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CARDIOVASCULAR ADAPTATIONS TO PHYSICAL TRAINING

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The principal features of the cardiovascular responses to endurance training in normal subjects were well documented by the late 1960s (2, 23, 35, 84, 88) and are illustrated in Table 1. They include an increase in maximal oxygen uptake, stroke volume, and cardiac output with no change or a small decrease in maximal heart rate. Systemic vascular conductance increases and there is also an increase in the maximal systemic arteriovenous oxygen difference. Cardiac output at submaximal levels of work does not change significantly but the increase in stroke volume is associated with a relative bradycardia at rest and at any given submaximal level of oxygen uptake. These cardiovascular changes are produced by a complex set of central and peripheral mechanisms operating at multiple levels—e.g. structural, metabolic, and regulatory (13, 14, 97). Our understanding of how these adaptations combine to extend aerobic capacity is still incomplete.

The classical concept that maximal oxygen uptake is limited by the oxygen transport capacity of the cardiovascular system (37) was challenged during the early 1970s (46) and the oxidative capacity of skeletal muscle was then by some considered to be the primary limiting mechanism. More recent work has reinforced the conclusion that functional capacity of the cardiovascular system is the principal limiting factor. Here we review the interaction between training-induced adaptations affecting the heart, the

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Table 1 Cardiovascular and pulmonary functional capacities determined during maximal exercise in college students and Olympic athletes[a]

	Students			
	Control	After bedrest	After training	Olympic athletes
Maximal oxygen uptake, liters/min	3.30	2.43	3.91	5.38[b]
Maximal voluntary ventilation, liters/min	191	201	197	219
Transfer coefficient for O_2, (ml/min)/(mmHg)	96	83	86	95
Arterial O_2 capacity, vol %	21.9	20.5	20.8	22.4
Maximal cardiac output, liters/min	20.0	14.8	22.8	30.4[b]
Stroke volume, ml	104	74	120	167[b]
Maximal heart rate, beats/min	192	197	190	182
Systemic arteriovenous O_2 difference, vol %	16.2	16.5	17.1	18.0

[a] Mean values, n = 5 and 6. Age, height, and weight similar. Modified after Johnson (44). Data from Saltin et al (88) and Blomqvist et al (8).

[b] Significantly different from college students after training, $p < 0.05$.

peripheral vasculature, skeletal muscle, and the autonomic nervous system. The various steps involved in the utilization and transport of oxygen provide a convenient framework.

MECHANISMS LIMITING MAXIMAL OXYGEN UPTAKE

Oxidative Capacity of Skeletal Muscle and Substrate Utilization

Maximal oxygen uptake could theoretically be limited by the intrinsic oxidative capacity of skeletal muscle or by the availability of substrate and oxygen for energy transformation. Endurance training produces large increases in the activities of the oxidative enzymes of skeletal muscle. There is little or no effect on the enzymes of the glycolytic pathway (32). Saltin & Rowell (92) and Gollnick & Saltin (31) have recently reviewed the physiological implications of these metabolic adaptations. They noted that both longitudinal and cross-sectional studies on endurance training have demonstrated much larger and more rapid effects on the oxidative enzymes than on maximal oxygen uptake. Thus there is little evidence for a direct causal link. However, the increased oxidative capacity following training is associated with an increased endurance capacity, defined as time to exhaustion at submaximal work load levels. This was well documented in a recent study in the rat (21). The change in endurance was quantitatively related to the enhanced capacity for oxidation. Mitochondrial volume in skeletal muscle doubled after training. Maximal oxygen uptake increased but not in proportion to the enlarged mitochondrial capacity.

Lack of substrate (glycogen) is a performance-limiting factor only during prolonged exercise at high but still submaximal intensities (4). The training-induced cellular adaptations, including increased mitochondrial volume and increased levels of mitochondrial enzymes (e.g. carnitine acyltransferase and the enzymes in the β-oxidation pathway), favor entry into the citric acid cycle of acetyl units derived from fatty acids (31). The overall effects are an increased use of fats as substrate during exercise and a decrease in both aerobic and anaerobic utilization of carbohydrates, particularly muscle glycogen. These changes have no effect on maximal oxygen uptake, but the preferential use of fats improves endurance by postponing the development of performance limitations due to glycogen depletion and/or lactate accumulation. The greater use of fats occurs without any changes in the plasma levels of fatty acids (48).

