known whether moderate resistance training would induce similar arterial stiffening. Second, because regular aerobic exercise has been shown to increase arterial compliance [10,11], simultaneously performed endurance training may negate the effects of resistance training, thereby attenuating or preventing arterial stiffening. Neither of these possibilities has been tested, however.

Accordingly, the primary aim of the present study was to determine the effects of moderate-intensity resistance training as well as the combined strength and endurance training intervention on carotid arterial compliance. We hypothesized that the compliance of carotid arteries would not change following moderate-intensity resistance training as well as combined resistance and aerobic training. At the completion of the exercise intervention period, we implemented a period of detraining. We reasoned that if the observed changes in arterial compliance were induced by the prescribed exercise training, values should return to the baseline levels when the stimuli of exercise training were removed.

Methods

Participants

A total of 39 young healthy men were studied. None of the men had participated in any resistance or endurance training on the regular basis. All subjects were normotensive (< 140/90 mm Hg), non-obese (body mass index < 30 kg/m^2), and free of overt chronic diseases as assessed by medical history, physical examination, and a complete blood chemistry and hematological evaluation. Candidates who smoked in the past 4 years were taking cardiovascular-acting medications or anabolic steroids, or had significant intima–media thickening, plaque formation, and/or other characteristics of atherosclerosis (e.g. ankle–brachial index < 0.9) were excluded. All subjects gave their written informed consent to participate, and all procedures were reviewed and approved by the Institutional Review Board. Subjects were randomly assigned into either the moderate-intensity resistance training group (MODE, $n = 12$), the combined high-intensity resistance training and moderate-intensity aerobic exercise training group (COMBO, $n = 11$), or sedentary control group (CONTROL, $n = 16$). No endurance-training group was included because the primary focus of the present study was on resistance training. Before the intervention period, there were no significant differences in any of the variables between the groups (Table 1).

Table 1 Selected subject characteristics at baseline

Variable	CONTROL group	MODE group	COMBO group
N	16	12	11
Age (years)	22 ± 1	20 ± 1	21 ± 1
Height (cm)	172 ± 1	169 ± 2	171 ± 2
Body weight (kg)	68 ± 2	65 ± 2	66 ± 2
Body mass index (kg/m^2)	22 ± 1	23 ± 1	23 ± 1
Body fat (%)	21 ± 1	18 ± 2	21 ± 1
Lean body mass (kg)	55 ± 2	51 ± 1	53 ± 1
Peak oxygen consumption (ml/kg per min)	49 ± 3	52 ± 2	49 ± 2

Data presented as the mean ± SEM. CONTROL, sedentary control group; MODE, moderate-intensity resistance training group; COMBO, combined high-intensity resistance training and moderate-intensity aerobic exercise training group.

Measurements

The exercise intervention groups were studied five times: before training (baseline), at 2 months (midpoint of exercise training), at 4 months (completion of exercise training), at 6 months (midpoint of detraining), and at 8 months (completion of detraining). The non-exercising control group was studied three times: baseline, at 4 months, and at 8 months. In order to avoid potential diurnal variations, subjects were tested at the same time of day throughout the study period [9,10]. Furthermore, prior to each testing, subjects abstained from caffeine and fasted for at least 4 h; most subjects were studied after overnight fast. Subjects in the intervention groups were studied 20–24 h after their last exercise training session to avoid the acute effects of exercise [12], but while they were still considered to be in their normal (i.e. habitually exercising) physiological state.

Incremental exercise

To demonstrate that the participants had been sedentary, we measured the maximal oxygen consumption during an incremental cycle ergometer exercise [13]. The oxygen consumption, heart rate, and ratings of perceived exertion were measured throughout the protocol.

Strength testing

Maximal muscular strength in the intervention groups was assessed before and after resistance training using the following exercises: half squat, bench press, leg extension, leg curls, lat row, and abdominal bend. After 10 warm-up repetitions, one-repetition maximum (1 RM) values were obtained according to established guidelines. The day-to-day coefficient of variation for 1 RM strength in our laboratory is 4 ± 2%. The 1 RM test was not performed in the control group due to the potential risks involved in the testing.

Body composition

The body composition was determined using the bioelectric impedance method (coefficient of variance, 4 ± 2%) [14].

Arterial blood pressure at rest

Chronic levels of arterial blood pressure at rest were measured with a semi-automated oscillometric device (Form PWV/ABI; Colin Medical, Komaki, Aichi, Japan) over the brachial and dorsalis pedis artery. Recordings were made in triplicate with participants in the supine position.

Carotid artery intima–media thickness

The carotid artery intima–media thickness (IMT) was measured from the images derived from an ultrasound machine equipped with a high-resolution linear-array broad-band transducer as previously described [8]. Ultrasound images were analyzed by use of computerized image analysis software. At least 10 measurements of IMT were taken at each segment, and the mean values were used for analysis. This technique has excellent day-to-day reproducibility (coefficient of variance, $3 \pm 1\%$) for the carotid IMT.

Carotid artery stiffness and compliance

A combination of ultrasound imaging of the pulsatile common carotid artery with simultaneous applanation of tonometrically obtained arterial pressure from the contralateral carotid artery permits non-invasive determination of arterial compliance [10,15]. The carotid artery diameter was measured from images derived from an ultrasound machine equipped with a high-resolution linear-array transducer. A longitudinal image of the cephalic portion of the common carotid artery was acquired 1–2 cm distal to the carotid bulb. To assess the effects of peripheral artery compliance, the same procedure was repeated on the common femoral artery. All image analyses were performed by the same investigator who was blinded to the group assignments.

Pressure waveforms and amplitudes were obtained from the common carotid artery with a pencil-type probe incorporating a high-fidelity strain-gauge transducer (SPT-301; Millar Instruments, Houston, Texas, USA) [10,16]. Because baseline levels of blood pressure are subjected to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial and diastolic blood pressure to the brachial artery value [9,10]. In addition to arterial compliance [17], we also calculated the β-stiffness index, which provides an index of arterial compliance adjusted for distending pressure [18]. Arterial compliance and the β-stiffness index were calculated using the equations $[(D_1-D_0)/D_0]/[2(P_1-P_0)] \times \pi \times (D_0)^2$ and $[\ln(P_1/P_0)]/[(D_1-D_0)/D_0]$, where D_1 and D_0 are the maximal and minimum diameters, and P_1 and P_0 are the highest and lowest blood pressures. The blood pressure obtained at the ankle (Form PWV/ABI; Colin Medical) was used to calculate the femoral artery compliance. The day-to-day coefficients of variation were 2 ± 1, 7 ± 3, and 5 ± 2 for the carotid artery diameter, pulse pressure, and arterial compliance, respectively. The coefficient of variance for femoral arterial compliance was $7 \pm 4\%$.

Left ventricular dimensions, mass and function

Echocardiography was used to measure the left ventricular dimensions, wall thickness, and stroke volume according to established guidelines [19] as previously described [8]. The left ventricular mass and stroke volume were normalized for the body surface area. The ratio of the average left ventricular wall thickness to the left ventricular internal end-diastolic diameter was used as an index of relative wall thickness [8].

Exercise training intervention

In the first 4 months of study period, participants in all training groups underwent three supervised resistance training sessions per week. During each training session, participants in the COMBO group completed three sets of 8–12 exercises at 80% of 1 RM and subjects in the MODE group completed three sets of 14–16 exercises at 50% of 1 RM, in the following order: leg extension, seated chest press, leg curls, lateral row, squat, and sit-ups. The resistance of each exercise was increased progressively throughout the resistance training period. The recovery time between exercise bouts was controlled at 2-min intervals. Each resistance training session lasted approximately 45 min. Subjects in the COMBO group performed a cycle exercise at 60% of the maximal heart rate for 30 min immediately after each resistance training session. Training assistants verbally encouraged the subjects and ensured proper form and technique at each exercise session. Participants were instructed to refrain from any other regular exercise during the entire study period. Participants in the sedentary control group were instructed not to alter their normal activity levels throughout the study period.

Statistical analyses

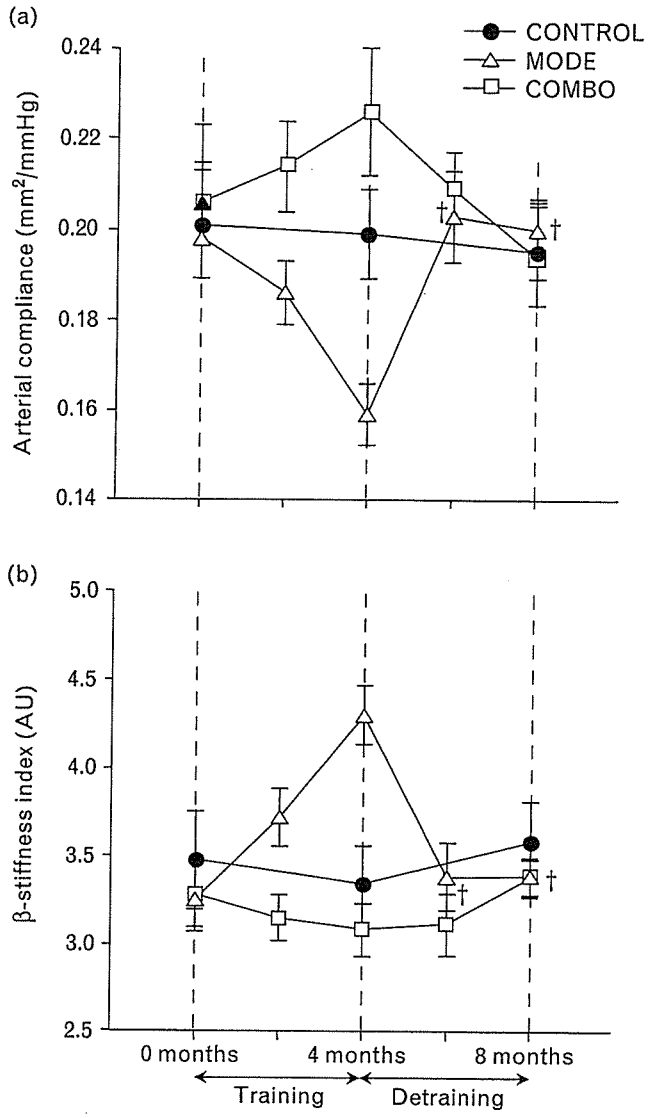
Changes were assessed by two-way analysis of variance (group × time) with repeated measures. In the case of significant F-values, a post-hoc test (Newman–Keuls method) was used to identify significant differences among mean values. To determine whether the changes in arterial compliance and the β-stiffness index were independent of changes in stroke volume, analysis of covariance was performed with stroke volume as the covariate. Pearson's correlation and regression analyses were performed to determine the relation between variables of interest.

