Influence of acute plasma volume expansion on $\dot{V}O_2$ kinetics, $\dot{V}O_2$ peak, and performance during high-intensity cycle exercise

Nicolas J. A. Berger, Iain T. Campbell, Daryl P. Wilkerson, and Andrew M. Jones

1Department of Exercise and Sport Science, Manchester Metropolitan University, Alsager; and 2Department of Anaesthesia, Withenshawe Hospital, Manchester, United Kingdom

Submitted 7 February 2006; accepted in final form 9 May 2006

Berger, Nicolas J. A., Iain T. Campbell, Daryl P. Wilkerson, and Andrew M. Jones. Influence of acute plasma volume expansion (APVE) on oxygen uptake ($\dot{V}O_2$) kinetics, $\dot{V}O_2$ peak, and time to exhaustion during severe-intensity exercise. Eight recreationally active men performed “step” cycle ergometer exercise tests at a work rate requiring 70% of the difference between the gas-exchange threshold and $\dot{V}O_2$ max on three occasions: twice as a “control” (Con) and once after intravenous infusion of a plasma volume expander (Gelofusine; 7 ml/kg body mass). Pulmonary gas exchange was measured breath by breath. APVE resulted in a significant reduction in hemoglobin concentration (preinfusion: 16.0 ± 1.0 g/dl; $P < 0.001$) and hematocrit (preinfusion: 44 ± 2 vs. postinfusion: 41 ± 3%; $P < 0.01$). Despite this reduction in arterial O2 content, APVE had no effect on $\dot{V}O_2$ kinetics (phase II time constant, Con: 33 ± 15 vs. APVE: 34 ± 12 s; $P = 0.74$), and actually resulted in an increased $\dot{V}O_2$ peak (Con: 3.90 ± 0.55 l/min; $P = 0.006$) and time to exhaustion (Con: 365 ± 58 vs. APVE: 424 ± 64 s; $P = 0.04$). The maximum O2 pulse was also enhanced by the treatment (Con: 21.3 ± 3.4 vs. APVE: 22.7 ± 3.4 ml/beat; $P = 0.04$). In conclusion, APVE does not alter $\dot{V}O_2$ kinetics but enhances $\dot{V}O_2$ peak and exercise tolerance during high-intensity cycle exercise in young recreationally active subjects.

Blood volume; endurance; $O_2$ kinetics; performance

There is powerful evidence that the delivery of $O_2$ to the working muscles is the principal determinant of the maximal $O_2$ uptake ($\dot{V}O_2$ max) attained during large muscle group exercise (22). For example, acute alterations of red cell mass caused by the withdrawal (9, 18, 54) and reinfusion (18, 55) of whole blood have consistently resulted in changes in $\dot{V}O_2$ max that are proportional to changes in the hemoglobin concentration ([Hb]). An alternative method for altering [Hb], and thus the arterial $O_2$ content, is through acute plasma volume expansion (APVE). However, the influence of the hypervolemia caused by APVE on $\dot{V}O_2$ max is controversial, with reports of no changes (38, 39, 46, 57), and even increases (15, 16, 42) in $\dot{V}O_2$ max appearing in the literature. The possibility of an unchanged or increased $\dot{V}O_2$ max with APVE (which reduces [Hb]) might seem intuitively paradoxical. However, it has been demonstrated that APVE increases stroke volume (SV) and thus cardiac output (Q) by the Frank-Starling mechanism (30, 31, 38, 42, 46, 57). This effect is apparently capable of offsetting the reduced [Hb] with APVE such that muscle $O_2$ delivery is preserved, or even enhanced, during maximal-intensity exercise (21, 30, 31). The extent to which APVE can increase $Q$ and $\dot{V}O_2$ max appears to depend on the training status of the subjects (endurance-trained subjects already have an enlarged plasma volume; Ref. 12) and the volume of fluid infused (15, 16, 42, 57).

The influence of APVE on exercise tolerance is similarly ambiguous. APVE has been reported to reduce (15, 38, 39), improve (16, 43), or have no effect on (46, 57) time to exhaustion during endurance exercise. Whether APVE results in an enhanced endurance exercise capacity might be related to the interaction of the possible positive effects of APVE on $\dot{V}O_2$ max and the possible negative effects of APVE on muscle lactate production and blood buffering capacity (15, 16, 43). One factor that has not been considered as a possible explanation for the changes in endurance performance invoked by APVE is the magnitude of the “$O_2$ deficit” incurred across the transition from rest to exercise. A lower muscle $O_2$ delivery caused by a reduced [Hb] with APVE could increase the $O_2$ deficit and impair exercise performance by increasing the “anaerobic” contribution to energy transfer, with consequently greater perturbation to intracellular homeostasis (e.g., decreased muscle phosphocreatine concentration and pH; increased inorganic phosphate and lactate accumulation). On the other hand, an increased Q with APVE could result in an unchanged (or reduced) $O_2$ deficit and an enhanced $\dot{V}O_2$ max, potentially enhancing exercise performance.

