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Magnetic Resonance Imaging and Spectroscopy in Studying Exercise in Children

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The widely held but largely intuitive notion that vigorous physical activity occurs more frequently in children and adolescents than in adults is increasingly supported by scientific investigation [20, 51]. Moreover, there are intriguing data suggesting that physical activity of childhood and adolescence influences the very process of growth and development by modulating anabolic agents at the cellular level [22]. Despite the unique and important role of exercise in the lives of children, our understanding of developmental aspects of cardiorespiratory responses to exercise is limited.

Methodological difficulties are, of course, a major stumbling block in probing mechanisms of adaptation to exercise in children and young adults. Only minimally invasive studies are ethically acceptable in this population, and even simple tasks like breathing on a mouthpiece and/or pedaling on an ergometer at a regular frequency require a level of cooperation and attention often beyond the developmental capabilities of many otherwise willing and enthusiastic subjects. Magnetic resonance imaging (MRI) and spectroscopy (MRS) provide researchers with powerful noninvasive tools that can be used in children. In this chapter, we review recent insights into structural and functional adaptive responses to exercise during the period of growth and development. Our focus is on application of MRI techniques to this specific biological question, rather than on the mechanics of MRI itself. We refer the interested reader to published review for further discussion of exactly how MRI works (e.g., see ref. 57).

GROWTH AND DEVELOPMENT OF CARDIORESPIRATORY RESPONSES TO EXERCISE

The adaptation to physical activity in children represents the unique interaction of two distinct biological processes, human development and physical exercise, each of which is characterized by tissue plasticity. Physical activity plays a profound role in tissue anabolism, growth, and development. Yet, surprisingly little is understood about the mechanisms linking exercise with muscle hypertrophy [60], increased capillarization and mitochondrial capacity [12], stronger bones [43], changes in body composition [4, 5], and improved cardiorespiratory dynamics [15].

The interaction between physical activity and growth is not limited to individuals engaged in competitive sports and athletics. Disuse atrophy—the reduction in muscle mass and bone density that accompanies bed rest, limb immobilization, or neural injury—occurs even in sedentary individuals [13]. This implies that a sizeable anabolic stimulus arises from the relatively modest physical activity of daily living. Moreover, the existence of the "training effect"—the ability to improve performance with repeated exercise—suggests a "dose-response" relationship between activity and anabolic effect.

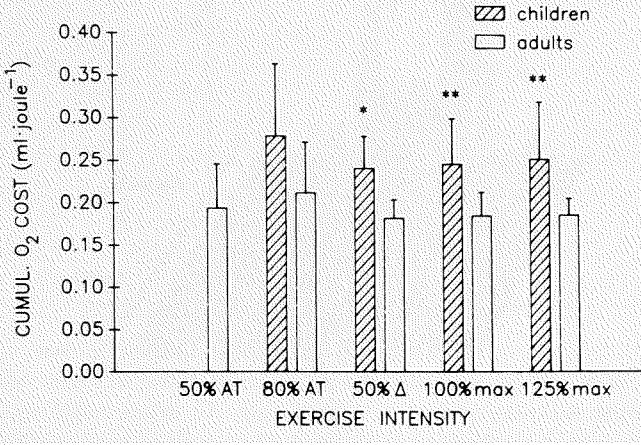
There is increasing evidence suggesting that the metabolic pathways essential for physical activity mature during growth in children. The gas exchange response (measured at the mouth, breath by breath) to high-intensity exercise in children has been shown to be qualitatively and quantitatively different from that of adults. The oxygen cost of high-intensity exercise normalized to the actual work done (O_2/J) is higher in children, suggesting less dependence on anerobic metabolism [77] (Fig. 15.1). After vigorous exercise, blood and muscle lactate concentrations are lower in children, reflected by lower levels of metabolic acidosis [32, 59]. Consistent with this phenomenon is our recent observation that the early exponential increase in $\dot{V}O_2$ during constant work rate, high-intensity exercise is greater in children than in adults, but the slower additional $\dot{V}O_2$ (which has been shown to correlate with the magnitude of blood lactate [64] is less [2]. The growth-related differences in the adaptive response to high-intensity exercise might be related to maturation of muscle metabolic pathways, but no definitive mechanism has been established.

The use of phosphorus nuclear magnetic resonance spectroscopy (^{31}P MRS) now provides safe and noninvasive means of monitoring intraceullular inorganic phosphate (P_i), phosphocreatine (PCr), adenosine triphosphate (ATP), and pH [18] (Fig. 15.2) that are acceptable for studies in children. These variables, in turn, allow the assessment of muscle oxidative metabolism and intramuscular glycolytic activity [18]. As leg muscle work rate increases, adenosine diphosphate (ADP) and P_i are released from the breakdown of ATP and PCr. One current theory holds that ADP and P_i may regulate the rate of oxidative phosphorylation exactly, so that homeostasis of the ATP concentration is obtained until very heavy levels of exercise are encountered [7, 8, 18]. As ATP hydrolysis approaches the maximal rate of oxidative phosphorylation, glycolysis (similarly activated by ADP and P_i) assumes an increasing proportion of the metabolic burden [18].

We hypothesized that the growth-related changes in whole-body O_2 uptake and O_2 cost of exercise observed during high-intensity exercise reflect a maturation of the kinetics of high-energy phosphate metabolites in muscle tissue. This hypothesis was tested by comparing P_i, PCr,and pH kinetics in calf muscles during progressive incremental exercise in children and adults [76].

In adult healthy subjects, the relationship between P_i:PCr and work rate is characterized by an initial, almost linear portion. The slope of P_i:PCr to

FIGURE 15.1.
*Cumulative O_2 cost per joule at different work intensities in adults and children. Values are means ± SD. Cumulative O_2 cost was not affected by increasing work intensity in children and adults. However, cost was significantly higher in children than in adults at higher work rates. 50% Δ refers to a work rate above the subject's anerobic threshold (AT) by exactly 50% of the difference between the AT and $\dot{V}O_{2max}$. 100% max and 125% max refer to the subject's $\dot{V}O_{2max}$. (*P < .001; **, P < .01). Reproduced from ref. 77.*



work rate is a function of mitochondrial density and reflects the sensitivity of respiratory control [27] (Fig. 15.3), which is followed by a second steeper slope that is associated with acceleration of glycolysis and increased lactic acid production suggestive of anerobic metabolism [18]. Production of lactic acid, which is dissociated at physiological pH, results in increasing $[H^+]$. Therefore, ^{31}P MRS can indirectly monitor glycolyic activity by measuring intracellular pH.