Oxygen Transport

The rate of oxygen transfer from ambient air to the tissue could be limited at any of several steps in the oxygen transport chain (44). Pulmonary transport includes ventilation, diffusion into blood, and chemical reaction with hemoglobin. Cardiac or aortic transport capacity is equal to the product of maximal cardiac output and arterial oxygen capacity. The final links include distribution of cardiac output and diffusion to sites of tissue utilization. Table 1, modified after Johnson (44), details average pulmonary and cardiovascular functional capacities in a group of young college students before and after bed rest followed by a two-month training program (88) and in a group of Olympic athletes (8). Training produced a significant increase (+18.5%) in maximal oxygen uptake in the group of students but their final level corresponded to only 73% of the mean value for the athletes. The large residual difference presumably reflects the combined effects of different genetic backgrounds (51, 52) and the prolonged intensive training in the athletes.

Measurements relating to pulmonary function were similar in both groups. Further analysis demonstrated that the overall capacity for pulmonary oxygen transport also was similar, 5.6 liters/min in the students after training and 6.2 liters/min in the athletes. Most of the difference in maximal oxygen uptake was accounted for by different capacities for cardiovascular oxygen transport, 4.0 and 5.8 liters/min. The data show that variations in physical activity have little effect on pulmonary function. They also indicate that cardiovascular and pulmonary oxygen transport capacity are closely matched in champion athletes whereas sedentary normal subjects utilize only about two thirds of their pulmonary capacity. Thus the conventional concept that pulmonary function is of no consequence as a limiting factor does not apply to superior athletes. Pulmonary diffusion generally becomes

limiting at sea level when maximal oxygen uptake reaches about 6 liters/min (44) and athletes are likely to have relatively larger declines in performance at altitude than average subjects. The magnitude of the decrease is a function of the ratio between sea level maximal oxygen uptake and pulmonary diffusing capacity (8). Pulmonary diffusing capacity is not affected by prolonged exposure to hypoxia and high altitude in adult life, but recent studies (R. L. Johnson, Jr., personal communication) have demonstrated a large increase in dogs raised at 3100 m from the age of 2 months to adulthood.

Data on the systemic arteriovenous oxygen difference (Table 1) suggest that the final step in the oxygen transport chain, distribution of cardiac output and/or the extraction by the tissues, is more efficient in well-trained subjects. A more efficient distribution of cardiac output can be achieved by an increase in vascular conductance in active tissue. An increased systemic A-V O_2 difference after training has been a consistent finding in longitudinal studies of sedentary young men and patients with ischemic heart disease but not in women or older men (13, 14, 87, 97). A more efficient utilization of available oxygen, reflected by decreased venous oxygen content in the absence of significant changes in arterial oxygen levels, may account for as much as one half of the improvement in maximal oxygen uptake produced by a short-term training program in young men (Table 1).

The training-induced widening of the systemic arteriovenous oxygen difference has been attributed to an increase in mitochondrial volume in skeletal muscle (97). However, it is unlikely that changes in mitochondrial volume are crucial. Immobilization causes a decrease of the aerobic capacity of skeletal muscle with no change or a decrease in mitochondrial volume (80, 88), but the maximal systemic A-V O_2 difference is maintained or increases slightly after bed rest (88) (Table 1). Myoglobin levels are elevated after training in rodents (73). This may contribute to an improved oxygen utilization, but human studies have failed to demonstrate any significant variations in myoglobin content (42, 69).

The high systemic A-V O_2 difference after both training and deconditioning can be explained if vascular adaptations are responsible for the efficient oxygen extraction. A wide systemic A-V O_2 difference after bed rest may reflect a relative prolongation of the mean transit time through skeletal muscle capillaries. Maximal cardiac output, and, presumably, maximal skeletal muscle blood flow are significantly reduced after a bed rest period of less than a month whereas there is little or no short-term change in capillary density (88, 90).

Increased usage of muscle causes a proliferation of the capillary bed (40) with an increase in the number of capillaries (41, 72, 90) and their dimensions (68)—i.e. an increase in capillary blood volume. A larger muscle blood

flow following training can therefore be accommodated with little or no change in the capillary transit time. Furthermore, oxygen extraction is facilitated by the increased capillary density and the decreased diffusion distances. However, primary control of perfusion is exerted at the arteriolar level.

The improved utilization of the systemic capacity for oxygen transport only accounts for a small fraction of the large difference in maximal oxygen uptake between athletes and sedentary subjects. A superior systemic aerobic capacity clearly requires superior cardiac pump performance with a large stroke volume during exercise.