In this respect, it is noteworthy that the rate at which pulmonary [and, by inference (23), muscle] $\dot{V}O_2$ rises after the onset of constant-work-rate exercise (i.e., the $\dot{V}O_2$ “kinetics,” an important determinant of the $O_2$ deficit) has been reported to be significantly faster after only 4–7 days of endurance exercise training in previously sedentary subjects (20, 47, 64). This adaptation has been reported to occur more rapidly than the increase in muscle oxidative capacity, and it has been speculated that this could be related to an enhanced cardiovascular response to exercise (47). One of the earliest adaptations to endurance training is a rapid expansion of the plasma volume; a 12–20% increase in plasma volume has been reported after just 4–8 days of intense training (12–14, 24, 25). Therefore the early speeding of $\dot{V}O_2$ kinetics noted with endurance training might be related, at least in part, to adaptations in Q and muscle $O_2$ availability resulting from the training-induced hypervolemia. Surprisingly, the influence of APVE on $\dot{V}O_2$ kinetics and the $O_2$ deficit has not been specifically investigated.

The principal purpose of this study was to investigate the influence of APVE on pulmonary $\dot{V}O_2$ kinetics during severe-
intensity upright cycle ergometer exercise. A secondary purpose was to examine the effect of APVE on \( \dot{V}_O_2 \) peak and exercise tolerance. To mimic the early effects of endurance training on plasma volume, we recruited active but not specifically trained subjects and used a moderate level of plasma volume expansion (7 ml/kg). We hypothesized that APVE would result in 1) a speeding of the \( \dot{V}_O_2 \) kinetics; 2) an increased \( \dot{V}_O_2 \) peak; and, therefore, 3) an enhanced exercise performance.

**METHODS**

**Subjects.** Eight healthy men (age 27 ± 4 yr; height 1.84 ± 0.05 m; body mass 83.7 ± 5.0 kg; means ± SD) volunteered and gave written, informed consent to participate in this study, which had received approval from the local Research Ethics Committee. The subjects were occasionally active in recreational sports activities but were not highly trained. They were fully familiar with the exercise testing procedures employed in the study. The subjects were instructed to arrive at the laboratory at the same time of day (±1 h), having performed no heavy exercise during the previous 24 h, and having consumed no food, caffeine, or alcohol during the previous 3 h.

**Procedures.** The subjects attended the laboratory on four occasions over a 4-wk period to perform exercise tests on the cycle ergometer. The first visit was used to establish \( \dot{V}_O_2 \) max and to estimate the gas-exchange threshold (GET). On each of the three subsequent visits, subjects completed a single bout of severe-intensity exercise to the limit of tolerance: “control” bouts were completed on two occasions, whereas the exercise trial was preceded by APVE on the remaining occasion. The APVE and control bouts were presented to the subjects in random order and were each separated by 7–10 days. It has been reported that control plasma volume is reestablished within 7 days of APVE (14). The APVE trial was completed only once because of ethical concerns over the physiological effects of repeated cannulation and plasma volume expansion.

All testing was performed on an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands) in a well-ventilated laboratory at a temperature of 20–22°C. During the first visit to the laboratory, the ergometer was adjusted so that each subject was comfortable, and the settings were recorded and replicated during all subsequent exercise tests. After measurement of height and body mass, subjects performed a “ramp” incremental exercise test to determine \( \dot{V}_O_2 \) max and GET. This test consisted of 3 min of pedaling against no external resistance, followed by a continuous ramped increase in work rate of 30 W/min until the limit of tolerance. The pedal rate selected by each of the subjects in this test (typically 80–85 rpm) was employed during all subsequent tests. All gas-exchange and ventilatory variables were averaged and displayed over 10-s intervals. The \( \dot{V}_O_2 \) max was determined as the highest \( \dot{V}_O_2 \) measured over 30 s, and the GET was determined using the V-slope method (6). The work rate corresponding to 70% “\( \Delta \)” (i.e., 70% of the difference between GET and \( \dot{V}_O_2 \) peak, i.e., “severe” exercise; Ref. 49) was calculated by linear regression of \( \dot{V}_O_2 \) vs. work rate with account taken of the lag in \( \dot{V}_O_2 \) relative to work rate that exists during ramp incremental exercise (58).