We found that during progressive exercise, muscle P_i:PCr ratio increases to a smaller extent in children, compared with that in adults, even when the data are related to work rate normalized to body weight (Fig. 15.4). In addition, children showed a smaller drop in intramuscular pH. A slow and fast phase of P_i:PCr increase and pH decrease was noted in 75% of adults and 50% of children. The initial linear slope was the same in children and adults, suggesting a similar rate of mitochondrial oxidative metabolism during low-intensity exercise. However, the different responses of the P_i:PCr ratio and pH during high-intensity exercise in children, compared with those in adults, indicate growth-related differences in energy metabolism (limited primarily to the high-intensity exercise range).

Our data might suggest that children may either deliver O_2 more effec-

FIGURE 15.2.
^{31}P MRS spectra from right calf of an 8-yr-old boy at rest, during incremental exercise, and recovery. Reproduced from ref. 76.

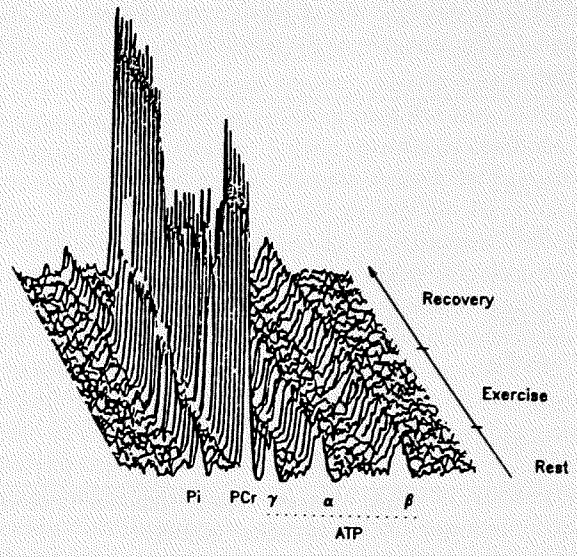


FIGURE 15.3.
P_i:PCr and pH at rest and during incremental exercise in a 33-yr-old man. Arrows transition points between slow and fast phases of P_i:PCr increase and pH reduction. Reproduced from ref. 76.

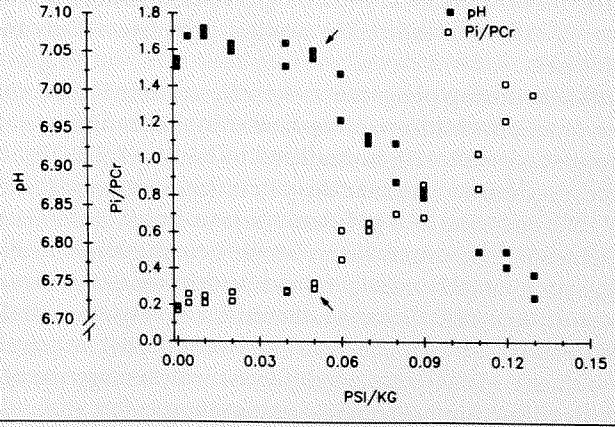
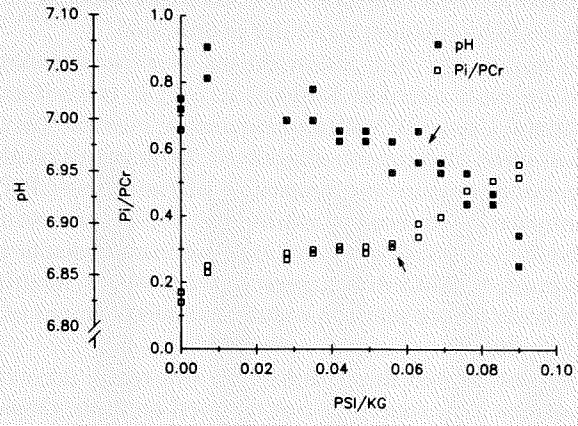


FIGURE 15.4.
P_i:PCr and pH at rest and during incremental exercise in a 9-yr-old girl. Arrows, transition points between slow and fast phases of P_i:PCr and pH changes. Reproduced from ref. 76.



tively to the mitochondria than adults, be less able to facilitate anerobic pathways, or have tissue O_2 requirements during exercise that are not found in adults. More effective O_2 use could result from factors that influence mitochondrial oxidative ATP resynthesis, such as delivery of oxygen from the capillary blood, delivery of substrates, or greater density of mitochondria. Each of these factors might be responsible for a greater oxygen-dependent ATP generation, lower P_i:PCr ratio, and higher pH during exercise in children.

But a more effective oxygen delivery in children alone should not inhibit the glycolytic capability. As work rate increases, children, like adults, will eventually require anerobic glycolysis, with concomitant lactate production as an additional mechanism of ATP rephosphorylation. This phenomenon is observed in trained athletes: Although anerobic metabolism occurs at higher work rates than that in untrained subjects, lactate levels ultimately achieved are much higher. It is noteworthy that the threshold in the slope of P_i:PCr to work rate occurred at the same relative work rate in children and adults (0.05 psi/kg), indirect evidence against the idea of greater aerobic capacity in children. It appears, therefore, that when the work rate exceeds a threshold value, the ability to stimulate anerobic metabolism is less in children, compared to that in adults. Ultimately, the work performed is less in children.

There could be less glycolytic capability in children, so that the rate of glycolysis may not contribute sufficiently to muscle energy requirements, resulting in early muscle exhaustion. The minimal drop in pH seen in children

for heavy exercise demonstrates that even after the transition point, i.e., when further energy sources appear to be required, the glycolytic processes play less of a role. Moreover, children achieved an end-exercise P_i:PCr value of 0.54 ± 0.12 (only 27% of adult values), which indicates that soon after the threshold, when the oxidative rate has presumably reached its maximum, children can no longer sustain muscular contraction.

A reduced muscle glycolytic ability during exercise, compared with that of adults, was recently noted by Kuno et al. [47] in trained and untrained boys 12–17 yr old. Using ^{31}P MRS and exhaustive exercise (in the magnet), the findings of these investigators supported the previous results in our laboratory of generally higher intramuscular pH and lower P_i:PCr ratios in children, compared with those in adults (Fig. 15.5). Interestingly, Kuno et al. found no effect of training on end exercise intramuscular pH or P_i:PCr ratios. In contrast, ^{31}P MRS data suggest that training in healthy adults and patients with heart failure tends to reduce the development of intramuscular acidosis [49, 70].