MYOCARDIAL ADAPTATIONS

The increased stroke volume that is a salient effect of training in normal subjects can be achieved simply by increasing cardiac dimensions or by improving the performance characteristics of the heart. Pump performance may be increased by (*a*) enhancing the intrinsic contractile properties of the myocardium and the responses to inotropic stimulation and (*b*) extramyocardial adaptations that have secondary effects on performance—e.g. by increasing ventricular filling or decreasing myocardial work.

Comprehensive analysis of myocardial function includes simultaneous consideration of force, velocity, and fiber length (64). The velocity axis can often be disregarded without serious loss of information in the analysis of the performance of the intact heart. The ventricular pressure-volume relationship (34, 86, 106, 115) provides a useful framework for analysis and a link between muscle mechanics and ventricular function. It is also helpful when considering peripheral or extracardiac factors. The pressure-volume relation defines contractile state as the maximal pressure (or tension) that can be developed at any given volume (or fiber length). Maximal ventricular pressure is normally a linear function of volume. Implicit in the concept is that the amount of shortening or stroke volume that can be achieved from any given diastolic volume or fiber length can be increased only by reducing afterload or by enhancing contractile state. Similarly, an increase in the amount of shortening at a given afterload requires either an increased end-diastolic volume or an increased contractile state. The linear relationship between peak systolic pressure and end-systolic volume closely approximates the relation between maximal tension and volume. End-systolic volume is independent of preload. This model makes it feasible to evaluate intra- and interindividual physiological differences in ventricular contractile performance even if the experimental conditions make it impossible to control preload and afterload. However, the slope and intercept of the systolic pressure-volume relationship are affected both by the basal or in-

trinsic properties of the myocardium and by the response to neural and humoral inotropic stimulation.

The normal human cardiac response to the demands of exercise with increasing systolic pressure and peak wall tension includes a combination of increased preload or end-diastolic volume—i.e. a Starling effect—and increased contractile state (76). The increased contractile state is manifest as decreasing end-systolic volume and increasing ejection fraction (the ratio stroke volume/end-diastolic volume).

Cardiac Dimensions

There is a large body of older, mainly German and Scandinavian data on the relationship between heart size and physical performance in athletes and normal subjects. In general, total heart size as estimated from bi-plane radiographs has in cross-sectional studies been found to correlate closely with maximal oxygen uptake, cardiac output, and stroke volume (3). The results from longitudinal series are less consistent; they range from a close correlation between changes in maximal oxygen uptake and stroke volume and total heart size in young normal subjects (88) to no correlation in middle-aged men (36, 99). Activity-related dimensional changes can develop within weeks (88) but former endurance athletes, including young women who have trained intensely over several years and later adopted a level of relative inactivity, maintain a large total heart size (25, 39, 77, 89).

Recent studies based on echocardiographic and radionuclear techniques have generated detailed dimensional data, particularly on the left ventricle. The results support the older radiographic observations. Cross-sectional studies comparing sedentary subjects and highly trained young and older athletes have demonstrated significant differences that can be related to the different demands of different forms of athletic activity. Morganroth et al (66) noted that endurance training—i.e. frequent exposure to conditions producing increased ventricular filling with high stroke volume and cardiac output—causes an increase in left ventricular end-diastolic volume without major changes in wall thickness, whereas isometric exercise, which primarily imposes a pressure load, produces an increased wall thickness without any change in left ventricular volume. Their findings have been confirmed by several subsequent studies, reviewed by Péronnet et al (75). The internal left ventricular end-diastolic diameter is about 10% larger in endurance athletes than in sedentary subjects. This corresponds to a ventricular volume difference of about 33%. Recent studies indicate that both dynamic and isometric training cause an increase in absolute left ventricular mass, but only endurance training increases mass normalized with respect to lean or total body mass (49, 61).

Péronnet et al (75) also assembled echocardiographic data from eight short-term longitudinal studies (≤ 20 weeks) of endurance training in sedentary individuals. The gain in maximal oxygen uptake averaged 17%. At least some increase in left ventricular end-diastolic diameter at rest was recorded in most series, but the changes were generally small and were statistically significant in only three studies. The average increase in diameter was 1.3 mm or 2.5%, which approaches the limit of resolution of the method of measurement. However, ventricular volume is a third power function of the linear dimensions. The small average diameter change translates into a volume increase of 16%, which closely matches the change in maximal oxygen uptake. A post-training increase in end-diastolic diameter could reflect ventricular dilatation and be due simply to relative bradycardia, but left ventricular posterior wall thickness did not change or increased slightly in most series, implying a true increase in muscle mass.