On each of the three subsequent laboratory visits and prior to the commencement of the “step” exercise tests, the subjects rested for 10 min before blood samples from a prewarmed fingertip were collected into heparinized microhematocrit tubes (Hawksley and Sons, Sussex, UK) and microcuvettes (HemoCue AB, Angelholm, Sweden) for the determination of hematocrit (Hct; Hawksley 1560 Microhematocrit reader) and hemoglobin (B-Hemoglobin photometer, HemoCue AB), respectively. Blood pressure was measured using a manual sphygmomanometer, and mean arterial pressure (MAP) was subsequently determined as the diastolic pressure plus one-third of the pulse pressure. In both the control and experimental conditions, subjects then lay in the prone position for 35 min. In the experimental condition, a hand vein was cannulated and an infusion pump was programmed to administer 7 ml/kg body mass of a clinical plasma volume expander (Gelofusine; Braun, Sheffield, UK) over a 30-min period. The subjects then moved to the cycle ergometer and sat at rest for 10 min, after which blood samples were again collected and blood pressure was measured. The subjects then performed a single severe-intensity exercise bout to the limit of tolerance. In each case, the test commenced with 3 min of pedaling against no external resistance after which the work rate was abruptly increased to the target work rate. Subjects were given strong verbal encouragement throughout the exercise test, and the time to exhaustion was recorded to the nearest second. Within 30 s of the completion of the exercise test, a final set of blood samples for determination of Hct and [Hb] were collected, and blood pressure was again measured. Immediately before the onset of loaded exercise, every 2 min throughout exercise, and immediately upon the cessation of exercise, fingertip blood samples were collected into capillary tubes for the determination of blood lactate concentration by using a semiautomated analyzer (YSI 1500, Yellow Springs Instruments, Yellow Springs, OH).

Pulmonary gas exchange and ventilation were measured breath by breath with subjects wearing a nose clip and breathing through a low-dead space (90 ml), low-resistance (0.75 mmHg·l⁻¹·s⁻¹ at 15 l/s) mouthpiece and impeller turbine assembly (Jaeger Triple V). The inspired and expired gas volumes and gas concentration signals were continuously sampled at 100 Hz, the latter using paramagnetic (\( O_2 \)) and infrared (\( CO_2 \)) analyzers (Jaeger Oxycon Pro, Hoechberg, Germany) via a capillary line connected to the mouthpiece. The gas analyzers were calibrated before each test with gases of known concentration, and the turbine volume transducer was calibrated by using a 3-liter syringe (Hans Rudolph, Kansas City, MO). The volume and concentration signals were time aligned by accounting for the delay in the capillary gas transit and the analyzer rise time relative to the volume signal. \( \dot{V}_O_2, \dot{V}_CO_2 \) production, and minute ventilation were calculated by using the algorithms of Beaver et al. (5) and displayed breath by breath. Heart rate (HR) was measured every 5 s using short-range radio telemetry (Polar S610, Polar Electro Oy, Kempele, Finland). \( O_2 \) pulse was calculated as Q/HR.

The breath-by-breath data from the step exercise tests were used to estimate the \( \dot{V}_O_2 \) kinetics. The data were first manually filtered to remove outlying breaths, defined as breaths deviating by more than three standard deviations from the preceding five breaths. The data were subsequently interpolated to provide second-by-second values, and, for each individual, the data sets from the control condition were time aligned and averaged.

The first 20 s of data after the onset of exercise (i.e., the phase I response) were deleted and a nonlinear least-square algorithm was used to fit the data as described in the following biexponential equation:

\[
\dot{V}_O_2(t) = \dot{V}_O_2\text{baseline} + A_p(1 - e^{-(t-TD_p)/TD_p}) + A_l(1 - e^{-(t-TD_p)/TD_l})
\]

where \( \dot{V}_O_2(t) \) represents the absolute \( \dot{V}_O_2 \) at a given time \( t \); \( \dot{V}_O_2\text{baseline} \) represents the mean \( \dot{V}_O_2 \) in the final 2 min of the baseline period; \( A_p \), \( TD_p \), and \( \tau_p \) represent the amplitude, time delay, and time constant, respectively, describing the fundamental or primary increase in \( \dot{V}_O_2 \) above baseline; and \( A_l \), \( TD_l \), and \( \tau_l \) represent the amplitude, time delay, and time constant describing the development of the \( \dot{V}_O_2 \) slow component, respectively. An iterative process was used to minimize the sum of the squared errors between the fitted function and the observed values. The asymptotic value (\( A_\infty \)) of the exponential term describing the \( \dot{V}_O_2 \) slow component may represent a higher value than that actually reached at the end of the exercise and therefore the actual amplitude of the \( \dot{V}_O_2 \) slow component at the end of exercise was used and defined as \( A_\infty ' \).

