The Gas Transporting Systems: Limits and Modifications With Age and Training

Donald H. Paterson and David A. Cunningham

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Abstract/Résumé
The interplay of cardiovascular and cellular oxygen uptake determinants of aerobic performance and the system adaptations to training in different population samples are examined in order to describe the limitation. With VO$_2$max, a central limitation following myocardial infarction and ageing is modified with training. Peripheral adaptations occur and stroke volume may be increased primarily through improved diastolic filling. In submaximal perturbations, control of the increase in O$_2$ uptake at exercise onset (O$_2$ kinetics) is most often under peripheral metabolic control, but in exceptions may also be limited by central factors. In young and old the peripheral machinery is matched to the growth (puberty) and loss (ageing) of muscle mass. Cardiac stroke volume capacity may adjust following the changes in muscle mass. Submaximal endurance is closely influenced by the anaerobic threshold (θ$_m$) and peripheral factors of oxidative metabolism. Relative to VO$_2$max, the θ$_m$ is low in children and high in older adults, perhaps reflecting a slow time course in full development and loss of peripheral adaptations. Remarkable increases in endurance performance are related to relatively small changes in the maximal capacity and the relative intensity of performance.

L’interaction du transport de l’oxygène et de sa diffusion dans la cellule, facteurs de la performance aérobie, et les adaptations par l’entraînement de divers groupes d’individus sont analysées pour en connaître les limites. À propos du VO$_2$max, la limite du système de

The authors are with the Centre for Activity and Ageing, School of Kinesiology, University of Western Ontario, London, Ontario N6A 3K7.
transport suite à un infarctus du myocarde et au vieillissement est modifiée par l’entraînement. Des adaptations périphériques se manifestent et le volume d’éjection systolique peut être accru principalement par l’amélioration du remplissage diastolique. Au cours de perturbations sous-maximales, le contrôle de l’augmentation de la consommation d’oxygène au début de l’effort (cinétique de l’O₂) est le plus souvent dicté par le métabolisme périphérique mais il peut être exceptionnellement limité au niveau central. Chez les plus jeunes et les plus vieux, la machinerie périphérique est apparue à la croissance (puberté) et à la perte (vieillissement) de masse musculaire. La capacité d’éjection systolique peut s’adapter à la variation de la masse musculaire. L’endurance sous-maximale est directement influencée par le seuil anaérobie et les facteurs périphériques du métabolisme oxydatif. Relativement au VO₂max, le seuil anaérobie est bas chez les enfants et élevé chez les adultes, probablement parce que les adaptations périphériques sont lentes à se manifester totalement et à se retirer. Des améliorations notables de l’endurance sont associées à des variations plutôt faibles de la capacité de travail et à l’intensité relative de la performance.

Introduction

The conductance theorem, describing the continuum of processes from lung to cell respiratory capacity, sets the background upon which we examined the cardiorespiratory adaptations to endurance training. Adaptations are thought to occur most readily in factors that are the “bottlenecks” or limits. Adaptations in central (cardiac output, Q, and oxygen delivery) or peripheral (muscle O₂ utilization, arteriovenous oxygen [a-vO₂] difference) parts of the gas transporting system have been a focus of our research over the past 25 years. Thus this paper will review the interplay of these two system segments as well as their effect on endurance performance and their adaptation to endurance training.

A Look at Past Research

Early experimental work centered upon the role of exercise in rehabilitation from myocardial infarction. These early studies were important in examining exercise training and the adaptation of a compromised heart pump capacity to the ultimate improvement in aerobic power. In this scenario, the heart recovering from an infarct was the critical limitation. We therefore studied the effects of physical training (Rechnitzer et al., 1983) on cardiovascular function following myocardial infarction (Paterson et al., 1979). In a high intensity exercise group (HIE) there was a 12% increase in peak VO₂ with 6 months of training. At submaximal exercise, the heart rate (HR) reduction of 5–10 bpm resulted in a 5–8% reduction in Q (with stroke volume, SV, unchanged), and the VO₂ requirement was met by a widened a-vO₂ difference. From 6 to 12 months of training there was little further increase in peak VO₂. The feature of cardiovascular adaptation over this period was a significant increase in exercise SV by 6 to 11%.