Human echocardiographic studies have been limited to providing data on left ventricular dimensions at rest, but Rerych et al (79) recently used radionuclide angiography and demonstrated larger post-training left ventricular end-diastolic volumes during exercise as well as at rest.

Grande & Taylor (33) showed in an extensive review that active mammals generally have a higher heart-weight/body-weight ratio than inactive but otherwise similar breeds or species. Data from experimental longitudinal studies are less consistent, but it is evident that both swimming and running programs can produce at least a moderate degree of hypertrophy if defined as an increase in the heart-weight/body-weight ratio (29, 71, 95, 97). The extent of the hypertrophy is probably directly related to the intensity and duration of the training program and inversely related to age (10, 53, 67). The mode of exercise (e.g. running vs swimming) and the sex of the experimental animals may also be significant determinants of the degree of cardiac hypertrophy, but findings from several studies conflict (67). One problem is that a majority of the experimental studies have been performed in rodents, mainly rats. The rodent heart appears to be less responsive to exercise training than other mammalian hearts. Muntz et al (67) studied the effects of isometric exercise in the cat. Less than three minutes of daily isometric effort over a six month period produced an increase in left ventricular wall thickness and relative heart weight of about 30%. Significant changes in cardiac mass after endurance training have been reported also in the dog (11, 120), cat (121), and horse (101).

The exercise-induced cardiac hypertrophy appears to be global. Left atrial and right ventricular dimensions are consistently increased in subjects with left ventricular hypertrophy (67, 83, 108, 123). Characteristically, the normal heart muscle grows to match the work load imposed on the ventricle, maintaining a constant relationship between systolic pressure and the

ratio of wall thickness to ventricular radius, irrespective of ventricular size (27). This means that normally wall tension is kept constant according to the law of Laplace. The weight lifter's increased mass/volume ratio (49, 61, 66) is inappropriate relative to their blood pressure at rest, but the increased wall-thickness is most likely appropriate to the hemodynamic conditions *during* isometric exercise and strength training, which induce a marked pressor response. By similar reasoning, an increase in ventricular volume with a secondary small increase in wall-thickness is in line with the hemodynamic state during large-muscle dynamic exercise.

Dynamic or isometric exercise training causes only a moderate increase in heart size. Cardiac weights higher than 500 g are rarely seen in athletes (59) whereas valvular and myocardial disease may produce weights well above 1000 g. The primary mechanism in both the abnormal and physiological situation is hypertrophy of the individual muscle fiber and serial addition of sarcomere units. No convincing signs of hyperplasia have been described. Dynamic and isometric exercise training as well as experimentally induced hemodynamic overload tend to produce an increase in mean myocardial fiber diameter and an increased variability of fiber sizes (11, 67). An increased heart-weight/body-weight ratio may also be due to a decrease in body weight without any change in fiber diameter (71).

Contractile Performance

A variety of preparations have been used to evaluate training effects on myocardial function. Isolated papillary muscles and isolated perfused hearts have been employed to analyze the effect on intrinsic myocardial contractile properties—i.e. the performance of denervated heart muscle under rigidly controlled conditions. Nutter & Fuller (70) reviewed six studies of the effect of training on the mechanical performance of isolated left ventricular papillary muscles. Passive or diastolic myocardial length-tension relationships did not change. Isometric or isotonic contractile performance was increased in two series, decreased in two, and showed no change in two.

Several investigators have examined the effects of training on the performance of the isolated perfused heart. Scheuer and associates (5, 7, 94, 95) have made a systematic study of the response to different forms of training —i.e. running and swimming in male and female rats. They concluded (94) that both activities produce skeletal muscle adaptations (e.g. increased cytochrome oxidase activity) in both male and female rats and an increased heart-weight/body-weight ratio. Absolute increases in heart weight relative to weight-matched control rats occur only in female swimmers. They found evidence for improved contractile performance (measurements normalized with respect to heart weight and obtained at several levels of left ventricular

filling pressure) in male and female swimmers and male runners but not in female runners. These findings correlated closely with increased calcium binding in isolated sarcoplasmic reticulum and increased actomyosin ATPase (95). However, Fuller & Nutter (29), who studied the effects of running in male rats and essentially replicated the methods used by Scheuer and collaborators, were for reasons that are not apparent unable to demonstrate any training effects on contractile performance. Studies of the intact in situ heart of anesthetized rats (19) and in the awake chronically instrumented dog (11) have also failed to demonstrate any significant changes in myocardial performance attributable to training.