Results

Before the intervention period, there were no significant differences in any of the variables between the groups (Table 1). In all groups, there were no changes in height, weight, body mass index, and body surface area throughout the intervention periods.

All the exercise intervention groups increased 1 RM strength significantly in all muscle groups tested ($P < 0.05$ to $P < 0.0001$). Percentage increases in 1 RM strength for the MODE and COMBO groups were 6 and 25% for leg extension, 13 and 14% for leg curl, 10 and 25% for squat, 8 and 17% for lateral row, 6 and 21% for bench press, and 12 and 21% for abdominal bend, respectively.

Fig. 1



Changes in (a) carotid arterial compliance and (b) β-stiffness index for the sedentary control group (CONTROL), the moderate-intensity strength training group (MODE), and the combined aerobic and strength training group (COMBO). Data presented as the mean ± SEM. *$P < 0.05$ versus baseline; †$P < 0.05$ versus 4 months.

Table 2 Hemodynamic and vascular indices

Variable	Baseline	After training	After detraining	Interaction
Brachial systolic blood pressure (mmHg)				
CONTROL group	118 ± 2	119 ± 1	120 ± 2	$F = 2.130$
MODE group	120 ± 3	117 ± 3	115 ± 2	$P = 0.086$
COMBO group	115 ± 2	116 ± 2	115 ± 2	
Brachial diastolic blood pressure (mmHg)				
CONTROL group	68 ± 2	73 ± 2*	73 ± 1	$F = 5.475$
MODE group	71 ± 2	66 ± 2*	68 ± 2	$P > 0.001$
COMBO group	67 ± 1	67 ± 2	67 ± 2	
Brachial pulse pressure (mmHg)				
CONTROL group	49 ± 2	47 ± 1	47 ± 1	$F = 2.407$
MODE group	49 ± 2	52 ± 2	47 ± 2	$P = 0.057$
COMBO group	48 ± 2	49 ± 1	48 ± 1	
Carotid systolic blood pressure (mmHg)				
CONTROL group	101 ± 2	104 ± 2	104 ± 1	$F = 1.653$
MODE group	105 ± 3	105 ± 4	104 ± 3	$P = 0.170$
COMBO group	99 ± 2	97 ± 2	98 ± 2	
Carotid pulse pressure (mmHg)				
CONTROL group	33 ± 2	32 ± 1	32 ± 1	$F = 2.383$
MODE group	36 ± 2	39 ± 3	36 ± 2†	$P = 0.059$
COMBO group	31 ± 1	30 ± 1	32 ± 1	
Carotid lumen diameter (mm)				
CONTROL group	5.91 ± 0.11	5.94 ± 0.14	6.06 ± 0.11	$F = 1.839$
MODE group	6.03 ± 0.13	6.02 ± 0.10	6.02 ± 0.11	$P = 0.131$
COMBO group	5.79 ± 0.09	5.91 ± 0.07	5.81 ± 0.09	
Δ Carotid lumen diameter (mm)				
CONTROL group	0.66 ± 0.03	0.66 ± 0.04	0.63 ± 0.03	$F = 3.460$
MODE group	0.74 ± 0.02	0.66 ± 0.04*	0.76 ± 0.04†	$P = 0.012$
COMBO group	0.71 ± 0.04	0.72 ± 0.03	0.69 ± 0.04	
Carotid intima–media thickness (mm)				
CONTROL group	0.50 ± 0.01	0.52 ± 0.02	0.50 ± 0.02	$F = 1.803$
MODE group	0.46 ± 0.01	0.45 ± 0.02	0.46 ± 0.01	$P = 0.138$
COMBO group	0.47 ± 0.01	0.52 ± 0.01	0.51 ± 0.02	
Femoral compliance (mm²/mmHg)				
CONTROL group	0.10 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	$F = 0.950$
MODE group	0.08 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	$P = 0.441$
COMBO group	0.09 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	

Data presented as the mean ± SEM. CONTROL, sedentary control group; MODE, moderate-intensity resistance training group; COMBO, combined high-intensity resistance training and moderate-intensity aerobic exercise training group. *$P < 0.05$ versus baseline. †$P < 0.05$ versus after the training period.

The magnitude of increases was larger ($P < 0.05$) in the COMBO group than in the MODE group in all exercises except for the leg curl.

There were no significant differences in baseline arterial compliance and β-stiffness index between all four groups (Fig. 1). Carotid arterial compliance decreased after 4 months of MODE interventions ($P < 0.01$). In contrast, arterial compliance did not decrease, but rather tended to increase ($P = 0.06$), after 4 months of the COMBO intervention. Following the detraining period, arterial compliance values returned to the baseline level. Alterations in arterial compliance were primarily due to changes in arterial distension as the carotid pulse pressure remained unchanged (Table 2). In general, qualitatively similar results (although inverse in direction) were obtained by use of the β-stiffness index ($P < 0.01$). The femoral arterial compliance, an index of the compliance of peripheral (muscular) artery, did not change in any groups. In all groups, there were no significant changes in brachial and carotid systolic blood pressures, carotid IMT, and carotid lumen diameter (Table 2).

In all groups, there were no significant changes in heart rate at rest throughout the study period (Table 3). All the resistance training interventions increased the left ventricular mass index and the relative wall thickness ($P < 0.001$). In the COMBO group, the stroke volume index tended to increase during the training period ($P = 0.07$). There were no significant changes in the stroke volume index in any other groups. Following the detraining period, left ventricular structural and functional indices returned to baseline and were no longer significantly different from baseline. There were no such changes in the sedentary control group throughout the study period. To determine whether changes in stroke volume, a determinant of arterial compliance, could confound the interpretation of the present results, we performed several different analyses. When we performed a

Table 3 **Cardiac indices**

Variable	Baseline	4 months	8 months	Interaction
Heart rate at rest (beats/min)				
CONTROL group	58 ± 3	56 ± 2	57 ± 2	$F = 0.254$
MODE group	55 ± 3	54 ± 2	53 ± 2	$P = 0.906$
COMBO group	52 ± 3	48 ± 1	50 ± 1	
Left ventricular mass index (g/m^2)				
CONTROL group	131 ± 7	132 ± 7	131 ± 7	$F = 11.940$
MODE group	139 ± 4	151 ± 4*	137 ± 4†	$P < 0.001$
COMBO group	125 ± 5	143 ± 6*	127 ± 6†	
Relative wall thickness (%)				
CONTROL group	19.5 ± 0.4	19.7 ± 0.4	19.8 ± 0.4	$F = 15.793$
MODE group	19.0 ± 0.5	20.7 ± 0.5*	19.3 ± 0.5†	$P < 0.001$
COMBO group	19.0 ± 1.0	20.2 ± 0.9*	18.9 ± 0.9†	
Stroke volume index (ml/m^2)				
CONTROL group	47 ± 2	47 ± 2	46 ± 2	$F = 1.861$
MODE group	51 ± 1	50 ± 1	50 ± 1	$P = 0.130$
COMBO group	48 ± 2	50 ± 2	48 ± 2	

Data presented as the mean ± SEM. CONTROL, sedentary control group; MODE, moderate-intensity resistance training group; COMBO, combined high-intensity resistance training and moderate-intensity aerobic exercise training group. *$P < 0.05$ versus baseline. †$P < 0.05$ versus 4 months.

univariate correlation analysis between the stroke volume index and carotid arterial compliance in a pooled population, these two functions were not correlated ($r = 0.05$, $P = 0.93$). Additionally, changes in carotid arterial compliance were not associated with changes in stroke volume index in the combined exercise group ($r = 0.19$, $P = 0.26$). Moreover, when analysis of covariance was performed with the stroke volume as the covariate, the overall results on carotid arterial compliance were essentially the same.

Discussion

The major findings of the present study are as follows. First, resistance training performed at a moderate intensity produced a magnitude of arterial stiffening similar to high-intensity resistance training previously reported [9]. Second, concurrently performed endurance training minimized arterial stiffening that was accompanied by high-intensity resistance training. These results suggest that a simultaneously performed aerobic training could negate and prevent the stiffening of carotid arteries caused by resistance training.

