Slower $\dot{V}O_2$ Kinetics in Older Individuals: Is It Inevitable?

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ABSTRACT

MURIAS, J. M., and D. H. PATERSON. Slower $\dot{V}O_2$ Kinetics in Older Individuals: Is It Inevitable? *Med. Sci. Sports Exerc.*, Vol. 47, No. 11, pp. 2308–2318, 2015. **Introduction**: The mechanisms controlling the rate of adjustment of oxidative phosphorylation have been debated for several years. Although disagreement exists as to what the prevailing mechanisms controlling the speed of the oxygen uptake ($\dot{V}O_2$) kinetics are in both young and older individuals, it seems tenable that the slower $\dot{V}O_2$ kinetics response typically observed in older adults is at least partly imposed by an O_2 delivery limitation. **Results**: Several studies have demonstrated that different interventions can speed $\dot{V}O_2$ kinetics in older individuals so that this response can become similar to that observed in their young counterparts. These findings have opened the debate as to whether aging *per se*, or other factors that accompany aging, is responsible for the slower adjustment of oxidative metabolism in the elderly. This review focuses on the slower $\dot{V}O_2$ kinetics often observed in older populations and discusses potential mechanisms that might mediate the slower adjustment in oxidative phosphorylation. Furthermore, interventions that have been successful in speeding $\dot{V}O_2$ kinetics in the elderly are described to discriminate how the controlling factors determining the adjustment of $\dot{V}O_2$ might be regulated by specific perturbations. Importantly, this review shows that the slower adjustment of oxidative phosphorylation typically seen in older compared with young individuals can be completely abolished in some exceptional situations such as chronic endurance-exercise training, despite the age-related decrease in maximal $\dot{V}O_2$ still being present. **Conclusions**: Thus, this review focuses on the concept that although $\dot{V}O_2$ kinetics is often slower in the elderly, this slower increase in the rise of oxygen uptake during the exercise on-transient does not need to be considered an inevitable response. **Key Words:** OXIDATIVE PHOSPHORYLATION, AGING, BLOOD FLOW, O_2 EXTRACTION, NEAR-INFRARED SPECTROSCOPY, MODERATE-INTENSITY EXERCISE

BASIC SCIENCES

The study of $\dot{V}O_2$ kinetics has expanded our knowledge regarding the mechanisms controlling the dynamic adjustment of oxidative phosphorylation. During exercise transitions performed from a baseline intensity to a given and instantaneous increase in work rate within the moderate-intensity domain, the pulmonary $\dot{V}O_2$ ($\dot{V}O_{2p}$) response describes three distinctive phases (Fig. 1). Phase I (or cardiodynamic phase) reflects the circulatory transit delay of O_2 from the active tissues to the lungs. During this phase, changes in the $\dot{V}O_{2p}$ represent an increase in pulmonary blood flow and do not reflect the increased oxygen extraction occurring at the level of the muscle. Phase II, or the fundamental component, describes an exponential increase in $\dot{V}O_{2p}$ that is explained by the continued increase in pulmonary and muscle blood flow as well as the return of deoxygenated blood from the active muscles to the lungs. This phase is proposed to closely characterize the adjustments of oxidative phosphorylation in the active muscles (36,74), and it describes a monoexponential increase until a steady state is achieved (86,87). Phase III, during moderate-intensity exercise, represents the steady state of $\dot{V}O_{2p}$. The duration of that dynamic adjustment (Phase II) for the increase in $\dot{V}O_2$ is characterized by the $\dot{V}O_2$ time-constant ($\tau\dot{V}O_2$), which describes the time required for the $\dot{V}O_{2p}$ response to reach 63% of its steady-state value (with four $\tau\dot{V}O_2$ representing 98% of the adjustment and typically considered as the time needed to reach steady-state). Although pioneering work from Krogh and Lindhard (49) initially described the exponential increase in $\dot{V}O_2$ toward a steady-state response, the development of fast-response breath-by-breath gas analyzers and computer-based data modeling software promoted increased research in this area. This research has extended over the last 40 yr and resulted in a prolific scientific debate regarding the mechanisms controlling the $\dot{V}O_2$ kinetics response. Whereas some have postulated that in young healthy adults the main locus of control for the adjustment of oxidative phosphorylation resides intracellularly (32,34,35,67,68), others have proposed that O_2 provision to the active tissues

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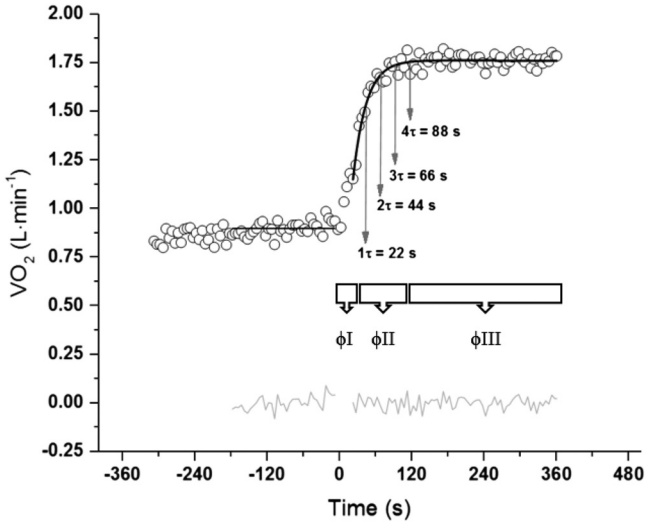

FIGURE 1—Representative fitting of the $\dot{V}O_2$ kinetics response in an older man. 1τ, 2τ, 3τ, and 4τ represent 63%, 86%, 95%, and 98%, respectively, of the time required for the amplitude of the $\dot{V}O_2$ response to reach steady state. ϕ I, Phase I of the $\dot{V}O_{2p}$ response; ϕ II, Phase II of the $\dot{V}O_{2p}$ response; ϕ III, Phase III of the $\dot{V}O_{2p}$ response. Residuals of the fit are depicted in light grey line at the bottom part of the figure.

plays a critical role in determining the dynamic response of $\dot{V}O_2$ (46,47,62,63).