The most appropriate approach for the computation of the \( O_2 \) deficit during high-intensity exercise that invokes a \( \dot{V}_O_2 \) slow component response is unclear (59) and so, in the present study, the \( O_2 \) deficit was estimated by using the following equation:

\[
\Delta [\dot{O}_2] = \frac{\dot{V}_O_2(t) - \dot{V}_O_2\text{baseline}}{\dot{V}_O_2\text{steady}}
\]
deficit over just the “primary” phase of the response was calculated by using the formula $(TD_p + \tau_p)/60 \cdot A_p$.

Statistical analysis. The results are presented as means ± SD. Analysis of variance was used to determine the significance of any differences between the hematological variables at rest and during exercise in the control and APVE conditions. When an overall difference was found, post hoc Bonferroni-adjusted paired $t$-tests were used to examine significant differences among means. Paired $t$-tests were used to examine differences between the APVE and control conditions with respect to $V_o_2$ kinetics, $V_o_2$ peak, and time to exhaustion. Statistical significance was accepted when $P$ was less than 0.05.

RESULTS

The $V_o_2$ max of the subjects measured during the ramp incremental test was $4.06 ± 0.42$ l/min (48.7 ± 6.6 ml·kg$^{-1}$·min$^{-1}$), and the highest work rate attained was 379 ± 37 W. The GET occurred at a mean $V_o_2$ of $2.05 ± 0.41$ l/min or $50 ± 6\% \ V_o_2$ max. The work rate equivalent to 70% $\Delta$ was 303 ± 33 W.

The influence of APVE on [Hb] and Hct is illustrated in Fig. 1. APVE resulted in an 8% reduction in [Hb] [preinfusion (pre): 16.0 ± 1.0 vs. postinfusion (post): 14.7 ± 0.8 g/dl; $P < 0.001$] and Hct [pre: 44 ± 2 vs. post: 41 ± 3%; $P < 0.01$], but there was no significant difference in the control condition for either [Hb] [pre: 15.8 ± 0.9 vs. post: 15.5 ± 0.8 g/dl; $P = 0.20$] or Hct [pre: 43 ± 1 vs. post: 43 ± 2%; $P = 0.51$]. Exercise was associated with a hemoconcentration in both conditions, but [Hb] remained significantly lower at the end of exercise after APVE [control (Con): 17.3 ± 0.9 g/dl vs. APVE: 16.0 ± 1.5 g/dl; $P < 0.05$; Fig. 1]. The mean change in plasma volume, calculated by the methods of Dill and Costill (17), was 14%. MAP was not significantly different between the conditions on first measurement [Con: 95 ± 7 vs. APVE: 97 ± 10 mmHg; $P = 0.66$], after the rest or infusion period [Con: 96 ± 12 vs. APVE: 99 ± 4 mmHg; $P = 0.56$], or immediately after exercise [Con: 115 ± 15 vs. APVE: 117 ± 12 mmHg; $P = 0.60$].

The model parameters describing the $V_o_2$ kinetic response to exercise are shown in Table 1, and the $V_o_2$ responses of a representative subject in the control and APVE conditions are shown in Fig. 2. APVE had no significant effect on baseline $V_o_2$ or on the parameters describing the primary phase of the $V_o_2$ response ($TD_p$, $\tau_p$, or $A_p$). Of particular importance with reference to the purpose of the present study was that the group mean $\tau$ was almost identical between the two conditions [Con: 33 ± 15 vs. APVE: 34 ± 12 s; $P = 0.74$]. The 95% confidence interval surrounding the estimate of $\tau_p$ was $4 ± 2$ s for Con and $5 ± 3$ s for APVE. The magnitude of the $O_2$ deficit incurred over the primary phase of the response did not differ between the Con and APVE conditions (Table 1). The model parameters describing the $V_o_2$ slow component response were also not significantly different between the two conditions [Con: 0.63 ± 0.16 vs. APVE: 0.86 ± 0.39 l/min; $P = 0.12$].

Compared with the control condition, APVE resulted in a small but statistically significant 6% increase in the highest (end-exercise) $V_o_2$ attained [Con: 3.90 ± 0.55 l/min; $P = 0.006$; Fig. 3]. However, the end-exercise $V_o_2$ values attained in the control and APVE step tests did not differ significantly from the $V_o_2$ max value attained during the initial ramp incremental exercise test (4.06 ± 0.42 l/min). The time to exhaustion was not significantly different between the first and second control tests (360 ± 68 and 369 ± 70 l/min).