Historically, resistance training had been regarded as unsafe for individuals at high risk for future cardiac events because of the abrupt increases in blood pressure and myocardial oxygen demand during high-intensity resistance training [20]. These marked increases in arterial blood pressure during resistance exercise were thought to be initiating factors for arterial stiffening [8]. The majority of recent studies, however, have documented that low to moderate resistance training is a safe and viable form of exercise training as blood pressure increases are within the clinically acceptable range during moderate-intensity resistance training [21]. For these reasons, we hypothesized that resistance training performed at a moderate intensity would not result in a decrease in arterial compliance. In contrast to our working hypothesis, moderate resistance training significantly decreased arterial compliance (from 0.20 ± 0.01 to 0.16 ± 0.01 $mm^2/mmHg$), and the magnitude of the reduction in arterial compliance was similar to that we previously observed in high-intensity resistance training (from 0.20 ± 0.02 to 0.16 ± 0.01 $mm^2/mmHg$) [9]. Moreover, these changes in arterial compliance returned to the baseline levels a few months after the cessation of training, confirming that the change in carotid arterial compliance was indeed due to the effect of the moderate resistance training intervention. Furthermore, reductions in arterial compliance were accompanied by significant increases in left ventricular mass index and relative wall thickness, important clinical correlates of arterial stiffening. Even moderate-intensity resistance training therefore appears to stiffen or harden the large elastic arteries. Our present study provides a warning that even moderate resistance training, which is typically recommended to the general public, should be prescribed cautiously, especially for high-risk populations. However, one important consideration that should be emphasized is that the volume (i.e. three sets) of moderate-intensity resistance training used in the present study was still greater than that typically recommended for comprehensive health programs, where only one set of resistance exercises is recommended [6,7]. We therefore cannot exclude the possibility that moderate-intensity resistance training performed with fewer sets may not result in a reduction in arterial compliance.

In contrast to resistance training, regular aerobic exercise is shown to be efficacious in preventing and reversing arterial stiffening in healthy adults [10,11]. We hypothesized that by combining the stiffening effects of resistance training and the destiffening effects of endurance training, both interventions would negate each other and would cause no changes in arterial compliance. In the present study, we demonstrated that simultaneously performed endurance training prevented the reduction in arterial compliance that was accompanied by high-intensity resistance training. Additionally, there was a tendency for arterial compliance to increase with combined endurance and resistance training. From the standpoint of exercise adherence and compliance, this type of 'cross-training' is highly beneficial as it is more enjoyable and breaks the boredom that often results from long-term participation in a single exercise mode [22,23]. Taken together, these findings suggest that combined resistance and aerobic training may be an effective countermeasure for the unfavorable effects of strenuous resistance training.

It is not clear what physiological mechanisms explain the effects of combined training on arterial compliance. Chronic or repeated increases in flow exert their effects on endothelial vasodilatation by modulating the expression of nitric oxide synthase [24]. Carotid arteries

experience increases in blood flow and shear stress during aerobic exercise bouts [25,26], whereas carotid blood flow does not appear to change during resistance exercises [27,28]. Consistent with this, endothelial function is improved with regular aerobic exercise [29,30] as well as with combined resistance and aerobic training [31,32]. Resistance training alone, however, appears to have no effects on flow-mediated vasodilation [33]. One possibility is therefore that the combined aerobic and resistance training may have increased nitric oxide bioavailability, which in turn may have negated the opposing effects of resistance training on the arterial wall. Future studies will be needed to determine the physiological mechanisms underlying the influence of resistance and aerobic training on carotid arterial compliance.

Although endurance training performed concurrently with resistance training prevented the stiffening of carotid arteries, the magnitude of increases was larger in the combined training group than in the moderate-intensity training group in all exercises except for the leg curl. The strength gains were consistently smaller in the combined training group compared with the previously studied high-intensity resistance training alone [9], especially in the lower limbs. This occurred despite the fact that the same training intensity and volume were prescribed to both groups. These results are consistent with a number of previous studies demonstrating that subjects who perform a combination of endurance and strength training achieve lower strength gains than subjects performing weight training alone [34–36]. It should therefore be noted that simultaneous endurance and resistance training may prevent arterial stiffening, but could attenuate optimum gains in muscular strength. In order to minimize the antagonistic effects of endurance training on strength gains, it is recommended that strength and endurance training be performed on alternate days [36]. A smaller strength gain in the combined training group might confound the interpretation of our findings. The moderate-intensity resistance training that achieved much smaller strength gains, however, experienced a similar magnitude of arterial stiffening to the high-intensity training group. The effect of resistance training on arterial compliance therefore does not appear to be dependent upon the training intensity or strength gains.

There are several limitations of the present study that should be emphasized. First, the combined training group that performed moderate-intensity resistance training was not included in the present study. Because simultaneously performed endurance training negated the effects of 'high-intensity' resistance training, however, it is fairly reasonable to assume that it would negate the effects of 'moderate-intensity' (i.e. lesser stimuli) resistance training as well. Second, although arterial compliance and blood pressure often change simultaneously with interventions, changes in arterial compliance were not associated with the corresponding changes in blood pressure in the present study. Because changes in the elastic property of arteries appear to precede changes in blood pressure [37], it is possible that a longer duration of resistance training may have increased blood pressure. Third, we studied relatively small numbers of subjects in each group ($n = 11–16$), and included only young healthy men. Future studies targeting high-risk populations (e.g. the elderly) are needed.

In light of the current recommendation that resistance training should be incorporated into exercise prescription [5–7], the effects of resistance training to stiffen large elastic arteries are of particular concern. We examined two strategies that potentially prevent arterial stiffening associated with resistance training. We demonstrated that moderate-intensity resistance training produced significant reductions in arterial compliance. In contrast, combined resistance and aerobic training did not result in decreases in carotid arterial compliance. These results suggest that in order to negate and prevent the stiffening of carotid arteries caused by resistance training, aerobic training should be performed simultaneously with resistance training.

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ORIGINAL ARTICLE

Central circulatory and peripheral O_2 extraction changes as interactive facilitators of pulmonary O_2 uptake during a repeated high-intensity exercise protocol in humans

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Abstract It has frequently been demonstrated that prior high-intensity exercise facilitates pulmonary oxygen uptake ($\dot{V}O_2$) response at the onset of subsequent identical exercise. To clarify the roles of central O_2 delivery and/or peripheral O_2 extraction in determining this phenomenon, we investigated the relative contributions of cardiac output (CO) and arteriovenous O_2 content difference (a-$\bar{v}DO_2$) to the $\dot{V}O_2$ transient during repeated bouts of high-intensity knee extension (KE) exercise. Nine healthy subjects volunteered to participate in this study. The protocol consisted of two consecutive 6-min KE exercise bouts in a supine position (work rate 70–75% of peak power) separated by 6 min of rest. Throughout the protocol, continuous-wave Doppler ultrasound was used to measure beat-by-beat CO (i.e., via simultaneous measurement of stroke volume and the diameter of the arterial aorta). The phase II $\dot{V}O_2$ response was significantly faster and the slow component (phase III) was significantly attenuated during the second KE bout compared to the first. This was a result of increased CO during the first 30 s of exercise: CO contributing to 100 and 56% of the $\dot{V}O_2$ speeding at 10 and 30 s, respectively. After this, the contribution of a-$\bar{v}DO_2$ became increasingly more predominant: being responsible to an estimated 64% of the $\dot{V}O_2$ speeding at 90 s, which rose to 100% by 180 s. This suggests that, while both CO and a-$\bar{v}DO_2$ clearly interact to determine the $\dot{V}O_2$ response, the speeding of $\dot{V}O_2$ kinetics by prior high-intensity KE exercise is predominantly attributable to increases in a-$\bar{v}DO_2$.

Keywords High-intensity exercise · Cardiac output · Arteriovenous O_2 content difference

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Introduction

It has been consistently demonstrated that the pulmonary oxygen uptake ($\dot{V}O_2$) response to a bout of high-intensity [i.e., supra-lactate threshold (LT)] exercise is faster throughout the transient when recently preceded by a similar high-intensity bout, i.e., a "double-transition" protocol (e.g., Gerbino et al. 1996; MacDonald et al. 1997; Burnley et al. 2000; Fukuba et al. 2002). The majority of these studies (using cycle ergometer exercise) point to an attenuation of the $\dot{V}O_2$ slow component as the main mediator of this phenomenon (e.g., Burnley et al. 2000; Gerbino et al. 1996; Koppo and Bouckaert 2000; MacDonald et al. 1997). However,

even for a single high-intensity transition, there is still debate regarding the relative contributions of O_2 delivery to the exercising muscles (i.e., vascular limitation) and O_2 extraction (i.e., metabolic "inertia") consequent to intramuscular enzyme-linked control mechanisms (e.g., Grassi 2001; Hughson et al. 2001; Poole et al. 1994; Whipp et al. 2002) in determining the $\dot{V}O_2$ kinetic response. The characteristics of the $\dot{V}O_2$ kinetic response to the double-transition protocol has been widely addressed (see Jones et al. 2003 for review), but the details of the potential cardiovascular determinants still remain to be elucidated. For example, to what extent does the magnitude and time course of the cardiac output (CO; reflective of the central component) and the arteriovenous O_2 content difference (a-$\bar{v}DO_2$; indicative of the peripheral O_2 extraction component) contribute to the differences in $\dot{V}O_2$ between the first and second bouts of the double-transition protocol?

There are, to our knowledge, no studies that have tracked central cardiovascular changes throughout the double-transition protocol to establish their potential proportional contributions. Recent advances in continuous-wave Doppler ultra-sonography provide the opportunity for CO to be assessed continuously throughout the transients from measurements at the ascending aorta. We have, therefore, determined the magnitude and time course of the CO response simultaneously with that of $\dot{V}O_2$ throughout a high-intensity knee-extension double-transition exercise protocol in humans, thereby also allowing the dynamic features of the a-$\bar{v}DO_2$ response to be calculated via the Fick equation.

