

## Physical Conditioning Can Modulate Endothelium-Dependent Vasorelaxation in Rabbits

Hsiun-ing Chen and Hsing-Tan Li

To investigate whether exercise training can modulate endothelium-dependent vasorelaxation, male New Zealand White rabbits were divided into either control or training groups. The training animals were trained on a treadmill with a running speed of 0.88 km/hr on a 0° grade for 10–60 minutes/day, 5 days/week for 8 weeks. After exercise training, the resting heart rate was lowered ( $p < 0.05$ ). At the end of the experiments, three vessel segments, i.e., the thoracic aortas, the pulmonary arteries, and the common carotid arteries, were isolated and precontracted with norepinephrine. Acetylcholine-stimulated endothelium-derived relaxing factor (EDRF) release was assessed by bioassay in the presence of indomethacin ( $10^{-5}$  M). Basal release of EDRF was examined by the addition of hemoglobin. In addition, the relaxing responses of the thoracic aortas and pulmonary arteries to A23187, a calcium ionophore, and to sodium nitroprusside, a direct vasodilator of vascular smooth muscle, were compared between control and trained groups to further investigate possible underlying mechanisms. The results indicated that after exercise training 1) both the thoracic aorta and pulmonary artery, but not the carotid artery, became more sensitive to acetylcholine-induced vasorelaxation; 2) no significant differences in basal release of EDRF between control and trained rabbits were observed; and 3) there were no significant differences in the vascular responses to A23187 or sodium nitroprusside between the two groups. Our data suggest that exercise training may enhance endothelium-dependent vasodilation to acetylcholine via the stimulated EDRF release and that this elevated sensitivity to acetylcholine may not be caused by the alteration of the relaxing response in vascular smooth muscle. (*Arteriosclerosis and Thrombosis* 1993;13:852–856)

**KEY WORDS** • endurance exercise • endothelium • acetylcholine • rabbits • endothelium-derived relaxing factor

The vascular endothelium is the layer of squamous epithelial cells that is in direct contact with the blood. It not only serves as a diffusion barrier but also displays a variety of biological functions. In 1980, Furchgott and Zawadzki<sup>1</sup> discovered that the response of vascular strips to acetylcholine (ACh) was strongly dependent on the presence of the endothelial cell layer. Their experiments suggested the existence of a mediator passing from endothelial cells to induce the relaxation of vascular smooth muscle. This mediator has been termed endothelium-derived relaxing factor (EDRF). Since then, it was noticed that endothelial cells exert a significant role in the modulation of local vascular tone by the release of endothelium-derived constricting factor and EDRF.<sup>2,3</sup> Under pathophysiological conditions, the net balance between dilatory and constricting signals is disturbed. Previous studies have indicated that endothelium-dependent relaxation is significantly impaired in atherosclerosis and hypertension, and they suggested that decreased EDRF release may be the principal underlying mechanism re-

sponsible for the abnormal endothelium-dependent vasorelaxation.<sup>4–10</sup>

Based on epidemiological, clinical, and pathological studies, physical activity seems to play an important role in the prevention and treatment of several cardiovascular diseases.<sup>11–14</sup> Therefore, it is believed that appropriate physical activity may be a valuable tool in the therapeutic regimens for the control and amelioration of cardiovascular disease.<sup>15</sup> Since most of the evidence comes from retrospective and cross-sectional analyses of subject populations, the underlying mechanisms of this “exercise hypothesis” are still unclear. According to the above studies, we speculated that regular aerobic exercise may enhance endothelium-dependent vasorelaxation. In 1991, Rogers et al<sup>16</sup> found a decrease in responsiveness of canine coronary vascular smooth muscle to vasoactive relaxants after exercise training. However, no reports indicate whether endothelium-dependent vasorelaxation response would be altered by exercise training. Therefore, we conducted this study to evaluate the effects of exercise training on endothelium-dependent vasorelaxation in normal rabbits. Since flow could induce EDRF release,<sup>17,18</sup> we also wanted to know whether vessels that have various responses in blood flow during exercise would have different responses after exercise training. Therefore, the thoracic aortas in the systemic circulation, the pulmonary arteries in the pulmonary circulation, and the common carotid arteries

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in the cerebral circulation were studied. Furthermore, vascular responses to A23187, a calcium ionophore that induces EDRF release from endothelial cells without receptor activation, and the responses to sodium nitroprusside (SNP), a vasodilator that acts directly on smooth muscle, were also compared to investigate possible underlying mechanisms.