Table 1. Parameters of the $V_o_2$ kinetic response to severe-intensity cycle exercise with and without acute plasma volume expansion $V_o_2$

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>APVE</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline $V_o_2$, l/min</td>
<td>0.75±0.06</td>
<td>0.80±0.11</td>
<td>0.74</td>
</tr>
<tr>
<td>Primary time delay, s</td>
<td>11±6</td>
<td>9±7</td>
<td>0.55</td>
</tr>
<tr>
<td>Primary time constant, s</td>
<td>34±12</td>
<td>33±15</td>
<td>0.74</td>
</tr>
<tr>
<td>Primary amplitude, l/min</td>
<td>2.54±0.40</td>
<td>2.33±0.35</td>
<td>0.11</td>
</tr>
<tr>
<td>“Primary” $O_2$ deficit, liters</td>
<td>1.98±0.56</td>
<td>1.63±0.46</td>
<td>0.22</td>
</tr>
<tr>
<td>SC time delay, s</td>
<td>131±34</td>
<td>109±61</td>
<td>0.41</td>
</tr>
<tr>
<td>SC amplitude, l/min</td>
<td>0.63±0.16</td>
<td>0.86±0.39</td>
<td>0.12</td>
</tr>
<tr>
<td>End-exercise $V_o_2$, l/min</td>
<td>3.90±0.56</td>
<td>4.12±0.55</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are means ± SD. APVE, acute plasma volume expansion; $V_o_2$, $O_2$ uptake; SC, slow component.
The principal findings of this study were that APVE (at 7 ml/kg body mass; 500–650 ml) had no effect on \( \dot{V}_\text{O}_2 \) kinetics (and thus the O2 deficit) but resulted in significant enhancements of \( \dot{V}_\text{O}_2 \) peak, and exercise tolerance during severe-intensity constant-work-rate cycle ergometer exercise in healthy, recreationally active subjects. These effects occurred despite a significant reduction in [Hb] and Hct after APVE and indicate that the reduction in arterial O2 content achieved with APVE did not adversely influence \( \dot{V}_\text{O}_2 \) kinetics, \( \dot{V}_\text{O}_2 \) peak, or the performance of high-intensity exercise.
Influence of APVE on [Hb] and Hct. APVE resulted in an 8% reduction of [Hb] and Hct (equivalent to a 14% expansion of the plasma volume; Ref. 17), both before and after exercise (Fig. 1). The magnitude of the effects observed are entirely consistent with the results of previous studies in which similar volumes of fluid were infused (15, 16, 30, 57). Also, these effects are similar to those observed after a few days of intense endurance training in previously untrained subjects where plasma volume is typically elevated by 12–20% (12–14, 24, 25, 27). Our experimental design was therefore successful in artificially reproducing the physiological expansion of the plasma volume that occurs shortly after the commencement of an endurance training program.

Influence of APVE on VO₂ kinetics. To our knowledge, this is the first study to directly investigate the influence of APVE on VO₂ kinetics and the O₂ deficit after the onset of high-intensity constant-work-rate exercise. The rate at which VO₂ rises after the onset of exercise is finite and might be limited in different situations either locally by an inertia of the oxidative metabolic enzymes in the contracting myocytes, or systemically by the delivery of O₂ to its sites of utilization (32, 37). If O₂ delivery represents an important limitation to VO₂ kinetics, then the reduced [Hb] brought about by APVE might be hypothesized to result in a slower VO₂ response after the onset of exercise. The fact that VO₂ kinetics was not influenced by APVE in the present study therefore suggests either that 1) muscle O₂ delivery does not limit VO₂ kinetics during severe-intensity upright cycle exercise in healthy young subjects or 2) adjustments in muscle blood flow, or in muscle O₂ extraction, across the exercise transient were sufficient to negate the effect of the reduced arterial O₂ content.

With regard to the first possibility, several studies have examined the effect of interventions designed to either reduce muscle O₂ delivery [using, for example, hypoxia (19, 45), altered body position or perfusion pressure (41, 44, 63), β-blockade (35), and blood letting (9)], or to enhance muscle O₂ delivery [using, for example, hypoxia (45, 61), prior exercise models (8, 56), and human recombinant erythropoietin (RhEPO) treatment (11, 62)], with equivocal results. The consensus view is that VO₂ kinetics are principally regulated by intracellular mechanisms but that muscle O₂ availability might represent an additional limitation in some circumstances (depending on a combination of factors including the exercise intensity, the exercise modality, and the characteristics of the subjects studied; Ref. 37). It is therefore possible that a small reduction in muscle O₂ delivery caused by APVE did not impact on VO₂ kinetics because muscle O₂ delivery exceeded the capacity of the muscle to extract O₂ in the control condition, as suggested by the results of several previous investigations (2, 23, 63).

