensities  $>80\%$   $\dot{V}O_{2\max}$  of sustained exercise, the diaphragm consistently shows fatigue at end exercise, as demonstrated using bilateral phrenic nerve stimulation (147). An important consequence of high levels of respiratory muscle work and respiratory muscle fatigue is vasoconstriction and reduction in blood flow to the working locomotor muscles, accompanied by changes in vascular resistance (115, 117), which can compromise exercise tolerance, as has been demonstrated in male cyclists.

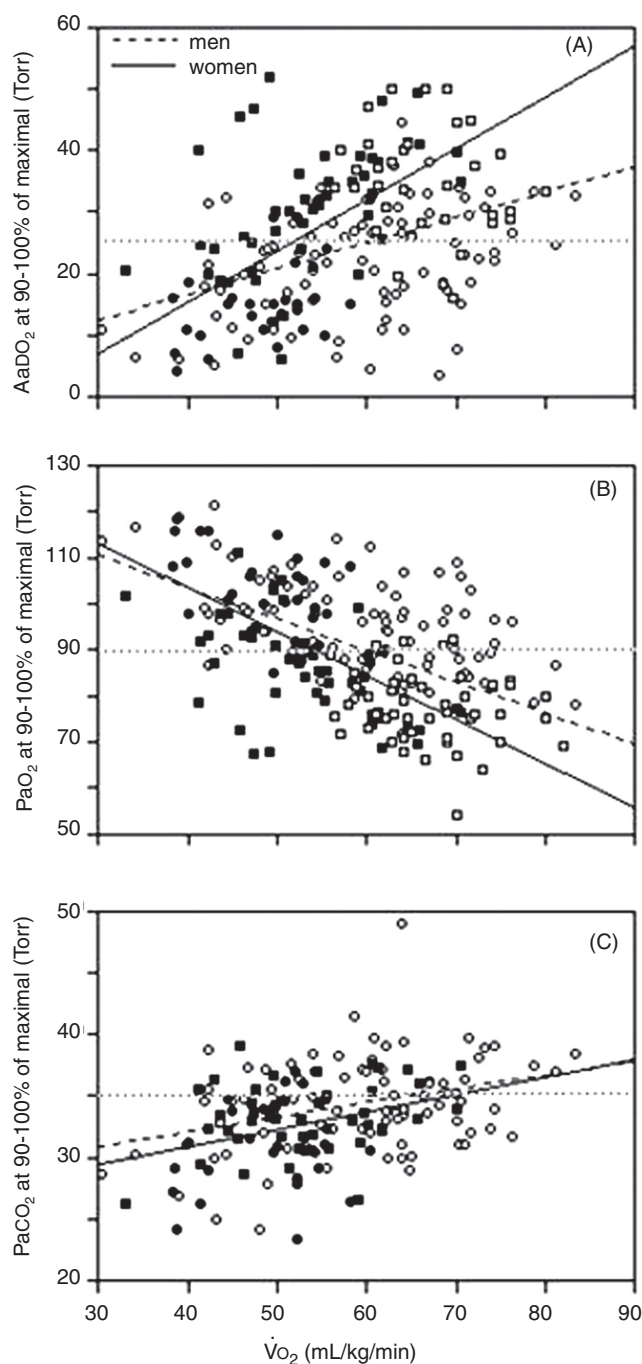
## Gas exchange

A significant reduction in the arterial partial pressure of oxygen ( $P_{aO_2}$ ) ( $<90$  mmHg) during heavy exercise, termed exercise-induced arterial hypoxemia (EIAH) has been well documented in some fit adult men over the past several decades (62, 63, 118). The cause of EIAH is believed to be due to an excessive widening of the alveolar arterial oxygen difference, an insufficient hyperventilatory response (63), and to a lesser extent, intrapulmonary arteriovenous shunts. Evidence suggests that even mild EIAH can have a significant detrimental effect on limiting  $O_2$  transport during heavy exercise (117).

To date, there are few published temperature corrected arterial blood gas data directly comparing pulmonary gas exchange between genders. A recent review has discussed in detail gender and pulmonary gas exchange during exercise (134). From this review, data in Figure 19 compiled from previously published studies (62, 116, 133, 216) in 57 women ( $\dot{V}O_{2\max}$  32-70 mL/kg/min) and 135 men ( $\dot{V}O_{2\max}$  30-83 mL/kg/min) show that the slope of the relationship of the  $A\text{-}aDO_2\text{-}\dot{V}O_2$  relationship during heavy to maximal exercise is greater in women than men. From these data, 12% of the women with a  $\dot{V}O_{2\max}$  of less than 50 mL/kg/min had evidence of gas exchange impairment. For men of the same fitness level, less than 2% have evidence of gas exchange impairment. These differences in gas exchange are reflected in the  $P_{aO_2}$  data and women have a greater negative slope of the  $P_{aO_2}/\dot{V}O_2$  relationship than do men. Approximately 10% of women with a  $\dot{V}O_{2\max}$  less than 50 mL/kg/min had a  $P_{aO_2}$  of less than 90 mmHg during heavy and maximal exercise compared to less than 2% of the men. It should be kept in mind that when lung size and fitness level are controlled for, many of the gas exchange differences between genders seem to be lost. Clearly, more testing is needed to determine: (i) the prevalence of EIAH among the normal population of women, (ii) if women are more susceptible to EIAH than men, and (iii) the mechanisms responsible for the EIAH.

## Maximal aerobic capacity

Sex differences in  $\dot{V}O_{2\max}$  are not clear cut. While it is generally thought that women typically have  $\dot{V}O_{2\max}$  values that



**Figure 19** Gender differences in arterial blood gases during exercise at 90% to 100% of  $\dot{V}O_{2\max}$ . Closed symbols are data from women and open symbols are data from men. Circles are cycle data and squares are running data. Faint dotted line represents level at which impairment is suggested to occur (see text for details). The  $A\text{-}aDO_2$  (A) is increased and the  $P_{aO_2}$  (B) is less in women compared to men at any level of  $\dot{V}O_2$ . However, alveolar ventilation is not reduced in women compared to men, as the  $P_{aCO_2}$  if anything, is lower in women at any given  $\dot{V}O_2$ . Data from Dempsey et al. (62); Harms et al. (116); Hopkins et al. (133); Olfert et al. (216).

are 15% to 30% below men (321), this may not always be the case. It has been reported over 40 years ago that considerable variability exists in  $\dot{V}O_2\text{max}$  within each sex as well as between sexes (125). Although the  $\dot{V}O_2\text{max}$  values of women and men are similar until puberty, many comparisons of  $\dot{V}O_2\text{max}$  values of normal nonathletic women and men beyond puberty might not be valid. Such data likely reflect an unfair comparison of relatively sedentary women with relatively active men. Thus, reported differences would reflect the level of conditioning as well as possible sex-specific differences. Saltin and Astrand (265) compared  $\dot{V}O_2\text{max}$  values of men and women athletes. In comparable events, the women had 15% to 30% lower  $\dot{V}O_2\text{max}$  values. However, more recent data suggest a smaller difference (55, 219). Elite female runners had substantially higher values than untrained men and women. Some women's values were even higher than a few of the elite male runners' values, but when considering the average for each elite group, women's values were still 8% to 12% lower than those of the elite male runners.