Earlier studies (Degré et al., 1977) had suggested that postcoronary patients showed a widened a-vO₂ difference with training, but not a central adaptation. These adaptations and the sequence of peripheral, then central, improvements were similar in persons with angina, younger and older, regardless of the recovery time since their heart attack (Paterson et al., 1990). Thus we observed a specific interplay of peripheral followed by central adaptation in the response to endurance training.
in middle-aged postmyocardial infarction subjects. As well, in light of today’s encouragement of a more active lifestyle, it is notable that the low intensity exercise group (LIE) showed minimal changes in cardiorespiratory fitness or cardiovascular responses to light or heavy exercise, and possibly a decline of SV.

Subsequent to the early concern with myocardial infarction patients, in many of our studies we have examined different population groups and age groups. This research design has provided models for understanding the roles of central and peripheral gas transport and utilization responses. Figure 1 summarizes the cardiac output/oxygen uptake relationship during submaximal exercise in different subject groups. A study of boys ages 10 to 15 years characterized the development of these components of endurance capacity in normally active and very active hockey players. The longitudinal study of the development of cardiorespiratory function in circumpubertal boys (Cunningham et al., 1984) used multiple regression analysis to examine whether the variance in VO\textsubscript{max} among the boys was a function of central aspects (i.e., primarily accounted for by differences in SV) or of peripheral aspects (i.e., accounted for by differences in a-vO\textsubscript{2} difference). Also examined was the influence of pubertal factors on the interplay of potential determinants of VO\textsubscript{max}. Of course, VO\textsubscript{max} (L·min\textsuperscript{-1}) increased markedly during the period from prepuberty to adolescence, in this case 67%, and was proportional to mass with a scaling exponent of 1.02 (Paterson et al., 1987).

The purpose of these studies was to examine the extent and pattern of change with growth of the components of the cardiorespiratory system. The findings indicated that VO\textsubscript{max} or VO\textsubscript{2} at a given HR, was determined primarily by the size of SV throughout this age range (Cunningham et al., 1984). At HR\textsubscript{50}, a 58% increase in VO\textsubscript{2} from age 11 to 15 years was accompanied by a 66% increase of SV, with a-vO\textsubscript{2}

![Figure 1](image-url)  
Figure 1. Data from our laboratory for cardiac output to oxygen uptake relationship in young boys (11 & 15 yrs), older men (60+ yrs), and men post-myocardial infarction (45–55 yrs). All groups show a slightly hypokinetic cardiac output in exercise compared to healthy adults, with peak stroke volume of: boys (11 yrs), 60 ml; (15 yrs), 90 ml; older men, 95 ml; post-MI, 100 ml.
difference increasing only 8% across this age span, even though body mass showed a large increase. However, when data were analyzed with respect to each subject’s maturational (peak height velocity, PHV) age, SV showed the largest increase following the age of PHV. In fact, the SV lagged during the stage of peak growth.

It appears the increased muscle mass at maturation occurs first, followed by SV development to meet the new capacity. A widened a-\(\text{vO}_2\) difference was a critical component of the increased \(\text{VO}_2\) during the year preceding PHV. Maturation-dependent changes, including oxidative enzymes and capillary-to-fibre ratio, may be implicated. The conclusion in relation to the interplay of central and peripheral factors in \(\text{VO}_2\) max or endurance capacity is one of an asynchronous development of SV and a-\(\text{vO}_2\) difference at various stages of growth and development.

Similarly, the question of central and peripheral components of endurance performance has been addressed in our investigations of older adults in which a year of exercise training increased \(\text{VO}_2\) max in recently retired men with little change in the control group (Cunningham et al., 1987). Ehsani et al. (1991) determined that a 1-year vigorous training program in older adults did elicit increases in SV. Our analyses with older adults have focused on explaining the loss of \(\text{VO}_2\) max with age. Thomas et al. (1993) measured the cardiovascular responses during light through heavy exercise in 96 men of mean age 62 years. The Q-\(\text{VO}_2\) regression (\(Q = 4.6 \text{ VO}_2 + 4.2\)) suggested a slight circulatory hypokinesis of 10% during exercise. The increased \(\text{VO}_2\) across work rates was achieved with significant increases in Q and HR, and a widened a-\(\text{vO}_2\) difference. SV remained constant over the first two work rates, then declined 5% in heavy work. Additionally, the a-\(\text{vO}_2\) difference predicted for maximum exercise of 160 ml \(\cdot\) L\(^{-1}\) was within 10% of peak values reported for young adults.

