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Systematic analysis of adaptations in aerobic capacity and submaximal energy metabolism provides a unique insight into determinants of human aerobic performance

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Vollaard NB, Constantin-Teodosiu D, Fredriksson K, Rooyackers O, Jansson E, Greenhaff PL, Timmons JA, Sundberg CJ. Systematic analysis of adaptations in aerobic capacity and submaximal energy metabolism provides a unique insight into determinants of human aerobic performance. *J Appl Physiol* 106: 1479–1486, 2009. First published February 5, 2009; doi:10.1152/japplphysiol.91453.2008.—It has not been established which physiological processes contribute to endurance training-related changes (Δ) in aerobic performance. For example, the relationship between intramuscular metabolic responses at the intensity used during training and improved human functional capacity has not been examined in a longitudinal study. In the present study we hypothesized that improvements in aerobic capacity ($\dot{V}O_{2max}$) and metabolic control would combine equally to explain enhanced aerobic performance. Twenty-four sedentary males (24 ± 2 yr; 1.81 ± 0.08 m; 76.6 ± 11.3 kg) undertook supervised cycling training (45 min at 70% of pretraining $\dot{V}O_{2max}$) 4 times/wk for 6 wk. Performance was determined using a 15-min cycling time trial, and muscle biopsies were taken before and after a 10-min cycle at 70% of pretraining $\dot{V}O_{2max}$ to quantify substrate metabolism. Substantial interindividual variability in training-induced adaptations was observed for most parameters, yet "low responders" for $\Delta\dot{V}O_{2max}$ were not consistently low responders for other variables. While $\dot{V}O_{2max}$ and time trial performance were related at baseline ($r^2 = 0.80$, $P < 0.001$), the change in $\dot{V}O_{2max}$ was completely unrelated to the change in aerobic performance. The maximal parameters $\Delta\dot{V}E_{max}$ and ΔVeq_{max} ($\Delta\dot{V}E/\dot{V}O_{2max}$) accounted for 64% of the variance in $\Delta\dot{V}O_{2max}$ ($P < 0.001$), whereas Δperformance was related to changes in the submaximal parameters Veq_{submax} ($r^2 = 0.33$; $P < 0.01$), muscle Δlactate ($r^2 = 0.32$; $P < 0.01$), and Δacetyl-carnitine ($r^2 = 0.29$; $P < 0.05$). This study demonstrates that improvements in high-intensity aerobic performance in humans are not related to altered maximal oxygen transport capacity. Altered muscle metabolism may provide the link between training stimulus and improved performance, but metabolic parameters do not change in a manner that relates to aerobic capacity changes.

phosphocreatine; maximal oxygen uptake capacity; lactate; low responder

AEROBIC CAPACITY ($\dot{V}O_{2max}$) is one of the most widely obtained variables in exercise physiology. Measured as the maximal attainable rate of oxygen consumption in a laboratory setting, $\dot{V}O_{2max}$ is deemed to have implications for both health and exercise performance. A high $\dot{V}O_{2max}$ is associated with reduced risk of metabolic and cardiovascular disease (9, 35, 50), and training-induced changes in $\dot{V}O_{2max}$ have been shown to correlate with changes in risk factors for metabolic and cardiovascular disease and mortality (29, 51). $\dot{V}O_{2max}$ is also widely considered a determinant of aerobic performance. An increase in $\dot{V}O_{2max}$ is a common method of demonstrating a training effect in endurance training studies (3), and $\dot{V}O_{2max}$ is often used to quantify and standardize exercise intensity for training studies (13, 18, 38), submaximal time-to-exhaustion performance trials (28, 37), and studying metabolic responses to submaximal exercise (1, 41).

The link between $\dot{V}O_{2max}$ and aerobic performance is deemed strong enough for researchers to search specifically for training techniques optimizing increases in $\dot{V}O_{2max}$ to improve performance (31). In support of this view, $\dot{V}O_{2max}$ and aerobic performance are positively correlated in athletes of mixed ability (15, 24, 27, 42), with well-trained endurance athletes achieving values for $\dot{V}O_{2max}$ over twice those of sedentary individuals (42). However, in well-trained athletes $\dot{V}O_{2max}$ remains stable even when performance is shown to increase (3, 4), and in these athletes the correlation between $\dot{V}O_{2max}$ and aerobic performance can be poor (10, 26). Moreover, although rarely acknowledged, in the small longitudinal studies that have linked changes in $\dot{V}O_{2max}$ with changes in aerobic performance, the data have been unconvincing. Indeed, studies using chronic obstructive pulmonary disease patients (33), recreationally active subjects (20, 40), and endurance-trained athletes (5, 23) did not observe a correlation between the magnitude of training-induced improvements in $\Delta\dot{V}O_{2max}$ and aerobic performance. Moreover, Paavolainen et al. (36) observed a significant negative correlation between $\dot{V}O_{2max}$ and the improvement in a 5-km run ($r^2 = 0.27$). Conversely, Esfarjani and Laursen (14) reported a positive correlation ($r^2 = 0.58$), but five "no training" control subjects who demonstrated neither an improvement in $\dot{V}O_{2max}$ nor performance were included with the 12 subjects in the training groups, invalidating the analysis. Finally, Smith et al. (43) showed a significant positive correlation ($r^2 = 0.61$) between $\Delta\dot{V}O_{2max}$ and Δperformance in nine well-trained athletes following 4 wk of treadmill interval training, but not in an additional nine athletes following a similar training program at a higher intensity. Thus a link