With regard to the second possibility, it was evident that neither HR nor O₂ pulse were altered across the exercise transient after APVE (Figs. 4 and 5). Another explanation for the unaltered VO₂ kinetics after APVE is therefore that SV (and hence Q and muscle blood flow) was increased across the exercise transient in the APVE condition so that muscle O₂ delivery was not appreciably different from the control condition (16, 30, 42) and/or that muscle O₂ extraction was enhanced. Accordingly, Calbet et al. (10) have recently reported a significantly increased leg blood flow and O₂ extraction with APVE so that muscle O₂ delivery and uptake were unchanged relative to the control condition during submaximal exercise. The available evidence therefore indicates that 5–8% reductions in [Hb] caused either by APVE (present study) or by blood letting (9) do not measurably impact on VO₂ kinetics, whereas reductions in muscle perfusion pressure (brought about by altering body position; Refs. 33, 41, 44; but see also Ref. 63) or in O₂ driving pressure from the muscle capillary to the mitochondrion (achieved in hypoxia; Refs. 19, 34) have the potential to slow VO₂ kinetics. Presumably these latter interventions result in more substantial reductions in muscle O₂ availability that cannot be easily negated by compensatory increases in muscle blood flow.

In the present study, APVE was induced “artificially,” i.e., through intravenous infusion of fluid. However, a similar effect occurs physiologically after the commencement of an endurance exercise training program. Indeed, increases in plasma volume of 400–600 ml or more have been measured after the completion of just a few training sessions and linked to improvements in markers of aerobic fitness (12–14, 25, 27). Interestingly, VO₂ kinetics also appear to adapt remarkably quickly to endurance training with a speeding of the primary VO₂ response being manifest within 4–7 days of the commencement of training (20, 47, 64). Phillips et al. (47) reported that this speeding of VO₂ kinetics occurred before any measurable increase in citrate synthase activity (a key mitochondrial enzyme) and suggested that alterations in cardiovascular regulation ultimately manifesting in an increased leg blood flow might have been responsible for the effects observed. Plasma volume expansion has been demonstrated to enhance SV and Q (30, 31, 38, 42, 46, 57), and therefore hypervolemia might be hypothesized to contribute, in part, to the early speeding of VO₂ kinetics observed soon after the commencement of endurance exercise training, assuming that any increase in Q translated into an increased leg blood flow and O₂ delivery (see Limitations). However, there was no evidence to support this hypothesis in the present study because VO₂ kinetics and the O₂ deficit were unchanged after APVE. Therefore, the speeding of the VO₂ kinetics observed during the first 4–7 days of endurance...
training must be explained by other factors such as a better local matching of blood flow to metabolic rate (36) and/or upregulation of the key rate-limiting enzymes for oxidative metabolism (7). The available evidence suggests that a significant increase in muscle capillarity is not evident until after some 10–21 days of training (1, 26, 32), indicating that changes in the muscle microcirculation are not responsible for the early speeding of the \( \dot{V}O_2 \) kinetics that has been reported. Interestingly, in contradiction to Phillips et al. (47), Burgomaster et al. (7) have recently reported a 38% increase in maximal citrate synthase activity after 3 days of high-intensity training. These data suggest that an increased muscle oxidative capacity might play an important role in the rapid enhancement of the \( \dot{V}O_2 \) response dynamics caused by endurance training.

After the onset of exercise above the GET, pulmonary \( \dot{V}O_2 \) rises toward the “initially anticipated” steady-state requirement for the work rate (3); however, after some 2–3 min, a secondary component of the \( \dot{V}O_2 \) response emerges (60). This \( \dot{V}O_2 \) “slow component” reduces metabolic efficiency by elevating \( \dot{V}O_2 \) above the expected value (for all work rates above the GET); for all work rates above the so-called “critical power,” \( \dot{V}O_2 \) is set on a trajectory toward its maximum (49). For this reason, and because its development is associated both with a metabolic acidosis and a continued decline in intramuscular phosphocreatine concentration (51), the \( \dot{V}O_2 \) slow component has been assumed to be inextricably linked to the fatigue process (48). In the present study, however, exercise tolerance was enhanced despite there being no significant alteration in the amplitude of the \( \dot{V}O_2 \) slow component. The relationship between the magnitude of the \( \dot{V}O_2 \) slow component and exercise tolerance is clearly not straightforward and will depend, in part, on the extent to which experimental interventions influence the amplitude of the primary phase of the response and/or the \( \dot{V}O_2 \) peak (Refs. 8, 9, 61, 62; present study).