Radionuclide angiocardiography studies in a subgroup showed increased SV from rest to exercise, concurrent with a decrease in end systolic volume. Ejection fraction increased from 66% at rest to 76% in peak exercise. Thus we observed only a modest limitation of left ventricular performance in older subjects. In older adults, then, the loss of \(\text{VO}_2\) max and endurance capacity are not entirely accounted for by losses in HR max, as there are also small losses in SV and in a-\(\text{vO}_2\) difference. These central and peripheral losses appear to be of similar magnitude. Indeed, the SV and a-\(\text{vO}_2\) difference declines (as opposed to loss in HR max, alone) are reflected by a decline of the maximum oxygen pulse of approximately 40% across age (Paterson, 1992).

In our most recent analysis of data from a large randomly selected sample of men and women ages 55 to 85 years, the decline in \(\text{VO}_2\) max with age was analyzed in terms of the rate of decline toward a minimum compatible with maintaining independence. In that analysis, the oxygen pulse showed the fastest rate of decline across this age span, approximately 30% (Cunningham et al., 1997). Data from that study revealed a similar loss in \(\text{VO}_2\) max in men and women when expressed relative to fat-free mass, suggesting the mirror image of the finding in children, that is, that the loss of muscle mass with age may be a confounding factor and may precede the loss of SV.

Subsequent studies have examined potential central limitation to \(\text{VO}_2\) max in older subjects with impaired left ventricular diastolic function. Petrella et al. (1994) reported the effects of a centrally acting calcium channel blocker (verapamil) on Doppler echocardiography measures of left ventricular diastolic function. The rate
of diastolic relaxation and early (E) and late (A-atrial) diastolic filling are important in adequate left ventricular filling and Q in exercise. In 70-year-old hypertensive and normotensive subjects, but not in young, with verapamil, the early : late filling was increased, and the isovolumetric relaxation time decreased, particularly in the hypertensive subjects. With these changes, both older groups showed significant improvements in VO₂ max.

As the left ventricular dysfunction is believed to involve a slowed re-uptake of intracellular calcium by the sarcoplasmatic reticulum after the systolic phase of the cardiac cycle, the improved diastolic filling measures with verapamil suggest improved calcium re-uptake. Thus, the impaired diastolic function appears to have been a limitation to the exercise capacity in sedentary elderly, both in the presence and absence of underlying hypertension. Further, a follow-up study (Petrella et al., 1996) found that older active subjects (with VO₂ max 27 ml · kg⁻¹ · min⁻¹, vs. 22 ml · kg⁻¹ · min⁻¹ in sedentary) showed no evidence of diastolic dysfunction, and thus regular physical activity even at low levels was associated with some maintenance of left ventricular filling.

Most recently (Petrella et al., 1997; Petrella et al., submitted), sedentary older subjects showed a significant decrease of isovolumetric relaxation time and increased early : late ventricular filling following a 5-day exercise training program. The VO₂ max increase of 12% was significantly correlated with the indices of diastolic function, suggesting the VO₂ max had been limited by, and was improved with, left ventricular filling and central haemodynamics.

Early studies in our laboratory had attempted to elucidate the mechanism of the increase of SV as an adaptation to endurance training. Wolfe et al. (1979) examined whether endurance training of men age 35 years resulted in left ventricular structure and function changes. With 6 months of jogging, the resting echocardiographic findings indicated an increased resting SV, which appeared to be due to increased end-diastolic dimensions secondary to greater ventricular filling. Although the ventricular dimensions with training did not approach the differences that had been observed in endurance athletes compared to sedentary individuals (Wolfe et al., 1978), it appears from the studies of Petrella et al. (1997) and Wolfe et al. (1979) that left ventricular filling, and preload, are critical adaptations in increasing the SV with endurance training.

Further exercise training studies on different population groups have yielded other interesting observations and differences in the cardiorespiratory adaptations to endurance training. Cunningham et al. (1979) examined the time course of central and peripheral adaptations to 12 weeks of intensive continuous or interval cycle training in young women. VO₂ max increased 21% with continuous training and 23% with interval training. At exercise of 40 to 95% VO₂ max, SV showed a 5 to 10 ml · beat⁻¹ increase, which was not significant, whereas a-VO₂ difference was significantly increased in heavy work by 9% in the continuous group and 20% in the interval group. Thus, strenuous training and high intensity exercise as in the interval group may provide the stimulus for peripheral adaptations, and central cardiac adaptations may be limited with cycle work.