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Table 1. *Adaptations to 6 wk of aerobic exercise training: changes in performance, maximal and submaximal parameters, and mitochondrial enzyme activity*

	Pretraining	Posttraining
Time trial performance, kJ	219.7±37.1	251.2±36.1***
Maximal exercise		
$\dot{V}O_{2max}$, l/min	3.81±0.58	4.31±0.60***
W_{max}, W	315±48	356±44***
HR, beats/min	192±8	190±6
$\dot{V}E$,l/min	141.5±23.0	158.8±21.0***
Veq	38.7±7.0	37.7±4.5
RER	1.24±0.07	1.18±0.04**
Submaximal exercise		
HR, beats/min	168±14	151±15***
$\dot{V}O_2$, l/min	2.61±0.51	2.57±0.41
$\dot{V}E$,l/min	71.2±16.1	62.1±11.0***
Veq	27.6±4.7	24.3±2.9***
RER	1.01±0.07	0.94±0.05***
Mitochondrial enzyme activity, $\mu mol \cdot min^{-1} \cdot g^{-1}$ wet wt		
Citrate synthase	35.9±6.1	45.1±7.2***
Complex I	3.6±1.5	4.5±1.7**
Complex IV	11.4±3.5	14.0±3.7***

Values shown are mean ± SD (n = 24). Difference between pre- and posttraining: ** $P < 0.01$; *** $P < 0.001$.

between improvements in the oxygen transport system and the magnitude of improvement in aerobic performance requires detailed reappraisal in a larger study.

Perhaps even more surprising, no study has determined metabolic control within skeletal muscle under training intensity conditions, so it has not been evaluated if the degree of altered energy metabolism explains alterations in aerobic capacity or human performance. The aim of the current study was therefore to determine in a relatively large cohort of previously untrained individuals (n = 24) whether training-induced improvements in $\dot{V}O_{2max}$, aerobic performance, and metabolic control are related, to provide greater insight into determinants of human physiological performance.

METHODS

Subjects. Twenty-four healthy men (24 ± 2 yr; 1.81 ± 0.08 m) volunteered to take part in the study. Body mass did not change during the study period (76.6 ± 11.3 vs. 77.0 ± 10.8 kg). Mean resting blood pressure (systolic/diastolic) and heart rate were 126 ± 11/72 ± 5 mmHg and 70 ± 13 beats/min, respectively. Subjects were previously sedentary (i.e., they did not undertake any regular sporting activities in the 6 mo prior to the study) and abstained from strenuous exercise during the 3 wk prior to obtaining pre-training muscle biopsies. Each of the volunteers provided written informed consent. Molecular responses to the exercise training program have been reported elsewhere (22, 47, 48). The clinical study was approved by the Ethics Committee at the Karolinska Institutet, Stockholm, Sweden.

Experimental procedures. Subjects performed a fully supervised 6-wk training program consisting of four 45-min cycling sessions per week at an intensity corresponding to 70% of pretraining $\dot{V}O_{2max}$ (compliance was 100%). Before commencing training, subjects performed five cycling tests. $\dot{V}O_{2max}$ and a number of additional cardiorespiratory variables [maximal heart rate, RER_{max}, $\dot{V}E_{max}$, maximal ventilatory equivalent (Veq_{max}: $\dot{V}E_{max}/\dot{V}O_{2max}$)] were determined during two exhaustive incremental cycling tests (Rodby, Sweden), with continuous analysis of respiratory gases using a SensorMedics ventilator. At $\dot{V}O_{2max}$ the respiratory exchange ratio exceeded 1.10 on all occasions. For each parameter the highest value for the two tests was taken. Next, a 10-min submaximal cycling test (70% of pretraining $\dot{V}O_{2max}$; 192 ± 31 W) was performed. Vastus lateralis muscle biopsies were taken before and directly after cycling and analyzed for a range of metabolites and enzymes. Submaximal heart rate was determined and respiratory gases were collected to determine submaximal $\dot{V}O_2$, RER, $\dot{V}E$, and Veq. Finally, aerobic performance was measured as the highest total amount of work done (kJ) in two separate 15-min self-paced cycling time trials (Linear mode, Lode, The Netherlands; test-retest variability <5%). The submaximal cycling test was repeated 24 h after the last training session. In subsequent days two additional incremental cycling tests and two time trials were performed to determine training-induced changes in maximal parameters and performance. Changes from pre- to posttraining are denoted with a Δ sign, except for metabolic parameters for which the Δ sign denotes the change from pre- to postsubmaximal exercise.