Methods

Subjects

Nine healthy Japanese subjects (5 women and 4 men: age = 29.1 ± 9.1 years; height = 165.8 ± 7.6 cm; body weight = 58.9 ± 14.0 kg, mean ± SD) were selected for the study on the basis of being able to provide high-quality Doppler signals from the ascending aorta. The subjects were all volunteers and were aware of all the testing procedures, having given informed consent to participate as approved by the ethics committee of the local institution (in accordance with the Declaration of Helsinki).

Exercise protocols

During preliminary investigations using high-intensity cycle ergometry, we found that the continuous measurement of loud, high-pitched audio signals and bright visual signals (required for accurate determination of the ascending aortic flow) was technically challenging due to the cardiac movement and interference from respiratory and body movements. In this study, we therefore adopted knee extension (KE) exercise with the subject strapped to the table by belts placed across the iliac spines and shoulder that allowed stable measurement of blood flow in the ascending aorta from continuous echo-Doppler applied via the supra-sternal notch. This both minimized the effects of body (especially thoracic) movement and allowed the subject to perform bilateral KE exercise in the supine position with the hips flexed and stabilized at an angle of approximately 150°: the lower leg being free to move over the required range of motion. The bilateral KE exercise involved lifting and lowering a weight at 1-s intervals (i.e., 60 cycles per min) for each leg in an alternating pattern. The weight was connected to the ankle by a wire-and-pulley mechanism. Timed audio signals provided the subjects with a constant rhythm to cue exercise cadence. Soft rubber was used to cushion the heel during knee flexion and to minimize eccentric muscle activation and maximize concentric muscle activation. A bar (that the subjects were required to touch with their toes on each leg excursion) was used to set the range of motion during the KE exercise, which was continuously monitored (and verbal feedback provided) to ensure a consistent lifting distance. The average lifting distance for this KE exercise protocol was 16.5 cm.

Initially, the subjects each performed a stepwise incremental KE exercise test (0.5 kg each 30 s, from a baseline of 0.5 kg) to the limit of tolerance, which occurred at a peak work rate of 18.3 ± 3.3 W for each leg. The main components of the protocol (each performed on different days) consisted of an initial 3-min resting control phase immediately followed by two consecutive 6-min KE exercise bouts separated by a 6-min resting recovery phase (a double-transition protocol). This was followed by a 6-min resting recovery. The work rate selected was 70–75% of the peak power achieved on the incremental test that consistently resulted in the development of a $\dot{V}O_2$ slow component but also ensured that each subject was able to sustain the 2 × 6-min exercise durations required by the double-transition protocol. Each subject performed the protocol on two occasions at the same time on different days.

Measurements

Ventilatory and gas exchange responses were determined breath-by-breath using a computerized meta-

bolic measuring system (RM-300, Minato Medical Co., Japan). Prior to each exercise test, a hot-wire flow-sensor and gas analyzers were calibrated by inputting a known volume of air (at several mean flow rates) and gas mixtures of known concentrations, respectively.

The time-serial CO was obtained using continuous-wave Doppler, a two-dimensional and M-mode echocardiography apparatus (SSD-2000, Aloka, Japan) to measure the mean blood velocity (V_{mean}) and diameter of the ascending aorta (just above the aortic valve), i.e., similar to standard, previously described, methods (Christie et al. 1987; Miyachi et al. 1998; Rowland et al. 1998; Nottin et al. 2002; Sugawara et al. 2003). Briefly, the ascending aorta was assumed to be circular, and its cross-sectional area (CSA) was calculated using the diameter measured by two-dimensional and M-mode echocardiography during supine rest. The insertion point of the aortic valve tips at end-diastole was set using two-dimensional imaging in the parasternal long axis view. The subsequent M-mode echocardiogram was recorded at the same level. The aortic diameter was measured at mid-systole and end-diastole from the mean of 3–5 consecutive cardiac cycles by the leading edge to leading edge method. Continuous-wave Doppler echocardiographic recordings of the ascending aortic blood velocity were obtained with a small-dedicated 2.0 MHz non-imaging transducer (SSD-870, Aloka, Japan) held in the supra-sternal notch. The ascending aortic flow was identified by a loud, high-pitched audio signal and a bright well-defined video display. The Doppler and simultaneous ECG signals were stored on S-VHS video during the protocol. They were subsequently digitally converted and analyzed using image analysis software (NIH image). The V_{mean} throughout a cardiac cycle was determined between consecutive R spikes by planimetry. The velocity integral was calculated as the product of V_{mean} and ejection time during a cardiac cycle. The stroke volume (SV) was calculated as the product of the velocity integral and aortic CSA. The CO was, therefore, calculated as the product of the SV and the simultaneous heart rate (HR). The arteriovenous O_2 content difference (a-$\bar{v}DO_2$) was calculated from the Fick equation by dividing $\dot{V}O_2$ by CO. A second-by-second time course was calculated for each variable by interpolation and then stored on disk for further analysis.

Data analysis

The temporal profiles of variables at the onset of both bouts of high-intensity KE exercise were displayed by 10-s averaged data. We did not, however, perform further model-based analyses of the response transients (such as time constants, gains or amplitudes) due to the limited confidence of the estimation resulting from the small-step increment of work rate and limited number of repetitions (Lamarra et al. 1987). Instead, the summarized data from all subjects were displayed at distinct time points: 0, 10, 30, 50, 90, 180 and 360 s after the onset of each bout (where time = 0 is the baseline value averaged from the 30 s immediately preceding the exercise onset). The value at each representative time was determined as average for a 10-s bin placed equidistant around each corresponding time point. Then, the difference between the $\dot{V}O_2$ values in bout 1 and bout 2 were determined [$\dot{V}O_2$ (second)/$\dot{V}O_2$ (first)] and used to calculate the relative contributions of CO and a-$\bar{v}DO_2$ to this difference in each subject i.e., similar to the method previously used by De Cort et al. (1991) and MacDonald et al. (2001). Briefly, the relative contribution of a-$\bar{v}DO_2$ to the speeding of the $\dot{V}O_2$ kinetics observed in bout 2 can be evaluated by assuming that the CO kinetic profile is unchanged between bouts. Consequently, the relative contribution of a-$\bar{v}DO_2$ can be calculated from a-$\bar{v}DO_2$ (second)/a-$\bar{v}DO_2$ (first). The same process can be applied to a-$\bar{v}DO_2$ (i.e., assuming both bouts follow the measured bout 1 profile) in order to calculate the relative contribution of CO [CO(second)/CO(first)] to the speeding of the $\dot{V}O_2$ kinetics observed in bout 2. The difference between the $\dot{V}O_2$ kinetic profiles during the double-transition protocol (i.e., the degree of speeding of the $\dot{V}O_2$ kinetics) can thereby be attributed to the quantitative contributions of CO and/or a-$\bar{v}DO_2$.

The increment in $\dot{V}O_2$ between 180 and 360 s of each exercise bout ($\Delta\dot{V}O_{2(6-3)}$) was used to estimate the magnitude of the $\dot{V}O_2$ slow component. In addition, the increment in $\dot{V}O_2$ between 120 and 360 s of each exercise bout ($\Delta\dot{V}O_{2(6-2)}$) was also calculated to aid direct comparison with other recently published data (e.g., Koppo et al. 2002).

The values are expressed as mean ± SD. The time-serial changes in the variables were tested with respect to the differences between first and second bouts by repeated-measures ANOVA with time. When a significant difference was detected, this was further examined by Tukey's post-hoc test. All statistical analyses were performed with SPSS for Windows (SPSS Inc.). The statistical significance was accepted at $P < 0.05$.

Results

Examples of the 10-s averaged $\dot{V}O_2$ and cardiac responses (i.e., HR, SV and CO) for a representative

subject during the double-transition KE protocol are shown in Fig. 1. The group mean on-transient responses are shown in Fig. 2 at 0, 10, 30, 50, 90, 180 and 360 s of each bout (where $t = 0$ represents the baseline preceding exercise onset). The temporal profile of $\dot{V}O_2$ after the onset of bout 2 was consistently and significantly higher than that in bout 1 for all values from 10 to 180 s, consistent with speeded $\dot{V}O_2$ kinetics. Note also that $\dot{V}O_2$ had recovered to its prior control value by the start of the second exercise bout ($\dot{V}O_2$ values at $t = 0$ were the same for both bouts). The $\Delta\dot{V}O_{2(6-3)}$ was significantly higher in bout 1 (78 ± 44 ml min^{-1}) compared to bout 2 (57 ± 36 ml min^{-1}). This was also the case for the $\Delta\dot{V}O_{2(6-2)}$ index (bout 1, 132 ± 51 ml min^{-1} vs. bout 2, 94 ± 42 ml min^{-1}).