The sex difference in  $\dot{V}O_2\text{max}$  has generally been ascribed to differences in body composition and hemoglobin concentration (see above). Thus, the average male generates more total aerobic energy simply because he possesses more muscle mass and has less fat than the average female. Several studies have shown that differences between the sexes disappear when  $\dot{V}O_2\text{max}$  is expressed relative to fat-free mass or active muscle mass (233), yet some studies continue to demonstrate differences even when adjusted for differences in body fat. Factors other than lower body fat and higher hemoglobin concentrations may also explain male-female aerobic capacity differences. For example, normal physical activity levels differ between the average male and average female (104). These findings suggest a biologically inherent and unalterable component to the sex difference in aerobic capacity.

There is no reason to suspect that training differences in  $\dot{V}O_2\text{max}$  are different between sexes. In fact, one study has demonstrated that endurance-trained women have considerable higher capillary-to-fiber ratios than untrained women (102). These values are similar to those reported in men of similar training status (231). With cardiorespiratory endurance training, women experience the same relative increase (~10-50%) in  $\dot{V}O_2\text{max}$  that has been observed in men. The magnitude of change noted generally depends on the intensity and duration of the training sessions, the frequency of training, and the length of the study.

### Submaximal aerobic capacity

Little if any difference is found between women and men for the same absolute power output. However, at the same absolute submaximal work rate, women usually are working at a higher percentage of their  $\dot{V}O_2\text{max}$  (289). As a result, their blood lactate levels are higher, and lactate threshold occurs at a lower absolute power output. Peak blood lactate values are generally lower in active but untrained women than in active but untrained men (129). Also, limited data suggest that elite

female middle distance and long distance runners have peak lactate values that approximately 45% lower than similarly trained elite male runners (219, 231). The reason for these sex differences is unknown. Lactate threshold values appear to be similar between equally trained men and women when values are expressed in relative but not absolute terms. Lactate threshold appears to be closely related to the mode of testing and to the individuals' state of training. Thus, sex-specific differences likely do not exist.

After endurance training, women's oxygen uptake at the same absolute submaximal work rate does not appear to change (289), although several studies have reported decreases (194, 265). Women's blood lactate levels are reduced for the same absolute submaximal rates of work, peak lactate levels generally are increased, and the lactate threshold increase with training (129). Finally, endurance training also improves women's ability to use free fatty acids for fuel, and adaptation that is very important for glycogen sparing (301). In fact, it appears that women, during submaximal exercise, obtain a greater percentage of their energy from fat compared with men, in both the untrained and trained state (see below) (136, 301).

### Anaerobic capacity

Large sex differences exist in absolute anaerobic power capacity (82, 263). These differences can be explained by the clear sex differences in factors that affect absolute anaerobic power output capacity (187, 210). For example, given fat-free leg volume, the peak oxygen deficit during supermaximal cycling remained significantly higher in men than in women (328). These differences averaged about 20%, even after adjusting for the estimated difference in active muscle mass between sexes. Possible differences in the relative cross-sectional areas and metabolic capacities of the two fiber types and the catecholamine response to exercise may contribute to men's generally greater anaerobic capacity.

### Endocrine function and metabolism

Basal metabolic rate averages 5% to 10% lower in women than in men (229, 302). This does not necessarily reflect a true sex difference in the metabolic rate of specific tissues. Rather, it results largely because women generally possess more body fat (and less fat-free tissue) than men of similar size, and fat tissue has lower metabolic activity than muscle. Changes in body composition, either a decrease in fat-free mass and/or increase in body fat during adulthood (105) usually explain the 2% to 3%/decade BMR reduction observed for adult men and women (229).

Research suggests that women do not increase glycogen storage when dietary carbohydrate increases from 60% to 75% of total caloric intake (302). Other data support the notion of significant sex differences in carbohydrate metabolism in exercise before and after endurance training. During submaximal exercise at equivalent percentages of  $\dot{V}O_2\text{max}$ , women



derive a smaller proportion of the total energy from carbohydrate oxidation than men (146). This sex difference in substrate oxidation does not persist into recovery (136).

With similar endurance training protocols, both women and men show a significant decrease in glucose flux for a given submaximal power output (40, 96). However, at the same relative workload after training, women show an exaggerated shift toward fat catabolism, whereas men do not (146). This suggests that endurance training induces greater glycogen sparing at a given relative submaximal exercise intensity for women than men. Sex differences in exercise substrate metabolism may reflect differences in sympathetic nervous system adaptation to training (i.e., more blunted catecholamine response for women). A glycogen sparing metabolic adaptation to training could benefit women's performance during high-intensity endurance competition.

### Muscular strength and power

Men typically show greater strength than women. No differences exist in muscle quality (i.e., characteristics of muscle) of men and women, however. The difference in maximal strength is mainly explained by a difference in size of the individual muscle fiber. For example, the cross-sectional area for slow twitch fibers in untrained women is approximately 70% of the men's size and for fast twitch fibers it is about 85% (53, 54). Despite smaller fiber size in women, capillarization is similar between men and women (235). Clearly individuals with the largest muscle cross sections generate the greatest absolute force. The maximal strength per unit of cross-sectional area of the skeletal muscle, however, is about the same in women and men, irrespective of age (142). This suggests that the innate qualities of muscle and its mechanisms of motor control are similar for women and men (268).