Metabolic and enzyme measurements. Muscle biopsy samples were obtained from the vastus lateralis muscle before and after each of the two 10-min exercise bouts using a percutaneous needle biopsy as previously described (46). Each sample was taken ~3–5 cm apart on each visit, and the same leg was sampled for the pre- and postsubmaximal metabolism assessment. Biopsy samples were frozen in liquid nitrogen within 10–15 s of sampling, and stored at −80°C until analysis. One freeze-dried portion was dissected free from visible connective tissue and blood, powdered, and extracted in 0.5 M perchloric acid containing 1 mM EDTA. Following centrifugation the supernatant was neutralized with 2.2 M $KCHO_3$ and used for spectrophotometric determination of ATP, PCr, and lactate (21) and for the determination of free carnitine and acetyl-carnitine (ALCAR) by enzymatic assays using radioisotopic substrates (7). Freeze-dried muscle powder was also used for the determination of muscle glycogen (21). Activities of citrate synthase (CS), complex I (CI), and complex IV (CIV) were determined as previously described (16).

Statistical analyses. All data are presented as means ± SD. Statistical analyses were performed using SPSS statistical software (SPSS). Differences between pre- and posttraining mean values for all measured parameters were determined using paired sample t-tests. Subsequently, subjects were grouped into low responders (n = 8; $\Delta\dot{V}O_{2max}$: 4 ± 3%), medium responders (n = 8; $\Delta\dot{V}O_{2max}$: 13 ± 4%), and high responders (n = 8; $\Delta\dot{V}O_{2max}$: 23 ± 5%) for changes in $\dot{V}O_{2max}$. Differences in training response between low and high responders for all parameters were determined using independent sample t-tests. Multivariate linear regression analysis (stepwise criteria: probability-of-F-to-enter ≤0.05, probability-of-F-to-remove ≥0.10) was performed with either percentage change in $\dot{V}O_{2max}$ or time trial performance as dependent variables and either the baseline value or the training-induced change in the independent variables HR_{max}, $\dot{V}E_{max}$, Veq_{max}, RER_{max}, $\dot{V}E_{submax}$, Veq_{submax}, HR_{submax},

Table 2. *Adaptations to 6 wk of aerobic exercise training: changes in metabolic substrate levels ($mmol \cdot kg^{-1}$ dm) with submaximal exercise*

	Pretraining		Posttraining	
	Preexercise	Postexercise	Preexercise	Postexercise
Glycogen	370±70	269±82[i]	499±93[c]	459±92[d,h]
Lactate	8.8±3.0	39.8±20.0[i]	8.6±2.5	13.6±8.4[f,g]
ATP	25.2±2.6	25.6±2.2	26.0±2.5	27.0±2.8
Phosphocreatine	87.7±8.2	43.9±18.2[i]	83.8±5.3	58.2±15.5[e,i]
Creatine	49.2±8.5	93.0±18.6[i]	54.0±10.2	78.0±17.9[e,i]
Carnitine	16.8±3.5	8.2±3.4[i]	14.9±3.1[b]	10.8±3.9[f,i]
Acetyl-carnitine	4.7±2.8	15.5±4.5[i]	4.9±2.4	9.5±3.8[f,i]

Values shown are means ± SD (n = 24). Difference between Pre- and posttraining resting levels: [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$; Pre- and posttraining change with submaximal exercise: [d]$P < 0.05$, [e]$P < 0.01$, [f]$P < 0.001$; Pre- and postexercise: [g]$P < 0.05$, [h]$P < 0.01$, [i]$P < 0.001$.