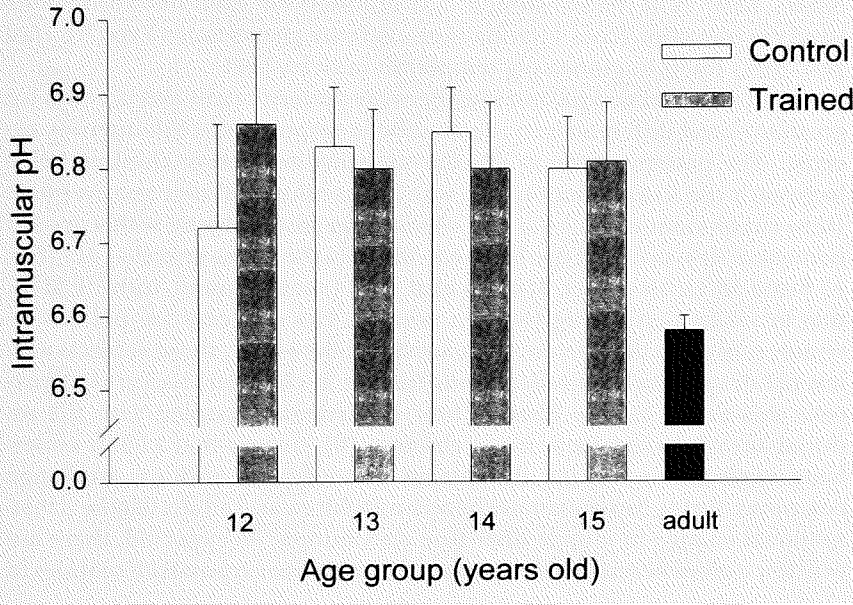
It could also be argued that children do not reach their real maximal work rate, because they simply do not try hard enough. Objective criteria for maximal effort are not easy to define, even for cycle ergometry, let alone single-leg treadle exercise. The children were told that they would be doing a hard exercise and were actively encouraged throughout the test. In addition, a transition in the P_i:PCr to work rate slope, i.e., a critical point in the cellular energy metabolism, was observed in 50% of the children at 62% of the maximal work rate. The same value (62%) was reported for the ratio of anerobic threshold to $\dot{V}O_{2max}$ in children of comparable age during maximal cycle ergometer exercise [23].

These results are consistent with those of previous studies, which reported growth-related differences in gas exchange response to high-intensity exercise. A higher CO_2:O_2 cost ratio (ie., higher acidosis) for 1 min of heavy exercise was observed in adults, compared to that of with children [3]. Bar-Or reported a lower anerobic capacity (measured by a supramaximal 30-s cycle ergometer test, the Wingate anerobic test) in young children, compared to adolescents and adults [6]. In addition, in the few invasive studies that have been done, blood and muscle lactate concentrations at high-intensity exercise are lower in children than in adults [32, 59].

Our results can not be explained by a faster lactate removal or subsequent metabolism in children. If glycolysis had increased with a simultaneous increase in lactate removal, then we ought to have found a more rapid increase in P_i without a parallel drop in pH in children. This was not the case, as the relationship between P_i:PCr and pH was the same in children and adults.

Both phosphofructokinase (PFK) and glycogen phosphorylase are key regulatory enzymes of glycolysis, but little attention has been paid to possible maturational pattern of their activity. Eriksson et al. reported a lower

FIGURE 15.5.
The values of intracellular pH at exhaustion in thigh muscles of well-trained and untrained children and adolescents. All children and adolescent values were significantly greater than those found in adults. There was no effect of training on intramuscular pH at the end of exercise in the children or adolescents. Data redrawn from ref. 47.



muscle concentration of PFK in 11- to 13-yr-old children, compared to that in adults [31]. In addition, studies in rats showed a 17-fold increase in total PFK activity, occurring during the first 2 mo of age (equivalent to birth to puberty in humans). This was accompanied by a dramatic decrease in C-type PFK subunit and an increase in M-type subunit, the isozyme best suited for glycolysis [30]. Finally, low levels of C-type PFK subunit have been shown to promote increased affinity for fructose-6-phosphate and diminished susceptibility to ATP inhibition [28, 29].

^{31}P MRS was used to study muscle metabolism during exercise in one adult subject with PFK deficiency [1]. A normal slope of the initial linear relationship of P_i:PCr to work rate, no drop in pH, and a gradual increase of phosphomonoester levels were observed during exercise. We did not observe a phosphomonoester peak in any of our children, which might simply reflect a much milder PFK impairment, compared to that of the subject affected by the myopathy.

Maturation of the muscle metabolic response to exercise might be re-

lated to the hormonal changes (increase in testosterone, estradiol, growth hormone, and insulin-like growth factor-1) occurring during puberty [52]. To date, little is known about the effect of these hormones on functional and structural muscle growth. Testosterone has been shown to increase sarcotubular and mitochondrial enzymes [65] in mature male subjects. In addition, Kelly et al. demonstrated that testosterone administration stimulated the transition from Type IIa (fast oxidative glycolytic) to Type IIB (fast glycolytic) fibers in guinea pig temporalis muscles [44].

A maturation of skeletal muscle fiber-type pattern might also account for growth-related differences in the metabolic response to high-intensity exercise. The pattern of rise in $\dot{V}O_2$ during heavy exercise in children [2]—large early rise to a greater O_2 cost, with less continued slower rise over time (slow component of $\dot{V}O_2$)—is also observed in adult subjects with a greater percent of slow twitch (Type I) muscle fibers in the vastus lateralis [41] (Fig. 15.6 and 15.7). Moreover, Mizuno et al. [55] recently found, with ^{31}P MRS, that in adults performing forearm exercise, the end exercise pH was inversely related to the percent of slow twitch fibers—i.e., those subjects with less pH drop (which is similar to our finding in children) had greater percent slow-twitch muscle fibers. These observation, coupled with the reduced anerobic capacity noted in children [6], suggest that a likely underlying explanation for the differences in metabolic and gas exchange responses during heavy exercise between children and adults may be a maturational change in muscle fiber type distribution. As expected, there are very few studies of systematic changes in muscle fiber types from biopsies in

FIGURE 15.6.

Group mean O_2 cost of below anerobic threshold (AT)-intensity (A, 80% AT) and above-AT (B, 75%Δ) intensity exercise in children and adults. For both low- and high-intensity exercise, average O_2 cost was significantly higher in children. Compare these results with those of adults with different fiber type proportions, shown in Figure 15.7. Reproduced from ref. 2.