Women are reported to be 40% to 60% weaker than men in upper body strength but only 25% to 30% weaker in lower body strength (128, 268). Additionally, MRI data suggest that men have more skeletal muscle than women and that these sex differences are greater in the upper body (144). Comparisons of muscular strength on an absolute score basis (i.e., total force in lb or kg) indicate that men possess considerably greater strength than women for all muscle groups. This gender disparity generally coincides with gender-related difference in muscle mass distribution (34). When lower body strength is expressed relative to body weight, women are still 5% to 15% weaker than men, but when expressed relative to fat-free mass, this difference disappears (34). Women have a higher percentage of their muscle mass in the lower body when compared with men. In addition and probably related to this muscle mass distribution, women use the muscle mass of their lower bodies much more than they used their upper body muscle mass, particularly when compared with use patterns in men. This indicates the importance of neuromuscular recruitment and synchronization of motor unit firing in the ultimate determination for strength.

The amount of absolute muscle hypertrophy with resistance training represents a primary sex difference. Variation in hypertrophic response probably results from sex-specific differences in hormonal levels that exert strong anabolic effects, particularly the average 20 to 30 times higher testosterone levels in men (169). Importantly, testosterone levels exist along a continuum; some women normally possess concentrations as high or higher than men (170). Without doubt, men experience a greater absolute change in muscle size because of their larger initial muscle mass, but muscular enlargement on a percentage basis remains similar between sexes (58, 217). Sex-related differences in hormonal responses to resistance exercise (e.g., increased testosterone and decreased cortisol) may determine any ultimate sex differences in muscle size and strength adaptations with prolonged training (168, 343). It has been suggested that women are more dependent on physical activity than adult men to develop strength (104). Differences between individuals in the internal muscle architecture, in limb length, and in joint structures are important factors capable of influencing strength (186). Women tend to show greater resistance to fatigue compared with men (129). The reason for this greater resistance to fatigue is not yet known but could be related to the amount of muscle mass recruited, substrate utilization, muscle fiber type, difference in muscle blood flow (occlusion) and neuromuscular activation.

### Thermoregulation

The typically smaller female possesses a relatively large external surface per unit of body mass exposed to the environment, offering a favorable dimensional characteristic for heat dissipation (32). Consequently, under identical conditions of heat exposure, women tend to cool faster than men. Sweating represents the distinct sex difference in thermoregulation. Women sweat less prolifically than men, despite possessing more heat-activated sweat glands per unit skin area (32). Women start to sweat at higher skin and core temperature; they also produce less sweat than men for a comparable heat exercise load, even after equivalent acclimatization (66). Despite a lower sweat output, women have a heat tolerance similar to men of equal aerobic fitness at the same exercise level (287). Women probably use circulatory mechanisms for heat dissipation, whereas men make greater use of evaporative cooling. Clearly, producing less sweat to maintain thermal balance protects women from dehydration during exercise at high ambient temperatures.

The available evidence shows that women require lower evaporative cooling both in hot and wet environments and in hot and dry environments (278). Women have a lower tissue conductance in cold and a higher tissue conductance in heat than do men. This indicates a greater variation in the peripheral reaction to climatic stress in women. This fact does not appear to be important for the performance of work, however. Active women performed exercise of equal relative intensity in dry heat as well as active men (135). Also, no differences were determined in sweating efficiency between sexes in the

dry heat, but women maintain a significantly higher sweating efficiency than the men in humid heat (98). In both environments, men recruit a significantly lower percentage of their available sweat glands than women.

Fitness is an important factor when men and women are compared in the heat. When fitness levels are similar, the previously reported sex-related differences in response to an acute heat exposure seem to disappear (12). Women generally tolerate the thermal stress of exercise at least as well as men of comparable aerobic fitness and level of acclimatization. Both sexes also acclimatize to the same degree (287). When comparing men and women at similar workload or %  $\dot{V}O_2\text{max}$ , thermoregulatory differences between sexes became less pronounced (121).

Women have a slight advantage over men during cold exposure because they have more subcutaneous body fat (69). But their smaller muscle mass is a disadvantage in extreme cold because shivering is the major adaptation for generating body heat. The greater the active muscle mass, the greater the subsequent heat generation. Muscle also provides an additional insulating layer.

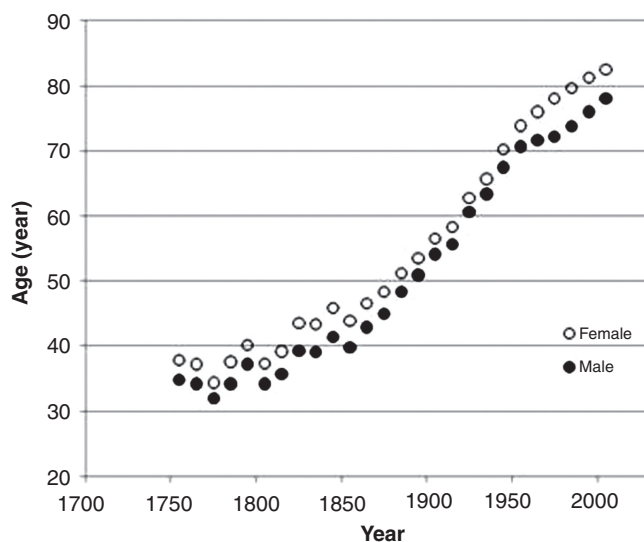
### Future directions

Increasing evidence suggests that there are a number of physiological sex differences that influence performance. However, historically the vast majority of scientific studies have focused on these responses in men with relatively little attention given to women or to sex differences. It is only in the past couple of decades that exercise and training responses and differences between the sexes has emerged. Future studies should continue to investigate sex differences in body composition, cardiovascular function, pulmonary function, substrate metabolism, and thermoregulation as specified in this article to specifically elucidate the mechanistic basis for performance differences between men and women.