Overend et al. (1992b) followed on this hypothesis in testing different interval training regimens, versus continuous, with 10 weeks of training in young men. The increase in VO₂ max was 11% while the ventilatory threshold increased 13%, yet no between-group differences were detected. It is possible the continuous train-
ing was quite vigorous (80% VO₂ max) and a higher intensity with interval training was not required in these nonathletic subjects.

Another attempt to stress peripheral adaptations was the study of central and peripheral adaptations to one-legged training (Thomas et al., 1981). Young subjects trained for 4 weeks with one-legged cycling, followed by 4 weeks using the other leg. The first 4 weeks of training resulted in a 20% increase in peak VO₂ during exercise of the trained leg, with significant increases in Q and SV, and a-VO₂ difference. The untrained leg showed a nonsignificant 5% increase in peak VO₂, with small changes in both SV and a-VO₂ difference. The other leg, trained in the second 4 weeks, showed a 17% increase in peak VO₂, with a significant increase in Q but not a-VO₂ difference. Echocardiographic estimates of left ventricular dimensions at diastole showed no changes, and biopsy samples did not reveal enhanced oxidative potential. The adaptations in Q during exercise of the trained limb, but not the untrained limb, together with the lack of change in echocardiographic measures, suggested that the increased Q was due to vascular adaptations of the trained leg. Specifically, an enhanced capillarization and decreased total peripheral resistance may explain the increased Q observed only during exercise with the trained leg; i.e., the increased Q was due to peripheral vascular adaptations.

Our studies with groups representing different models that included old and young, sedentary and active, and different models of the intensity of exercise training have addressed the interplay of central and peripheral responses in the limitations to VO₂ max. It appears that a widened a-VO₂ difference may be an early response to exercise training, growth, and ageing changes in normally active individuals. Strenuous endurance training, however, may enhance the adaptation. Important changes in cardiac function appear to depend on left ventricular diastolic filling; these adaptations may also occur early in training, and a moderate stimulus appears appropriate. Cardiac adaptations, consequent to dimensional changes of the heart or to properties of contractility, may require a longer training period.

Also important for understanding endurance performance and adaptations to endurance training over the past couple of decades has been the introduction and understanding of other aerobic parameters. Whipp et al. (1981, 1982) characterized four aerobic parameters: VO₂ max, the anaerobic threshold (θₘₐₓ), efficiency, and oxygen kinetics. We have studied these aerobic parameters in different population groups.

The θₘₐₓ is a concept that has engendered much controversy, and we became involved in the discussion with a paper by Marsh et al. (1991). In that study a progressive exercise ramp protocol of wrist flexion was used in conjunction with ³¹P-NMR spectroscopy to determine whether intracellular thresholds (IT) could be observed in high-energy phosphate compounds and pH. In analysis, the Pi/PCr ratio approximates changes in muscle oxygen consumption. Several possible mechanisms, either directly or indirectly involving PCr, have been proposed for the control of mitochondrial respiration (Bessman and Carpenter, 1985; Chance et al., 1986; Mahler, 1985). The ramp exercise caused an increase in log Pi/PCr with an initial slow and later fast component, and a distinct nonlinear response best fit by a piecewise regression. Thus, the results established the existence of a threshold in skeletal muscle metabolism suggesting that the lactate and ventilatory thresholds may be indicative of changes in respiration occurring at the cellular level. The log Pi/PCr breakpoint coincided with the point at which pH began to decline, i.e.,
coincident thresholds in intracellular phosphorylation potential and pH during progressive exercise.

Subsequently (Marsh et al., 1993b), forearm training using a wrist flexion exercise resulted in a 14% increase in the power output at onset, or threshold, of intracellular acidosis, and a 34% increase in endurance time for a submaximal wrist flexion test. Thus the training program delayed the onset of intracellular acidosis during progressive exercise and increased the capacity for submaximal work. In addition, venous occlusion plethysmography measures suggested that these effects did not depend on an increase in muscle blood flow. Therefore, the change in IT was understood to noninvasively detect changes in the oxidative capacity of muscle.