## Methods

### Animals

This study was conducted in conformity with the policies and procedures detailed in the *Guide for the Care and Use of Laboratory Animals*. Male New Zealand White rabbits were fed a standard diet and were housed in an environmentally controlled room. These animals weighed 0.8–1.2 kg at the beginning of the study and they weighed 2.7–3.5 kg at the end of the experiments. All animals were subcutaneously implanted with electrocardiographic electrodes under anesthetic conditions (30 mg/kg body wt ketamine and 20 mg/kg body wt sodium pentobarbital i.v. via the marginal ear vein). After a recovery period of 1 week, they were randomly assigned to either the control or the training group. Heart rates of the awake animal, either at rest or during exercise, could be monitored on a polygraph (Gould 2200S Recorder, Cleveland, Ohio).

### Exercise Protocols

The training protocol was modified from DiCarlo and Bishop.<sup>19</sup> After 1 week of familiarization, the training group ran on a leveled treadmill (model Q50, Quinton Instrument Co., Seattle, Wash.) in a Plexiglas cage at a speed of 0.88 km/hr for 10 minutes for the first week. During subsequent training weeks, the running time was extended 5–10 minutes each week up to 60 minutes/day. The rabbits were trained for 5 days/week for 8 weeks. The training intensity was approximately 70% of their maximal exercise capacity, which was estimated from heart rates. The control rabbits were regularly placed in the treadmill for similar periods of time. During the training period, resting heart rates before exercise were monitored weekly after 30 minutes of rest.

### Bioassay for ACh-Stimulated and Basal EDRF Release

To avoid the short-term effects of exercise, at least 48 hours after training the animals were anesthetized with ketamine (30 mg/kg i.v.) and pentobarbital (20 mg/kg i.v.), and the vessel segments were immediately obtained. All the vessels were dissected from the animals during the same period of time during the day to avoid diurnal variation. Rings of thoracic aorta, common carotid artery, and pulmonary artery (each 3 mm long) were carefully excised and submerged in organ chambers containing a Krebs-Ringer solution gassed with 95% O<sub>2</sub> and 5% CO<sub>2</sub> (37°C, pH 7.4). This solution had the following composition (in mM): 118.0 NaCl, 4.8 KCl, 2.5 CaCl<sub>2</sub>, 1.2 MgSO<sub>4</sub>, 1.2 KH<sub>2</sub>PO<sub>4</sub>, 24 NaHCO<sub>3</sub>, 0.03 Na<sub>2</sub>-EDTA, and 11.0 glucose. In addition, indomethacin (10<sup>-5</sup> M) was added to the solution to prevent the formation of endogenous prostaglandins.

After these vessel rings had been mounted on a force transducer, they were progressively stretched to the optimal passive tension at which the contractile re-