## Aging

### Introduction

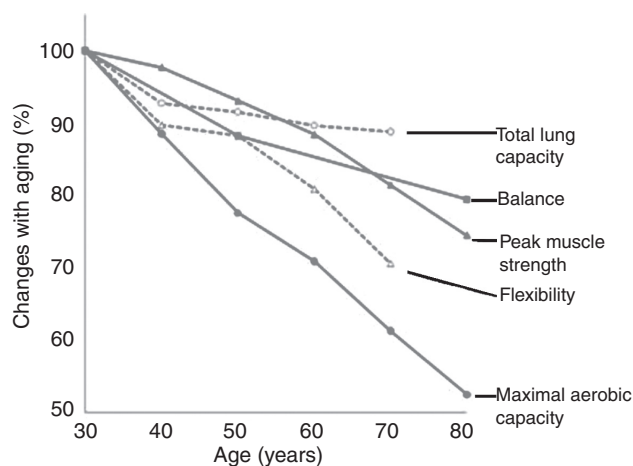
Average life expectancy at birth is an indication of the functional life span. Maximum life expectancy has apparently remained unchanged at  $\sim 120$  years. Yet average life expectancy at birth experienced dramatic increases in the last few century of human history (Fig. 20) (139). These changes have been attributed largely to the improvements in medicine and technology. Ironically, the same technological advances have contributed to a remarkable decrease in habitual level of physical activity over the year. More importantly, the prevalence of the sedentary lifestyle increases markedly with advancing age and is highest among the elderly (22). An increasingly older population coupled with the greater prevalence of sedentary lifestyle in older adults is a deadly combination and could place a potentially unmanageable burden on our society and the health care system due to increased morbidity and hos-



**Figure 20** Life expectancy at birth (Sweden). Life expectancy at birth has increased remarkably over the past 200 years, contributing to the ever-increasing population of the elderly. Data from the Human Mortality Database, University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Available at [www.mortality.org](http://www.mortality.org). (139).

pitalization. As such, primary and secondary prevention of age-related dysfunction is of paramount importance. Lifelong physical activity is essential for preserving or delaying the onset of functional disability and chronic metabolic diseases.

As elegantly displayed by Shock (280), different physiological functions decline with age with widely varying rates. Various measures of physical fitness also undergo different rates of declines with advancing age (Fig. 21). These aging changes accumulated throughout the physiological systems



**Figure 21** Age-associated reductions in physical fitness. There are substantial differences in the age-related rates of declines in physical fitness components that are routinely measured in exercise physiology. Data from Einkauf et al. (75), Tanaka et al. (293), Duncan et al. (72), and Lindle et al. (180).

reduce the capacity to cope with the stress and maintain homeostasis. In this subsection, age-associated changes in body composition, muscle strength and power, maximal aerobic capacity are described. Additionally, vascular disease that is known to increase markedly with advancing age is discussed.

## Structure and function

### Body composition

According to the National Health and Nutrition Examination Survey (NHANES) involving >4000 men and >4000 women varying in age, height appears to be maintained up to 40 to 50 years of age (189). Thereafter, height decreases very slowly with aging with an average rate of 1 cm/decade both in men and women (132, 189). Age-associated decreases in height do not appear to be modulated by the physical activity status (293, 338). Body mass, total body fat, and abdominal adiposity all increase with advancing age in sedentary adult humans (132). However, increases in body mass are plateaued around 50 to 60 years of age, and body mass starts to decline after the age of 70 years both in men and women (189). This decline, however, is not large in magnitude, since the rate of reduction does not exceed 0.3% of body mass per year (279). Body fat content, as assessed by underwater weighing, increase linearly at least until 70 years of age (95, 132). This marked increase in body fatness is in contrast to fairly stable body mass index with aging (99). This is because aging is also associated with the corresponding reductions in fat-free mass (99, 132). Another important index of obesity, particularly in the context of metabolic syndrome that increases in prevalence with aging, is abdominal obesity, as conveniently assessed by waist circumference. Waist circumference increases  $\sim 0.7$  cm/year with aging at least until 80 years of age (211). Even within the abdominal area, there appears to be an increase in visceral fat and the corresponding reduction in subcutaneous fat (345). Interestingly, intermuscular adipose tissue, which is the adipose tissue within the fascia surrounding skeletal muscle, also appears to increase with advancing (196). Although the metabolic significance of the intermuscular fat is not clear, high degree of intermuscular fat is associated with muscle weakness (107) and could contribute to sarcopenia (145).

The increases in body mass and adiposity are presumably due to age-related reductions in energy expenditure that are disproportionately greater than the reductions in energy intake that occur with advancing age (228). There are three primary components of energy expenditure: resting (basal) metabolic rate, thermic effects of food, and physical activity thermogenesis. There are other small components of energy expenditure that might contribute to the increases in body mass and adiposity, such as changes in energy expenditure associated with medications (e.g., thyroxine) and stress or anger. Thermic effect of physical activity is the most variable component and makes up  $\sim 15\%$  of the total energy expenditure in sedentary adults, but its proportion can increase to 30% or more in physically active adults. Declines in the amount of physical activity

may contribute to age-associated elevations in body mass and body fatness (132, 228). One component of activity thermogenesis that has attracted a lot of attention in recent years is nonexercise activity thermogenesis (NEAT), the energy expenditure that is not from sleeping, eating or exercise/sports. It ranges from the energy expended through sitting, standing, walking, typing, toe-tapping, and fidgeting (176). Similar to thermogenesis associated with exercise/sports, NEAT is also significantly lower in older compared with young adults (119). Resting metabolic rate, which accounts for 60% to 75% of daily energy expenditure, decreases with advancing age (230, 253, 318). Another determinant of total energy expenditure that contributes to its decline with aging is a reduction in the thermic effect of food (150, 228). The mechanisms responsible for the age-related reduction in diet-induced energy expenditure have not been elucidated. An inability to activate the sympathetic nervous system activity has been hypothesized as a mechanism (228) but such hypothesis has not received much experimental support (150).

Compared with that observed in sedentary adults, the age-associated increases in body mass are markedly smaller or even absent in those who exercise regularly (166, 293, 317). However, percent body fat in middle-aged and older athletes is significantly higher than that in young athletes although the magnitudes of such age-related differences are substantially less than that in the sedentary counterparts (166, 293, 317). No age-related changes in body mass in face of the increase in body fatness appear to be odd, but it is because chronic endurance training does not appear to be effective in preserving muscle mass or muscle cross-sectional area with advancing age (163, 285, 292). Consequently, measurement of body mass alone may ignore important changes in body adiposity with advancing age. Smaller age-related differences in body mass and adiposity in athletes could be due, at least in part, to their high physical activity-related energy expenditure. It should, however, be noted that there is no evidence that high levels of exercise training intensity and volume, which result in high total caloric expenditure, can be maintained for period longer than 10 years, especially at older ages (65, 232, 299). Thus, in addition to the direct caloric cost of exercise, it is likely that other components of total energy expenditure would contribute. For example, the age-related decline in resting metabolic rate in sedentary adults is not observed in adults who regularly perform endurance exercise (318).