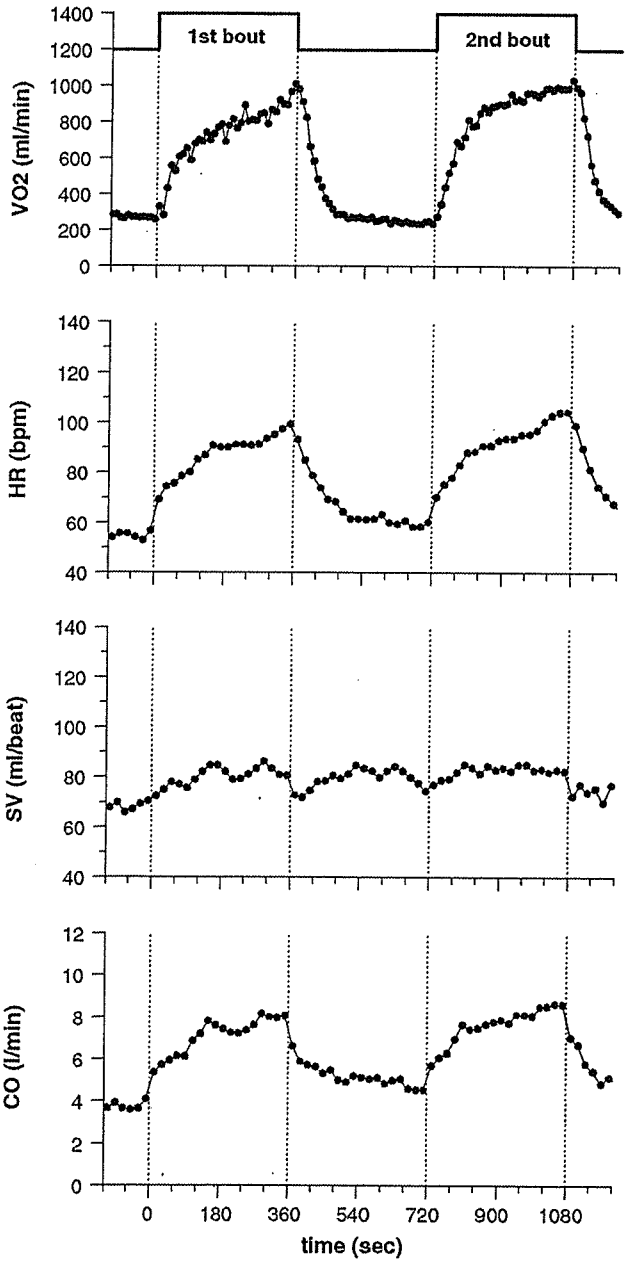

Fig. 1 The pulmonary $\dot{V}O_2$, heart rate (*HR*), stroke volume (*SV*) and cardiac output (*CO*) responses (averaged every 20 s) during repeated bouts of high-intensity knee extension exercise in a representative subject

Following the initial 20 s, CO showed a very similar temporal response during both exercise bouts, with the CO only being greater ($P < 0.05$) at 0 and 10 s of bout 2. In contrast, the HR remained significantly elevated throughout the bout 2, including the baseline prior to the exercise onset (Fig. 2). The a-$\bar{v}DO_2$ was significantly lower at the onset of the bout 2 as a consequence of the high CO residual from the prior exercise (Fig. 2). The difference of a-$\bar{v}DO_2$ between the bouts gradually widened after phase I and was significantly higher in bout 2 (compared to bout 1) by 180 s (Fig. 2). It is salient to note that the qualitative difference between the bouts in the $\dot{V}O_2$ profiles was closer to that of a-$\bar{v}DO_2$ than CO. We could not discern a slow component-like phase in the CO response in either bout: $\Delta CO_{(6-3)}$ bout 1, 0.21 ± 0.46 vs. bout 2, 0.40 ± 0.31 l min^{-1}. However, Δa-$\bar{v}DO_{2(6-3)}$ was significantly lower in bout 2 (–0.071 ± 0.401 ml 100 ml) compared with bout 1 (0.635 ± 0.388 ml 100 ml).

The relative contributions (expressed in %) of CO and a-$\bar{v}DO_2$ to the speeding of $\dot{V}O_2$ observed in bout 2 between 0 and 180 s (i.e., the region encompassing phase II) are displayed in Fig. 3. Using the 90 s time point as an example, the absolute mean values for $\dot{V}O_2$ increased from 617 ml min^{-1} in bout 1 to 656 ml min^{-1} in bout 2: an increase of 6.3%. The corresponding values for CO and a-$\bar{v}DO_2$ were 8.41 l min^{-1} and 73.34 ml l^{-1}, respectively, during bout 1, and 8.60 l min^{-1} and 76.31 ml l^{-1}, respectively, during bout 2. If it is assumed that CO did not change between bouts (i.e., was 8.41 l min^{-1} at 90 s in both bouts), then the expected increase in $\dot{V}O_2$ would be 8.41 l min^{-1} multiplied by 76.31 ml l^{-1}, or 642 ml min^{-1}. This can then be used to estimate the relative contribution of a-$\bar{v}DO_2$ to the speeded $\dot{V}O_2$ kinetics observed in bout 2, i.e., 642/617 ml min^{-1}, or 4%. A similar calculation for CO (assuming unchanged a-$\bar{v}DO_2$) yields an expected $\dot{V}O_2$ of 631 ml min^{-1} (i.e., 8.60 l min^{-1} multiplied by 73.34 ml l^{-1}). The relative contribution of CO was therefore estimated to be 631/617, or 2.3%.

These calculations were repeated for each individual at each time point. The increase in the $\dot{V}O_2$ of bout 2 was approximately 6–7% throughout the transient phase (i.e., until 180 s; Fig. 3). Using the approach described above, approximately 2–3% was attributable to a-$\bar{v}DO_2$ during the first 30 s, after which this con-

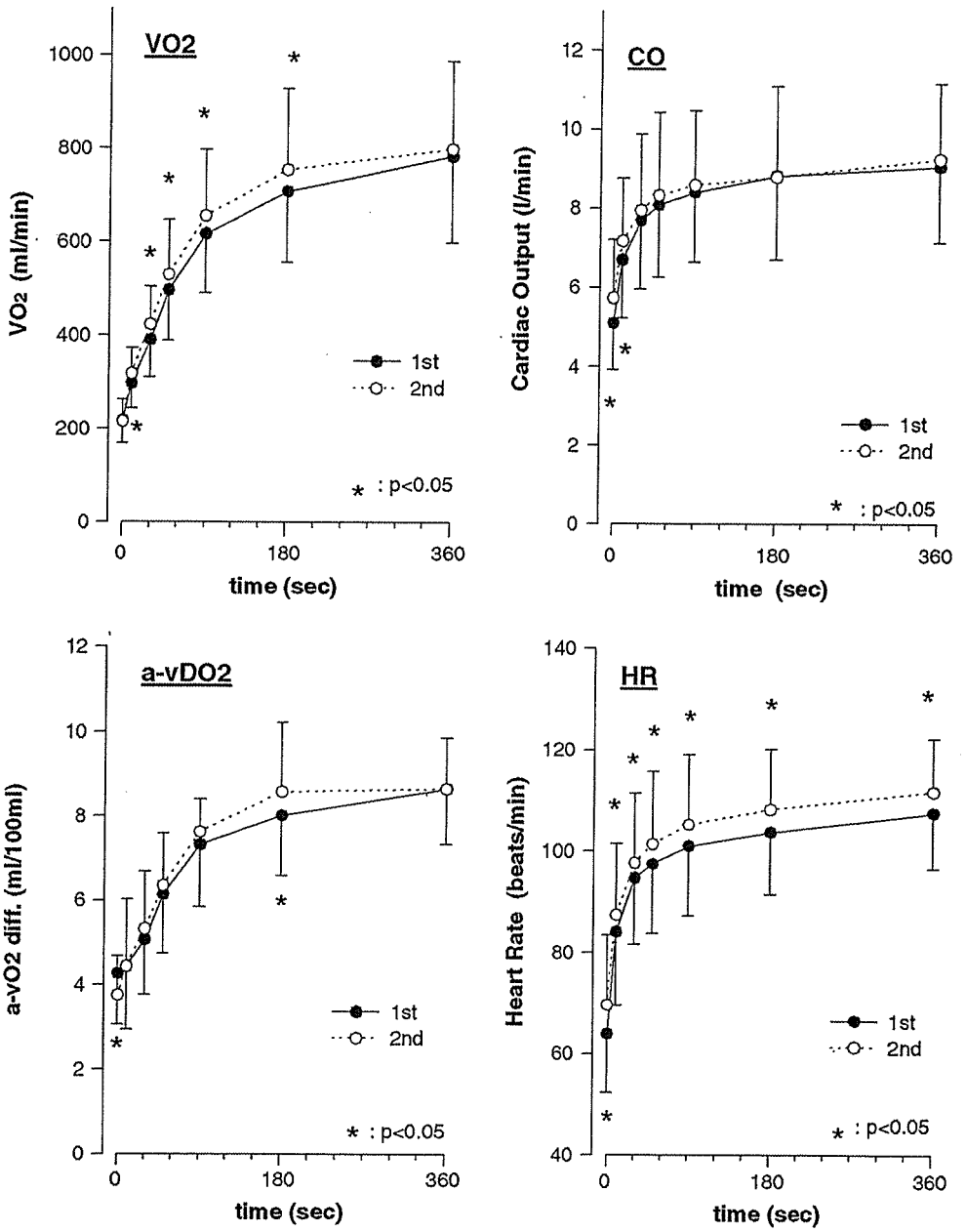

Fig. 2 The superimposition of pulmonary $\dot{V}O_2$, cardiac output (*CO*), arteriovenous O_2 content difference (a-$\bar{v}DO_2$) and hear rate (*HR*) responses determined at district time points during bout 1 (*filled circle*) and bout 2 (*open circle*) of repeated high-intensity KE exercise (group mean and SD). The values at time 0 represent the average of the 30 s baseline just prior to the exercise onset. *Asterisks* represent significant difference between first and second bouts ($P < 0.05$)

tribution continuously increased reaching 7% by 180 s. The higher $\dot{V}O_2$ measured at 180 s in bout 2 (compared to bout 1) could, therefore, be entirely attributed to a proportional increase in a-$\bar{v}DO_2$ by the end of phase II. The proportional contribution of CO showed the opposite trend. At 10 s, the higher $\dot{V}O_2$ in bout 2 could be entirely attributed to a proportionally higher CO. However, this proportional contribution fell rapidly over the initial 30 s and subsequently continued to decrease, such that by 180 s, none of the $\dot{V}O_2$ speeding could be attributed to CO (Fig. 3). There were statistical differences between contributions of both CO and a-$\bar{v}DO_2$ at 10 and 180 s (Fig. 3). Overall, following high-intensity KE exercise, the $\dot{V}O_2$ response to a second identical exercise bout 2 was ~7% greater at each time point considered from 0 to 180 s. This was consequent to interactive contributions by both O_2 delivery and extraction, with the predominant proportion attributable to a progressively increasing extraction (greater a-$\bar{v}DO_2$) following the initial 30 s of exercise (i.e., rising from 43 to 107% between 30 and 180 s of exercise).