The \( \theta_{ao} \) has proved, at least, to be an important concept in understanding endurance performance. The \( \theta_{ao} \) (or respiratory ventilatory threshold, \( T_{ve} \)) concept implies that, at a certain exercise intensity, aerobic metabolism can no longer supply the required energy, and consequently the rate of glycolysis is abruptly increased to provide additional ATP. The \( \theta_{ao} \) has proved useful in evaluating cardiorespiratory endurance capacity (Whipp et al., 1981), and a strong correlation has been noted between \( \theta_{ao} \) and endurance performance (Kumagai et al., 1982; McLellan and Skinner, 1985). Indeed, as illustrated by Paterson and Whipp (1991), as exercise intensity increases beyond the \( \theta_{ao} \), there is a significant slow component of increased oxygen uptake (and demand); this decreased aerobic efficiency appears critical in endurance efforts. As noted earlier (Marsh et al., 1993b), differences or changes in the \( \theta_{ao} \) are related to peripheral (oxidative metabolism) differences or adaptations. Thus the threshold provides information on submaximal work performance that may be independent of \( VO_2 \) max. Thomas et al. (1985) proposed a U-shaped empirical relationship between \( T_{ve}/VO_2 \) max and \( VO_2 \) max, with a high relative \( T_{ve} \) noted both in those with low \( VO_2 \) max and in those with high \( VO_2 \) max, and a lower relative threshold in the inactive with modest \( VO_2 \) max.

In the longitudinal study of active boys ages 10 years through puberty (Paterson et al., 1987), we analyzed the year-to-year changes in \( T_{ve} \) and \( VO_2 \) max. The \( VO_2 \) max followed a growth function of greatest gains coinciding with growth velocity, whereas the \( T_{ve} \) increments were consistent year-to-year (shown by similar mean year-to-year changes when subject responses were aligned with PHV). Given their very active lifestyle as reflected in their \( VO_2 \) max increasing from 60 to 68 ml \( \cdot \) kg\(^{-1} \) \( \cdot \) min\(^{-1} \) across the age span, the \( T_{ve} \) as a % of \( VO_2 \) max was low. As the boys grew older, \( T_{ve} \) occurred at a slightly higher proportion of \( VO_2 \) max from 56 to 62% (at the base of the ascending right arm of the U of Thomas et al., 1985, with increasing \( VO_2 \) max but smaller changes in \( T_{ve}/VO_2 \) max). This increase in \( T_{ve} \) relative to \( VO_2 \) max occurred before the years of greatest growth in height. In conclusion, whereas the value of the \( T_{ve} \) of 25 to 40 ml \( \cdot \) kg\(^{-1} \) \( \cdot \) min\(^{-1} \) in these boys suggests a good ability to perform endurance events, the \( T_{ve} \) as a % \( VO_2 \) max was lower than expected. Growth factors may have dominated during this period, and the training adaptations resulting in a high relative AT may not have added to the stimulus of growth and maturation factors alone.

In older adults we have characterized the \( T_{ve} \) (Cunningham et al., 1985; Thomas et al., 1985). Consistently in our studies \( T_{ve} \) has occurred at a higher percent of \( VO_2 \) max in older subjects (i.e., on the left arm of the U of Thomas et al., 1985), reflecting the greater rate of decline across age in \( VO_2 \) max versus \( T_{ve} \). Data from our large cross-sectional study in men and women ages 55 to 85 years showed
the T_{VE} to decline at half the rate of VO_{max} decline (Paterson et al., submitted). It was suggested that the threshold may be maintained at a minimal level by normal everyday activities, with the implication that as long as individuals are somewhat active in their daily activities, the θ_{ao} and muscle metabolic processes of oxidative phosphorylation are reasonably maintained.

In the study of Poulin et al. (1992), older men, mean age 67 years, underwent training for 9 weeks. In that study we measured the endurance performance before and after training as the time-to-fatigue on a standardized heavy exercise treadmill protocol. VO_{max} increased by 11% and T_{VE} by 10%. The time-to-fatigue on the treadmill increased 180% from 7 to 20 min. Thus, adaptations to aerobic training resulted in substantial increases in endurance capacity during constant-load submaximal exercise—indeed, endurance time is a function of the relative intensity and increases exponentially with decreasing relative exercise rate. In addition, the endurance time-to-fatigue improvement was related most closely, not simply to the increase in VO_{max} or to the change in T_{VE}, but to the relative change in the delta between T_{VE} and VO_{max} from an average of 88 to 73%; that is, the largest changes in performance were seen in those who showed the greatest increases in both T_{VE} and VO_{max}.