### Muscle strength and power

Skeletal muscle strength, one of the representative measures of functional capacity, begins to decline after age 30, with a more exponential decrease in strength after the age of 50 (110, 240). Between the ages of 30 and 80, humans lose an average of 30% to 40% of their muscle strength (around 40% in the leg and back muscles and 30% in the arm muscles) (110, 132). Dynamic muscular power declines at a much faster rate than static or isometric strength in healthy aging men (4, 193, 283, 344). A loss in static strength with aging appears to

occur sooner and at a faster rate in the lower body than in the upper body (11, 23). On the other hand, dynamic muscular power declines similarly in the upper and lower body with advancing age (4, 183). The age-associated decline in peak muscular power generation has important clinical and functional implications for independent living among the elderly (85). The ability to perform many activities of daily living may be compromised by low muscular strength and power even in healthy elderly persons (257). The consequences of sarcopenia can be extensive because there is an increased susceptibility to falls and fractures, impairment in the ability to thermoregulate, a decrease in basal metabolic rate, as well as an overall loss in the functional ability to perform daily tasks (73). Moreover, muscle strength is inversely and independently associated with death from all causes, even after adjusting for aerobic fitness (262).

The primary mechanism underlying the decrease in muscle strength with age is a decline in muscle mass and, to a lesser extent, a decrease in muscle strength per unit muscle cross-sectional area (i.e., neural activation or muscle quality) (73, 160, 322). Age-related loss in skeletal muscle mass is primarily caused by the selective atrophy of type II fibers as demonstrated by the measurements of fiber cross-sectional area and myosin heavy chain expression (177). Evidence from human skinned single muscle fiber experiments indicates no age-related differences in peak force when fibers are normalized for cell size (310), consistent with the notion that the reduction in muscle strength with advancing age is regulated primarily by a loss in muscle cross-sectional area. The decrease in muscle cross-sectional area with aging is attributed to a structural imbalance between muscle protein synthesis and degradation. Although some studies reported reduced basal muscle protein synthesis rate in older versus young adults (18, 258), more recent studies demonstrate no differences in basal muscle protein synthesis rates between young and older adults (157, 322, 323). The current hypothesis is that basal muscle protein synthesis and/or degradation rates are generally preserved with aging (323). Attenuated rate of muscle protein synthesis in response to lower physical activity and the ingestion of amino acids or protein is believed to be one of the key factors responsible for the age-related decline in skeletal muscle mass (157, 167). The proportion of type I and II muscle fibers as determined by histochemical staining of myosin ATPase does not appear to change with advancing age in human studies using muscle biopsy samples (41, 84). These biopsy data are supported by an autopsy study of whole muscle cross-sections showing that the proportion of muscle fiber types in the vastus lateralis is not affected with increasing age (178).

A number of intervention studies have demonstrated that chronic resistance training provides substantial stimuli to enhance muscle strength in older adults (276). Indeed, older adults are capable of achieving the same relative magnitude of gains in muscle strength as their younger counterparts (97). These muscular benefits, combined with the preservation of bone mineral density, help prevent the deleterious effects of

aging on functional capability, including balance loss, falls, and loss of functional independence. These musculoskeletal adaptations are important, and these unique benefits appear to be attributable only to resistance training because chronic endurance training does not appear to confer similar benefits to muscle mass or muscle cross-sectional area with advancing age (163, 285, 292). As is apparent in the stereotypic appearance of Masters endurance-trained runners, regular aerobic exercise does not induce obvious muscle hypertrophy (292, 322), although an increase in both type I and IIa muscle fiber area has been observed after intense endurance training in previously sedentary older adults (42). Additionally, endurance training does not appear effective in preserving muscle mass and in ameliorating the progression of sarcopenia (163, 285, 292). Thus, resistance training is currently the most effective strategy to combat sarcopenia and its sequela.

A clinically and functionally important question is whether the rate of decline in muscle strength and power with age is attenuated or absent in adults who perform regular resistance exercise. The notion that strength training performed on the daily basis will attenuate or prevent loss of muscle strength with age is a very positive message from the public health standpoint, and such notions have been promoted and described in textbooks (336). Surprisingly, only a few published studies are available to provide insight into this issue. In a study that compared Masters weightlifters and healthy untrained adults varying widely in age (222), both peak muscle isometric strength and peak lower-limb explosive power declined with increasing age at a similar relative (%) rate in the weightlifters and sedentary controls. When the data in peak muscle power was expressed in absolute unit (in W/year), the rate of decrease was ~60% greater in strength-trained adults (222). Similar relative rates of age-related decline in anaerobic power have also been reported between power-trained Masters athletes and sedentary peers (108). Thus, the available evidence is not consistent with the notion that regular strength training would prevent loss of muscle strength and power with increasing age. However, it is important to note from the standpoint of preventive gerontology that the absolute levels of muscle strength and power in strength-trained adults are substantially higher than those of their sedentary peers throughout the adult age range (222). Accordingly, strength-trained adults possess higher levels of muscular fitness and lower risks of premature morbidity than do sedentary adults at any age.

Resistance exercise interventions have been shown to be effective in increasing skeletal muscle mass, strength, and functional capacity in older adults, particularly when protein is ingested before, during, and/or after exercise (167). The additional health benefits of engaging in regular resistance training include an increase in basal metabolism and limb perfusion, bone mineral density, as well as improved insulin sensitivity, and lipid and lipoprotein profiles (3, 141, 233, 334). Although the list of benefits induced by resistance training is impressive, the magnitude of these health benefits may be smaller than those achieved by endurance

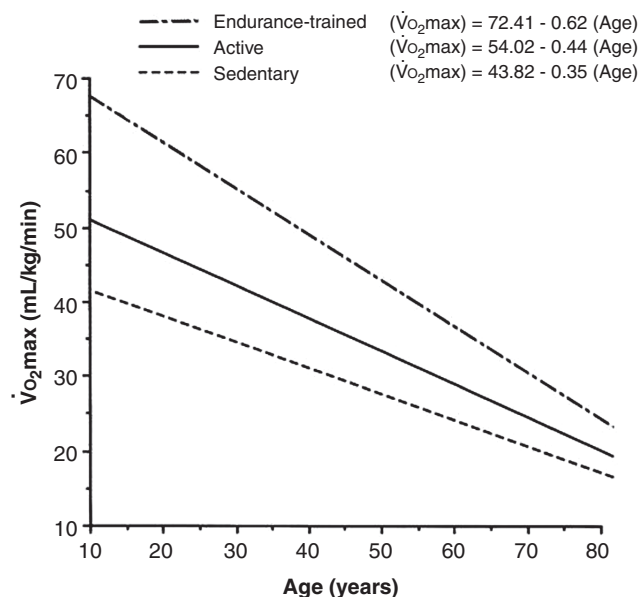


training (233, 334) and there may be unintended effects associated with resistance training as well. Recent studies have reported that individuals habitually performing strength training exhibit a greater rate of age-related arterial stiffening (25, 197) and that a period of strenuous resistance training may increase arterial stiffness in young adults (52, 158, 198). Because arterial stiffening precedes and may even initiate the development of elevated blood pressure (179), resulting in the hypertension that often leads to a major clinical event, these findings are alarming. Fortunately, endurance training concurrently performed with resistance training appears to negate the arterial stiffening effects of resistance training (44, 158). This exercise regimen is consistent with the current physical activity recommendation to perform both endurance and resistance training on a daily basis (205). Other comparative studies have also demonstrated that the combination of resistance and endurance training results in better cardiovascular adaptations than endurance training alone, especially in older cardiac patient population (60).