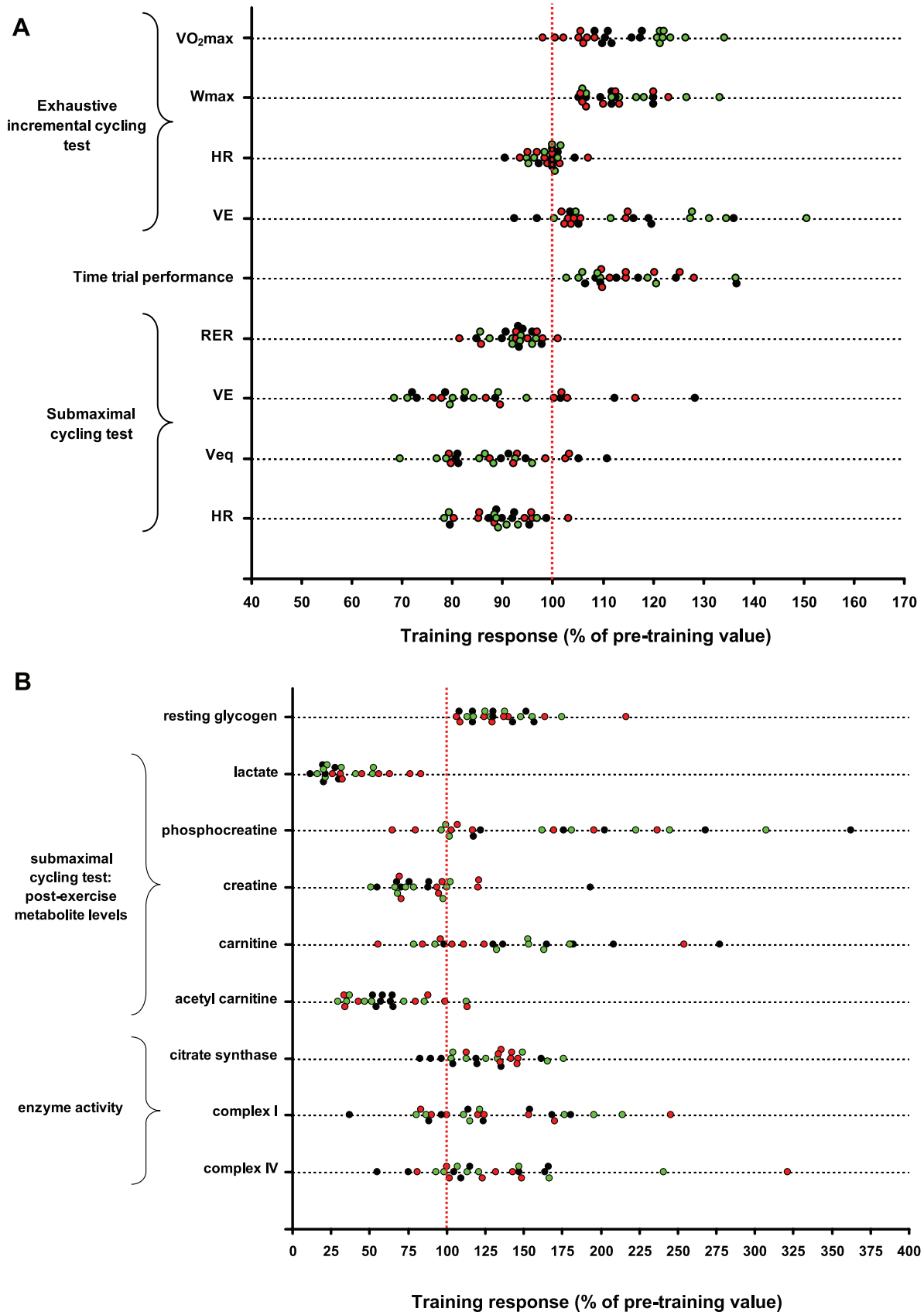

Fig. 1. Variation in response to training for variables measured during the $\dot{V}O_{2max}$ test, time trial performance, and cardiorespiratory variables determined during the submaximal cycling test (*A*), and resting glycogen, post-submaximal cycling metabolite levels, and enzyme activity (*B*). Dots represent the training adaptation for individual subjects ($n = 24$) as a percentage of their individual pretraining value (i.e., 90% represents a 10% decrease, 110% represents a 10% increase). Dots are colored by response for $\dot{V}O_{2max}$, with the highest 8 responders colored green and the lowest 8 responders colored red (remaining 8 subjects colored black).

$\dot{V}O_{2submax}$, RER_{submax}, glycogen degradation, phosphocreatine degradation, carnitine utilization, lactate accumulation, creatine accumulation, acetyl-carnitine accumulation, resting glycogen levels, and activity of citrate synthase, complex I, and complex IV. Bivariate correlations were assessed using Pearson's correlation coefficient. Significance was accepted at $P < 0.05$.

RESULTS

Aerobic training improves a range of classic physiological parameters. With the current 6-wk supervised cycling training program, commonly reported training-induced adaptations in a range of classic parameters were reproduced (Tables 1 and 2). Both aerobic capacity ($\dot{V}O_{2max}$; 13%; $P < 0.001$) and aerobic time trial performance (14%; $P < 0.001$) significantly improved. Posttraining, maximal exercise testing was associated with increases in maximal power output (13%; $P < 0.001$) and maximal minute ventilation (12%; $P < 0.001$), as well as a decrease in maximal RER (−4.6%; $P < 0.01$), but no changes were observed for maximal ventilatory equivalent or maximal heart rate. Submaximal heart rate (−10%), minute ventilation (−13%), ventilatory equivalent (−12%), and RER (−7.7%) were all reduced following training ($P < 0.001$). Furthermore, submaximal exercise was associated with lower increases in muscle levels of lactate (−84%; $P < 0.001$), creatine (−45%; $P < 0.01$), and acetyl-carnitine (−58%; $P < 0.001$), as well as lower breakdown of muscle glycogen (−61%; $P < 0.05$) and phosphocreatine (−42%; $P < 0.01$), and less acetylation of carnitine (−53%; $P < 0.001$). Finally, resting glycogen levels increased (35%; $P < 0.001$), as did the activities of the mitochondrial enzymes citrate synthase (26%; $P < 0.001$), complex I (23%; $P < 0.01$), and complex IV (23%; $P < 0.001$). Together these results suggest greater aerobic capacity, improved metabolic control, and greater reliance on lipid oxidation during submaximal exercise. Thus the physiological and biochemical findings of the current study are in agreement with the large body of work previously published. However, as no previous studies have simultaneously examined both the maximal and submaximal physiological and biochemical parameters presented, we were able to examine their interrelationships for the first time.