When we measure these parameters of aerobic function, we can quantify the endurance performance, and notably, relative to the aerobic parameters, it is the same for young and old and shows a similar improvement with endurance training. Along a similar line, Overend et al. (1992a) examined critical power as the highest rate of work that can be performed for an extended period. Whereas critical power was 35% lower in the old versus young, during a 24-min exercise at the individually determined critical power there were no differences relative to maximum values between old and young for ventilation or HR. In fact, the VO_{2} represented 92% of max in the older group and 85% in the younger group. Additionally, blood lactate values were significantly lower in the elderly versus young (6.5 vs. 8.1 mmol · L^{-1}). Of interest in this study, relative to the topic of endurance performance is the figure (c.f. Overend et al., 1992a, Fig. 4) showing that performance time could be predicted from the percentage of critical power at which individuals were working, and old and young again followed the same relationship.

The aerobic parameter of oxygen kinetics has received our attention most recently and is the focus of much of our most recent research. At the American College of Sports Medicine meetings, Whipp (1998) presented a paper titled "Oxygen kinetics: Stamen of stamina." The rate of response of oxidative metabolism in adjusting to changes in work rate may be a critical component of endurance, particularly in the many team sports involving intermittent exercise and frequent changes in the pace or intensity of exercise from coasting or walking to short duration sprints (basketball, hockey, squash, etc). The faster the oxygen kinetics, the lesser the reliance on easily fatigueable anaerobic energy contribution—in each and every transition from rest to exercise to recovery, or from light to heavy exercise.

In terms of the interplay of central and peripheral factors determining this aerobic parameter, it is widely held that blood flow to the muscle is abundant and quickly available, and that the inertia of the processes of increased oxidative phosphorylation controls the rate of oxygen kinetics (Whipp and Mahler, 1980). We have contributed some of the evidence favouring this hypothesis (Marsh et al., 1993a) using magnetic resonance spectroscopy to study the transient changes in muscle high-energy phosphates during moderate exercise. The rate of PCR brak-
down and recovery in the muscle at the onset and cessation of moderate-intensity wrist flexion exercise were aptly described by a first-order model with a rate parameter (time constant, τ) close to 30 sec.

Theories of mitochondrial respiratory control imply that the kinetics of phosphocreatine hydrolysis are indicative of the kinetics of muscle VO₂ during this moderate-intensity exercise. Indeed the follow-up study of McCreary et al. (1996) showed during calf exercise a similar rate for the kinetics of PCR and Phase 2 pulmonary VO₂ kinetics. Thus, PCR and Phase 2 VO₂ kinetics (which reflect muscle O₂ kinetics) occur at similar rates during moderate-intensity planter flexion exercise with a time constant of approximately 45 sec. Therefore, measures of pulmonary VO₂ kinetics can be used to infer metabolic kinetics for specific muscles.

Again, we have used the older population to examine pulmonary VO₂ kinetics as a reflection of metabolic kinetics at exercise onset. Whereas the variance in kinetics among a sample of young very fit to very unfit is small, in our studies of old we found some with very slow oxygen kinetics (Babcock et al., 1994b; Cunningham et al., 1993). This slow time constant in older adults allowed us to examine the physiological cause of these slow kinetics, and the potential limitation to endurance capacity in some activities. The first question was whether the lengthening of kinetics was caused by physiological changes that occur with aging, or was the result of reduced activity in older people. Indeed, with 6 months of cycle training, the VO₂max and Tₜ, both increased 20% and the τ changed from 62 to 32 sec (Babcock et al., 1994a). Remarkably, the VO₂ time constant in the older men after training was comparable to that seen in young subjects following training.

One explanation of the faster time course of O₂ uptake with aerobic training would be an increased mitochondrial content and oxidative capacity. The counter hypothesis would be faster circulatory adaptation including HR kinetics and Q, and adaptations favouring improved muscle blood flow.

We have used different population groups to explore possible central limitations that may slow oxygen kinetics. Heart transplants, with cardiac denervation, represent a unique group for studying physiological control systems in humans. In such patients the HR response to exercise onset is greatly delayed because of cardiac denervation, therefore this may impose the limitation to VO₂ kinetics. Indeed the kinetics were very slow in the transplants, τ of 77 sec compared to 45 sec in age-matched controls; and the HR by 3 min of exercise had risen only 7 bpm in the transplant group compared to 19 bpm in the controls (Paterson et al., 1994). Thus the slow VO₂ kinetics of the heart transplant recipients appeared to reflect a central limitation at the onset of exercise. Nevertheless, with a second transient to exercise, initiated after 6 minutes and before the HR had returned to baseline, the kinetics of the transplant patients was 46 sec. It appeared the greater cardiac output at the second transient was adequate to overcome this limitation, and the VO₂ kinetics of the second transient may reflect the bioenergetic processes controlling the rate of oxidative metabolism in the exercising muscles.