Discussion

This investigation provides, we believe, the first description of the relative contributions of CO and

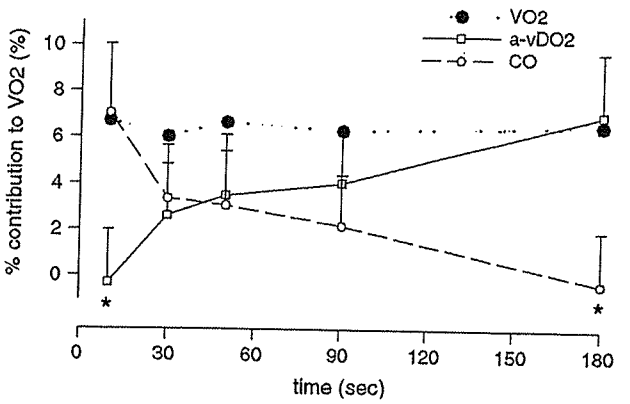

Fig. 3 The percentage contribution of arteriovenous O_2 content difference (a-$\bar{v}DO_2$) (*square*) and cardiac output (*CO*) (*circle*) throughout the transient, to the difference in $\dot{V}O_2$ (*closed circle*) between the first and second exercise bouts. See the detailed explanations in the text. *Asterisks* represent significant difference between CO and a-$\bar{v}DO_2$ contributions ($P < 0.05$)

a-$\bar{v}DO_2$ to the faster $\dot{V}O_2$ response manifest during the transient phase of the second bout of a repeated high-intensity exercise protocol. In order to determine both $\dot{V}O_2$ and CO in concert (and calculate a-$\bar{v}DO_2$) we used KE exercise, not cycle ergometry as is more typical. However, through solving the Fick equation using these measurements during KE exercise, we have elucidated the relative and interactive contributions to $\dot{V}O_2$ from central circulatory and peripheral O_2 extractive components. The findings suggest that the ~7% speeding of the $\dot{V}O_2$ kinetics in the second bout of the double-transition protocol are mainly derived from a gradually widening a-$\bar{v}DO_2$ (relative to that of the first bout). However, during a very early stage of the transition (the first 50 s after onset) the CO contributes to a greater degree to the speeding of $\dot{V}O_2$ in repeated bouts.

In the present study, we chose a conservative strategy to analyze the time-serial data without identifying kinetic parameters (see section Limitations). However, it should be noted that the relationships among CO, $\dot{V}O_2$ and a-$\bar{v}DO_2$ in the present study are compatible to those previously reported for a single transition of cycling exercise (e.g., Cummin et al. 1986; De Cort et al. 1991). Even without estimation of the kinetic parameters, it is clear from the profiles shown in Fig. 2 that the time course of CO is relatively faster than that of $\dot{V}O_2$ in both exercise transitions. Despite these faster kinetics, the magnitude of the CO increase (relative to that of $\dot{V}O_2$) is not adequate to prevent slow increases in a-$\bar{v}DO_2$ throughout the transient. By comparing the $\dot{V}O_2$ kinetics of two bouts of repeated high-intensity exercise, we were able to calculate the relative contributions of CO and a-$\bar{v}DO_2$ to the $\dot{V}O_2$ speeding in the second bout. To do this, we assumed that either of the two variables contributing to $\dot{V}O_2$ (i.e., CO or a-$\bar{v}DO_2$) would have the same absolute value throughout the bout 2 transition as that measured during bout 1. That is, with a-$\bar{v}DO_2$ assumed to respond in bout 2 precisely as it did during bout 1, we can calculate the degree to which an augmented CO may have contributed to the greater $\dot{V}O_2$ measured. Comparison of these calculated and measured $\dot{V}O_2$ values allows a relative weighting to be placed on either of the two components, CO or a-$\bar{v}DO_2$. These data suggest that CO had a relatively important contribution to the increment in $\dot{V}O_2$ during phase I and the following few seconds of bout 2 (the first ~50 s; Fig. 3). Consequently, mechanism(s) related to the peripheral extraction and utilization of oxygen seem to be relatively more important than central circulatory factors in determining the speeding of the phase II and III (i.e., 50–180 s after the exercise onset) pulmonary $\dot{V}O_2$ kinetics during the high-intensity double-transition protocol; although, of course, the interaction of both factors ultimately determine the $\dot{V}O_2$ kinetics.

We are aware of only one study with respect to "double-transition" protocol that has experimentally addressed the potential contribution of circulatory factors in determining the faster $\dot{V}O_2$ kinetics during bout 2. MacDonald et al. (2001) used a similar strategy to the present study to explore the relative contributions of peripheral "blood flow" (BF) and a-vDO_2 (where *v* means antecubital venous blood) to exercising limb $\dot{V}O_2$ (not pulmonary $\dot{V}O_2$) during repeated bouts of forearm exercise (lateral handgrip). In that study, the forearm $\dot{V}O_2$ was raised by ~30% at 30 s after exercise onset in bout 2 compared to bout 1. They calculated (using the same methods as those used here) that the increase in $\dot{V}O_2$ was consequent to a 25.1% increase in forearm BF and 3.7% increase in a-vDO_2. MacDonald et al. (2001) concluded that this relative contribution indicated that the major factor influencing exercising-limb $\dot{V}O_2$ was the increase in BF.

The main discrepancy between the study of MacDonald et al. (2001) and the present findings is the exercising muscle mass and the intensity of the exercise bouts. The limb $\dot{V}O_2$ in the study of MacDanolad et al. (2001) reached a plateau within 2 min and there was no evidence of a slow component, suggesting a light or moderate intensity (see Fig. 2 in MacDonald et al. 2001). During larger muscle mass exercise (such as cycling or KE), a speeded $\dot{V}O_2$ response is typically only manifest if the preceding exercise is above LT and $\dot{V}O_2$ consequently manifests a slow component. The discrepancy between the studies may, therefore, be derived from the difference in the relative intensity of

the exercise for the involved muscle mass adopted (e.g., Shephard et al. 1988). We suggest that when a larger, locomotory muscle mass is engaged in exercise, the predominant cause of speeded $\dot{V}O_2$ kinetics is an increase in a-vDO_2. In support of this notion, Endo et al. (2003) recently demonstrated that attenuation of central circulatory dynamics (reducing HR by cold face stimulation; CFS) applied at the onset of bout 2 during high-intensity cycling had no effect on the pulmonary $\dot{V}O_2$ response. This supports the notion that the speeded $\dot{V}O_2$ response during the double-transition protocol is not dominated by central factors.

Attenuation of the magnitude of the $\dot{V}O_2$ slow component by prior exercise was a characteristic of the present study. This is similar to previous observations during a double-transition protocol using cycle ergometry (e.g., Burnley et al. 2000; Gerbino et al. 1996; Koppo and Bouckaert 2000; MacDonald et al. 1997). However, in the present study the reduced $\dot{V}O_2$ slow component was not associated with an alteration of CO during KE exercise. Here, CO did not show evidence of a slow component-like phase, with $\Delta CO_{(6\text{-}3)}$ being essentially zero (bout 1: 0.21 ± 0.46 vs. bout 2: 0.40 ± 0.31 l min^{-1}). Rather the attenuation of the $\dot{V}O_2$ slow component was more closely associated with the profile of a-$\bar{v}DO_2$. This also indicates that O_2-extractive factor(s) appear to be more important in speeding the overall $\dot{V}O_2$ response dynamic using a double-transition protocol.

The present result revealed a relatively dominant contribution of a-$\bar{v}DO_2$ to the augmentation of the $\dot{V}O_2$ response during the high-intensity double-transition protocol. While it was, of course, determined by the effective interaction of both central circulatory and peripheral extractive factors, we calculated that a-$\bar{v}DO_2$ contributed to over 50% of the $\dot{V}O_2$ speeding (i.e., from 50 s onwards, or the majority of phase II). In line with previous suggestions, these findings indicate that the predominant determinants for the speeding of $\dot{V}O_2$ kinetics by prior exercise (and the consequent reduction of the $\dot{V}O_2$ slow component) is likely to be attributable to factors more proximal to the exercising limb (the lower limb in this case). One candidate was within the peripheral bulk circulation; that is a more efficient distribution of CO to the exercising limb. However, a recent study from our laboratory utilizing kinetic analyses (Endo et al. 2005) indicated that the optimization of femoral artery blood flow could not explain the faster pulmonary $\dot{V}O_2$ kinetics during the second bout of repeated high-intensity KE exercise. For blood flow to be responsible for a greater proportion of the speeded $\dot{V}O_2$ response, a flow optimization that is more peripheral than the femoral artery would be required. Such a mechanism is yet to be elucidated.