Interindividual variability in training response is high. Although aerobic capacity improved significantly for the group as a whole, individual training adaptations ranged from a 2% decrease to >30% increase. Similarly, interindividual variability in training response was high for all other variables, with a proportion of the subjects not demonstrating a training-induced adaptation for a number of variables (Fig. 1). Critically, low responders for $\dot{V}O_{2max}$ (red dots in Fig. 1) were not consistently lowest responders for all variables: whereas the change in $\dot{V}O_{2max}$ for the eight subjects with the lowest increase (low responders; 4 ± 3%) was sixfold lower than for the eight highest responders (high responders; 23 ± 5%; $P < 0.001$), the training adaptations of low responders were not significantly different from high responders for any other variable except $\dot{V}E_{max}$ (6 ± 5% vs. 23 ± 16%; $P < 0.05$).

Changes in aerobic capacity and aerobic performance are not related and associate with distinct biological parameters. Although there were strong positive correlations between $\dot{V}O_{2max}$ and time trial performance both pretraining ($r^2 = 0.80$, $P < 0.001$; Fig. 2*A*) and posttraining ($r^2 = 0.74$; $P < 0.001$; Fig. 2*B*), the change in $\dot{V}O_{2max}$ was not related to the change in time trial performance (Fig. 2*C*). Multiple linear regression analysis identified the maximal variables $\Delta\dot{V}E_{max}$ and ΔVeq_{max} to account for 64% of the variance in $\Delta\dot{V}O_{2max}$ ($P < 0.001$). Correcting $\dot{V}O_{2max}$ for body weight did not affect the analysis. For Δperformance, 33% of variance was accounted for by the submaximal variable ΔVeq_{submax} ($P < 0.05$). Bivariate correlations indicated no training-induced changes in submaximal parameters were related to $\Delta\dot{V}O_{2max}$. Conversely, apart from ΔVeq_{submax}, Δperformance was related to the training-induced changes in Δlactate ($r = 0.56$; $P < 0.01$) and ΔALCAR ($r = 0.54$; $P < 0.05$), but not to any maximal parameters.

Baseline determinants of training adaptation. The magnitude of training adaptations for most parameters, but not $\Delta\dot{V}O_{2max}$ and Δperformance, was significantly correlated with their respective baseline levels (Table 3). To determine whether low baseline values for particular parameters affected the magnitude of adaptations in either aerobic capacity or aerobic performance, correlations between baseline values for maximal and submaximal parameters, and $\Delta\dot{V}O_{2max}$ or Δperformance were analyzed. Critically, no baseline parameters correlated with $\Delta\dot{V}O_{2max}$ and thus improvements in aerobic capacity cannot be predicted using the extensive range of physiological and biochemical parameters in this study. In contrast, baseline muscle Δlactate (Fig. 3; $r = 0.48$; $P <$

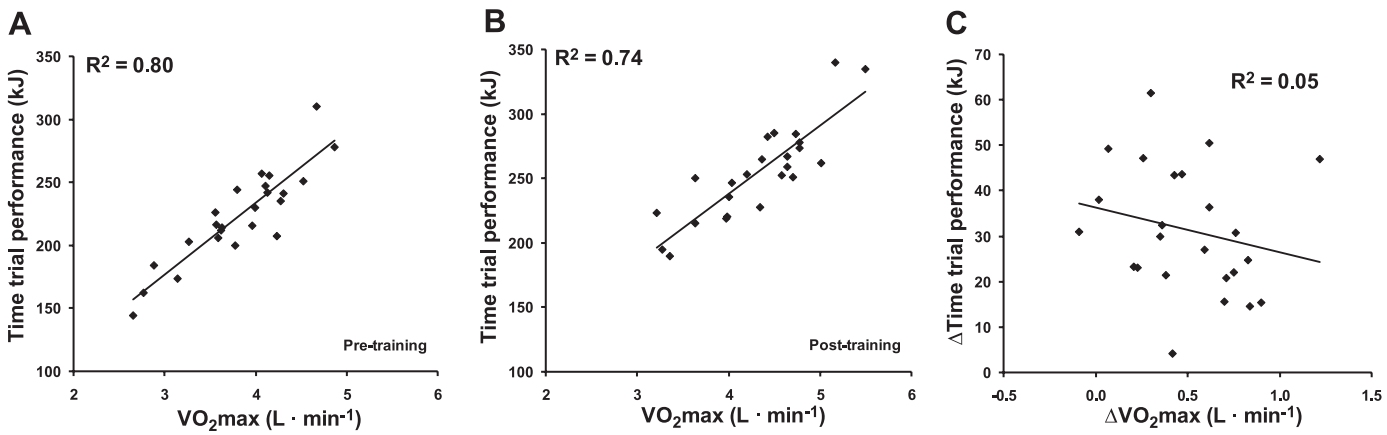

Fig. 2. Correlations between $\dot{V}O_{2max}$ and time trial performance pretraining (*A*; $P < 0.001$) and posttraining (*B*; $P < 0.001$), and between $\Delta\dot{V}O_{2max}$ and Δperformance (*C*).