Two groups of recent studies on the limitation and control of oxygen uptake kinetics in older adults have examined the interplay of central versus peripheral limitations. Studies by Petrella et al. (1997; and paper submitted), as detailed earlier, examined potential central limitation to VO₂max and also measured the VO₂ kinetics in these older subjects with impaired left ventricular diastolic function. With enhanced diastolic function consequent to verapamil treatment (Petrella et al., 1996), or to short-term exercise training, either perturbation resulted in faster
\( \text{VO}_2 \) kinetics, from a \( \tau \) of 60 sec to \( \tau \) of 40–50 sec (Petrella et al., submitted). Thus, a limiting factor to \( \text{VO}_2 \) kinetics of the response rate of the central circulation was apparently overcome by perturbations acting to improve cardiac filling, and the \( \text{VO}_2 \) kinetics then appeared to reflect the rate of metabolic control of muscle oxidative phosphorylation.

The studies of Chilibeck et al. (1996a, 1996b, 1997, 1998a, 1998b) also focused on older adults and oxygen kinetics. These experiments with active older adults demonstrated that the \( \text{VO}_2 \) kinetics were significantly slow compared with young subjects during cycle exercise, but there was no significant difference during plantar flexion exercise, an activity similar to their daily walking (Chilibeck et al., 1996b). \( \text{VO}_2 \) kinetics during treadmill walking were slowed in older subjects compared to younger ones, but not to the extent observed during cycling. The slow \( \text{O}_2 \) kinetics on the cycle and treadmill were associated with slow HR kinetics (used to approximate \( Q \) dynamics), and this suggested that the slowed \( \text{VO}_2 \) kinetics in the older group may be related to slow central \( \text{O}_2 \) delivery. During exercise of a small muscle mass (plantar flexion), circulatory demand may not be challenged and it is unlikely that \( \text{O}_2 \) supply would be limiting.

However, the slower \( \text{O}_2 \) kinetics in older subjects during cycling, while possibly influenced by slow HR kinetics, may also relate to the use of muscle groups not accustomed to activity and therefore suggests a peripheral limitation to such activity. The older subjects were all active walkers. Presumably this walking maintained the activity level of oxidative enzymes in plantar flexors and other muscle groups challenged during the treadmill exercise. In fact, Chilibeck et al. (1997) found that accompanying the similar kinetics during plantar flexion exercise in older active walkers compared to younger subjects, the older group also showed similar muscle capillarization and estimated \( \text{O}_2 \) diffusion distance. Thus, it appears that \( \text{VO}_2 \) kinetics (and PCR kinetics, Chilibeck et al., 1998b) during exercise of a muscle group accustomed to everyday activity were well maintained, as were peripheral factors of capillarization (Chilibeck et al., 1997) and also oxidative enzymes (Chilibeck et al., 1998a).

Therefore, the limiting factors for maximum oxygen uptake or oxygen kinetics apparently depend on the subjects in the study, and the answer to whether it is the central or the peripheral aspects that are limiting may be as variable as the differences between groups tested. The adaptations to endurance training do seem to relate to adaptations in the limiting central or peripheral factors of the groups under study, and to the exercise training stimulus in terms of intensity and length of training.

The interplay of central and peripheral factors in endurance training appear to have a time course that depends largely on the starting point related to initial cardiorespiratory capacity. For example, young children progressing through growth and development of puberty may demonstrate an increase in \( \text{VO}_2 \) max related to the increase in mitochondrial machinery, whereas the loss in old age may reflect the process in reverse. The factors that dictate limitations in young to older healthy adults may also vary but appear to be more consistent with oxygen delivery limitations at maximal exercise whereas at submaximal power output, peripheral limitations are critical.

A moderate degree of physical activity seems to preserve normal heart function and muscle metabolism even into older age. However, strenuous exercise training can yield remarkable improvements in both central and peripheral capacity, and a threefold improvement in endurance performance.
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