Human echocardiographic data from longitudinal and cross-sectional studies provide no evidence for any significant training effects on contractile performance (75). Physical training has the potential of altering not only cardiac dimensions but also autonomic state, preload, and afterload. It is therefore difficult to separate cardiac and extra-cardiac training effects on ventricular performance. If anything, the training-induced bradycardia at rest tends to be associated with a negative inotropic effect, presumably reflecting a decreased sympathetic drive. Data on myocardial performance during exercise are unfortunately scarce. Rerych and associates (79) found no effect on ejection fraction during submaximal and maximal exercise in a longitudinal study.

Thus the overall effects of physical training on intrinsic myocardial function remain uncertain. A large number of experiments, based on a variety of methods applied to humans and animals, have failed to demonstrate any significant training effects that can be attributed to an enhanced intrinsic contractile state—i.e. an improved quality of the myocardium. On the other hand, the careful studies by Scheuer and associates have documented significant improvement of myocardial function in isolated hearts of trained rats with parallel changes in myocardial myosin ATPase and calcium handling. Data on left ventricular performance during maximal exercise in humans (76, 79) suggest that there is little to be gained from an isolated improvement of contractile performance. The ejection fraction is very high and the end-systolic volume is very low in normal subjects irrespective of the state of training.

Several factors complicate the interpretation of the experimental data on myocardial contractile performance. Maximal oxygen uptake has rarely been measured in subhuman species. The rat, the most often used experimental animal, has obvious advantages over larger mammals, particularly in terms of cost, but there are also potentially important disadvantages. Hypertrophy is often only relative—i.e. consists of an increased heart-weight/body-weight ratio that is due to a lower total body weight in the trained animals rather than to an increased absolute heart weight. Body

growth normally continues throughout adult life. Furthermore, the rat has myocardial membrane characteristics that differ significantly from those of other mammals (78). Other animal models also present problems in terms of applicability of findings to humans. The dog has a very high native aerobic capacity, often well above the levels recorded in olympic athletes. The heart-weight/body-weight ratio is also about twice as high as in humans—i.e. 8 g/kg body weight vs 4–5 in humans (96). The horse (101) and pig (93) may provide models in which baseline characteristics and responses to training more closely resemble those in humans.

EXTRAMYOCARDIAL ADAPTATIONS

Coronary Blood Flow

Dynamic exercise at graded work load levels causes a progressive increase in myocardial work with increasing heart rate, wall tension, and velocity of fiber shortening—i.e. the principal determinants of myocardial oxygen demand—but there is no indication that exercise produces ischemia in normal subjects. Myocardial ischemia causes left ventricular dysfunction, but performance is normally enhanced during exercise. Tension development and ejection fraction increase progressively and maximal values are reached during maximal exercise (76). Direct measurements of coronary flow in normal human subjects have also demonstrated that a linear relationship between myocardial work and coronary blood flow is maintained during heavy exercise (38, 45). Furthermore, recent studies in the pig (117) have shown that a coronary vasodilator reserve is present also during maximal exercise.

Longitudinal studies (104, 105) have demonstrated that changes in coronary flow patterns occur very early after the onset of a training program, which suggests significant regulatory adaptations. There is also experimental evidence for a training-induced increase in the size of the *coronary vascular bed* (40, 67, 97, 122) with changes involving both capillaries and larger vessels. The extent to which the increase in vascularity exceeds the increase in muscle mass in the normal heart remains to be determined. Schaible & Scheuer (95) have reported increases in coronary flow proportional to the degree of training-induced increase in heart weight. Others (53, 102, 107) have described an increase in the size of the coronary tree after training even in the absence of changes in heart weight. Neogenesis of coronary capillaries is suggested by studies based on light- and electronmicroscopy and autoradiographic techniques (53, 60, 62) as well as by data on the rate of incorporation of ^{3}H-thymidine in myocardial capillaries in young rats exercised by swimming (60). Older animals may be less responsive (109). The larger heart size in wild animals than in domestic sedentary

species (33) is also associated with an increased capillary density of the myocardium (112–114).

Eckstein (22) observed that exercise training promotes collateral flow in dogs with experimental coronary artery narrowing. A larger number of subsequent studies have produced conflicting results (17, 96). Multiple studies in the dog and pig indicate that exercise produces no increase in collateralization in the absence of coronary lesions (17, 93).