sponse evoked by norepinephrine (NE) was maximal. Our preliminary study showed that the optimal passive tension of these vessels was the same between control and trained groups, i.e., 9 g for the thoracic aorta, 8 g for the pulmonary artery, and 2 g for the common carotid artery. Functional integrity of the endothelium was confirmed by the fact that ACh could induce at least 80% relaxation in NE-precontracted specimens. After optimal tension had been obtained, vessel rings were equilibrated for 120 minutes. These specimens were then precontracted by a concentration of NE that was approximately equal to its median effective dose (ED<sub>50</sub>), i.e., 10<sup>-7</sup> M for thoracic aorta, 10<sup>-6</sup> M for common carotid artery, and 10<sup>-6</sup> M for pulmonary artery. NE-induced vasoconstriction was repeated at least three times until the response was stable. Dose responses of ACh-induced vasorelaxation were then evaluated by adding ACh cumulatively to the chamber solution. The ED<sub>50</sub> of ACh ([ACh]<sub>ED<sub>50</sub></sub>) for each vessel segment was obtained from its semilog dose-response curve. The geometric means of [ACh]<sub>ED<sub>50</sub></sub> were then analyzed. At the same passive tension described above, basal release of EDRF in each vessel ring was determined by the enhanced tension with addition of hemoglobin: 10<sup>-5</sup> M for the thoracic aorta and the pulmonary artery and 1.5×10<sup>-5</sup> M for the common carotid artery. Immediately after each experiment, the chambers were washed at least twice with Krebs-Ringer solution. Before starting the next experiment, more than 45 minutes' incubation was allowed as the equilibration time. The integrity of the vascular endothelium was proved by silver staining at the end of each experiment.<sup>20</sup> All chemicals used in this study were purchased from Merck (Darstadt, FRG), except NE, indomethacin, A23187, and hemoglobin, which were obtained from Sigma Chemical Co. (St. Louis, Mo.).

### Vascular Responses to A23187 and SNP

Since the statistical analysis of our experimental results indicated that both thoracic aortas and pulmonary arteries showed training-induced effects on ACh-induced vasorelaxation (see "Results"), the following experiments were also performed on those vessels to further investigate the possible underlying mechanisms of training effects.

Vessel rings were submerged in organ chambers and were progressively stretched to their optimal passive tension as described above. After optimal tension had been obtained, they were equilibrated for 120 minutes. The vessel rings were then precontracted by NE concentrations approximately equal to their respective ED<sub>50</sub>s. Dose responses of A23187-induced or SNP-induced vasorelaxation were then evaluated by adding these reagents cumulatively to the chamber solution. The ED<sub>50</sub> for each vessel segment was obtained from its semilog dose-response curve. The geometric means of each ED<sub>50</sub> were then analyzed for these two reagents.

### Statistics

Data in this study are presented as mean±SEM; the sample size represents the number of animals used. With the SPSS-PC+ statistical software package, the results were analyzed by using an unpaired Student's *t* test. Differences between control and trained groups were considered significant at *p*<0.05.

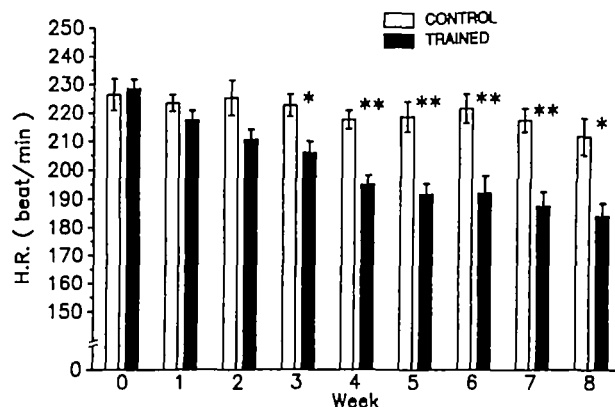


FIGURE 1. Bar graph showing comparison of resting heart rates (H.R.) between control and trained rabbits during the experimental period. Resting heart rates were significantly lowered after 3 weeks of endurance training. Data are presented as mean  $\pm$  SEM. \* $p<0.05$ ; \*\* $p<0.01$ .

### Results

#### Resting Heart Rates

After endurance exercise training, the trained rabbits had significantly lower resting heart rates than the control rabbits (Figure 1). This physiological finding indicated that our training protocol indeed had training effects.