**Influence of APVE on \( \dot{V}O_2 \) peak and exercise tolerance.** APVE resulted in a 6% increase in the highest \( \dot{V}O_2 \) attained during the exercise test despite the simultaneous 8% reduction in [Hb] caused by the procedure. Because \( \dot{V}O_2 \)max during large muscle group exercise such as cycle ergometry is believed to be principally dependent on muscle \( O_2 \) delivery (22), these results suggest that APVE enabled the attainment of a higher maximal \( Q \) (and thence muscle \( O_2 \) delivery) that more than compensated for the reduced arterial \( O_2 \) content. There was a significantly higher maximum \( O_2 \) pulse after APVE (Fig. 5). According to the Fick principle, \( Q/HR = SV \times C(a-v)O_2 \), where \( C(a-v)O_2 \) is the arterial-mixed venous \( O_2 \) content difference. Therefore, the increased maximum \( O_2 \) pulse observed after APVE might have resulted from an increased SV. At the same maximum HR (as was observed in the present study; Fig. 4), the increased SV would increase the maximum \( Q \). There is substantial evidence that SV is increased by APVE as a result of increased preload and diastolic filling that enhances ventricular emptying by the Frank-Starling mechanism (30, 31, 38, 40, 42, 46, 57). In this light, our results appear to be consistent with the study of Krip et al. (42) in which a 10% expansion of the plasma volume resulted in a 9% increase in SV and \( Q \) and a 7% increase in \( \dot{V}O_2 \)max.

The MAP measured shortly after the termination of exercise was not significantly different between the two conditions in the present study, suggesting that any increase in \( Q \) was counterbalanced by a reduction in total peripheral resistance. There might be little scope for further redistribution of \( Q \) toward the working muscles during high-intensity exercise of the type investigated in the present study (52), and it is unclear what proportion of the increased \( Q \) might have been directed to the exercising muscles relative to other vascular beds. The latter will depend, in part, on possible changes in norepinephrine spillover across the legs relative to these other vascular beds. Calbet et al. (10) reported that leg vascular conductance was increased by APVE, although the mechanism(s) responsible for this effect were unclear. When the work of breathing was reduced by use of a proportional-assist ventilator during maximal-intensity exercise, \( Q \) was reduced but leg blood flow and \( V_2 \) were increased as a consequence of a reduction in muscle sympathetic nerve activity (and therefore leg vascular resistance) at similar MAP (28, 29). In a similar fashion, it is possible that APVE might reduce the output of the pulmonary reflexes (through as yet undefined mechanisms), leading to less vasoconstriction in the exercising limb, and enabling exercise to be continued longer and a higher \( V_2 \) to be attained.

The increased maximum \( O_2 \) pulse after APVE could also be explained by an increased maximal \( C(a-v)O_2 \). However, this might be considered unlikely because muscle \( O_2 \) extraction would be near maximal during high-intensity exercise of this type (10, 28). Indeed, any increase in intracapillary spacing of erythrocytes after APVE might be predicted to reduce muscle \( O_2 \) diffusing capacity (38, 54). On the other hand, APVE would be expected to reduce blood viscosity and this might, in turn, enable a faster blood flow through the muscle capillaries such that \( O_2 \) extraction is preserved, as shown by Calbet et al. (10). It is, however, difficult to know what effect systemic changes in Hct might have on capillary Hct and hemodynamics. For example, Sarelius (53) reported that neither capillary red blood cell flux nor velocity were different in hamster cremaster muscles when the systemic Hct was reduced to either 49 or 32% of normal and concluded that tissue \( O_2 \) delivery from capillaries cannot be predicted from measured changes in systemic \( O_2 \) transport capacity.

The influence of APVE on \( \dot{V}O_2 \)max is equivocal, with previous studies reporting either no change (10, 38, 39, 46, 57) or enhancements (15, 16, 42) of \( \dot{V}O_2 \)max after APVE. The divergent results might be explained by an interaction of the magnitude of the plasma volume expansion and the training status of the subjects (15, 16, 42, 57). It is possible that a particularly large reduction in [Hb] caused by a substantial expansion of the plasma volume (i.e., >700 ml) might exceed the potential for compensatory alterations in SV and \( Q \) to maintain muscle \( O_2 \) delivery, such that \( \dot{V}O_2 \)max is reduced. Aerobic exercise training results in a physiological hypervolemia (12), and therefore endurance athletes might be especially sensitive to a reduction in \( \dot{V}O_2 \)max if plasma volume undergoes substantial “additional” expansion using artificial means (16, 30, 57). Clearly, the potential for APVE to enhance \( \dot{V}O_2 \)max depends on striking a delicate balance between the potentially negative effects of a reduced [Hb] and the potentially positive effects of an increased SV. It appears logical that lesser trained subjects, such as those used in the present study, would stand to benefit more from larger blood volume loading than would better trained subjects in whom the plasma volume is already elevated (12). Previous studies indicate that the infusion of fluid volumes of ~250–500 ml might positively impact on \( \dot{V}O_2 \)max and exercise performance in untrained subjects (15, 16, 42, 43), whereas...
volumes of greater than ~650 ml might have a detrimental effect (16, 38, 39). The present study demonstrates that positive effects on aerobic function are still possible when fluid volumes of ~500–650 ml are infused in recreationally active subjects.