Peripheral Vascular Adaptations

INCREASED PRELOAD There is evidence to suggest an increased preload during exercise after training. Changes in physical activity and maximal oxygen uptake are paralleled by small but statistically significant changes in total blood volume (88), usually without major changes in hemoglobin concentration or hematocrit. Well-trained athletes have higher cardiac outputs and pulmonary arterial wedge pressures during maximal supine exercise than sedentary normal subjects (6, 24).

Measurements during maximal exercise following volume overload in sedentary and highly trained subjects provide further insights into the role of ventricular filling as a potential primary limiting factor. Robinson et al (82) studied exercise performance in a group of essentially normal subjects (maximal oxygen uptake 3.2 liters/min) before and after autotransfusion of 1.0–1.2 liters whole blood. This was sufficient to cause an increase in central venous pressure of 7 mmHg but there was no significant change in stroke volume or cardiac output during maximal work. Fortney et al (28) examined a group with slightly higher maximal oxygen uptake (3.5 liters/min) and found a small but significant increase in maximal stroke volume after blood volume expansion. Spriet et al (100) reported a large increase in maximal stroke volume (+31%) and cardiac output after reinfusion of 800 ml whole blood in highly trained athletes. Kanstrup & Ekblom (47) also examined a group of subjects with high maximal oxygen uptake (4.4 liters/min), stroke volume, and cardiac output. Plasma volume expansion averaging 700 ml produced a 20% increase in stroke volume and a 13% increase in maximal cardiac output. The combined data from these four studies seem to indicate a difference between sedentary and well-trained subjects with respect to the cardiovascular response to an acute blood volume increase. Analysis of the pooled individual data demonstrate that there is a strong linear relationship between maximal stroke volume at the control study (SV_0, ml) and the magnitude of the increase (ΔSV, ml) after volume loading ($\Delta SV = 0.51\ SV_0 - 48$, $r^2 = 0.49$). It is tempting to speculate that endurance training alters the apparent ventricular compliance characteristics by modifying right/left ventricular-pericardial interactions. The result is an increase

in diastolic reserve capacity. Experimental studies of chronic volume overload have demonstrated increased effective left ventricular diastolic compliance due to pericardial rather than to myocardial adaptations (55). Measurements of left ventricular volumes in sedentary subjects during exercise are also consistent with a stroke volume limitation imposed by the effective left ventricular diastolic compliance. Poliner et al (76) obtained scintigraphic measurements of left ventricular volumes during submaximal and maximal exercise and found that left ventricular end-diastolic volume reached a plateau at low–intermediate submaximal work load levels. Intracardiac pressures were not measured in their study but other investigators have found progressively increasing left ventricular filling pressure with increasing work loads (6, 24). Intrapleural pressures also become increasingly negative with increasing ventilation (63). This contributes to a further increase in effective or transmural diastolic pressure which nevertheless fails to produce an increase in volume.

DECREASED AFTERLOAD Afterload reduction is a crucial component of the integrated cardiovascular responses to training. Based on data from both cross-sectional and longitudinal studies Clausen (13, 14) has demonstrated a strong inverse and curvilinear relationship between maximal oxygen uptake and systemic peripheral resistance. The relationship is defined by the equation $y = 11.8 \cdot x^{-.72}$ where y is maximal O_2 uptake in liters/min and x is the ratio mean arterial blood pressure (mmHg)/cardiac output (liters/min).

A marked reduction in peripheral resistance enables the athlete to generate a cardiac output of up to 40 liters/min compared to 20 in the sedentary subject at similar arterial pressures during maximal exercise. Arterial pressures would be twice as high in the athlete if systemic resistance did not change and the same cardiac output were attained. However, analysis of the performance characteristics of the normal heart suggests that any potential gain in stroke volume that could be achieved by a training-induced increase in heart size would largely be negated by the increased afterload unless training also induced a decrease in systemic resistance.

The increase in the size of the capillary bed of skeletal muscle is a striking feature of the training response, but by far the largest portion of the resistance to systemic blood flow is exerted at the arteriolar level. The primary mechanisms responsible for the reduction in systemic resistance are poorly defined. They are likely to affect the arterioles and to be regulatory rather than anatomical.

Experiments based on exercise and exercise training involving a smaller muscle mass than both legs have demonstrated that blood flow to the working limb is affected by both systemic and local factors. The capacity

of the cardiovascular system to deliver oxygenated blood to active tissue exceeds the demand when only a small fraction of the total muscle mass is active. Local vascular conductance is most likely limiting oxygen delivery although blood flow may be quite high also in untrained muscle. Recent studies utilizing thermodilution techniques indicate that maximal exercise with the knee-extensors of one limb produces a muscle flow of at least 200 ml/100 g/min (1).

