Effects of one-legged endurance training on femoral arterial and venous size in healthy humans

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Received 6 December 2000; accepted in final form 19 January 2001

Miyachi, Motohiko, Hirofumi Tanaka, Kenta Yamamoto, Akira Yoshioka, Kouki Takahashi, and Sho Onodera. Effects of one-legged endurance training on femoral arterial and venous size in healthy humans. J Appl Physiol 90: 2439–2444, 2001.—The cross-sectional area (CSA) of large-conductance arteries increases in response to endurance training in humans. To determine whether training-induced changes in arterial structure are systemic in nature or, rather, are confined to the arteries supplying exercising muscles, we studied 10 young men who performed one-legged cycle training [80% of one-legged peak O2 uptake (V̇O2 peak), 40 min/day, 4 days/wk] for 6 wk and detraining for another 6 wk. There were no significant differences in baseline one-legged V̇O2 peak and CSA of the common femoral artery and vein (via B-mode ultrasound) between experimental and control legs. In the experimental leg, one-legged V̇O2 peak increased 16% [from 3.0 ± 0.1 to 3.4 ± 0.1 (SE) l/min], arterial CSA increased 16% (from 84 ± 3 to 97 ± 5 mm²), and venous CSA increased 46% (from 56 ± 5 to 82 ± 5 mm²) after endurance training. These changes returned to baseline during detraining. There were no changes in one-legged V̇O2 peak and arterial CSA in the control leg, whereas femoral venous CSA in the control leg significantly increased 24% (from 54 ± 5 to 67 ± 4 mm²) during training. Changes in femoral arterial and venous CSA in the experimental leg were positively and significantly related to corresponding changes in one-legged V̇O2 peak (r = 0.86 and 0.76, respectively), whereas there were no such relations in the control leg (r = 0.10 and 0.17). When stepwise regression analysis was performed, a primary determinant of change in V̇O2 peak was change in femoral arterial CSA, explaining 70% of the variability. These results support the hypothesis that the regional increase in blood flow, rather than systemic factors, is associated with the training-induced arterial expansion. Femoral arterial expansion may contribute, at least in part, to improvement in efficiency of blood transport from the heart to exercising muscles and may facilitate achievement of aerobic work capacity.

maximal cardiac output and maximal arteriovenous O2 difference (19). Because as much as 80% of training-induced increase in maximal cardiac output is directed to working skeletal muscles during exercise (15), skeletal muscle blood flow capacity is known to increase with exercise training (19). According to the close coupling in systemic cardiovascular circulation (11, 16), large- and medium-sized conductance vessels between the heart and exercising skeletal muscles may also have to increase their size to accommodate the increased blood flow during dynamic exercise.

Several cross-sectional studies have documented larger luminal diameters in the main conduit artery of trained limbs in young adults who perform regular endurance exercise than in their untrained peers (9, 23, 28, 29). Consistent with these cross-sectional observations, we recently documented that several months of regular leg-cycling intervention increased cross-sectional area (CSA) of ascending aorta and abdominal aorta in young healthy men (13). However, it is not known whether the training-induced adaptation in large conduit arteries is systemic in nature or is localized to regions that receive increased blood flow.

Animal studies demonstrated that chronic increases in blood flow would result in dilatation of conductance arteries (5, 7, 26). These changes in arterial diameter appear to be endothelium dependent (10), and the flow-induced release of the endothelium-derived relaxing factor is thought to play an important role in modulating changes in vascular tone (20). Thus it is plausible to speculate that the regional increase of blood flow to exercising muscle is associated with the training-induced expansion of conductance vessels. However, this issue has not been directly addressed. Accordingly, we determined the effects of changes in blood flow induced by endurance training on the size of the femoral artery and vein in humans. To address effectively this aim, we employed a one-legged exercise training model (8). During one-legged cycle exercise, blood distribution to the exercising leg increases, whereas blood flow to the nonexercising leg decreases.

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exercise; ultrasound; vascular remodeling
or does not change (2). We reasoned that if arterial and venous expansion were obtained only in the experimental leg, the flow-induced process would be the underlying mechanism in the training-induced expansion of conductance vessels. Additionally, we used the detraining regimen after endurance training to determine whether the training-induced expansion observed after endurance training would be reversed.

METHODS

 Subjects. Ten young healthy men (22 ± 2 yr) volunteered for the study. Subjects were informed about the experimental procedures, potential risks, and discomfort and signed informed consent forms. The experiments were carried out with the approval of the Ethical Committee of the Kawasaki University of Medical Welfare.