### Cardiopulmonary functional capacity

Maximal oxygen consumption ( $\dot{V}O_2\text{max}$ ) is generally considered a primary determinant of endurance performance among young endurance-trained athletes (152, 298). Among middle-aged and older adults, it is the best index of the functional capacity of the cardiovascular system. Since a classic study by Robinson in 1938 (252), it has been well recognized that  $\dot{V}O_2\text{max}$  declines with advancing age with the average rate of  $\sim 10\%$  per decade after the age 25 to 30 in healthy but sedentary adults of both sexes (83, 89, 226, 293). This reduction results in a decrease in functional capacity that would contribute to a loss of independence, increased incidence of disability, and reduced quality of life and cognitive function with age (27, 132, 221, 316, 330). Additionally, maximal aerobic capacity is an independent risk factor for cardiovascular and all-cause mortality (28). Given this, lifestyle factors that may affect the rate of decline in  $\dot{V}O_2\text{max}$  with advancing age are of considerable public health interest.

Early investigations reported that the rate of decline in  $\dot{V}O_2\text{max}$  with advancing age is substantially (as much as 50%) smaller in endurance-trained athletes than sedentary counterparts (122, 156). However, more recent studies reported that when expressed as percent decrease from early adulthood, the relative (%) rate of decline in  $\dot{V}O_2\text{max}$  with age is not dependent on physical activity levels (83, 89, 92, 131, 226, 293, 338). In fact, endurance-trained men and women demonstrate rather greater absolute (mL/kg/min) rates of decline in  $\dot{V}O_2\text{max}$  with age than their sedentary counterparts (Fig. 22) (83, 89, 226, 293). It is interesting to note that the greater rate of age-related declines in  $\dot{V}O_2\text{max}$  in endurance-trained versus sedentary states has also been observed in rats (349). It should be noted that the absolute values of  $\dot{V}O_2\text{max}$  in endurance-trained adults are substantially greater than those of their sedentary peers throughout the age range. As such, endurance-trained adults possess higher levels of physiolog-



**Figure 22** Maximal oxygen consumption and age in three groups separated by their activity status. Rate of decline was smallest in sedentary women and greatest in endurance-trained women. Data from FitzGerald et al. (89).

ical functional capacity (330) and lower risks of premature mortality (81), than do sedentary adults at any age.

Maximal oxygen consumption has an exact physiological definition that is expressed by the Fick equation: maximal cardiac output  $\times$  maximal arteriovenous  $O_2$  difference. The exact contribution of the central (i.e., cardiac) and peripheral (i.e., oxygen extraction) factors to the age-related decline in  $\dot{V}O_2\text{max}$  remains unknown. Attempts to assess the effects of active aging on the Fick determinants of  $\dot{V}O_2\text{max}$  have relied almost exclusively on cross-sectional studies comparing young and older endurance-trained athletes.

Although there is a previously held view that maximum cardiac output is maintained with advancing age (254), this observation has not been confirmed by the majority of other studies (140, 153, 214, 251, 264). Given the well-established fundamental relation between oxygen consumption (i.e., metabolism) and cardiac output (i.e., blood flow), it is reasonable that maximal cardiac output decreases with advancing age as  $\dot{V}O_2\text{max}$  declines (110, 236). In endurance-trained athletes, maximal cardiac output is reduced in older adults (60-70 years) to 80% to 90% of that measured in younger adults (20-30 years) (214, 251). The age-related reductions in maximal cardiac output are mediated by reductions in both maximal stroke volume and maximal heart rate.

Maximal heart rate was viewed as a primary factor for influencing age-related reductions in maximal cardiac output and  $\dot{V}O_2\text{max}$  in endurance-trained men (112, 122). However, the subsequent cross-sectional and longitudinal studies of older elite distance runners demonstrated that maximal heart rate declines with age at a rate similar to sedentary men and

women at a rate of 0.7 beats/min/year (297). This rate of reduction deviates from the prevailing equation (maximal heart rate =  $220 - \text{age}$ ), and the reliance on the traditional equation could underestimate maximal heart rate in older adults. The age-associated reduction in maximal heart rate appears to be mediated by a slower conduction velocity, a reduced responsiveness of the myocardium to  $\beta$ -adrenergic stimulation (93) and a decreased intrinsic heart rate (151), with the latter playing by far the greatest role in determining maximal heart rate (38).

Maximal stroke volume is also reduced with advancing age in older adults (60-65 years of age) to 80% to 90% of that measured in young adults (214). There is very limited information as to how the age-related reduction in maximal stroke volume in endurance-trained adults is attributed to the three major determinants of stroke volume (i.e., the preload, the afterload, and the contractility of the heart). The exercise training-induced increase in maximal stroke volume is almost always associated with an increase in preload or left ventricular end-diastolic dimension, and this has been viewed as a "hallmark" cardiovascular adaptation to endurance exercise (74). However, it is unclear if a reduction in left ventricular filling plays a role in the age-associated decline in maximal stroke volume in endurance-trained adults. Previous studies indicating that left ventricular preload, as expressed as left ventricular end-diastolic dimension, area, or volume, is not related to age in healthy relatively active adults (90) do not support this concept. In young adults, total blood volume exerts an important influence on maximal stroke volume and maximal oxygen consumption (43). But total blood volume does not seem to explain the lower maximal stroke volume observed in older endurance-trained subjects as they do not demonstrate the age-related reductions in total blood volume (149). One possibility is that other determinants of the cardiac preload, including LV end-diastolic pressure, diastolic filling time, venomotor tone, myocardial compliance, and/or a combination of these factors, contribute to the age-related decline (5, 271).