Measurements in the same individual during one-leg and two-leg maximal exercise shows a significantly lower flow to the active limb during two-leg exercise with little or no difference in arterial pressures—i.e. evidence for an increase in local vasoconstrictor activity when a larger muscle mass is activated and the systemic oxygen demand exceeds the supply (14, 15, 50, 91). Maximal oxygen uptake during one-leg work is normally about 75% of the absolute or two-leg maximum. Plasma norepinephrine levels during maximal work are proportional to the active muscle mass (9).

Training of only one leg (20, 30, 91) or of both legs separately (50) produces a large increase in one-leg maximal oxygen uptake (20% or more), a much smaller increase in two-leg maximum (10% or less), and no change during maximal exercise of the untrained leg. Changes in submaximal heart rates are reciprocal to the changes in maximal oxygen uptake. Maximal oxygen uptake during exercise with the trained leg also represents a larger portion of the two-leg maximum, 85–90% after training. There is a significant post-training increase in leg blood flow and conductance during maximal work with the trained leg but little or no change during two-leg maximal exercise. Analogous results have been reported from experiments in which either the lower or upper limbs have been trained and both pairs tested separately. The most prominent training effects are always evident when exercise is performed with the trained limb(s) (13–16). The combined data from these experiments support the concept that training causes an important increase in the maximal vascular conductance of working skeletal muscle. This increase is limited to the trained limb or limbs—i.e. mediated primarily by local rather than systemic mechanisms.

Older studies based on ^{133}Xe clearance rates have generated conflicting data on the effects of training on maximal flow rates in skeletal muscle (14). However, the ^{133}Xe method severely underestimates flow (1).

The extent to which the increase in the capacity to vasodilate can be translated into an increased maximal oxygen uptake is clearly modified by an opposing vasoconstrictor drive. The strength of this drive is determined by the relation between systemic oxygen demand and transport capacity. Thus changes in systemic oxygen transport capacity and the systemic impact of the local vascular adaptations are interdependent. Local adaptations with increased vascular conductance are prerequisites for effective utiliza-

tion of a training-induced increase in cardiac capacity due to the inverse relationship between stroke volume and afterload. Similarly, the gain in aerobic capacity of a trained limb contributes effectively to an increased maximal systemic oxygen uptake only if associated with an increase in the capacity for systemic oxygen transport.

The precise manner in which central vasoconstrictor and local vasodilator mechanisms interact in working muscle is still poorly understood. There is no doubt that the metabolic state of muscle is the key factor. However, the metabolic response to exercise has the potential to enhance both vasoconstrictor and vadodilator drives. Several changes in the composition of the extracellular fluid of metabolically active tissues can produce vasodilation by direct inhibitory effects on smooth muscle cells. Some of these conditions—e.g. acidosis, hyperosmolarity, and release of adenosine—also have an inhibitory effect on adrenergic neurotransmission (110). On the other hand, impulses originating in skeletal muscle receptors responding to changes in metabolic state may contribute to the central vasoconstrictor drive whereas the role of reflex-induced β-adrenergic vasodilatation remains uncertain (98).

Autonomic Regulatory Mechanism

The complexity of the training-induced regulatory changes is well illustrated by the effects on heart rate. The normal heart rate response to exercise is mediated by a combination of vagal withdrawal and β-adrenergic stimulation (81). The essentially linear relationship between relative load (actual load as a fraction or percentage of individual maximum) and heart rates during exercise is not altered by training or deconditioning, but sinus bradycardia at rest and decreased heart rate at any absolute level of submaximal oxygen uptake are hallmarks of a cardiovascular training effect. In Scheuer & Tipton's review (97), ample evidence is presented that there is at rest after training an increased parasympathetic activity that causes bradycardia, but the results of various studies performed during exercise conflict. An enhanced parasympathetic drive may still be important at low work loads and heart rates. However, complete vagal blockade in humans will only produce a heart rate of about 130 beats/min. Any increase above this level must be mediated primarily by β-adrenergic mechanisms. Early studies produced inconclusive data on changes in adrenergic responses after training—i.e. reduced, unchanged, and elevated plasma or myocardial epinephrine or norepinephrine levels (97). Recent studies have generated more uniform results. There are no significant changes in myocardial tissue concentrations or in the plasma levels of epinephrine or norepinephrine at rest (12, 18, 74). Plasma concentrations are lower at any absolute submaximal work load after training but there are no differences when comparisons are