Despite the disagreements in terms of the prevailing mechanisms controlling the speed of the $\dot{V}O_2$ kinetics response in young individuals, there seems to be agreement that older adults typically display a slower dynamic adjustment of $\dot{V}O_2$ (3,8,22,40,57,58) and that a limitation in O_2 delivery to the working muscles may be, at least, partly responsible for the greater $\tau\dot{V}O_2$ observed in older compared with young individuals (57,58,68,69). Importantly, recent studies have shown that different interventions can decrease $\tau\dot{V}O_2$ in older individuals to values similar to those observed in their young counterparts (23,39,57,58), opening the debate as to whether aging *per se*, or other factors that normally accompany, but are not requisite with, aging (such as poorer cardiovascular function and decreased mitochondrial enzymes activity likely related to reduced fitness levels), is responsible for the slower rate of adjustment in the $\dot{V}O_2$ response in the elderly.

Thus, this review will focus on the slower $\dot{V}O_2$ kinetics response typically observed in older populations, and it will discuss the mechanisms that are likely to mediate the slower adjustment in oxidative phosphorylation. In addition, interventions that result in speeding of $\dot{V}O_2$ kinetics in the elderly will be described to discern the limiting factors that may be ameliorated by specific perturbations.

$\dot{V}O_2$ KINETICS IN OLDER ADULTS

Although there is extensive literature on the study of $\dot{V}O_2$ kinetics during exercise performed within the moderate-intensity domain in healthy young adults, relatively fewer studies have examined this response in older individuals. An early study by Babcock and colleagues (1) in 79 subjects age 30–84 yr estimated the $\dot{V}O_2$ kinetics as the mean response time (the total lag time of the increasing $\dot{V}O_2$ for the increasing work rate) for the $\dot{V}O_2$ increase during a ramp incremental increase in work rate. The mean response time for $\dot{V}O_2$ kinetics increased with a linear slope of 0.7 s·yr^{-1}. This slower $\dot{V}O_2$ kinetics response of older adults was confirmed using other forcing functions; with a cycling exercise step ("square wave") protocol, Babcock and colleagues (3) again observed an increase in $\tau\dot{V}O_2$ of ~0.7 s·yr^{-1} in 46 men spanning the age range of 30–80 yr (39 s to 61 s) and a sinusoidal protocol on the treadmill in women elicited a $\tau\dot{V}O_2$ of 34 s in young and 55 s in old (age, 62–73 yr) (20). It is now generally accepted that $\dot{V}O_2$ kinetics becomes progressively slower with aging. Studies evaluating the $\dot{V}O_2$ kinetics responses in older individuals (generally, age 65 yr and older) have shown $\tau\dot{V}O_2$ values ranging from ~30 s to ~60 s for the group average response (2,3,8,12–15,22,23,38,40,41,57,58,61,76,80), whereas the average group mean $\tau\dot{V}O_2$ in young subjects normally ranges between 20 s and 45 s (11–15,22–24,36,38,40,48,57,58,61,76). From these group mean values reported in older and young populations, it seems evident that, although older participants display an overall slower adjustment of $\dot{V}O_2$ during exercise transitions from baseline to a higher intensity within the moderate-intensity domain, there is also an "overlapping" area where older and young individuals have a similar $\dot{V}O_2$ kinetics response. This suggests that the slower dynamic adjustment of oxidative phosphorylation typically observed in older individuals might be secondary to other factors such as training status, instead of being exclusively determined by aging *per se*. Indeed, in three other studies in which $\dot{V}O_2$ kinetics responses were compared in older and young individuals, the rate of adjustment of oxidative phosphorylation was similar between groups (12,13,38). In addition, a recent paper has demonstrated that older, chronically trained men have $\dot{V}O_2$ kinetics that is similar to those of young individuals (39). This is an important characteristic of this response, as it shows not only that some older participants might display a "fast" $\dot{V}O_2$ kinetics but also that young, healthy individuals might exhibit a "slow" response as previously demonstrated (62,63). Figure 2, derived from different studies conducted in our laboratory, illustrates this point.

A recent study has challenged the notion that older adults have slower $\dot{V}O_2$ kinetics than those observed in young healthy individuals (54). In that study, the authors suggested that given that older participants exhibited a lengthened Phase I $\dot{V}O_{2p}$ and that an association between Phase II $\dot{V}O_{2p}$ duration and the circulatory dynamics during exercise has been proposed (4), then modeling the Phase II $\dot{V}O_{2p}$ data from a fixed value (typically ~20 s) would likely result in an overestimation of the $\tau\dot{V}O_2$ measured in older individuals. Although the data from that study supported that contention, a subsequent investigation suggested a limitation in the analysis and corroborated that the $\tau\dot{V}O_2$ values previously reported in the literature for older individuals were correct since using a range of different values as the onset of the

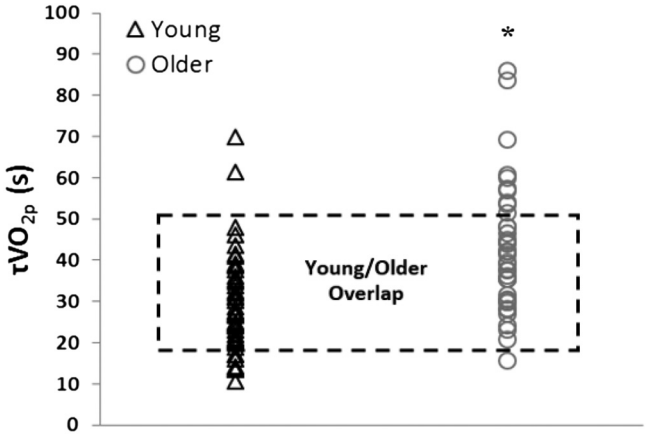

FIGURE 2—Individual $\tau\dot{V}O_2$ responses from different studies conducted in our laboratory comparing older ($n = 41$) and young ($n = 49$) individuals. Although the overall $\dot{V}O_2$ kinetics response is slower in older (42 ± 15 s) compared with young (29 ± 12 s) individuals ($P < 0.05$), the area within the dashed lines represents the "overlapping" $\tau\dot{V}O_2$ responses in these two groups. Data presented in this figure represent preintervention values (i.e., no exercise training or prior heavy-intensity warm-up) so that no "speeding" effect biases the interpretation. *Group mean significantly different from young.