It is well established that arterial walls stiffen with advancing age. The increase in arterial stiffness can lead to an excessive rise in aortic input impedance as well as vascular afterload, thereby impeding the increase in stroke volume and cardiac output during exercise stress (36, 204). Although the degree of arterial stiffening with advancing age is substantially attenuated in endurance-trained adults, they still experience moderate aortic stiffening with age (295). This could contribute to the decline in maximal stroke volume seen in older endurance-trained adults presumably through increases in the afterload. On the other hand, there is also a contradicting report that the afterload, as indirectly assessed by mean arterial pressure or total peripheral resistance, are not different between young and older endurance-trained men (251). It is very difficult to evaluate the contractility of the heart due to the complex interactions among multiple modulators of the cardiac function, and there is no satisfactory index of contractility totally independent of preload and afterload in humans

(90, 103). Animal studies using the isolated perfused heart preparation demonstrated that the contractility declines significantly with advancing age in endurance-trained rats and that the magnitude and the rate of the decline is similar to sedentary rats (286).

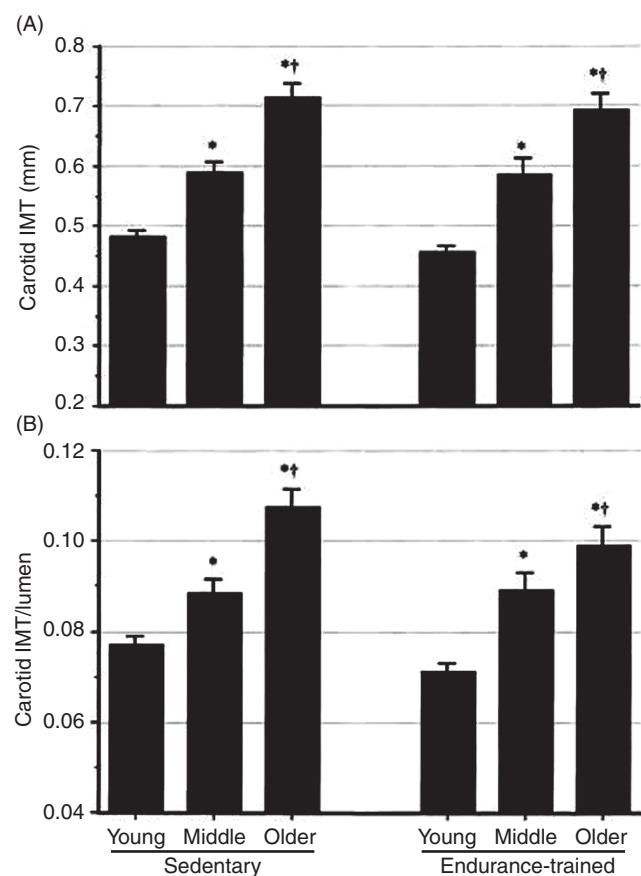
Maximal arteriovenous  $O_2$  difference reflects the capacity of the skeletal muscle to extract and consume oxygen from the blood for ATP production. In sedentary adults, maximal arteriovenous  $O_2$  difference clearly declines with advancing age. These findings fit well with the results of histochemical and enzymatic studies demonstrating marked reductions in capillary density per unit fiber area and mitochondrial enzyme activities with age (41, 281). Even in endurance-trained men, peripheral oxygen extraction appears to contribute to the decline in  $\dot{V}O_{2\max}$  with age as maximal arteriovenous  $O_2$  difference declines modestly (5-10% in the span of  $\sim 30$  years) with age (112, 251, 264). The decline in oxygen extraction with age is associated with  $\sim 25\%$  reduction in mitochondrial enzyme activity in the span of 20 years (311). As skeletal muscle mass is closely related to maximal aerobic capacity among healthy humans across the adult age range (91), a decline in maximal arteriovenous  $O_2$  difference may be secondary to age-related loss of skeletal muscle mass. However, even if maximal oxygen consumption was expressed per unit skeletal muscle, it was still lower in the older compared with the young adult athletes (237). It is a matter of debate as to whether this reflects reductions in maximal oxygen delivery or extraction. Fat-free mass may exert its permissive influence on maximal oxygen consumption via an effect on central circulatory function involving blood volume, stroke volume, and cardiac output (140).

### Vascular disease risks

Cardiovascular disease, in particular coronary heart disease, is the leading cause of morbidity and mortality in the United States and other industrialized countries (259). As it is the case for most chronic degenerative diseases, the prevalence and incidence of cardiovascular disease increase markedly with advancing age in both men and women (259). Older age is now considered one of the major risk factors for cardiovascular disease (171). Very little attention, however, has been devoted to aging as a risk factor for coronary heart disease. This may be due to the prevalent notion that aging is a nonmodifiable and unpreventable risk factor that is not manageable. However, this notion is no longer tenable.

There are several explanations for dominating effects of age on cardiovascular disease risks. A traditional view is that aging simply provides an increased exposure time to the other age-associated risk factors. Indeed the concept that aging process is closely coupled to vascular changes is not new. As early as 17th century, a famous clinician Thomas Sydenham stated, "a man is as old as his arteries." However, an emerging view is that age-associated changes in vascular structure and function alters the substrate on which specific pathophysiological mechanisms become superimposed (171, 209).

Arteries, in particular large elastic arteries, such as the aorta, are reported to dilate with advancing age resulting in an increase in arterial lumen size (269, 320). Aging is also associated with the longitudinal morphological changes in the aorta (i.e., the aortic length) (68). It is generally thought that the aorta and large elastic arteries become longer and tortuous with aging (114, 208, 327). However, age-related elongation of the aorta appears to confine only to the ascending aorta (290). The thickness of arterial wall, as measured by the intima-media thickness (IMT), increases linearly with advancing age (Fig. 23) (269, 296, 320). Age-associated intima-media thickening on the carotid artery is often ascribed to subclinical atherosclerosis or diffuse plaque formation on the intima layers (341) probably because high-resolution ultrasonography cannot distinguish between the intimal and medial layers (272). A part of the increase in arterial wall thickness is due to intimal thickening as a postmortem study conducted in populations with low incidence of atherosclerosis clearly shows (320). However, increases in IMT are also mediated by thickening of the media layers as has been shown in nonhuman primates (239) as well as in beagle dogs



**Figure 23** Age-related differences in carotid artery intima-media thickness (IMT) in sedentary and endurance-trained adults. In both sedentary and endurance-trained groups, carotid IMT and IMT/lumen ratio were progressively higher in the young, middle-aged, and older men. There were no statistically significant differences between sedentary and endurance-trained men at any age. \* $P < 0.05$  versus young. † $P < 0.05$  versus middle. Data from Tanaka et al. (300).

that do not develop atherosclerosis (113). Although there is no detailed information regarding the physiological factors involved in progressive arterial wall thickening with aging, intravascular hemodynamic changes related to increases in local (carotid) blood pressure appear to play a role (296).