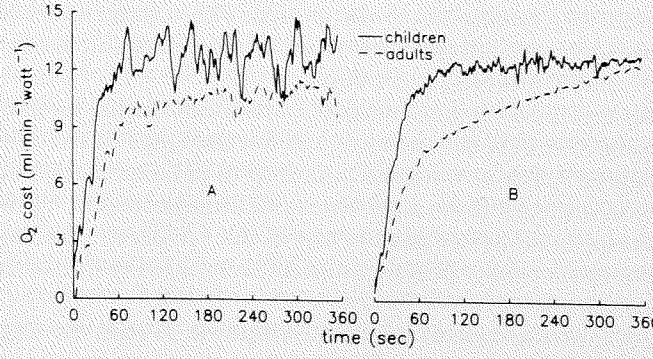
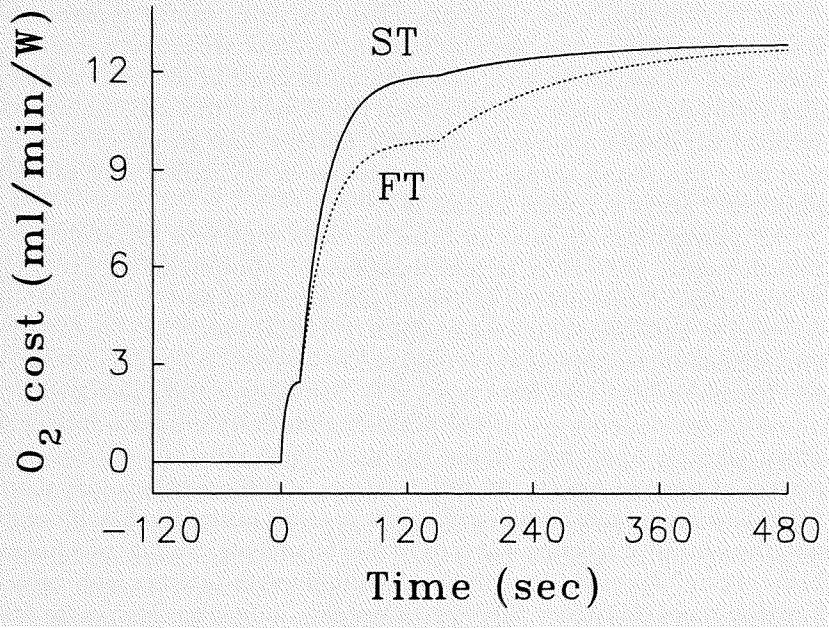


FIGURE 15.7.
Schematic of rise in $\dot{V}O_2$ during heavy exercise, scaled as O_2 cost by dividing by work rate. FT represents a subject with predominance of fast-twitch (Type II) fibers in vastus lateralis, whereas ST is the idealized response of the subject with majority of slow-twitch (Type I) fibers. Data from ref. 41. Compare these results with those of Figure 15.6.



children. However, several studies examining biopsies of human diaphragm [42] and hindlimb muscles [10] demonstrated that fiber-type differentiation occurs relatively early in life, and by 6 yr of age, the skeletal muscle histochemical profile is similar to that of a young adult. Obviously, work is needed to determine the ultimate role of fiber-type maturation in the overall development of the cardiorespiratory response to exercise.

In conclusion, muscle high-energy phosphate kinetics during high-intensity exercise is different between children and adults. In this range of work, children seem to rely less on anerobic glycolytic metabolism than adults do. ^{31}P MRS has proved to be a noninvasive unique technique to gain sight into muscle metabolism during exercise in children. Our results suggest a potentially important role of ^{31}P MRS spectroscopy during exercise in identifying abnormal muscle metabolism and in assessing the value of therapeutic approaches designed to improve exercise tolerance in children with a variety of disease.

PHOSPHODIESTER PEAK

In our studies, a phosphodiester (PDE) peak between the P_i and PCr peaks (at a chemical shift of 2.9–3 from the PCr) was observed in some of the subjects. In these subjects, PDE area was used to calculate the PDE:PCr ratio. The phosphodiester peak was observed in all adults; this peak was not observed in seven children.

The physiological meaning of this difference is not readily apparent, but it is intriguing to consider the possible mechanisms. We found significantly lower PDE/PCr peaks in girls, as compared to those of the other subjects, and although not statistically different, the value of this ratio in boys was substantially smaller than in adult males. Two previous groups of investigators have also found an age-related increase in the appearance of phosphodiester peaks in resting muscle [67, 75].

The phosphodiester peak in muscles likely represent glycerol-3-phosphorylcholine [14] and/or serine ethanolamine phosphodiester [16]. Age- or sex-related differences in glycerol-3-phosphorylcholine may reflect differences in lipid membrane metabolism or breakdown. The role of serine ethanolamine phosphodiester is not known; however, it has been shown to be characteristic of slow fiber types [17]. Satrústegui and coworkers [67] noted the age-dependence of PDE accumulation and the appearance of another phospholipid breakdown product, lipofuscin, a well-described marker of aging in muscle [26, 40]. Satrústegui and coworkers speculated: "The detection of phosphodiester by MR *in vivo* is one of the few, if not the only, non-invasive biochemical tests of the 'biochemical aging' of a human body organ." Precisely how these phosphodiesters interact with muscle function is not yet known. Whether or not our finding is evidence for fiber type maturation or change during growth, or represents another process related to aging, remains an important topic for future research.

MRI AND STRUCTURE-FUNCTION RESPONSES TO EXERCISE

Body size is a major determinant of maximal physiological function, and allometric equations quantify the relationships of body size (e.g., muscle mass) to metabolic rate (e.g., peak $\dot{V}O_2$ during exercise). Allometric analyses are used to assess size-structure relationships in mature animals of different sizes and species [71] as well as of those in a single species during the period of growth and development [9, 21, 68, 69]. The objective of the following study performed in our laboratory [78] was to examine the relationship between muscle size and the peak $\dot{V}O_2$ ($\dot{V}O_2$ peak) and work rate (WRpeak) in a group of children and adults.

$\dot{V}O_2$peak and WRpeak were measured from a progressive cycle ergometer test. Muscle size was estimated using MRI of the calf musculature. MRI is a noninvasive method not requiring ionizing radiation and is, therefore,

more feasible for studies in healthy children. MRI provided a means of measuring muscle cross-sectional area (CSA) and allowed us to account for bone and subcutaneous fat, factors that substantially limit the accuracy of limb diameter alone in estimating muscle size.

Allometric equations have the general form $q \propto a \cdot M^b$, where q indicates a metabolic rate (e.g., $\dot{V}O_2$), M is a parameter related to body dimension (e.g., mass), a is the mass coefficient, and b is the dimensionless mass exponent or the scaling factor [36]. The scaling factor relating body mass to $\dot{V}O_2$ peak in mature mammals of different sizes is about 0.75 [71]. In contrast, in cross-sectional studies of children and young adults performed in our laboratory, the scaling factor was found to be 1.01 [23], a value significantly greater than 0.75.

The observation of different scaling factors implies that the mechanisms accounting for size-function relationships are not entirely the same during growth in children as among mature animals of different sizes. A. V. Hill [39] in 1950 and T. A. McMahon [53] in 1984 reviewed the experimental data and theoretical considerations of size-function relationships during exercise in mature animals. Insight into the mechanisms governing size-function relationships during growth can be gained by testing certain assumptions reached by Hill and McMahon:

1. Peak muscle function $\propto$ muscle CSA^1. The inherent or intrinsic strength of a contracting voluntary muscle fiber is constant and independent of the size of an animal. A bigger muscle is capable of greater work and metabolic rate only because it is bigger, not because its inherent metabolic capacity is greater [39].
2. Peak muscle strength $\propto$ peak metabolic rate. In terms of a progressive exercise test, this could be stated as WRpeak $\propto \dot{V}O_2$ peak.