Phase II $\dot{V}O_{2p}$ (Phase I–Phase II transition) did not affect the parameter estimates of $\dot{V}O_2$ kinetics (61).

WHY IS $\dot{V}O_2$ KINETICS TYPICALLY SLOWER IN OLDER ADULTS?

A number of analyses have demonstrated that the slower dynamic adjustment of $\dot{V}O_2$ typically observed in older individuals is related to structural and functional changes in the O_2 transport system that affect the matching of O_2 delivery to O_2 utilization at the level of the active muscles (58,68). Although it is accepted that factors affecting the O_2 transport pathway contribute to the slower $\dot{V}O_2$ kinetics often seen in older individuals (58,68), intracellular mechanisms of control are not ruled out as a factor limiting the rate of adjustment of oxidative phosphorylation (22,25,40,41).

Limitations related to O_2 delivery to the active tissues could originate at the central (i.e., cardiac output (Q), heart rate (HR)) or peripheral circulation. Within the peripheral circulation, distinctions should be made between conduit arteries proximate to the active muscles (e.g., femoral artery) and the microcirculation within those muscles. This is important because even when conduit arteries are proximal to the active muscle fibers, circulation through these vessels can still be considered as "bulk" blood flow, whereas within the microcirculation, more precise adjustments are made in an attempt to adequately match local O_2 provision to O_2 demand.

From a cardiac output perspective, although the decreased absolute maximal cardiac output observed with aging results in reductions in whole-body maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$) (29), it has been shown that, at least during submaximal intensities of exercise, the Q to $\dot{V}O_2$ relationship shows a similar increase despite the fact that the Q may be somewhat lower in old (66,83) such that the relationship between the increase in cardiac output and $\dot{V}O_2$ is not altered by age neither in women nor in men (70). However, although the relationship between cardiac output and $\dot{V}O_2$ might be well preserved with aging, the dynamic adjustment of cardiac output during the transient to exercise might be affected by aging. In this regard, studies have examined the dynamic adjustment of HR, used as a proxy of the rate of adjustment of cardiac output and presumably bulk delivery of O_2 to the tissues (with the assumption that during the exercise-intensity transitions any increase in stroke volume is rapid, within the first few heartbeats, and thereafter remains constant (50)). Babcock and colleagues originally noted little change in the HR dynamics across age (30–80 yr) (3) and that with training the faster HR kinetics were not related to the faster $\dot{V}O_2$ kinetics (2). Nevertheless, other studies have found that τHR was significantly greater in older compared with young individuals (14,22,38) with a significant correlation ($r = 0.76$) between τHR and $\tau\dot{V}O_2$ in one of those studies (22). However, there are also data to support the idea that even if a slower adjustment of HR occurs in older participants, compensatory mechanisms might take place to distribute a larger percentage of the cardiac output to the active muscles so that muscle blood flow is not compromised (71).

In agreement with this idea, data from Bell and colleagues (9) demonstrated in a group of older adults that the dynamic adjustment of femoral artery blood flow (as derived by measures of mean blood velocity) was significantly faster than that of $\dot{V}O_2$, and that a smaller $\tau\dot{V}O_2$ observed after training occurred in the absence of changes in the adjustment of blood flow during the exercise on-transient. These data suggested that provision of O_2 to the active muscles would meet (or even exceed) the metabolic needs for O_2. duManoir and colleagues (28) also examined the dynamic responses of $\dot{V}O_2$ and femoral artery blood flow. Similar to the study of Bell and colleagues (9), this study found that the kinetics of blood flow in the femoral artery in older men was faster than the kinetics response of $\dot{V}O_2$, so that bulk delivery of O_2 did not seem to be responsible for the slower $\dot{V}O_2$ kinetics observed in older compared with young men. In fact, the τ blood flow in the femoral artery was not significantly different between older and young participants. Interestingly, a previous study (43) has shown (at least in young individuals) that although the kinetics adjustment of femoral blood flow was faster than that of $\dot{V}O_{2p}$, capillary blood flow was significantly slower than both of them, suggesting that the dynamic adjustment of blood flow within the microvasculature might impose a limitation to the rate of adjustment of oxidative phosphorylation. In addition, to further explore the role of O_2 transport to the active tissues in determining the rate of adjustment of $\dot{V}O_2$ in older compared with young individuals, duManoir and colleagues (28) added the measure of the near-infrared spectroscopy (NIRS)–derived deoxyhemoglobin [HHb] signal of the vastus lateralis muscle. The deoxygenation signal provides an indication of the balance of the O_2 delivery to O_2 utilization in the region. The deoxygenation to accomplish a given $\dot{V}O_2$ during the on-transient of the exercise was

compared with the relationship achieved in the steady state. A greater deoxygenation relative to the $\dot{V}O_2$ throughout much of the exercise on-transient (i.e., 30–90 s) would suggest a sluggish increase in the blood flow to the microvasculature in the region of the NIRS probe. The study of duManoir and colleagues (28) was the first to integrate the normalized $\dot{V}O_2$ (the proportion of the steady-state value achieved at any time in the transient) with the [HHb] (normalized) responses to indirectly assess the dynamic adjustment of microvascular blood flow. This study established a greater reliance on O_2 extraction for a given $\dot{V}O_2$ during the on-transient period in older compared with young men. The normalized [HHb] was described as showing an overshoot for a given $\dot{V}O_2$ in the transient relative to the relationship of the steady state. For example, when the $\dot{V}O_2$ had achieved 60% of its steady state, the [HHb] was 80% of its steady state. Thus, the normalized [HHb]/$\dot{V}O_2$ ratio (80%/60%) of 1.3 suggested a 30% greater deoxygenation to achieve a given $\dot{V}O_2$ during the transient compared with the steady-state data (for details on technical aspects of the [HHb] signal and [HHb]/$\dot{V}O_2$ ratio, please refer to the "Technical considerations" section in this paper). Interestingly, the study of duManoir and colleagues (28) did not consider the adjustment in the total-hemoglobin profile in the analysis. This is important as a recent study has suggested that total hemoglobin might be used as an indicator of changes in hemoglobin concentration during exercise (21). In this regard, Gurd and colleagues (40) showed that changes in total hemoglobin concentration from baseline to the end of the exercise transition were not different in older and young men. Although this might suggest that the total change in O_2 availability during exercise was similar in both older and young participants, no information was provided in terms of the dynamic changes in this response so that there is no certainty that the dynamic increase in total hemoglobin was similar in both groups. Nevertheless, although bulk delivery of O_2 measured in the femoral artery seems to be adequate to support the metabolic demand for O_2 during the exercise on-transient in older adults, microvascular delivery and/or distribution of O_2 within regions of the active muscle fibers might not be satisfactory to meet the metabolic needs, resulting in a mismatch between O_2 delivery and O_2 utilization during the kinetic adjustment to exercise.