#### Dose Response of ACh-Induced Vasorelaxation via Stimulated EDRF Release

Figure 2 illustrates a typical dose-response tracing of ACh-induced vasorelaxation. Since the response was executed in the presence of indomethacin ( $10^{-5}$  M) and was abolished by hemoglobin ( $10^{-5}$  M), an inhibitor of EDRF, the vasorelaxing effect was presumably caused by ACh-stimulated EDRF release. Figure 3 shows dose-response curves for the thoracic aorta and pulmonary artery in both groups. The results show that exercise training enhanced ACh-induced vasorelaxation in these two vessels. On the contrary, dose responses to ACh in the carotid artery were similar between control and trained groups (data not shown). In addition, the concentration of ACh that induced 50% of maximal vasorelaxation (i.e.,  $ED_{50}$ ) was compared between control and trained groups

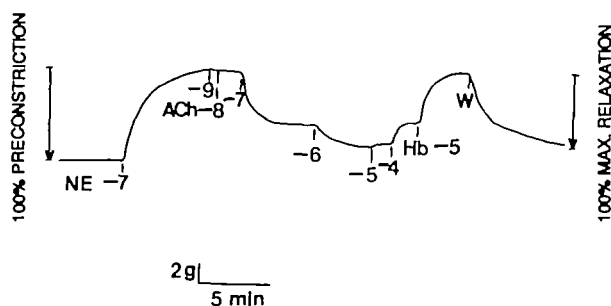


FIGURE 2. A typical tracing of vasorelaxation response induced by various concentrations of acetylcholine (ACh) ( $10^{-9}$ – $10^{-4}$  M) on a precontracted thoracic aorta. Hemoglobin (Hb) ( $10^{-5}$  M) was added at the end of this experiment to abolish endothelium-derived relaxing factor-related vasorelaxation. NE, norepinephrine; W, washout; max., maximal.

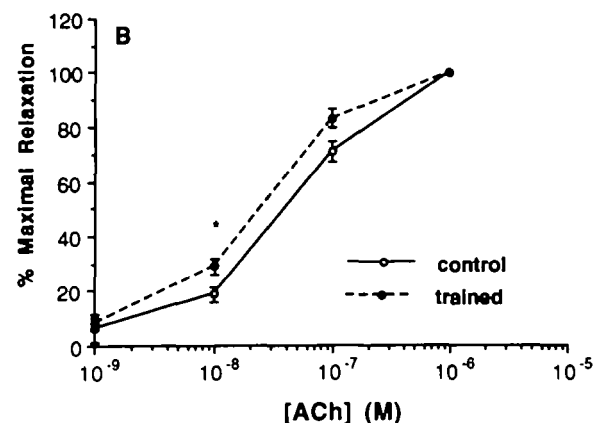
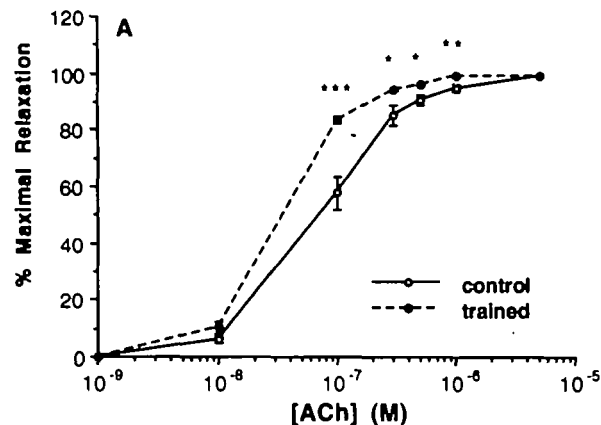


FIGURE 3. Line graphs showing dose-response relations of acetylcholine (ACh)-induced vasorelaxation after exercise training. Panel A shows relaxation response for the thoracic aorta; panel B shows relaxation response for the pulmonary artery. Each point represents the mean value of responses, and the vertical bars represent SEM. \* $p<0.05$ ; \*\* $p<0.01$ ; \*\*\* $p<0.001$ .

for the thoracic aorta, pulmonary artery, and carotid artery (Table 1). Our results show that the trained group had higher sensitivity of ACh-induced vasorelaxation, indicated by lower  $[ACh]_{ED_{50}}$ , in both thoracic aorta and pulmonary artery than did the control animals. Nonetheless, the common carotid artery was not significantly affected by exercise training. In addition, the concentrations of ACh needed to induce maximal vasorelaxation in the thoracic aorta and pulmonary artery were also reduced by exercise training (Table 1). In contrast, after exercise training there were no significant differences in ACh-induced maximal vasorelaxation responses, which was indicated by the reduction of vascular tension as percent of precontraction (Table 1).