These assumptions would then predict that: $\dot{V}O_2$ peak $\propto$ muscle CSA^1 and WRpeak $\propto$ muscle CSA^1.

We hypothesized that the scaling factor of 1.0, predicted from studies of mature animals, would not be found experimentally in children and adults. An important implication of finding a scaling factor other than 1 would be that the intrinsic strength and/or metabolic capacity of muscles change during growth and development.

The study population consisted of 20 children (age range, 6–11 yr, 11 boys and 9 girls) and 18 adults (age range, 23–42 yr, 10 men and 8 women). Each subject performed a ramp-type progressive exercise test on an electromagnetically braked cycle ergometer to determine maximal oxygen uptake. MRI was performed on a Picker 1.5-T whole body MRI system. A round (10 cm in diameter) surface coil was used for signal detection, while a proton body coil was used for radiofrequency (RF) transmission for imaging. The subject was positioned with the center of the receive coil at the largest circumference of the calf (as estimated by the investigator). The whole leg

was then moved into the isocenter of the magnet bore. Images were obtained from a coronal slice (2 cm in diameter) at isocenter with a 30-cm field of view providing single-slice pictures of muscle, fat, and bone.

Computerized planimetry was used to determine calf muscle CSA. The major muscles included: gastrocnemius, soleus, tibialis anterior and posterior, and peroneus longus and brevis. The investigator traced the circumference of the calf, using a pointing device. These areas were traced as well and, subsequently, were subtracted from the limb CSA to yield the muscle CSA. A similar approach was recently presented by Nishida and coworkers [56].

A log-log transform was used to calculate the scaling factor [36]. Linear regression was performed on the transformed data, and the slope of the regression is equal to the scaling factor. Because work done by all of the calf muscles is a major component of the total work done during cycle ergometry [34, 38], we used the ratios of $\dot{V}O_2$ peak to CSA and WRpeak to CSA as indicators of the relative contribution of this muscle group to maximal metabolic rate and maximal power output. These ratios were analyzed in several ways: first, we calculated the mean value for the four groups: boys, girls, men,and women. Secondly, we calculated the linear regression of the ratios as a function of body weight in all male subjects, all female subjects, and in the group as a whole.

The mean peak $\dot{V}O_2$ normalized to body weight was 39.9 ± 8.6 (SD) ml/min/kg in the adults and 38.8 ± 7.4 in children (not significant).WRpeak per body weight in children (2.9 ± 0.6 W/kg) was significantly lower than in adults (3.9 ± 0.8 W/kg, $P < .001$). Both peak $\dot{V}O_2$ and WRpeak were similar to values found previously in our laboratory [23, 77].

Scaling Factors

The scaling factors, relating WRpeak and $\dot{V}O_2$ to muscle CSA, are shown in Table 15.1. Table 15.2 summarizes the linear regression analysis for WRpeak/CSA and $\dot{V}O_2$ peak/CSA as a function of body weight in males, females,and in the group as a whole. $\dot{V}O_2$ peak/CSA was not affected by body

TABLE 15.1.
Scaling Factors Relating Indices of Body Mass with Metabolic Function during Exercise

	Females		*Males*		*All Subjects*	
	Factor	*SEM*	*Factor*	*SEM*	*Factor*	*SEM*
WRpeak vs. CSA	1.25	0.22	1.40	0.16	1.37	0.12
$\dot{V}O_2$ peak vs. CSA	0.94	0.21	1.03	0.15	1.04	0.12

TABLE 15.2.
Regression Slope and Constant for the Equation $y = a \cdot x + {}^{a}b$

	Slope	*Constant*	*r*	*P*[a]
WRpeak/CSA♂	0.043	2.34	0.70	$P < 0.005$
WRpeak/CSA♀	0.045	2.17	0.57	$P < 0.05$
WRpeak/CSA, all	0.044	2.26	0.68	$P < .0001$
$\dot{V}O_2$peak/CSA,♂	0.13	47.2	0.24	NS
$\dot{V}O_2$peak/CSA,♀	0.18	41.3	0.25	NS
$\dot{V}O_2$peak/CSA, all	0.17	43.6	0.29	NS

[a]In this equation where y is either WRpeak/CSA or $\dot{V}O_2$peak/CSA; a is the slope, either as in watts per square centimeter per kilogram or milliters per square centimeter per kilogram; x is body weight in kilograms; and b is the constant in either watts per square centimeter or milliter per minute per square centimeter. The correlation coefficient is r and P values are calculated for significance of the difference of the slope from the value 0.

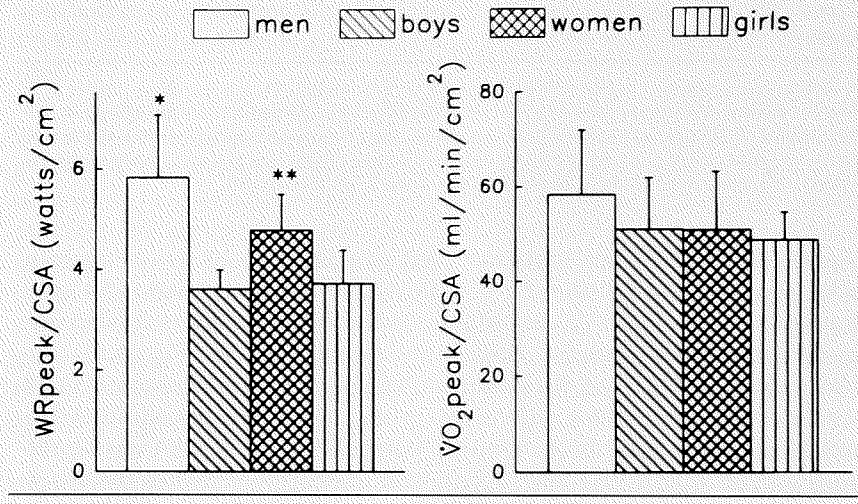
weight, but the WRpeak/CSA increased as a function of weight both in males ($P < .005$) and females ($P < .05$). No differences in $\dot{V}O_2$ peak/CSA were observed between children and adults. On the contrary, WRpeak/CSA was significantly higher in adults, compared to that in children (Fig. 15.8).

We found, as expected, that WRpeak, $\dot{V}O_2$ peak, and calf muscle CSA all increased with age and body size in this group of children and adults. As hypothesized, the scaling factor relating WRpeak to muscle CSA was significantly greater than 1.0 (Table 15.1), which was corroborated by the observations that the ratio WRpeak/CSA increased significantly with body weight, and that the mean values of WRpeak/CSA were less in boys and girls than in men and women (Fig. 15.8). (Note that these results were confirmed by analysis of covariance of the data as well.) A possible implication of this finding is that inherent muscle metabolic capacity increases with size during growth and maturation.