Table 3. *Correlations between baseline values and magnitude of adaptation*

		r^2
Maximal exercise	$\dot{V}O_{2max}$	0.04
	power output	0.16
	$\dot{V}E$	0.24*
	Veq	0.60‡
	RER	0.64‡
	HR	0.52‡
Time trial	performance	0.03
Submaximal exercise	$\dot{V}O_2$	0.35†
	$\dot{V}E$	0.53‡
	Veq	0.62‡
	RER	0.60‡
	HR	0.10
	ΔATP	0.21*
	Δphosphocreatine	0.68‡
	Δcreatine	0.70‡
	Δcarnitine	0.54‡
	Δacetyl-carnitine	0.69‡
	Δglycogen	0.55‡
	Δlactate	0.81‡
Preexercise biopsies	glycogen	0.19*
	citrate synthase	0.22*
	complex I	0.08
	complex IV	0.19*

Correlation significant at: *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

0.05), ΔALCAR ($r = 0.46$; $P < 0.05$), and Veq_{submax} ($r = 0.42$; $P < 0.05$) correlated with Δperformance. Although it is tempting to conclude from these data that subjects with poor pretraining metabolic control were able to improve aerobic performance to a larger extent, it is more likely that these correlations are due to the way the training intensity was standardized, i.e., as a fixed percentage of $\dot{V}O_{2max}$. The muscle lactate response to submaximal exercise (Δlactate) was positively correlated ($r^2 = 0.39$, $P < 0.001$) with the percentage of "performance power output" at which the submaximal test was performed (i.e., submaximal cycling power output expressed as a percentage of pretraining time trial power output; Fig. 4). Thus, considering the variable metabolic response to training sessions for individual subjects, it is not surprising that subjects training at an intensity closer to their performance power output tended to improve their performance to a larger extent ($r^2 = 0.14$, $P = 0.07$; Fig. 5A). Conversely, $\Delta\dot{V}O_{2max}$ was negatively correlated with training power output as a percentage of performance power output ($r^2 = 0.21$ $P < 0.05$; Fig. 5*B*), further demonstrating the poor link between aerobic capacity and aerobic performance.

DISCUSSION

Presentation of the physiological and biochemical adaptations to endurance training in a group of subjects as average responses largely ignores the observation that for most parameters no measurable response will be observed in certain members of that group. A logical hypothesis is that human performance will reflect the integration of a variety of physiological and biochemical capacities. $\dot{V}O_{2max}$ is often presented as a critical determinant of aerobic performance, yet we demonstrate that training-induced changes in $\dot{V}O_{2max}$ and aerobic performance are not related even in untrained subjects. Moreover, we demonstrate that $\dot{V}O_{2max}$ and aerobic performance associate with distinct and separate physiological and biochemical endpoints, suggesting that proposed models for the determinants of endurance performance may need to be revisited, especially to take into account the true heterogeneous nature of training-induced responses in humans. The data obtained in this detailed human study may also help identify which proposed molecular regulators of training-induced adaptations in aerobic capacity and aerobic performance are consistent with our in vivo human physiological and biochemical observations.

Linking physiological and biochemical mediators to improved exercise performance. Previously, it has been concluded that $\dot{V}O_{2max}$ sets the upper limit for aerobic performance (3, 11), but this has little relevance for maximal work performance over extended durations, where it is not possible to maintain exercise at $\dot{V}O_{2max}$. As maximal aerobic performance

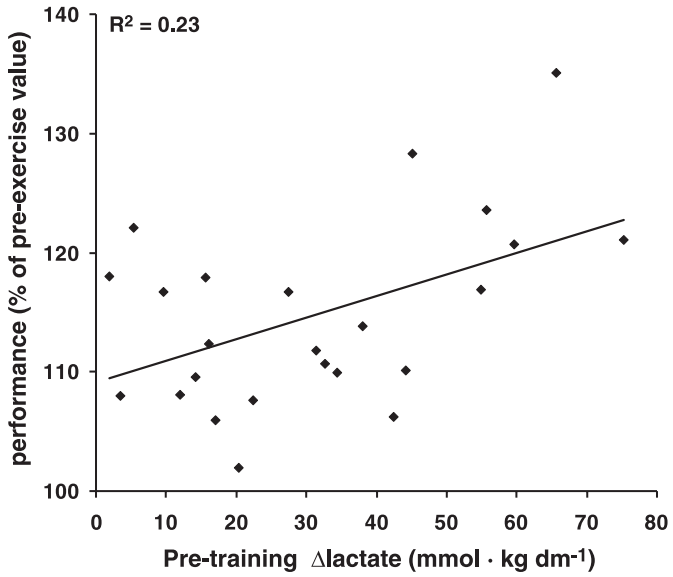

Fig. 3. Correlation between the pretraining increase in muscle lactate with submaximal cycling and the training-induced improvement in time trial performance ($P < 0.001$).