#### Basal Release of EDRF

The basal release of EDRF was illustrated as the increased isometric vascular tension generated by adding hemoglobin. There was no significant difference due to training in EDRF basal release among the three studied vessel rings (Table 2).

#### Vascular Responses to A23187

Since the thoracic aorta and pulmonary artery, but not the common carotid artery, showed increased sen-

TABLE 1. Effects of Exercise Training on ACh-Induced Vasorelaxation

	Thoracic aorta		Pulmonary artery		Carotid artery	
	C (n=11)	T (n=12)	C (n=8)	T (n=11)	C (n=11)	T (n=12)
[ACh] <sub>ED<sub>50</sub></sub> (-log M)	7.15±0.08	7.51±0.02*	7.46±0.06	7.65±0.06†	7.30±0.16	7.50±0.02
[ACh] <sub>max</sub> (-log M)	5.24±0.12	5.82±0.08*	5.86±0.20	6.31±0.05†	4.64±0.24	4.98±0.15
Maximal relaxation (%)	94±3	100±3	85±2	83±1	105±2	107±3

ACh, acetylcholine; C, control rabbits; T, trained rabbits; ED<sub>50</sub>, median effective dose; Maximal relaxation (%), percent of the precontracted tension induced by norepinephrine. Data are expressed as mean±SEM. The numbers in parentheses are sample sizes.

\**p*<0.001; †*p*<0.05 (control vs. trained by unpaired Student's *t* test).

sensitivity to ACh-induced vasorelaxation, vascular responses to A23187 were carried out in these two vessels. The results indicate that the same amount of A23187 caused similar vasorelaxation; for instance, in the thoracic aorta, 10<sup>-7</sup> M A23187 reduced tension by 92.8±3.9% of precontracted tension for the control group, and this same concentration of A23187 caused a 96.2±3.1% reduction in the trained group. Similarly, 10<sup>-6</sup> M A23187 relaxed the pulmonary artery by 68.3±4.7% of the precontracted tension in the control and by 70.0±5.6% in the trained group. Table 3 shows no significant differences in ED<sub>50</sub> of A23187 between the two groups.

#### Vascular Responses to SNP

There were no significant differences in ED<sub>50</sub> of SNP between control and trained groups either in the thoracic aorta or in the pulmonary artery (Table 4). SNP (10<sup>-5</sup> M) relaxed the thoracic aorta of the control group by 91.4±1.7% of the precontracted tension and that of the trained group by 87.6±4.2%. Similarly, 10<sup>-5</sup> M SNP reduced pulmonary artery tension of the control group by 80.9±3.9% and that of the trained group by 74.4±7.9%.

#### Discussion

Our data demonstrated that after 8 weeks of endurance exercise training in normal rabbits, 1) both the thoracic aorta and pulmonary artery, but not the carotid artery, became more sensitive to ACh-induced vasorelaxation; 2) no significant difference in the basal release of EDRF was observed; and 3) there were no significant differences in response to A23187 and to SNP in either the thoracic aorta or pulmonary artery.