Intramuscular mechanisms, that are thought to determine $\dot{V}O_2$ kinetics, have been investigated during the double-transition protocol by Rossiter et al. (2001). These authors suggested that attenuation of the $\dot{V}O_2$ slow component following prior exercise in humans was consequent to an intramuscular "sparing" of [PCr] degradation. This suggestion that the $\dot{V}O_2$ slow component is determined by intramuscular mechanisms was in accordance with the findings of Poole et al. (1991), who showed that ~80–90% of the pulmonary $\dot{V}O_2$ slow component could be accounted for by an increase in the leg $\dot{V}O_2$. Consequently, the control of the $\dot{V}O_2$ slow component is typically ascribed to intramuscular factors in the exercising limb, rather than to the rest of the body. Therefore, the attenuation of the slow component by prior exercise (and perhaps the speeding of phase II kinetics) ought also to be determined by intramuscular events, such as the pattern of motor unit recruitment and/or fatigue (Barstow et al. 1996; Rossiter et al. 2002), intracellular factors other than O_2 availability (Hogan 2001; Behnke et al. 2002), which may arise from either activation of the pyruvate dehydrogenase complex (Timmons et al. 1998; Howlett and Hogan 2003; Rossiter et al. 2003), and/or be related to the attenuation of the blood lactate increase (Gerbino et al. 1996), or altered phosphate-mediated feedback control (Rossiter et al. 2001). Identifying the intramuscular source of the faster $\dot{V}O_2$ kinetics is, however, beyond the scope of this study.

Limitations

The development of the Doppler ultrasound technique for the measurement of time-resolved CO has made it possible to observe the kinetics CO throughout an exercise transition in greater detail than has previously been possible. Traditional non-invasive methods, such as CO_2 or acetylene rebreathing or prolonged exhalations (e.g., Sackner 1987), have poor time resolution and are therefore not ideal for kinetic observations. However, the continuous Doppler wave method is itself sensitive to signal "noise" derived from several technical and spontaneous sources. We attempted to minimize these by averaging two identical repetitions for each subject with simultaneous $\dot{V}O_2$ measurement. The $\dot{V}O_2$ kinetic responses were further enhanced by additional repetitions, with particular care not to induce significant training effects. Despite this, the CO responses were not sufficiently noise-free to confidently estimate kinetic parameters. We, therefore, chose a conservative strategy to analyze the time-serial

data without estimation of kinetic parameters in any of the measured or calculated variables. However, it should be noted that the relationships among CO, $\dot{V}O_2$ and a-$\bar{v}DO_2$ in the present study were very compatible to those previously reported for a single transition of leg dynamic cycling exercise (e.g., Cummin et al. 1986; De Cort et al. 1991).

In general, the KE exercise modality has frequently led to a reduction in the time constant of $\dot{V}O_2$ primary component (τ_p) as well as the magnitude of the $\dot{V}O_2$ slow component (e.g., Hughson et al. 2003; Fukuba et al. 2004; Rossiter et al. 2001). However, investigations using cycle ergometry typically find that prior exercise-induced changes are limited to the slow component region; in other words, the phase II $\dot{V}O_2$ τ_p is unaltered (e.g., Burnley et al. 2000; Endo et al. 2003; Gerbino et al. 1996; Koppo and Bouckaert 2000; Wilkerson et al. 2004). In addition, KE exercise can result in longer $\dot{V}O_2$ τ_p (~50 s) and higher fundamental gain ($\Delta\dot{V}O_2/\Delta W$; ~20 ml min^{-1} W^{-1}), compared to those seen during cycle erogmetry in healthy subjects (e.g., ~25–35 s; ~10 ± 1 ml min^{-1} W^{-1}) (e.g., Endo et al. 2005). The distinction between KE and cycle erogometry, therefore, may be of importance in this regard. Furthermore, because the KE exercise requires substantially high intramuscular force, there are presumably differences in circulatory adjustments (including CO) at the onset of KE exercise compared to cycle ergometry. Steady-state relationships among CO, $\dot{V}O_2$ and a-$\bar{v}DO_2$ in the present study (i.e., KE exercise) were, however, very compatible to those previously reported for a single transition of leg cycling ergometer exercise (e.g., Cummin et al. 1986; De Cort et al. 1991). Therefore, caution should be used in extrapolating the results of the present study to other modes of exercise, such as conventional cycling exercise.

In summary, this study demonstrated that: (1) the pulmonary $\dot{V}O_2$ was significantly higher between 10 and 180 s (and slow component reduced) after the onset of high-intensity KE exercise when preceded by an identical first bout of KE; (2) cardiac output manifests a faster on-transient time course than pulmonary $\dot{V}O_2$ throughout, but was unchanged between the phase II transient of the first and second exercise bouts; and (3) the apparent speeding of the $\dot{V}O_2$ response during the phase II region of bout 2 was initially greatly determined by a large contribution of CO, but later (and more predominantly), as a result of increased O_2 extraction. This suggests that the mechanism(s) modulating the speeding of the $\dot{V}O_2$ response during bout 2 of the double-transition protocol should be sought for in event(s) within the exercising muscles themselves.

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スポーツ用サプリメントの有効性と有害性

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スポーツ用サプリメントの有効性と有害性

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要旨

スポーツ用サプリメントは，競技成績やスポーツパフォーマンスを向上させ，試合や激しい練習で消費し不足する可能性がある栄養素を効率的に補うために用いられる。現在ではさまざまなスポーツ用サプリメントが市場に出回っており，トップアスリートからスポーツ愛好家まで幅広い人々に用いられている。エビデンスに基づき有効性が認められているサプリメントは，たんぱく質，炭水化物，重炭酸塩，クレアチン，カフェインであり，その数は多いとはいえない。単にその有効性のみならず，安全性，合法性と倫理性に照らし合わせ，適切に用いられるべきである。もし，本人が使用するべきか否か判断できない場合には，スポーツ科学に精通した科学者，医師，管理栄養士などの助言を仰ぐべきである。

はじめに

スポーツ用サプリメントは，①食品と同様の栄養成分を含み，便利さ，実用性，おいしさを組み合わせて具体的な必要を満たすもの，いわゆる栄養補助食品と，②一般に食物よりずっと多量の栄養成分を含み，特別な栄養ニーズを満たすというより薬理学的・生理学的作用を通じて機能補助または運動能力強化特性を持つもの，すなわちエルゴジェニックの二つの形態で市場に出回っており，比較的容易に購入することができる。

栄養補助食品は，**表1**に示す通り，清涼飲料水やスナック菓子などとほとんど区別がつかない形態や価格で市場に出回っている。アスリートやスポーツ愛好家だけではなく，運動習慣のない人もその味覚に魅かれたり，あるいは過剰に特定の効用を謳った広告などの影響を受け，摂取している場合が多い。栄養補助食品は基本的に食品なので，製品の広告やコマーシャルに謳われているほどの効果は期待できない。その一方で，副作用などの好ましくない影響もほとんどないので，安全性の面からは補助食品の摂取を強く否定する理由はない。

エルゴジェニックは運動能力強化特性を持つものとして売られており，**表2**の通り，筋量増加，成長ホルモン増産，脂肪減少，免疫機能，エネルギー産生，疲労回復などが効能として主張されている。しかし，これらの製品によって運動能力が向上することはまれである。仮に効果があると評価されているものでも，個人によって効果の程度は異なるかもしれない。また，そのような製品を不適切に使用して効果を低下させることもあるだろう。さらに，国際オリンピック委員会（IOC）や世界アンチ・ドーピング機構（WADA）の定める規則[1]により，「ドーピング」と考えられることもある。もしエルゴジェニック製品の使用を考えているならば，その有効性，安全性，合法性，適切な1回当たり摂取量についての最新情報を提供できるスポーツ科学者やスポーツドクターの専門的なアドバイスを求める必要がある。

アスリートやスポーツ愛好家がサプリメントを

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表1　スポーツ用栄養補助食品の製品形態

スポーツ栄養補助食品	含有物	使用方法
スポーツ・ドリンク	炭水化物6～7%／ナトリウム10～25 mmol/l	運動中の水分・炭水化物供給／運動後の水分・グリコーゲン回復
液状補助食	炭水化物50～70%／たんぱく質10～25%／ビタミン・ミネラル強化／液体でも粉末でもとれる	体重増加を助ける凝縮されたエネルギー供給源／運動後食欲がない場合に特に適した回復用スナック
炭水化物ローダー・パウダー	グルコース・ポリマー（ブドウ糖重合体）として炭水化物100%	レース前にグリコーゲン蓄積を最大化するために／運動後のグリコーゲン・レベルの回復
炭水化物ゼリー	袋当たり炭水化物20～30 g／各種添加物（アミノ酸，鉄分，カフェイン，ガラナ，ビタミンC・Eなど）	凝縮された炭水化物供給源／いつでも摂取できる
ビタミン・ミネラルのサプリメント	各ビタミンの食事からの推奨摂取量の全量を満たす／また特別なビタミン・ミネラルの大量摂取	エネルギー消費が少ない人／食事制限中や食品品質の保証がない国でレースする場合／欠乏症と診断された場合の治療
スポーツ・バー	炭水化物40～50 g／プロテイン10+g／ビタミン・ミネラル	凝縮された炭水化物供給源／いつでも摂取できる