Subsequent work from our group further explored the issue of matching between O_2 delivery and O_2 utilization within the microvasculature. Different studies demonstrated that older women (27,57) and men (58) had a significantly slower $\dot{V}O_2$ kinetics compared with their younger or trained counterparts and proposed that this slower adjustment in the $\dot{V}O_2$ response was associated with a poorer matching of O_2 delivery to O_2 utilization in the active tissues as suggested by a greater reliance on O_2 extraction for a given $\dot{V}O_2$ (i.e., a larger overshoot in the [HHb]/$\dot{V}O_2$ ratio; Fig. 3A, Panels 1 and 2). Although the [HHb] data can only be suggestive, several lines of research support the concept that aging results in poorer O_2 provision to the active tissues. For example, animal studies have described reductions in endothelium-dependent and flow-mediated vasodilation in feed arteries and 1A arterioles of the oxidative soleus muscle in old compared with young rats (55). Subsequently, Behnke and Delp (5) measured the dynamics of vasodilation in first-order arterioles in old and young rats and observed a blunted response in the old for both soleus and red gastrocnemius and concluded that the slower vasodilation would inhibit O_2 delivery and matching of O_2 delivery to O_2 consumption during the exercise on-transient. In addition, it has been shown that although resting and steady-state exercise hindlimb blood flow were similar in old and young rats, there was a shift toward more blood flow being distributed to glycolytic than to oxidative muscles in older animals (65), indicating a potential for a mismatch between O_2 delivery and O_2 utilization in the more active fibers during moderate-intensity exercise. Another factor that might affect gas exchange with aging is related to reductions in measures of capillarization (16,72), although this is not a consistent finding; Chilibeck and colleagues (12) found no difference in capillarization of old versus young men and noted that this was for biopsy of the lateral gastrocnemius and preservation of the capillarization in older adults may be related to the muscle use in daily activity especially walking. Regardless, it has been shown that the capillary structure is not necessarily compromised with aging as the ratio of capillary-to-fiber surface contact to oxidative capacity is substantially higher in the older rats (44,52). Thus, an O_2 diffusion limitation in the elderly might not be related to a reduction in the structural capacity for O_2 transfer *per se*, but rather, by the flux of red blood cells (RBC) within the capillaries. Related to this, older rats have shown a reduced lineal density of RBC-perfused capillaries running next to a fiber, which is compensated at rest by increases in RBC velocity so that O_2 delivery is similar in both old and young rats (75). However, old rats exposed to electrically induced muscle contractions do not display the same increase in capillary RBC velocity that their younger counterparts exhibit (19). In addition, it has been demonstrated that old rats exhibit a transiently reduced microvascular pressure of O_2 across the rest—contractions transition that is likely to impair O_2 exchange from the capillaries to the fibers (6). Taken together, these changes in capillary hemodynamics reported in older rats are likely to explain reductions in O_2 transport from the capillaries to the myocyte. Independently of what the precise mechanism controlling O_2 delivery/distribution to the active regions in the elderly is, the overshoot in the [HHb]/$\dot{V}O_2$ ratio in the aforementioned studies support the idea that older individuals experience a constraint in blood flow distribution within the active muscles during exercise on-transients.

Although limitations within the O_2 transport pathway seem to play a major role in determining the rate of adjustment of $\dot{V}O_2$ in the elderly, other mechanisms have been proposed that might contribute to the slower $\dot{V}O_2$ kinetics typically observed in older individuals. Gurd and colleagues showed (40) a greater $\tau\dot{V}O_2$ in older (~40 s) compared with young (~20 s) participants. The authors measured an increase in