But we had also hypothesized that the scaling factors for both $\dot{V}O_2$ peak and WRpeak to muscle CSA would be the same because WRpeak $\propto$ $\dot{V}O_2$ peak (Assumption 2). This was not the case: the scaling factor of $\dot{V}O_2$ peak to muscle CSA did not significantly differ from 1.0. This was corroborated by the observation that the ratio $\dot{V}O_2$ peak/CSA did not change with body weight. One implication of the discrepancy between the WRpeak and $\dot{V}O_2$ peak scaling factors is that the coupling of $\dot{V}O_2$ (measured at the mouth) to muscle work and metabolic rate may change during growth and maturation.

It is first necessary to address some of the methodological limitations of this study. Working with children imposes a number of real constraints: these subjects, although enthusiastic and cooperative, can become distracted rather quickly, particularly in the confines of a whole body magnet, and then start moving and fidgeting. Thus, images must be obtained

FIGURE 15.8.
*Peak work rate (WRpeak)/cross-sectional area (CSA) and peak oxygen uptake ($\dot{V}O_2$ peak)/CSA in adults (males and females) and children (boys and girls). *, WRpeak/CSA in men was significantly greater than in boys ($P < .05$) and girls ($P < .05$); **, WRpeak/CSA in women was significantly greater than in boys ($P < .05$). No differences were found in $\dot{V}O_2$ peak/CSA among the four groups. Data are expressed as means ± SD. Reproduced from 78.*



quickly. We chose to image the calf muscle simply because the investigator could easily and quickly identify the prominent gastrocnemius head, which invariably represents the largest diameter of the lower leg.

An inherent assumption of this study was that the calf muscle CSA accurately represents all muscles involved in ergometry exercise. The calf muscles (e.g., soleus and gastrocnemius) are used extensively in cycle ergometry and have electromyographic power spectra during cycle ergometry that are similar to the vastus medialis of the thigh musculature [34, 38], but our results cannot exclude the possibility that the recruitment of thigh and calf muscles in cycle ergometer actually change with age. For example, when children relied on thigh muscles to a greater extent than adults did in the performance of heavy-cycle ergometer exercise, than our results could be explained without necessarily concluding that muscle power per CSA is smaller in children than in adults.

The relative inability of MRI to identify *intramuscular* fat could also add to the error of this technique. When the muscle CSA in children reflected a higher fat-to-muscle ratio than that of adults, then the WRpeak:CSA ratio would likely be lower in children and not necessarily indicate differences in muscle tissue per se. But, in general, children are leaner than adults (note

that the BMI in children was 17.5 ± 2.9 kg/m^2, as compared with 23.2 ± 2.2 in adults), which suggests relatively *less* fat than in adults. Thus, if anything, an inability to account for intramuscular fat by MRI would mean that we had *underestimated* the true difference in WRpeak/CSA between adults and children.

As noted, we chose the calf because the prominence of the gastrocnemius heads makes it relatively easy to choose the largest circumference by inspection. But using only a single CSA could lead to possible errors attributable to position of the coil or maturational changes in calf muscle anatomy. MRI may yield other ways of assessing muscle size that could potentially improve this type of analysis. For example, Roman and co-workers [62] recently showed increases in muscle size in elderly men after upper arm resistance training by using 1-cm contiguous MRI-derived CSA and calculating the *volume* of the muscle in question.

Despite these possible confounding features of the methodology, our observations are consistent with previous studies focused on different aspects of muscle function. From our own laboratory, reanalysis of previous progressive exercise data in a large number of children and teenagers revealed that the ratio of WRpeak/kg body weight increased with age in children and teenagers [23, 77]. This was unexpected, because Assumptions 1 and 2 above would suggest that WRmax $\propto$ weight$^{2/3}$, and, therefore, that the ratio of WRmax/weight would *decrease* as body weight increased. Davies and coworkers [25] measured electrically evoked contractile properties of the triceps surae muscle in children and adults. They calculated the mean force per cross-sectional area (estimated by anthropometry and water displacement) to be greater in young adults (34 N/cm^2) than in children (29 N/cm^2), even though the children in their study were not as young (mean age, 13 yr) as those in our study. Finally, Parker and coworkers [58] found that isometric quadriceps strength in boys and male teenagers increased, even when growth in height and body weight had virtually ceased.

Along these lines, Bar-Or and others [6, 33] have suggested that there is an increasing "anerobic capacity" (the ability to produce ATP regeneration for muscular work anerobically) as children mature into adulthood. Whether or not such changes are related to the anabolic effects of puberty is not known; however, it is noteworthy that the increases in WRpeak/CSA were observed in both males and females. To the extent that our observations can be explained by hormonal changes occurring during the process of maturation, the role of *both* estradiol and testosterone—the hormones responsible for the female and male adolescent growth spurts [52]—must be considered.

As noted, unlike the WRpeak, the $\dot{V}O_2$ peak increased in direct proportion with muscle CSA—the scaling factor was not significantly differently from 1.0. Davies and co-workers [24] discovered that $\dot{V}O_2$ peak, when scaled to leg volume (determined by anthropometry and water displacement), ac-

tually decreased slightly with increasing age in a cross-sectional study of children and adults. Moreover, in previous studies in this laboratory we found that the oxygen cost of 1 min of high-intensity exercise—normalized to external work performed (in milliliters per minute per joule)—was actually *greater* in children, as compared to that in adults [77].

Maturation of the "anerobic potential" referred to above may shed light on the apparent discrepancy between WRpeak and $\dot{V}O_2$ peak. The $\dot{V}O_2$ during exercise does not necessarily represent the total metabolic cost of the work performed. In particular, ATP rephosphorylation derived from anerobic metabolism and from high-energy phosphagen stores, important components of the total metabolic cost of exercise [73], is simply not accounted for by gas exchange measured at the mouth. Our data may be explained by the following scenario: Muscles grow in size and gain potential for anerobic metabolism as children grow and develop. WRpeak increases out of proportion to the growth in muscle (i.e., the scaling factor for WRpeak and muscle CSA is greater than 1.0), but a greater proportion of the energy required to perform work is anerobically derived, not reflected in the $\dot{V}O_2$ peak. Consequently, as muscles become bigger, WRpeak scales differently with respect to muscle size than does the $\dot{V}O_2$ peak.

These observations support the notion that the changes in body size and function that occur during growth are not regulated by the same mechanisms that account for size-function relationships among mature mammals of different sizes and species. Moreover, some of the assumptions often used in allometric analyses of size-function relationships during exercise in adult animals of different species do not appear to hold when considering the size changes that occur during normal growth and development within a species such as humans. Our data suggest that the inherent metabolic capacity of muscles increases with age in human beings.