 Experimental procedures and training program. Before the experiments, all subjects were familiarized with the one-legged cycle exercise. Subjects then underwent one-legged cycle-endurance training for 6 wk. The experimental and the control leg were chosen at random. Exercise was performed at an intensity that elicited 80% of each subject's peak O₂ uptake (V̇O₂peak) of one-legged cycle exercise for 40 min/day and 4 days/wk. As each one-legged V̇O₂peak of the experimental leg increased during the training period, one-legged exercise intensity was gradually increased from week to week as required to elicit 80% of the actual V̇O₂peak in the experimental leg. After the endurance training period, each subject underwent 6 wk of detraining. Before and after each intervention period, one-legged V̇O₂peak of the experimental and control legs and two-legged V̇O₂peak during incremental cycle exercise, left ventricular and ascending aortic dimension, and CSA of the common femoral artery and vein of the experimental and control legs were measured. Each subject was tested at the same time of day and was advised to maintain equivalent physical activity, other than that prescribed, on the day of and the day before each testing session. In addition, all subjects fasted for 3 h before each testing session.

V̇O₂peak. To measure V̇O₂peak, the incremental cycle exercise began at a work rate of 60 W for one-legged exercise and 120 W for two-legged exercise. The work rate was increased thereafter by 15 W/min until the subject could not maintain the required pedaling frequency (60 rpm). Heart rate and rating of perceived exertion were monitored throughout the exercise. O₂ consumption and minute ventilation were monitored during the last 30 s of each exercise stage after the rating of perceived exertion reached 18. The expired air was collected in Douglas bags. Expired O₂ and CO₂ gas concentrations were measured by mass spectrometry (model MGA 1200, Westron), and gas volume was determined using a dry gas meter (model NDS-2A-T, Shinagawa Dev).

 Left ventricular and conductance vessel size. Subjects were studied under quiet resting conditions while they were in the supine position. Left ventricular end-diastolic diameters (LVEDD) and systolic ascending aortic diameter were measured by M-mode echocardiography (model SSD870, Aloka) with the 2.5-MHz sector probe as previously described (22). The ascending aorta was assumed to be circular, and its CSA was calculated by diameter measured with M-mode ultrasound images at the point where the aortic valve leaflets were recorded. The cross-sectional two-dimensional ultrasound images of the common femoral artery and vein were obtained using a 6- to 13-MHz linear active matrix array probe (model LOGIQ 500 PRO, GE). CSA of the femoral artery and vein was measured below the inguinal ligament, ~2–3 cm above its bifurcation into the profundus and superficial branch artery, to reduce variation due to the measurement site. These images were recorded on a computer and on a magnetooptical disk for later off-line analysis.

All ultrasound images were analyzed using computerized image analysis software (NIH Image). All image analyses were performed by the same investigator, who was blinded to the assignment of experimental and control legs. Vessel sizes were measured at peak systole and end diastole. At least 10 measurements of CSA were taken, and the mean values of systolic CSA are reported. When we performed data analyses using end-diastolic CSA, the results were essentially the same as those performed using peak systolic CSA (data not shown). The reliability of the aortic CSA was previously reported by our laboratory (13). The intraobserver reliability of the femoral arterial and venous CSA in our laboratory was established by duplicate determinations for all subjects. Mean femoral arterial CSA was 85 ± 3 and 86 ± 3 mm² for trials 1 and 2, respectively (not significant); the correlation coefficient between trials 1 and 2 was 0.95 (P < 0.001); standard error of estimation was 4.5 cm². Mean femoral venous CSA was 55 ± 5 and 57 ± 5 mm² for trials 1 and 2, respectively (not significant); the correlation coefficient between trials 1 and 2 was 0.92 (P < 0.001); standard error of estimation was 3.9 cm².

Statistics. Changes in the dependent variables in response to interventions were assessed by repeated-measures ANOVA. In the case of significant F values, a post hoc test using the Newman-Keuls method was used to identify significant differences among mean values. Pearson's correlation and regression analyses were performed to determine the relation between variables of interest. Forward stepwise regression analysis was performed to determine independent, significant predictors of changes in V̇O₂peak. Values are means ± SE. Statistical significance was set at P < 0.05 for all comparisons.