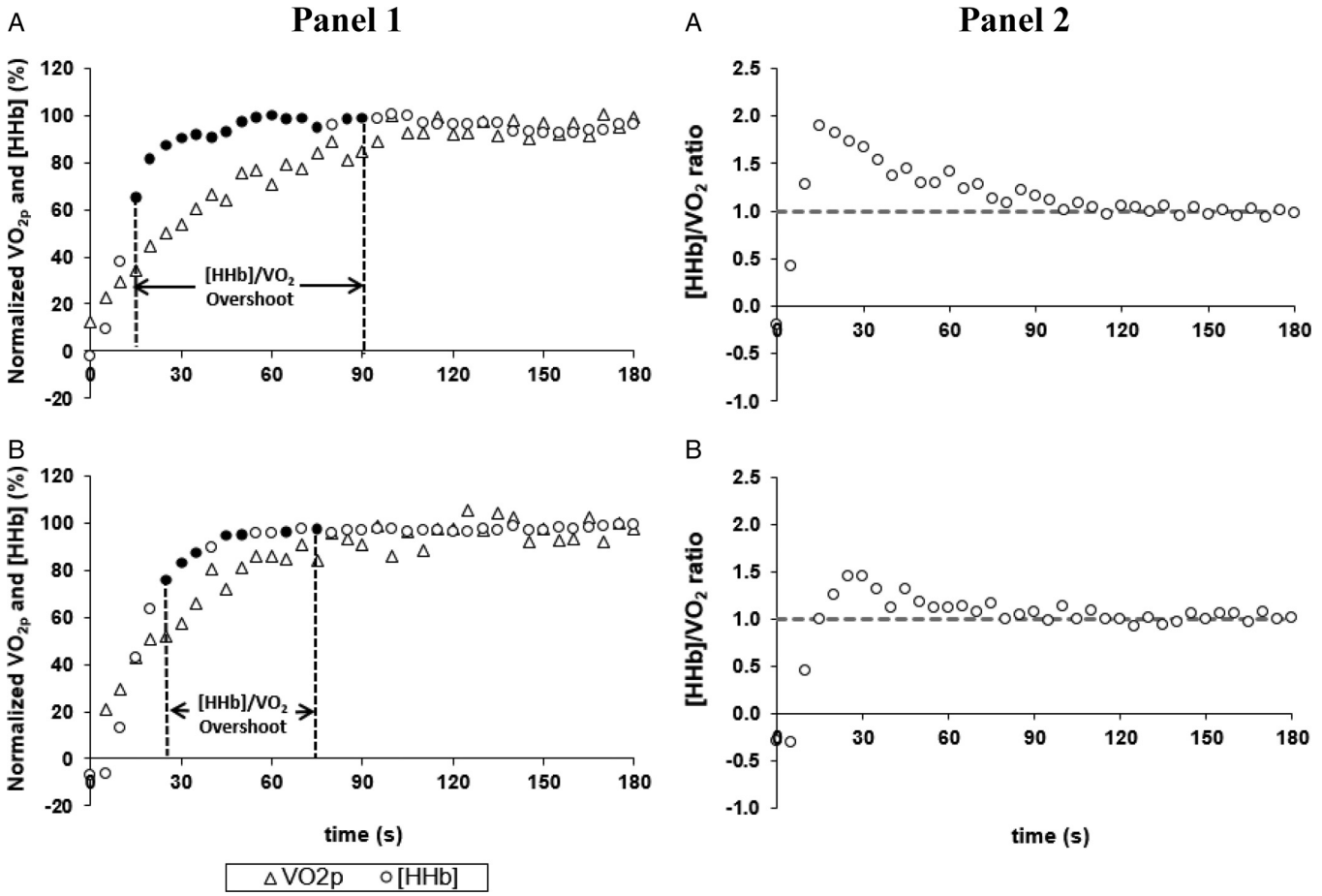

FIGURE 3—Panel 1, Group mean profiles for the adjustment of [HHb] (circles) and $\dot{V}O_{2p}$ (triangles) during the initial 180 s of a step-transition in work rate pretraining (A) and 3 wk after endurance training (B) in older men. *Filled circles* denote time points at which the relative increase of [HHb] is greater than the relative increase of $\dot{V}O_{2p}$ ($P < 0.05$). Panel 2, Group mean profiles for the adjustment of [HHb]/$\dot{V}O_{2p}$ ratio during a step-transition in work rate pretraining (A) and 3 wk after endurance training (B) in older men. Note that both the amplitude and the duration of the overshoot in the [HHb]/$\dot{V}O_{2p}$ ratio were reduced after 3 wk of training. Adapted from Murias et al., 2010 (58), used with permission.

pyruvate dehydrogenase (PDH) activity at 30 s into the exercise transition in young but not in the older participants, and a significant elevation in PDH activity in both groups at 6 min into the bout of moderate-intensity exercise. Given its role in controlling the entry of carbohydrate-derived substrate into the tricarboxylic acid cycle to provide reducing equivalents to the electron transport chain, and that PDH has been suggested as a site of "metabolic inertia," it was concluded that this slower adjustment in PDH activity, in combination with poorer O_2 delivery to the active tissues, was partly responsible for the slower $\dot{V}O_2$ kinetics in the older group. Although the correlation between $\dot{V}O_2$ kinetics and PDH activity at 30 s was not significant, it remains possible that the higher PDH activity contributed to the smaller $\tau\dot{V}O_2$.

The idea that slower $\dot{V}O_2$ kinetics in older adults may be attributed to intracellular control aspects has been difficult to study. A number of reports documented that older age affects various aspects of muscle metabolism. Short and colleagues (78) listed a 10%–40% lesser abundance of a number of mitochondrial proteins in older versus young muscle. Conley and colleagues (18) and Marcinek and colleagues (51) noted a lower mitochondrial oxidative capacity per mitochondria and a lower ATP production per O_2 used (although these data are not supported in humans where older and young individuals display similar increases in $\dot{V}O_2$ for a given increase in work rate (23,40)). Similarly, Hepple and colleagues (45) reported that aerobic power at matched O_2 delivery declined with age. However, other mechanisms of intracellular control that have been studied in young humans and animals have not been explored in older populations, and specific information on this group is missing. Thus, only inferences derived from data in young groups can be made regarding the role of other potential mechanisms of intracellular control, such as the role of the creatine kinase–catalysed PCr breakdown slowing the adjustment of oxidative metabolism by acting as a spatial and temporal buffer that delays the increase in ADP in the inner mitochondrial membrane (37); however, this is not the scope of this brief review (for an extensive review on the topic, refer to Poole and Jones (68,73)).

WHAT INTERVENTIONS HAVE BEEN SHOWN TO MODIFY THE $\dot{V}O_2$ KINETICS RESPONSE IN OLDER ADULTS?