MR ASSESSMENT OF FIBER TYPING

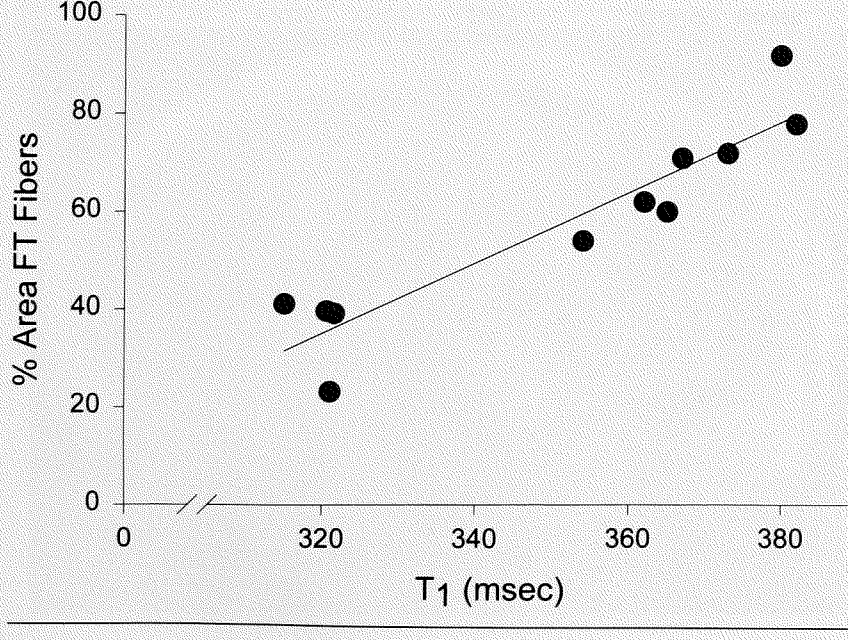
As noted above, the maturation of cardiorespiratory responses to exercise might be explained by fiber type changes; moreover, physical training can profoundly affect fiber type. A number of recent studies indicate that proton MR may be used to noninvasively assess fiber type in skeletal muscles. Kuno et al. [45, 46] studied the effect of strength training on the relationship between T_1 and T_2 relaxation times and muscle fiber composition. T_1 and T_2 relaxation times refer to the time it takes for the tissue to dissipate energy received after RF pulses. Five healthy men underwent a 5-mo heavy-resistance exercise training program and were compared with four control subjects. Needle biopsies from the vastus lateralis muscle were obtained before and after the experimental period, and cross-sectional area of fast-twitch (FT) fibers was significantly increased by training.

Both T_1 and T_2 relaxation times from proton MR analysis of the vastus

lateralis muscle significantly increased in the trained subjects. In addition, cross-sectional analysis of data from 21 subjects showed a significant correlation between T_1 and the proportion of FT fibers (Fig. 15.9). While the mechanism of the relationship between relaxation times and fiber type composition is not known, it is possible that the water content of fiber types differ [66]. Water content can be a major determinant of T_1 and T_2.

Noninvasive assessment of fiber type might also be possible, using ^{31}P MRS. Meyer and coworkers [54] used isolated in vitro preparations of cat soleus and biceps muscles to determine possible differences in phosphorus compounds between slow oxidative (SO) and fast-glycolytic (FG) fiber types, respectively. FG muscle had lower P_i and higher PCr, compared to that of SO fibers, these investigators suggested that the relative increase in P_i during muscle contraction would be greater in FG, as compared to that of SO muscles. More recently, Kushmerick et al. [48] studied a variety of surgically excised rat muscles. These workers noted about a 10-fold range in the P_i:PCr ratios in normal resting muscles, from 0.05 in fast-twitch fibers (Types IIa and IIb) to 0.5 in muscles containing predominantly Type I and IIx fibers. Clearly, more work is needed to further explore these intriguing

FIGURE 15.9.
Relationship between magnetic resonance longitudinal relaxation time and muscle fiber composition for a group of healthy subjects with a range of % fast-twitch (FT) fibers, as determined by muscle biopsy. Data redrawn from ref. 45.

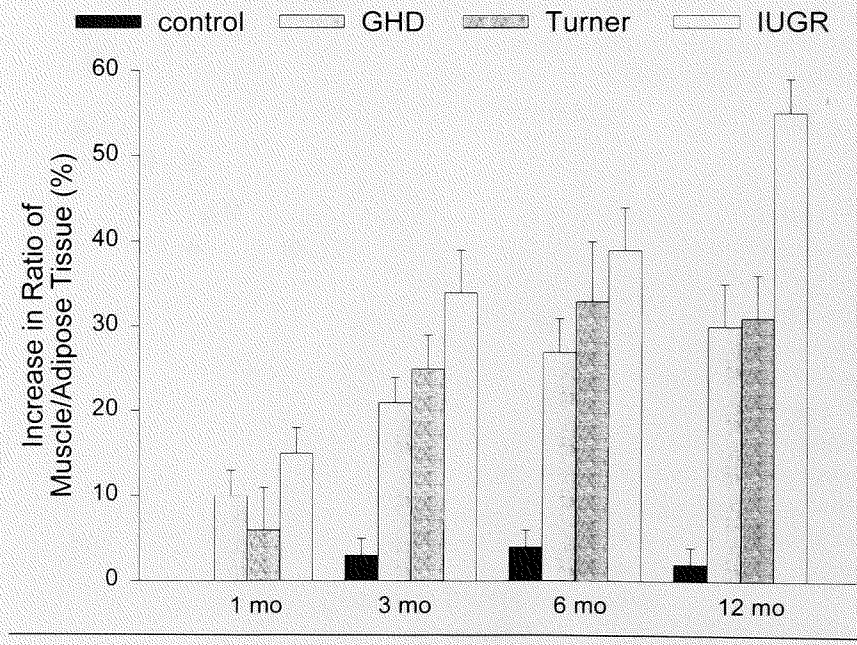


observations; such tools would be of great value in assessing maturation of cardiorespiratory responses to exercise in the growing child.

ASSESSMENT OF BODY COMPOSITION USING MRI

A variety of indirect techniques (e.g., skin-fold thickness or underwater weighing) have been used to estimate muscle mass and/or body fat content. But such techniques cannot quantify changes that occur in fat or muscle tissue at specific anatomical sites, which is important because training programs, for example, might increase the mass of a particular muscle group without measurably affecting overall body composition. Moreover, particular programs of exercise training might influence fat and muscle differently in different anatomical sites. Indeed, tissue-specific effects on adiposity have been documented when growth hormone is replaced in GH-deficient children [63].

FIGURE 15.10.
Mean increase (± SE) increase in the ratio of muscle:adipose tissue area in groups of children with growth impairments (growth hormone deficiency (GHD), Turner's syndrome, and intrauterine growth retardation (IUGR)) treated with GH and in untreated healthy children. The ratios were obtained from MRI of the midthigh. As can be seen, exogenous GH therapy increased the ratio of muscle:adipose tissue in the children with growth impairment. Data redrawn from ref. 50.