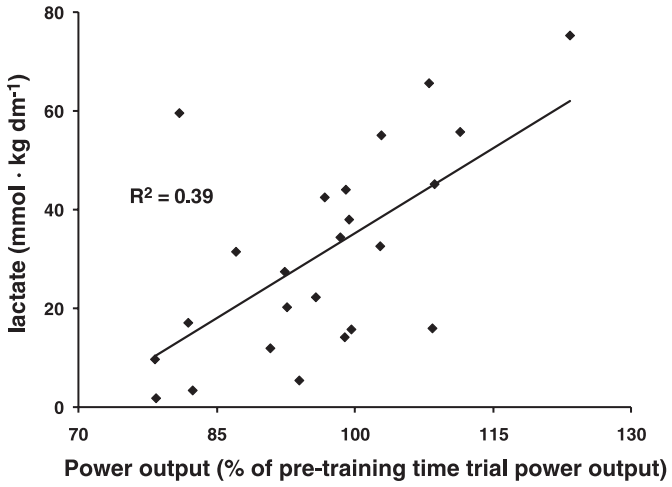

Fig. 4. Correlation between the intensity of the submaximal cycling test (expressed as a percentage of the power output during the pretraining time trial) and the increase in muscle lactate concentration during the pretraining submaximal cycling test ($P < 0.001$).

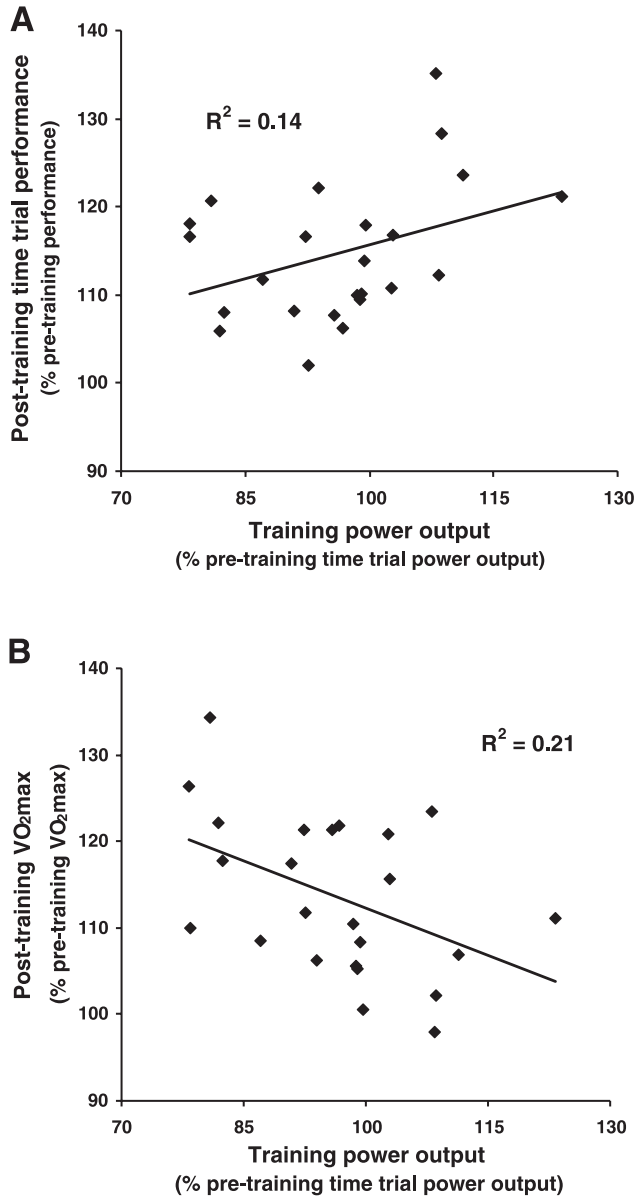

Fig. 5. Correlations between the power output during training sessions (expressed as a percentage of the power output during the pretraining time trial) and the training-induced changes in time trial performance (*A*; $P = 0.07$), and $\dot{V}O_{2max}$ (*B*; $P < 0.05$).

relies on a percentage of $\dot{V}O_{2max}$, this implies an "over capacity" of the aerobic system's ability to transport oxygen, which can only be used for short periods of time under conditions usually incorrectly referred to as "anaerobic" (45, 46). Ironically, an increase in the maximal oxygen transport capacity without simultaneous improvements in skeletal muscle metabolic control would actually lower the percentage of $\dot{V}O_{2max}$ achievable at maximal aerobic performance. Similarly, adaptations in the skeletal muscle that enable an individual to perform exercise at a higher percentage of $\dot{V}O_{2max}$ do not necessarily require improvements in the maximal capacity of the cardiorespiratory system to take up and transport oxygen to the muscle. Thus aerobic performance is not determined by $\dot{V}O_{2max}$ per se, rather $\dot{V}O_{2max}$ sets its theoretical (but not practical) upper limit.