A hallmark feature of vascular aging is the stiffening of arteries (261, 294). One can observe 40% to 50% differences in large elastic artery stiffness between age 25 and 75 years in apparently healthy adults (202, 295). Changes in the composition of the arterial wall are believed to be important mechanisms in mediating arterial stiffening with increasing age. In contrast to proximal elastic arteries (e.g., aorta and carotid artery), peripheral muscular arteries (e.g., brachial artery, femoral artery) do not obviously stiffen with aging in healthy humans (161, 294). The aorta and proximal elastic arteries distend and recoil approximately 10% with each heart beat, while peripheral muscular arteries distend only ~2% to 3% with each beat. Such differences in degree of stretch are the basis of the hypothesis that age-related arterial stiffening may be due to the material fatigue within the arterial wall (212). According to this hypothesis, with advancing age, repetitive pulsations (some 30 million/year) cause fatigue and fracture of elastin lamellae of central arteries, causing them to stiffen (and dilate). Studies using specimens of pig aorta demonstrated that the elastin undergoes structural alterations when millions of cyclic stretches are applied (109). Moreover, there is an accumulation of additional interstitial collagen in the arterial wall (282), which can react nonenzymatically with glucose, link them together, and produce advanced glycation end-products (AGEs) (282). AGEs accumulate slowly on long-lived proteins in the arterial wall to stiffen arteries (282).

In addition to the structural changes in the arterial wall, vasoconstrictor tone exerted by vascular smooth muscle cells also likely contributes. In marked contrast to the prevailing thought that arterial stiffness is a relatively static measure, arterial stiffness has a large “reserve” and can be altered over a much shorter period, even acutely (21, 30). The ability to acutely modify arterial stiffness is thought to be due to modulation of the contractile states of the vascular smooth muscle cells in the arterial wall (21, 30). Sympathetic nerve activity and bioactivity of locally synthesized molecules, such as nitric oxide and endothelin-1 are thought to be most potent modulators of smooth muscle tone (21, 30, 184, 291). Arterial stiffening with age does not appear to depend on the presence of atherosclerosis because it is observed in rural Chinese populations who have a low prevalence of atherosclerotic diseases (13), in rigorously screened healthy men and women (201, 295), and in animal species resistance to the development of atherosclerosis (113, 247).

Although regular exercise has never been shown to increase maximal lifespan (132), regular exercise is widely recommended and promoted in an attempt to prevent and treat premature vascular disease (205). A number of research studies have evaluated exercise interventions that target “traditional” risk factors for coronary heart disease. Indeed, a

physically active lifestyle is associated with a more favorable profile in traditional cardiovascular risk factors in middle-aged and older adults (274). Research studies that deal with the influence of regular exercise on vascular function and structure are now rapidly accumulating. Carotid lumen diameter and IMT are not different between sedentary and endurance-trained adults at any given age nor does it change in response to aerobic or resistance exercise interventions (Fig. 23) (197, 198, 202, 296). In contrast, repeated increases in femoral blood flow evoked by daily aerobic leg exercise induce expansive arterial remodeling in the femoral artery, characterized by reduced femoral IMT and greater lumen diameter, presumably to normalize arterial wall stress (67, 199).

The first evidence that habitual aerobic exercise might attenuate the age-related increase in arterial stiffness was observations from a cross-sectional study from the Baltimore Longitudinal Study of Aging that older males who performed endurance exercise on a regular basis demonstrated lower levels of aortic pulse wave velocity (PWV) and carotid augmentation index (AI) than their sedentary peers (315). A subsequent study reported that significant age-related increases in central arterial stiffness were absent in physically active women and that aerobic fitness was strongly associated with arterial stiffness (294). These cross-sectional findings provide a support for a role of regular aerobic exercise in the primary prevention of arterial stiffening. Results of follow-up intervention studies showed that daily brisk walking for 3 months reduced arterial stiffness in previously sedentary middle-aged and older men (295) as well as in postmenopausal women (201) to levels observed in age-matched endurance exercise-trained adults. Can older adults derive similar vascular health benefits from an exercise program as their younger counterparts? Not many studies to date have directly addressed this particular question. However, in one study (143), identical exercise programs induced considerably smaller reductions in blood pressure in older adults than in their younger counterparts.

### Future directions

Ever growing numbers of elderly population have led to increasing efforts in finding ways to preserve functional capacity and prevent premature cardiovascular disease. Available research indicates that participation in a regular exercise program is an effective strategy for the primary and secondary prevention of age-associated increases in physical dysfunction and cardiovascular disease. These data are certainly encouraging, but we are still in the initial stage of systematically addressing the benefits of physical activity in older adults. It is our mission to increase our capacity for maintaining physical function with advancing age and to identify some key physiological determinants of our ability to do so.

## Conclusion

Humans undergo remarkable changes in physiological functions with growth, development, and aging. There is a sub-

stantial body of experimental evidence indicating that regular physical activity can favorably modulate this developmental and aging process at any given age and beyond. Middle-aged and older adults can obtain similar health and functional benefits to their younger counterparts. Physical activity performed even in very early life may have both immediate and long-term health benefits. The understanding of this process can be complicated by important sex differences with regard to body composition, cardiopulmonary function, substrate metabolism, and thermoregulation. Although the effects of habitual exercise on health and function have been well established in male adults, much less is known about such effects in youth, elderly, and women. There is an increasing recognition that extrapolation of the physiological, genomic, and therapeutic data derived from young adult populations to children or elderly is clearly unjustified. Additionally, the notion that males and females respond similarly to both acute and chronic bouts of exercise is increasingly recognized as untrue. Clearly, more research is warranted to establish the effects of growth, development, and aging on physiological functions as well as its modulation by exercise and sex. It is our mission to properly link the beneficial impact of physical activity with the underlying biological mechanisms that could improve health and function of boys and girls and men and women throughout their lifespan.

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