Heavy-intensity "warm-up"is an acute intervention that has been shown to result in a reduced $\tau\dot{V}O_2$ during moderate-intensity exercise in older participants compared with the control condition (no prior heavy-intensity exercise) (23,41). Although this intervention results in increased O_2 provision to the tissues concomitant to increased activity of intracellular enzymes likely responsible for controlling the $\dot{V}O_2$ kinetics response, a recent study by Spencer and colleagues (79) showed that the faster $\dot{V}O_2$ kinetics observed in the post–warm-up step transition of moderate-intensity exercise was abolished when the increases in O_2 delivery were counteracted by hypoxic breathing. DeLorey and colleagues demonstrated not only that this intervention resulted in a faster adjustment of $\dot{V}O_2$ in older men but also that the age-related slower $\dot{V}O_2$ kinetics in the older compared with the young group was abolished (23). The authors suggested that improvements in local perfusion subsequent to the heavy-intensity 6-min bout of exercise were responsible for the faster $\dot{V}O_2$ kinetics in the older men. This conclusion was supported by a lack of changes in the dynamic adjustment of the HR response (providing an estimation of the dynamic adjustment of Q and "central" O_2 delivery) after the heavy-intensity warm-up, but in the presence of an increased oxygenation in the active muscles as reflected by greater concentrations of oxy- and total-hemoglobin (with the total hemoglobin increasing similarly in both young and older individuals and remaining elevated after the heavy-intensity warm-up, thus suggesting similar and sustained increases in hemoglobin concentration) in the area of NIRS interrogation, and a closer matching in the adjustment of the $\dot{V}O_2$ relative to the [HHb] signal. Similarly, Gurd and colleagues (41) demonstrated a faster $\dot{V}O_2$ kinetics response after prior heavy-intensity exercise in older adults. In agreement with the study of DeLorey and colleagues (23), NIRS-derived data supported the idea that increases in O_2 provision in the active muscles played a role in the speeding of $\dot{V}O_2$ kinetics after the heavy-intensity warm-up (as indicated by increased both oxy- and total hemoglobin concentrations). In addition, the authors proposed that greater availability of oxidative substrates in the second bout of moderate-intensity exercise also contributed to the smaller $\tau\dot{V}O_2$. This was supported by a higher PDH activity, with less decrease in the PCr and less increase in free ADP and Pi subsequent to the heavy-intensity warm-up. Although the correlations between changes in PDH activity at both baseline and 30 s into the bout of moderate intensity exercise and changes in $\tau\dot{V}O_2$ ($r = 0.63$ and $r = 0.61$, respectively) seemed high, the authors noted that they were not significant. This is an important observation because, whereas the availability of some oxidative substrates has been shown to contribute to the modulation of the adjustment of $\dot{V}O_2$ (37) and proposed to be of critical importance during the initial ~20 s of this adjustment (63), no study so far has established a clear association between changes in PDH activity and changes in $\tau\dot{V}O_2$ despite the sound theoretical reasoning behind this possibility.

Exercise training interventions have also been shown to result in a speeding of the $\dot{V}O_2$ kinetics response in older individuals (9,31,58,60). Early work from Babcock and colleagues demonstrated that after 6 months of endurance training exercise of vigorous intensity, older men experienced a ~50% reduction in the $\tau\dot{V}O_2$ value from ~62 s to ~32 s so that the $\dot{V}O_2$ response was similar to that often observed in young individuals (2). In this study, it was suggested that improvements in both the O_2 transport and utilization pathways might have been responsible for the faster adjustment of $\dot{V}O_2$. Subsequently, Bell and colleagues (9) showed that faster $\dot{V}O_2$ kinetics in older individuals after an exercise training intervention was not related to a faster bulk delivery of O_2, as represented by unchanged kinetics in the femoral artery blood velocity, but rather to improved O_2 utilization by the active muscles (9). More recent studies demonstrated faster adjustment of $\dot{V}O_2$ kinetics in older women (57) and men (58) after a 12-wk high-intensity endurance exercise training intervention. In both of these studies, it was shown that after only 3 wk of exercise training, older women and men displayed a significantly faster $\dot{V}O_2$ kinetics response (~35 s) compared with the pretraining evaluation (~50 s) that was similar to that observed in their younger counterparts before the start of the program (Fig. 3). In addition, measurements obtained at 6, 9, and 12 wk during the training program showed no further speeding of $\dot{V}O_2$ kinetics, suggesting that the mechanisms controlling the observed changes had to occur rapidly. Indeed, these studies proposed that improved matching of O_2 delivery to O_2 utilization, as reflected by a smaller [HHb]/$\dot{V}O_2$ ratio, was highly correlated ($r = 0.93$) to the faster dynamic adjustment of $\dot{V}O_2$ throughout the exercise training program (please refer to the "Technical considerations" section to gain further insights on the physiological significance of the [HHb]/$\dot{V}O_2$ ratio and its association with the $\tau\dot{V}O_2$ response). Based on these results, the authors speculated that increases in ACh-mediated and flow-induced vasodilation might have mediated the faster $\dot{V}O_2$ kinetics observed in response to exercise training. Indeed, improvements in ACh-mediated vasodilatory response have been reported to occur and peak between 24 and 48 h following an acute bout of exercise (42,56) and to remain elevated for 96 h after exercise (42) in young rats. Importantly, chronic exposure to exercise (6 wk) resulted in increases in vasodilatory responses that were twice as large and longer-lasting (~1 wk) compared with those observed with acute exercise (42). Similarly, ~10 wk of exercise training have been shown to restore endothelium- (81) and flow-dependent (82) vasorelaxation in the arterioles of the soleus muscle from old rats and also to redistribute blood flow to more oxidative muscles in trained compared with untrained old rats, thus improving the matching of O_2 delivery to O_2 consumption within the skeletal muscle (7). These rapid increases in vasodilatory responses to exercise have been also demonstrated in humans (77). In support of the idea that

endothelium-mediated mechanisms rather than adaptations requiring a longer time frame (such as increases in mitochondrial content or structural changes within the vasculature) were responsible for the improved matching of O_2 delivery to O_2 utilization observed in the aforementioned training studies (57,58), recent data from Zoladz and colleagues (89) have shown that a faster adjustment in the $\dot{V}O_2$ kinetics response precedes changes in mitochondrial biogenesis and increases in capillarization.