RESULTS

 Subject characteristics, V̇O₂peak, and central cardiovascular parameters. Body mass and heart rate decreased and LVEDD increased during endurance training (Table 1). These values returned to the base-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>After Training</th>
<th>After Detraining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass, kg</td>
<td>68.2 ± 1.9</td>
<td>67.3 ± 1.9*</td>
<td>68.5 ± 2.1†</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>106 ± 4</td>
<td>105 ± 5</td>
<td>107 ± 5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>74 ± 6</td>
<td>77 ± 5</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>63.9 ± 3.4</td>
<td>56.8 ± 1.7*</td>
<td>63.8 ± 2.0†</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>46.5 ± 1.2</td>
<td>48.7 ± 1.2*</td>
<td>46.8 ± 1.5†</td>
</tr>
<tr>
<td>CSA of ascending aorta, mm²</td>
<td>637 ± 19</td>
<td>690 ± 24*</td>
<td>689 ± 19*</td>
</tr>
<tr>
<td>Two-legged V̇O₂peak, l/min</td>
<td>3.26 ± 0.16</td>
<td>3.61 ± 0.14*</td>
<td>3.47 ± 0.15†</td>
</tr>
<tr>
<td>One-legged V̇O₂peak, l/min</td>
<td>2.89 ± 0.10</td>
<td>3.36 ± 0.10*</td>
<td>3.08 ± 0.11†</td>
</tr>
<tr>
<td>Experimental leg</td>
<td>2.89 ± 0.10</td>
<td>3.36 ± 0.10*</td>
<td>3.08 ± 0.11†</td>
</tr>
<tr>
<td>Control leg</td>
<td>2.91 ± 0.10</td>
<td>3.01 ± 0.09*</td>
<td>3.03 ± 0.12*</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVEDD, left ventricular end-diastolic dimension; CSA, cross-sectional area; V̇O₂peak, peak O₂ uptake. *P < 0.05 vs. baseline; †P < 0.05 vs. after training.
line values after the detraining period. There were no changes in systemic systolic and diastolic blood pressure throughout the intervention. The two-legged VO₂peak and CSA of the ascending aorta significantly increased with endurance training and remained elevated after the detraining period. There was no significant difference in baseline one-legged VO₂peak between the experimental and control legs. In the experimental leg, one-legged VO₂peak significantly increased after training and returned to near baseline during detraining.

**Femoral arterial and venous CSA.** There was no significant difference in baseline femoral arterial CSA between the experimental and control legs (Fig. 1). Endurance training increased femoral arterial CSA in the experimental leg. The elevated arterial CSA returned to baseline during the detraining period. There were no such changes in the control leg throughout the interventions.

There was no significant difference in baseline femoral venous CSA between the experimental and control legs (Fig. 1). In both legs, the femoral venous CSA showed a significant increase after the training. The femoral venous CSA in the experimental leg returned to baseline during detraining.

**Relations between one-legged VO₂peak and cardiovascular structure.** In the experimental leg, changes in one-legged VO₂peak during training (after training vs. before training) and detraining (after detraining vs. after training) were significantly and positively related to corresponding changes in femoral arterial CSA ($r = 0.86$, $P < 0.001$) and femoral venous CSA ($r = 0.76$, $P < 0.001$; Fig. 2). However, there were no such relations between these parameters in the control leg. Further-
more, changes in one-legged $\dot{V}O_2$ peak in the experimental leg were significantly and positively related to changes in LVEDD ($r = 0.58$, $P < 0.01$) and CSA of ascending aorta ($r = 0.74$, $P < 0.001$). When stepwise regression analysis was performed to determine a significant and independent predictor of changes in one-legged $\dot{V}O_2$ peak in the experimental leg, the first and only variable entered was the change in femoral arterial CSA, accounting for $\sim 70\%$ of the variability of changes in one-legged $\dot{V}O_2$ peak.

Changes in femoral arterial CSA in the experimental leg were significantly and positively related with changes in LVEDD ($r = 0.49$, $P < 0.05$) and CSA of ascending aorta ($r = 0.87$, $P < 0.001$). However, changes in femoral arterial CSA in the control leg were not significantly related to changes in LVEDD and CSA in ascending aorta.

**DISCUSSION**

The key new findings from the present study as follows. First, one-legged endurance training induced femoral arterial and venous expansion in the experimental leg. Second, structural changes in the femoral artery induced by training and detraining were positively and strongly associated with corresponding changes in one-legged $\dot{V}O_2$ peak. These results suggest that the regional increase of blood flow may play a mechanistic role in inducing arterial remodeling in large-sized conductance arteries. Additionally, the femoral arterial expansion may facilitate transport of increased blood flow to exercising muscle and, thereby, the increase in maximal aerobic capacity.

**Femoral arterial expansion.** Vascular size is determined primarily by the intrinsic wall property and smooth muscle tone, both of which are affected by systemic and regional factors. Systemic factors include the chronic influence exerted by sympathetic-adrenergic tone and humoral factors (e.g., ANG II). Regional factors include increases in blood flow and shear stress during exercise. The flow (shear stress)-induced release of the endothelium-derived relaxing factor plays an important role in arterial expansive remodeling and in modulating vascular tone (5, 7, 10, 20, 26). During one-legged cycle exercise in humans, blood distribution to the exercising leg increases, whereas blood flow to the nonexercising leg decreases or does not change (2). In the present study, we demonstrated that there was no change in femoral arterial CSA in the control leg during the training and detraining period. Thus the present results suggest that regional, rather than systemic, factors appear to be associated with the training-induced expansion of a conduit artery. Moreover, our present findings are consistent with the hypothesis that endurance training can induce expansion in large-sized conductance arteries in the trained leg, presumably via a flow-induced adaptation.