There is increasing use of MR assessment of fat and muscle tissue to guage the effects of hormonal therapy or exercise training. For example, Leger et al. [50] demonstrated a significant increase in muscle tissue and decrease in adipose tissue cross-sectional area from MRI images of thighs in children with growth retardation GH deficiency, Turner's syndrome, and intrauterine growth retardation) (Fig. 15.10). Treuth et al. [72] studied the effects of 16 wk of resistance training on 13 men (mean age, 60 yrs), and found substantial increases in body strength, as well as increases in midthigh muscle cross-sectional area and decreases in midthigh subcutaneous fat, as assessed by MRI. In our own laboratory, we are now using MRI assessment of muscle mass and abdominal fat to determine the effects of aerobic training in a group of 44 healthy female adolescents (Fig. 15.11 and 15.12).

FUTURE DIRECTIONS

The studies outlined above have, hopefully, demonstrated the ways in which these techniques have already substantially improved our ability to gain insight into cardiorespiratory, hormonal, and skeletal muscle adapta-

FIGURE 15.11.
An example of MRI of the abdomen at the umbilicus in a 15-yr-old girl. These images are being used in our laboratory to determine the effect of exercise training on body fat in specific anatomical locations.

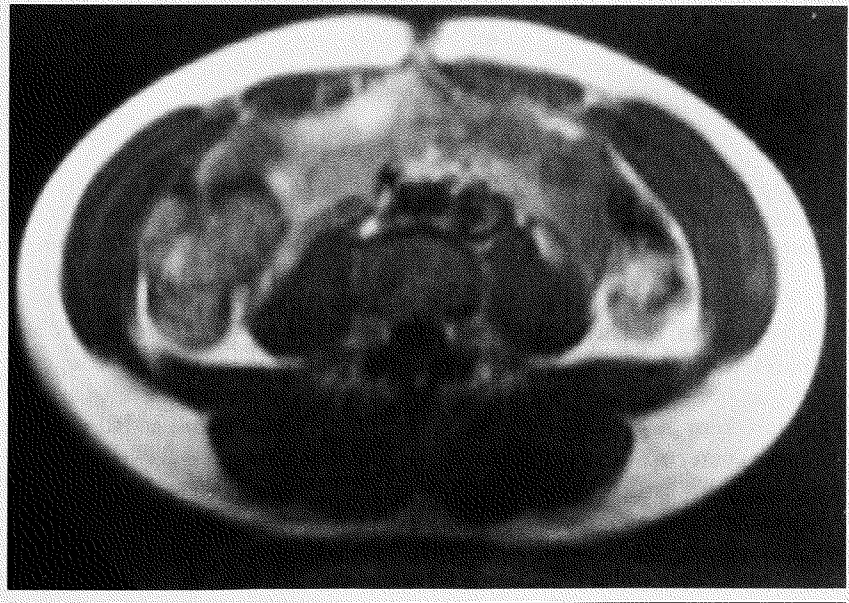
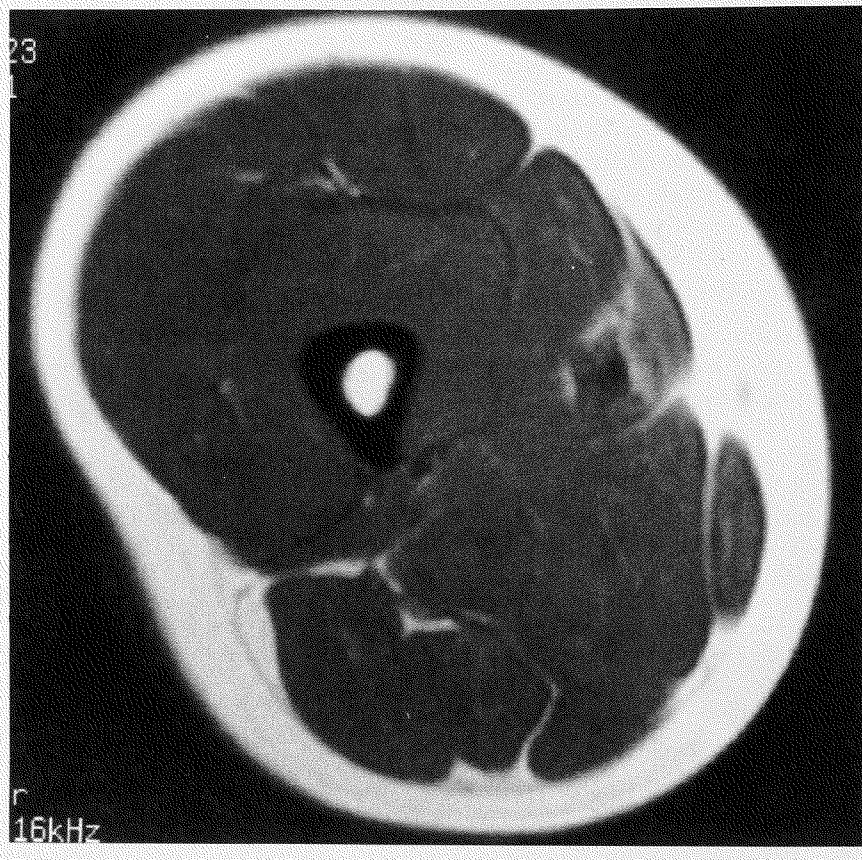


FIGURE 15.12.
An example of MRI of the midthigh in a 15-yr-old girl. These images are being used in our laboratory to determine the effect of exercise training on the mass of specific muscle groups. In addition, these images can be used to estimate the lean:fat ratio in the thigh.



tion to physical activity. It is unfortunate that the development of MR as a research tool is occurring in a period of downsizing in biomedical research. MRI is expensive; even for research purposes, 1 hr of magnet time may be about $500 or more, because of the high clinical load of most MRI centers. MR units can cost over a million dollars, and maintenance is expensive, requiring highly skilled technologists. It is unlikely, therefore, that the use of MRI to explore such questions as the development of high-energy phosphate responses to exercise in muscle tissues will proceed as rapidly as did research tied to new technologies in the 1970s and early 1980s.

Nonetheless, it is worth noting that MR techniques hold the promise of even more dramatic insights. MRI has been used to measure *pulmonary* blood flow in patients having undergone surgical repair of complex congenital heart disease [35, 61, 74] and can be used to measure blood flow to muscle groups as well [11, 19]. MRI studies of cerebral function in humans have yielded new insights into respiratory control [37], and such approaches could be used to focus on neural function during exercise. A number of possible uses of MR have yet to be fully developed; for example, greater understanding of the paramagnetic effects of oxygen to assess blood flow might provide researchers with tools that can be used in children, as well as in adults. In summary, MR is an impressive technological breakthrough with great potential for defining underlying mechanisms of cardiorespiratory adaptation to exercise in health and in disease. Whether or not this potential will be fully exploited in the near future remains to be seen.

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