Whereas we have suggested that metabolic control regulates $\dot{V}O_2$ kinetics in the range of 20 s and that slower $\dot{V}O_2$ kinetics may have a limitation in matching of O_2 delivery to the sites of active muscle utilization, Zoladz and colleagues (88) have proposed that muscle $\dot{V}O_2$ on-kinetics is mainly controlled/limited by intramuscular factors of metabolic activation. Based on a computer model of oxidative phosphorylation and metabolic control analysis, the increased ATP usage with exercise is accompanied by simultaneous activation of oxidative phosphorylation complexes (including Complexes I, III, IV, ATP/ADP). With exercise training, an acceleration of the $\dot{V}O_2$ kinetics from 28 to 23 s was explained in their model by an increase in the so-called each-step activation or parallel activation of the oxidative phosphorylation complexes. It remains to be seen whether this control theory applies when $\dot{V}O_2$ kinetics are slower (e.g., 30–40 s) as in older adults, or whether perturbations resulting in the acceleration of these slow $\dot{V}O_2$ kinetics would be explained by the "each-step activation" model.

CAN THE SLOWER $\dot{V}O_2$ KINETICS TYPICALLY OBSERVED IN OLDER INDIVIDUAL BE PREVENTED?

Although acute exercise and short-term exercise training interventions have been shown to result in faster $\dot{V}O_2$ kinetics responses in older individuals, it was still unclear whether or not chronically or long-term trained older adults could display further benefits that would result in even smaller $\tau\dot{V}O_2$ during moderate-intensity exercise. In other words, it was unknown if the slower adjustment of $\dot{V}O_2$ normally associated with aging could be abolished by chronic endurance exercise training. The results from different studies are equivocal. For example, Berger and colleagues (10) demonstrated that endurance-trained master athletes had a $\tau\dot{V}O_2$ of ~29 s and ~31 s for the 66- to 75-yr-old and the 76- to 85-yr-old groups, respectively. Although this $\tau\dot{V}O_2$ was significantly smaller than that observed in sprint-trained master athletes (~40 s and ~51 s for each age group, respectively), likely as a result of improved muscle blood flow and/or oxidative capacity related to the enhanced cardiovascular function in endurance versus sprint-trained participants, the $\dot{V}O_2$ kinetics response does not seem different from values previously reported after an acute bout of exercise (23) or a short-term endurance exercise training intervention (58). Similarly, Dogra and colleagues (27) demonstrated a faster $\dot{V}O_2$ kinetics response in endurance-trained older women (~35 s) compared with their untrained counterparts (~57 s), which was attributed to improvements in the matching of O_2 delivery to O_2 utilization within the active tissues, as shown by a reduced [HHb]/$\dot{V}O_2$ ratio in the trained women. However, once again, this faster $\dot{V}O_2$ kinetics response in chronically trained older women does not appear to be different from that observed in older women after 3 wk of endurance-training exercise (57). Thus, although the idea that short-term endurance-exercise training interventions result in rapid speeding of $\dot{V}O_2$ kinetics likely associated to changes in endothelium-dependent mechanisms, the suggestion that longer-term exercise programs resulting in structural improvements within the vascular network might further speed $\dot{V}O_2$ kinetics remained uncertain (58).

To further investigate this issue, a recent study by Grey and colleagues (39) evaluated chronically trained and normally active young, middle-age, and older men. This study demonstrated that there was a training effect, with the overall $\tau\dot{V}O_2$ being significantly smaller in trained compared with untrained individuals and, most importantly, that older trained individuals had a $\dot{V}O_2$ kinetics response that was as fast (~20 s) as that observed in the middle-age (~18 s) and young (~17 s) trained men, and the middle-age (~24 s) and young (~26 s) untrained, and significantly faster than that observed in the older untrained participants (~42 s). This faster response of the oxidative system occurred in the presence of an age-associated decline in $\dot{V}O_{2max}$ that was inevitable despite training. Regardless, in this study, the older untrained group was the only group showing a significant overshoot in the [HHb]/$\dot{V}O_2$ ratio, indicating that poorer matching of O_2 delivery to O_2 utilization within the active tissues was associated with the slower adjustment of oxidative phosphorylation. Although the differential responses observed in this study of chronically trained older individuals compared with previous ones (10,27) cannot be discerned at this point, it is important to note that the study of Grey and colleagues (39) is the first to demonstrate that chronic endurance-training exercise can prevent the slower $\dot{V}O_2$ kinetics response typically observed in older individuals. Thus, independently of whether improvement in metabolic components or vascular responsiveness were the main determinants of the faster $\dot{V}O_2$ kinetics response, what is critical is that factors other than aging *per se* are likely responsible for the slower adjustment of $\dot{V}O_2$ typically observed in older healthy populations. The authors speculated that the vascular remodeling occurring as a consequence of long-term endurance training improved the O_2 transport system so that an optimal delivery of O_2 was provided to meet the metabolic needs in the active muscles during these moderate-intensity exercise transitions. This concept is supported by structural vascular improvements in response to endurance training interventions of 3- to 12-month duration (16,17,59), and similar capillary density between chronically trained master athletes and training-matched young athletes (16). Similarly, it has been shown that the reduced endothelium-dependent vasodilation observed in older untrained men was preserved in older

trained individuals who regularly performed endurance exercise so that the age-associated decline in the vasodilatory response was abolished (26). These considerable improvements in measures of vascularization and endothelium-dependent vasodilation would improve the surface area for O_2 exchange, which might contribute to absence of an "overshoot" in the normalized [HHb]/$\dot{V}O_2$ ratio in the trained older compared with the untrained older men. Nevertheless, despite the suggestion that improved O_2 provision to the active tissues plays a critical role in controlling the faster $\dot{V}O_2$ kinetics observed in trained older individuals, mechanisms of intracellular control discussed in this review (34,35,40,41,68,88,89) are also to be acknowledged as "limiting" factors determining the rate of adjustment of oxidative phosphorylation.