APVE resulted in a 59-s (16%) increase in the time to exhaustion. This is consistent with some (16, 43), but not all (15, 38, 39, 46, 57), previous studies. During exhaustive exercise 6–7 min in duration, the $V_{\text{O2max}}$ is recognized to be (15, 38, 39, 46, 57), previous studies. During exhaustive exhaustion. This is consistent with some (16, 43), but not all subjects.

The measurement of SV, $Q_{\text{dot}}$, muscle blood flow, and $O_2$ uptake during the “fundamental” phase of the response, we presume that the increased exercise tolerance after APVE was secondary to the enhanced $V_{\text{O2peak}}$ (Fig. 2). During severe-intensity constant-work-rate exercise, there is evidence that the termination of exercise coincides with the attainment of a $V_2$ that is close to the $V_{\text{O2max}}$ attained during incremental exercise (49, 50, 56, 61). Muscle energy turnover continues to rise with time during high-intensity constant-work-rate exercise (51). Once the energy supplied through oxidative phosphorylation reaches its maximum rate, there is therefore likely to be a more rapid fall in the concentration of muscle high-energy phosphates and a greater accumulation of metabolites that have been linked to the fatigue process (i.e., hydrogen ions and inorganic phosphate). The increased $V_{\text{O2peak}}$ with APVE presumably delayed these effects and so enabled a prolongation of exercise performance.

We have recently examined the effect of blood withdrawal (which reduced [Hb] by 5%; Ref. 9) and RhEPO treatment (which increased [Hb] by 7%; Ref. 62) on the physiological responses to severe-intensity exercise in subjects of similar fitness to those of the present study. Blood withdrawal reduced $V_{\text{O2peak}}$ by 4% and time to exhaustion by 14% (9), whereas RhEPO treatment increased $V_{\text{O2peak}}$ by 7% and time to exhaustion by 22% (62). Although APVE reduced [Hb] to a greater extent than did blood withdrawal, the effects on $V_{\text{O2peak}}$ and time to exhaustion were similar to those reported after RhEPO treatment. This striking observation underlines the importance of both [Hb] and the total blood volume in the determination of $V_{\text{O2peak}}$ and endurance exercise performance (21, 38).

**Limitations.** The main purpose of the present study was to examine the influence of APVE on pulmonary $V_{\text{O2}}$ kinetics during large muscle group exercise (upright cycling). However, whereas our results might be interpreted in the light of previously published studies to indicate that muscle blood flow and/or $O_2$ extraction were enhanced after APVE (such that $V_2$ across the transient was preserved and $V_{\text{O2peak}}$ was enhanced), neither variable was directly measured in the present study. The measurement of SV, Q, muscle blood flow, and $O_2$ extraction is technically challenging during upright cycle exercise, and it is possible that the highly invasive nature of these measurements could adversely affect the fidelity of the pulmonary $V_2$ signal. The potential mechanism(s) for the effect of APVE on $V_{\text{O2peak}}$ therefore awaits further investigation. Another limitation to our study was that subjects were not blinded to the experimental intervention. However, we are confident that the performance test was reliable (<3% difference in time to exhaustion between the first and second control bouts) and that subjects gave a maximum effort on all occasions (end-exercise HR and blood lactate concentration were not significantly different between the APVE and control conditions).

In conclusion, despite causing a significant reduction in systemic [Hb], APVE (at 7 ml/kg body mass) did not alter $V_{\text{O2}}$ kinetics but did result in an increased $V_{\text{O2peak}}$ and an extended time to exhaustion during severe-intensity cycle exercise in recreationally active young men. The lack of effect of APVE on $V_{\text{O2}}$ kinetics suggests that muscle $O_2$ delivery does not limit oxidative metabolism in the transient phase of exercise of this type and/or that alterations in Q (mediated through an increased SV) or its distribution, or increased muscle $O_2$ extraction, are able to compensate for the reduced arterial $O_2$ content. The increased $V_{\text{O2peak}}$, maximum $O_2$ pulse, and exercise tolerance with APVE observed in the present study confirm the results of several previous studies and indicate that APVE enables an increased muscle blood flow and/or $O_2$ extraction that is sufficient to surmount the potentially negative effects of reduced [Hb] on muscle $O_2$ transport.

**ACKNOWLEDGMENTS**

Present address for N. J. A. Berger, D. P. Wilkerson, and A. M. Jones: School of Sport and Health Sciences, University of Exeter, St. Luke’s Campus, Heavitree Road, Exeter, EX1 2LU, UK.

**REFERENCES**