made on the basis of relative work intensity. The lower post-training plasma levels at any given absolute level of energy expenditure are consistent with the relative bradycardia and decreased vasoconstrictor tone. The sensitivity of the S-A node to exogenous β-adrenergic agonists appears to be unchanged. The same amount of isoproterenol causes similar heart rate increases in unconditioned and well-conditioned men according to Williams et al (119). They also noted that the lymphocyte β-receptor number and affinity are unaffected by training. These data suggest that training reduces the efferent sympathetic neural outflow to the S-A node. Some investigators have after training found a relatively larger increase in myocardial contractile state in response to exogenous β-adrenergic stimulation (103, 121), but others have reported decreased sensitivity; there is no demonstrable change in the number of β-adrenergic receptors in the heart (65, 118).

Nonneural mechanisms may contribute to the relative bradycardia after training. Several studies have demonstrated a significant decrease in intrinsic sinus node rate as measured after combined vagal and β-adrenergic blockade (56, 57). The exact mechanisms are not known. However, all intrinsic cardiac pacemakers respond to stretch with an increased rate of discharge (43). It is conceivable that the frequent exposure to increased atrial pressures during training affects the basic stress-strain relationships of the sinus node. A chronic stress relaxation phenomenon may in the trained state attenuate the chronotropic response to any given amount of stretch.

It may also be argued that the bradycardia is the result of a primary increase in stroke volume. Normal regulatory mechanisms, predominantly baroreflexes at rest and the poorly defined mechanisms that maintain a very tight link between cardiac output and oxygen uptake during exercise (9, 26), have the potential to produce relative bradycardia even in the absence of any autonomic adaptations.

Autonomic function is a major determinant of the acute response to exercise, and it is evident that training induces significant adaptive changes. Nevertheless, training effects can be produced also in the various abnormal autonomic states. Significant changes in maximal oxygen uptake and hemodynamic responses have been observed both in normal subjects and patients with coronary disease who during endurance training were treated with moderately high oral doses of β-blocking agents (54, 111, 116). Training effects have also been induced in a variety of experimental animal models with significantly altered autonomic and metabolic regulation (unilateral vagotomy, sympathectomy, diencephalic lesions, thyroidectomy, adrenalectomy, hypophysectomy, and genetic hypertension) (97).

Two recent reports present an opposing view and emphasize the importance of the β-adrenergic system. Sable et al (85) found that β-adrenergic

blockade abolished the training effect in a series of young healthy subjects. Liang et al (58) concluded that the major cardiovascular training effects can be elicited simply by β-adrenergic cardiac stimulation by chronic dobutamine infusion in dogs. However, the method used by Sable et al (85) to determine the intensity of training (equalization of heart rates, expressed as per cent of maximal heart rate measured during β-blockade and placebo treatment) is likely to have produced a lower relative intensity in the experimental group than in the control group. The results reported by Liang et al (58) included a large decrease in cardiac output during submaximal levels of exercise. This finding represents a significant deviation from the hemodynamic effects usually observed after training in normal subjects.

CONCLUSIONS

This review supports the concept that maximal oxygen uptake in general is limited by cardiovascular oxygen transport and that cardiovascular functional capacity can be enhanced by physical training. Cardiac pump performance, the ability to achieve a large stroke volume and cardiac output during exercise, is likely to be the immediate limiting factor. Training causes a moderate increase in cardiac dimensions with little or no change in intrinsic contractile performance—i.e. an increase in the quantity but not in the quality of the myocardium. An increase in diastolic reserve capacity is likely to be a significant factor. Systemic conductance increases in direct proportion to the increase in maximal VO_2 and cardiac output. Analysis of the performance characteristics of the normal heart indicate that an increase in dimensions would be unlikely to produce a significant increase in maximal stroke volume unless associated with an increase in maximal systemic conductance.

Data on skeletal muscle flow strongly suggest that significant vasoconstrictor tone normally is present also during maximal exercise. A release of vasoconstrictor activity is a crucial training-induced adaptation, but the potential for vasodilatation cannot be effectively utilized unless there is a simultaneous improvement in cardiac pump performance. The key to a better understanding of the cardiovascular effects of training is likely to be a better definition of how the local vasodilator and central vasoconstrictor mechanisms interact.

Further improvements of training techniques—yet to be defined—that induce even larger changes in cardiac pump performance and the potential for cardiovascular oxygen transport and delivery to skeletal muscle may unmask pulmonary diffusing capacity as the factor ultimately limiting performance.

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