It is curious that in the untrained individual, both parameters are tightly linked at baseline, suggesting that a common factor influences these capacities, yet this factor does not tightly couple the adaptive process that occurs during training. Although the overall stimuli for improving aerobic capacity and aerobic performance are identical (i.e., aerobic training), we demonstrate that these adaptations do not occur in proportion to each other and do not appear to be determined by the same physiological or biochemical parameters. It follows that the molecular mediators responsible for adaptations to aerobic capacity and aerobic performance are also likely to be unrelated. The potential for metabolic-responsive processes such as calcium-mediated signaling (8) or AMPK activation (32) as mediators of adaptations in aerobic performance would be consistent with our present analysis. Conversely, oxygen-related processes such as HIF-1α (2) and VEGF signaling promoting vascular remodeling (19) would seem less likely determinants of gains in functional capacity, but may be central for improvements in aerobic capacity (47). A role of local muscle energy metabolism as a critical determinant of whole body aerobic performance has been demonstrated in recent animal model systems (32). However, it should be noted that such studies involve performance during low-intensity, long-duration exercise in which fatigue is associated with muscle substrate depletion and little to do with either short-term aerobic performance, maximal aerobic capacity, or the type of fatigue an average human muscle encounters. It remains to be demonstrated whether any of these molecular mechanisms play a role in adaptations to high-intensity aerobic performance in shorter duration tests of human function as employed in the current study.

The importance of human variation. Human beings are characterized by their heterogeneity. However, in research, interindividual variability is largely ignored in favor of presentation of mean values. Numerous authors have focused on the average improvement in a range of classic parameters altered by aerobic training (12, 34, 38, 44), yet when one examines the data closely most of these parameters show no sign of change in a proportion of subjects (Fig. 1). More importantly, in the present study we find that low responders for one parameter are not necessarily low responders for another. Indeed, the fact that some individuals do not improve $\dot{V}O_{2max}$ in response to a standardized aerobic training program has been known for over two decades (25, 39) and was convincingly demonstrated by Bouchard et al. (6) in a large cohort in the HERITAGE Family Study. This study also showed considerable variation in training adaptations for parameters like blood pressure, HDL cholesterol, and heart rate at submaximal exercise (6). However, the present study is the first to present evidence that a low response for improvements in $\dot{V}O_{2max}$ does not associate with a low response to many other common physiological and metabolic adaptations associated with metabolic control or performance. In light of previous work suggesting a correlation between training-induced improvements in $\dot{V}O_{2max}$ and beneficial effects on risk factors of metabolic and cardiovascular disease (29, 51) our observations have potential implications in the search for the mechanisms by which aerobic exercise improves health.

Practical considerations derived from the present study. While maximal aerobic performance is often quantified as a percentage of $\dot{V}O_{2max}$, the ability to maintain a certain percent-

age of $\dot{V}O_{2max}$ during prolonged exercise has a large interindividual variability [~35–87% during 1–2 h of exercise (3)]. Therefore, while exercising at a fixed percentage of $\dot{V}O_{2max}$ may produce a similar stimulus to the cardiorespiratory system across subjects, we showed in the present study that standardizing in this manner results in a large range of metabolic responses within the exercising muscle. For example, even in our relatively homogenous cohort of subjects there was a 40-fold range in the increase in muscle lactate levels following submaximal exercise at 70% of $\dot{V}O_{2max}$. This observation has significant practical implications for various common uses of the $\dot{V}O_{2max}$ parameter in human physiology studies. First, standardizing training intensity to a set percentage of $\dot{V}O_{2max}$ in training studies aiming to study aerobic performance will result in large interindividual differences in the magnitude of the training stimulus (see Figs. 1 and 5). Second, the use of set percentages of $\dot{V}O_{2max}$ in studies investigating metabolic responses to exercise will also produce large interindividual variation. Finally, in studies determining changes in aerobic performance using time trials to exhaustion at a set percentage of $\dot{V}O_{2max}$, the metabolic response to exercise of individual subjects may vary considerably, potentially affecting any changes in performance measured or the underlying nature of fatigue (49). Indeed, in these cases it is advisable to standardize exercise intensity using measures more directly related to performance power output (e.g., maximal lactate steady state), rather than to a set percentage of $\dot{V}O_{2max}$. Therefore, as others have suggested (17, 30), the present study demonstrates that $\dot{V}O_{2max}$ cannot be considered a universal parameter to standardize aerobic exercise training studies. Based on the present data we conclude that plasticity of $\dot{V}O_{2max}$ is a poor determinant of improvements in aerobic performance in healthy young untrained males.

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