用いる理由は二つある。① 競技成績やスポーツパフォーマンスを向上させること，② 試合や激しい練習で消費し不足する可能性がある栄養素を効率的に補うことである。現在では，トップアスリートのみならず，一般スポーツ愛好家，ひいては習慣的にスポーツをしていない人であっても，少なくともスポーツドリンクなどの栄養補助食品を飲食した経験はあると思われる。このように，スポーツ用サプリメントの使用は，あらゆるレベルのスポーツマンに広がっているが，サプリメント，特にエルゴジェニックを使用するべきか否かについては，以下の三つの点を十分に考慮する必要がある。

1）有効か：期待されたパフォーマンス向上が見込めるか？
2）安全か：心身を障害するような作用はないか？
3）合法的かつ倫理的か：ドーピングに相当しないか？　個人の倫理観に抵触していないか？

以上三つの点のうち，どれか一つでも問題がある場合にはスポーツ用サプリメントの使用を控えなければならない。

スポーツ用サプリメントの有効性

スポーツ用サプリメントが有効か否かについて判断する材料には以下の3点がある。① 製品の広告や雑誌・インターネットの記事，② アスリート個人の経験と証言，③ 研究による考察である[2]。結論から先にいえば，③ 研究による考察のみが信頼できる判断材料といって良い。

1．製品の広告や雑誌・インターネットの記事

栄養補助食品やエルゴジェニックを製造している企業は，利益を生むことが目的なので，製品による利益を追求するあまり本当の効果と懸け離れた効能を謳った広告を行う可能性がある。広告によるごまかしの手法の代表として，実験計画や精度が不十分な研究による発見，スポーツ団体のお墨付きや推薦，特許の申請があげられるが，そのいずれも製品の有効性を示すものではない。また，インターネットなどの規制のかけにくい媒体に真実と異なる記事を掲載し，製品の広告をリンクさせる手法なども近年頻繁に用いられている。

2．アスリート個人の経験と証言

一流アスリートをキャラクターに登用して販売促進を行う会社もある。アスリート自身は，この製品を使ってパフォーマンスが向上したとはいわないとしても，それをみた消費者（特にそのアスリートに憧憬を抱いている者）は，通常は効果があるのではという印象を受けやすい。また，実際にそれを自分で試してみたところ，試合で調子が良くなったと感じるかもしれない。このような個人的体験は“プラセボ効果”によるところが大き

表2　エルゴジェニックの効能とその科学的根拠

分類と品目	効　能	科学的根拠
栄養学的エルゴジェニック		
水分補給	心循環機能低下予防，体温調節，脱水予防	あり
炭水化物サプリメント	高強度運動のエネルギー源の補給	あり
プロテイン	筋量増加，筋力増強，栄養バランスの保持	あり
アルギニン，リジン，オルニチン	筋量増加，体脂肪率減少	なし
BCAA's，グルタミン	成長ホルモンの増産，筋肉の成長を刺激，疲労軽減，耐久能力，免疫能力の向上	なし
アスパラギン酸塩	遊離脂肪酸の利用高進とグリコーゲン節約	なし
抗酸化物（例：ビタミンA・C・E）	練習による筋肉の酸化損傷を軽減する	不明
葉酸	DNA合成の補酵素で赤血球増加に関与	なし
鉄分	エネルギー利用とたんぱく質合成向上，ヘモグロビン合成	なし
マグネシウム	筋量増加，筋力増強	なし
カルシウム	筋収縮の円滑化やエネルギー代謝にかかわる酵素の活性化	なし
ホウ酸	テストステロン上昇に伴う筋量増加と脂肪量減少	なし
クロム	血糖を低下させ，インスリン感受性を高め，糖代謝を活発化	なし
リン酸塩	代謝に重要な役割を持ち，エネルギー代謝を活性化し，赤血球数を増加させる	不明
HMB	筋肉の損傷とたんぱく質の破壊を抑制し，筋肉増強を促進する	不明
朝鮮人参	スタミナ補給	なし
生理学的エルゴジェニック		
重炭酸ナトリウム	乳酸蓄積を緩衝し，ミドルパワー競技での持久力を保持	あり
クレアチン	繰り返し行われる集中度の高い練習による疲労回復を促進する	あり
コエンザイムQ10	高強度運動によるフリーラジカルによる細胞ダメージを防ぐ	なし
コリン塩，レシチン	神経伝達物質の増加を補助	なし
グリセロール（アミノ酸の一つ）	強力な水分補強剤で練習前の摂取により水分不足を減らし体温維持効果がある	不明
カルニチン	遊離脂肪酸の利用高進とグリコーゲン節約	なし
薬理学的エルゴジェニック		
カフェイン	脂肪代謝を促進，神経系統を刺激，集中度の高い練習と耐久能力を強化する	あり
アルコール	鎮静剤として心理ストレスの緩和作用	なし

い。このような場合には，製品の意図しない効果も併せて発揮される場合がある。真に有効なサプリメントは，それが意図した通りのパフォーマンス向上効果だけがみられるはずである。

3．研究による考察

スポーツ用サプリメントの有効性を確認するためには“適切な”研究成果の集積が必要である。“適切な”研究とは，以下の条件が整っているものと考えて良いであろう。正当な原理や学問的背景，適切な被験者群，スポーツパフォーマンスや生理学的指標の適切な評価，十分な習熟試行と研究への慣れ，プラセボを用いた無作為割り付け介入，二重盲検，テストや評価環境の制御，適切な統計処理といった条件である。

研究の成果は，審査済み論文として学術誌に掲載されている。情報源としては，①個別研究，②権威ある専門家による総説，③統計学を駆使したメタ解析の三つであるが，後者ほどエビデンスレベルが高いといって良い。

スポーツ用サプリメントの分類と利用法

スポーツ用エルゴジェニックは，①通常の食品にも含まれる栄養素からなる栄養学的エルゴジェニック，②自然な生理機能を高進する働きを持つ生理学的エルゴジェニック，③ホルモンや神経伝

表3　スポーツ用サプリメントの機能と分類

サプリメントの機能	分類		
	栄養学的	生理学的	薬理学的
身体パワー増加のためのサプリメント			
筋量増加	たんぱく質・アミノ酸	成長ホルモン	アナボリックステロイド
代謝高進	ビタミン類	カルニチン	興奮薬
エネルギー供給の増加	炭水化物	クレアチン	アルコール
エネルギー源運搬の向上	鉄	血液	カフェイン
蓄積物質の中和	抗酸化物	重炭酸ナトリウム	抗消炎薬
精神力向上のためのサプリメント			
興奮を誘発	アミノ酸	コリン	アンフェタミン
鎮静に導く	ビタミンB	重炭酸ナトリウム	鎮痛薬
バイオメカニクス的効率を高めるサプリメント			
体重や筋量の増加	たんぱく質・アミノ酸	クレアチン	アナボリックステロイド
体重や脂肪の減少	クロム	成長ホルモン	利尿薬

達物質と同様に作用するように設計された薬理学的エルゴジェニックの三つに分類される。

スポーツのパフォーマンスを高めるためには，①身体的パワーの向上，②精神力の向上，③バイオメカニクス的効率の向上の三つの機序が重要であるが，真に有効なサプリメントは予想される機序によって意図した通りにパフォーマンス向上に寄与する。

表2と**3**にサプリメントの分類と，どの機序に基づいて作用するのか示した。

有効なスポーツ用サプリメントの実際

表2に各サプリメントの有効性に関するエビデンスの有無について示した[3~7]。多くのサプリメントの中で，意図通りの運動パフォーマンス向上が期待できるというエビデンスが十分に得られているのは，①たんぱく質，②炭水化物，③炭酸水素ナトリウム，④カフェイン，⑤クレアチンである。

1）たんぱく質は筋などの体を構成する材料であるが，激しいトレーニングを行っているアスリートでは体重1kg 1日当たり1.5~2.0gの摂取が必要で，これは一般人の1.5~2倍に相当するため，一般人と同じ質の食事を摂る場合には相当な食事量を摂取する必要がある。プロテインパウダーのような形態のたんぱく質サプリメントは，アミノ酸がバランスよく配合されており，正しい食事とトレーニングとの組み合わせで，筋量や筋力の増加が期待できる。

2）炭水化物は，原則として食事により摂取されることが望ましいが，試合前や試合の合間などにエネルギーを手早く補給する必要がある場合には，炭水化物サプリメントなどを利用すると良い。特に長時間の試合や，もしくは複数の試合が繰り返されることによるエネルギー枯渇を防ぐことや，炭水化物ローディングによる筋グリコーゲンの増加などに有用であり，粘り強さを引き出すことができる。

3）重炭酸ナトリウムは，血中乳酸の増加に伴う血液のアシドーシスを抑制し，45秒~6分間続く，中・長距離走のような運動のパフォーマンスを高める。

4）クレアチンサプリメントの摂取は筋中のクレアチン量を増加させ，クレアチンリン酸の再合成を容易にする。したがって，短時間，反復，高強度の競技のパフォーマンスの向上に有用である。

5）カフェインは，有効と考えられる五つのサプリメントの中で唯一これまでドーピング規則により記載されている物質であった（2005年1月1日以降除外された）。しかし，コーヒーでカップ7杯以上を摂取しないと陽性と判定されなかったが，それ以下のカフェイン摂取でも，覚醒状態を保ち，交感神経興奮ならびに遊離脂肪酸の利用を高める効果により，特に長時間運動のパフォーマンスを向上させるのに有効である可能性がある。