Our study is the first to report a training effect on EDRF release. Although there was no significant difference in basal release of EDRF in the studied vessels between control and trained groups, the response of ACh-stimulated EDRF release in the thoracic aorta and

pulmonary artery was more sensitive in the exercise-trained group (Figure 3 and Table 1). There are several possible explanations for this. First, since physical activity can increase the density of muscarinic receptors on the hippocampus,<sup>21</sup> exercise training may also increase the density of muscarinic receptors on the endothelial cell membrane, which in turn enhances the response of ACh-stimulated EDRF release. In this study, we found that A23187, a calcium ionophore that stimulates EDRF release without activating receptors on the endothelial cell membrane, induced similar relaxation responses in both control and trained groups (Table 3). This implies that exercise training may upregulate muscarinic receptors, which in turn increase ACh-stimulated EDRF release. Second, since chronically elevated blood flow can enhance agonist-stimulated EDRF release,<sup>17</sup> increased blood flow during repetitive exercise<sup>22</sup> may change endothelial function and increase the sensitivity of stimulated EDRF release. This is consistent with our findings that such increased sensitivity of ACh-induced vasorelaxation only occurs in the thoracic aorta and pulmonary artery, where blood flow may increase severalfold during exercise, but not in the common carotid artery, where blood flow remains relatively constant during exercise.<sup>22</sup> Finally, endurance exercise alters serum lipid and lipoprotein patterns, which in turn could be partially responsible for lowering the risk of coronary heart disease or atherosclerosis.<sup>14,23</sup> Previous studies also revealed that lipoproteins could inactivate or inhibit EDRF release<sup>24-27</sup> and that intensive physical activity could largely correct the lipid abnormalities of atherosclerosis-prone rats.<sup>28</sup> Therefore, the third possibility is that endurance-type exercise training may change the lipid pattern and consequently enhance EDRF release. However, whether this training-induced lipid pattern change causes any regional difference along the vasculature remains to be investigated.

To rule out the possibility that vascular smooth muscle per se became more sensitive to nitrovasodilators after exercise training, we compared the vascular

TABLE 2. Comparison of the Basal Release of EDRF Between Control and Trained Rabbits

Vessel	Tension increase (g) induced by hemoglobin	
	Control (n=6)	Trained (n=8)
Thoracic aorta	0.18±0.07	0.14±0.06
Pulmonary artery	0.25±0.09	0.18±0.03
Carotid artery	0.23±0.03	0.21±0.06

EDRF, endothelium-derived relaxing factor. Data are expressed as mean±SEM. The numbers in parentheses are sample sizes.

TABLE 3. Comparison of ED<sub>50</sub> of A23187-Induced Vasorelaxation Responses Between Control and Trained Rabbits

Vessel	ED <sub>50</sub> (-log M)	
	Control (n=6)	Trained (n=6)
Thoracic aorta	8.63±0.06	8.74±0.03
Pulmonary artery	7.89±0.29	7.52±0.11

ED<sub>50</sub>, median effective dose. Data are expressed as mean±SEM. The numbers in parentheses are sample sizes.



**TABLE 4. Comparison of ED<sub>50</sub> of Sodium Nitroprusside-Induced Vasorelaxation Between Control and Trained Rabbits**

Vessel	ED <sub>50</sub> (-log M)	
	Control (n=6)	Trained (n=6)
Thoracic aorta	7.13±0.13	7.11±0.20
Pulmonary artery	7.26±0.19	7.15±0.10

ED<sub>50</sub>, median effective dose. Data are expressed as mean±SEM. The numbers in parentheses are sample sizes.

responses to SNP, a direct vasodilator that acts on smooth muscle cells, between control and trained groups. Our results indicated that there was no significant alteration in the sensitivity to SNP of smooth muscle cells. Besides, canine coronary smooth muscle has been reported to have a lowered responsiveness to vasoactive relaxants after training.<sup>16</sup> Therefore, the enhanced ACh-induced vasorelaxation response was probably not due to an increased sensitivity of vascular smooth muscle to EDRF.

It is well known that vasospasm usually occurs in cardiovascular diseases. In this study, we found that exercise training could enhance receptor-mediated endothelium-dependent vasorelaxation. It might be one possible underlying mechanism to explain why regular exercise would be beneficial to human health.

From our results, we conclude that 8 weeks of endurance exercise training in normal rabbits may affect ACh-stimulated EDRF release in certain regions of the circulation and that this alteration may be due to upregulation of muscarinic receptors, which in turn increase EDRF release.

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