Consistent with this concept, growing evidence suggests that expansive arterial remodeling is a nitric oxide (NO)-dependent process. Rudic et al. (21) determined flow-induced arterial remodeling in wild-type and endothelium-derived NO synthase-knockout mice and demonstrated that the knockout mice did not remodel their common carotid arteries in response to chronic reductions in blood flow. Thus, if the present results in humans do reflect a flow-induced remodeling process, it would seem reasonable to speculate that this may also be an NO-dependent process. Additionally, it is possible that increased matrix metalloproteinase activity may have played a role in inducing arterial enlargement, as has been shown in animal studies (1, 27). Clearly, further investigations are needed to determine the exact mechanism underlying this expansive remodeling process.

We wish to emphasize that the endurance exercise-trained state is not obviously associated with greater active limb conduit artery lumen size in experimental animals (12, 24). However, direct comparisons between these observations and those of the present investigation are difficult because of differences in species (e.g., bipeds vs. quadrupeds), training stimuli (e.g., forced treadmill running vs. voluntary cycling), and/or methodology (e.g., excised vs. intact artery).

**Femoral venous expansion.** Femoral venous expansion in response to endurance training was observed in the experimental leg, and this expansion was reversed during the detraining period. A previous cross-sectional study documented that young adult humans who perform regular endurance exercise demonstrate larger luminal diameters in inferior vena cava than untrained healthy controls (29). Additionally, we recently reported that several months of regular leg cycling increased CSA of abdominal inferior vena cava in young healthy men (14). To our knowledge, our findings are the first to demonstrate that endurance exercise can induce an increase in peripheral (femoral) venous size in healthy humans. These findings are consistent with the results from animal studies that postcapillary vascular resistance is decreased in hindlimbs from exercise-trained rats (6, 25). Taken together, these results are consistent with the hypothesis that endurance training exerts modulatory influences on the venous circulation.

Although the femoral arterial CSA did not change in the control leg, the femoral venous CSA in the control leg significantly increased during training. These results imply that regional and systemic factors may act on the training-induced expansion of the femoral vein. The regional factor of femoral venous expansion may be an increase of blood flow and shear stress to the wall of the femoral vein in the experimental leg. What systemic factors may be responsible for inducing venous expansion without increasing arterial size in the control leg? One possibility is the increase in blood volume. Endurance exercise is associated with increases in blood volume (3), and the increased blood volume may be distributed on the venous side of the vascular space, since the veins represent a more compliant reservoir (18). In this context, a previous study (4) indicated that 10 wk of endurance training elevated central venous pressure as well as blood volume.
Physiological significance of femoral vessel expansion. In the experimental leg, the changes in one-legged VO₂₇max during training and detraining were significantly and positively related to changes in femoral arterial and venous CSA. When we performed stepwise regression analysis to determine an independent predictor of changes in one-legged VO₂₇max, the first and only variable entered was the change in femoral arterial CSA, which explained ~70% of the variability. These results are in agreement with a recent study reporting that the diameter of the common femoral artery was strongly related to VO₂₇max (17). Collectively, these findings suggest that the femoral arterial expansion contributes, in part, to the adaptations in the efficiency of blood transport from the heart to exercising muscles and, in turn, may facilitate the achievement of maximal aerobic capacity.

Relations between central and peripheral adaptations. The one-legged endurance training and detraining also increased the size of the left ventricle and ascending aorta. Furthermore, these changes were significantly and positively related to changes in femoral arterial CSA in the experimental leg. Our present results are consistent with a previous study reporting that increase in stroke volume and decrease in leg vascular resistance during one-legged maximal exercise were closely associated with the increase in VO₂₇max induced by one-legged training (8). Taken together, these findings suggest that there is a coupling between central and peripheral cardiovascular adaptations in response to endurance training and that the cardiovascular coupling may result in the efficiency of blood transport from heart to exercising muscles.

Conclusions. Our findings support the hypothesis that the regional increase of blood flow, rather than systemic factors, is associated with the expansion of large-sized conductance arteries induced by exercise training. The femoral arterial expansion contributes, in part, to the improvement in the efficiency of blood transport from the heart to exercising muscles and may facilitate the achievement of maximal aerobic capacity in humans.

This study was supported by a grant-in-aid for scientific research from the Japan Society for the Promotion of Science and by a research grant from the Japanese Society for Rehabilitation of Persons with Disabilities.

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