TECHNICAL CONSIDERATIONS

A common objection to the role of O_2 delivery as a limiting factor in the rate of adjustment of oxidative phosphorylation is related to the lack of objective measures of blood flow within the microvasculature in humans. This is a limitation that is currently unsolvable; the [HHb] signal does not measure microvascular blood flow or O_2 delivery, and the microvascular hematocrit is not known. Thus, the [HHb]/$\dot{V}O_2$ is an index and some of the interpretations related to the use of the [HHb]/$\dot{V}O_2$ ratio as an indicator of the matching of O_2 delivery to O_2 distribution should be made with caution. For example, it could be argued that in order to characterize microvascular blood flow, $\dot{V}O_2$ should by divided by [HHb] (in place of arterial-venous O_2 difference) to effectively rearrange the Fick equation (30). However, some important limitations have been described for that approach (64). The [HHb]/$\dot{V}O_2$ ratio considers the inverse of this relationship. Although it is clear that this index cannot be produced by rearranging the parameters in the Fick equation, it reflects the concept that a faster adjustment of normalized [HHb] (normalized relative to the full scale of the steady state response) compared with the normalized $\dot{V}O_2$ response (i.e., greater deoxygenation for a given $\dot{V}O_2$) represents a mismatch in the balance of O_2 delivery relative to O_2 utilization and implies a transient limitation in O_2 provision to the active tissues. It could be argued that the greater relative deoxygenation during the transient represents the ability of the mitochondria to use the O_2 due alterations in the control of mitochondrial respiration. However, supportive data that this would occur during the transient in older adults with slower $\dot{V}O_2$ kinetics are not available. Validation of the interpretation of the [HHb]/$\dot{V}O_2$ ratio requires the development of precise measures of microvascular blood flow and O_2 delivery in humans. In the meantime, advantages and limitations of this approach are detailed elsewhere (62,64).

Another aspect to consider is that if a limitation in O_2 provision to the active fibers is responsible for the larger $\tau\dot{V}O_2$ typically seen in older, then an overshoot in the [HHb] signal should be expected, similar to the undershoot in microvascular PO_2 (reflecting O_2 extraction and likely similar to the [HHb] signal) in animal models (6,53). However, the "overshoot" in the [HHb] relative to the $\dot{V}O_2$ during the transient compared with the steady state is not a true overshoot of the [HHb] signal itself. This lack of a "true" overshoot in the [HHb] signal in the older participants should not be surprising. Unlike some animal models where fiber type is more compartmentalized by muscle groups, in the human muscle mosaic, it is likely that some of the fibers in the area of NIRS interrogation display an overshoot in the [HHb] (active fibers that did not receive sufficient blood flow to adjust to the greater metabolic demand, thus relying more on O_2 extraction), which is not detected in the overall [HHb] profile, because some inactive fibers may be supplied by blood flow, and even some active fibers may have adequate blood flow and limited need for increased extraction to meet their $\dot{V}O_2$ demand. Thus, after an initial delay in the [HHb] signal is overcome (likely reflecting a matched or even excess blood flow for a given O_2 demand due to a rapid increase in blood flow of unknown origin (84)), then a rapid decrease in intracellular PO_2 is compensated by a rapid increase in O_2 extraction (as seen in the [HHb] signal), so that the O_2 demand is met, regardless of the magnitude of the decrease in the intracellular PO_2 (85). Although the actual magnitude of the increase in O_2 extraction is uncertain from the [HHb] signal, as long as the intracellular PO_2 does not drop below critical levels (which does not occur in the moderate-intensity domain), an overshoot in [HHb] should not be expected. Thus, although not reaching "critical PO_2" levels to "impair" oxidative metabolism, it seems reasonable to suggest that the increase in O_2 extraction during the exercise transient, lowering microvascular PO_2, would affect (slow) the peripheral O_2 diffusion and intracellular oxidative metabolism.

One more factor to consider is that because of the shallow depth of penetration of the NIRS signal in the quadriceps muscle, data acquisition may be primarily arising from Type II muscle fibers, whereas exercise performed within the moderate-intensity would result in Type I muscle fibers being recruited. Nevertheless, it should be noted that the dynamic profile of the NIRS-derived [HHb] during square wave transitions to higher metabolic demands has been shown to resemble that of the arterial-venous O_2 difference, and to be a mirror image of the intracellular and microvascular pressures of O_2 (33). Thus, the temporal characteristics of this signal (as used in those studies examining the [HHb]/$\dot{V}O_2$ ratio) should still be an accurate representation of O_2 extraction within the area or NIRS interrogation.

Finally, it can be contended that changes in the [HHb]/$\dot{V}O_2$ ratio described in some studies might be explained by alterations in the adjustment of the $\dot{V}O_2$ response without changes being observed in the adjustment of [HHb] between different conditions or interventions. Although this possibility should be considered when interpreting the data, it should also be acknowledged that differences in the dynamic adjustment of $\dot{V}O_2$ in relation to the kinetics of [HHb] might reflect differences in the regulation of O_2 delivery. However, once again, this interpretation awaits confirmation

(or rebuttal) from newer techniques that permit direct measurement of microvascular blood flow in humans.

OVERALL CONCLUSION

An important reason for studying $\dot{V}O_2$ kinetics in older individuals has been the usually considerably slower $\dot{V}O_2$ kinetics observed in this population compared with their younger counterparts. This model has offered an approach to examine the underlying causes/mechanisms of the control of $\dot{V}O_2$ kinetics and the limitations constraining this response. Whereas in young individuals with often fast $\dot{V}O_2$ kinetics the majority of the perturbations that may speed or slow $\dot{V}O_2$ kinetics do not result in substantially large changes, the older adult provided a group more sensitive to changes in the dynamic adjustment of $\dot{V}O_2$ that allowed further understanding of the physiological mechanisms controlling the response of oxidative phosphorylation during the on-transient of exercise. This review showed that although the rate of adjustment of oxidative phosphorylation is typically slower in older compared with young individuals, there are exceptional situations such as chronic endurance-exercise training that can completely abolish this sluggish $\dot{V}O_2$ kinetics in the elderly, despite the age-related decline in $\dot{V}O_{2max}$ still being present. In addition, this review established that acute-exercise and short-term exercise-training interventions can significantly accelerate the adjustment of $\dot{V}O_2$ in older populations so that older individuals have a $\tau\dot{V}O_2$ that is similar to that observed in their younger counterparts preintervention. Although several mechanisms might be involved in this slower adjustment typically observed in the older participants, poorer matching of O_2 delivery to O_2 utilization in the active muscles and improvements in the O_2 delivery pathway seem to be important factors controlling the slower $\dot{V}O_2$ kinetics and its subsequent speeding in response to different exercise interventions.

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