

Regular Aerobic Exercise Augments Endothelium-Dependent Vascular Relaxation in Normotensive As Well As Hypertensive Subjects

Role of Endothelium-Derived Nitric Oxide

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Background—Several nonpharmacological interventions, including exercise, are recommended in primary prevention of hypertension and other cardiovascular diseases in which the pathogenetic role of endothelial dysfunction has been suggested. We studied the effects of long-term aerobic exercise on endothelial function in patients with essential hypertension.

Methods and Results—The forearm blood flow was measured by strain-gauge plethysmography. The responses of forearm vasculature to acetylcholine were smaller in the hypertensive patients than in the normotensive subjects. There was no significant difference in forearm vascular responses to isosorbide dinitrate in the normotensive and hypertensive subjects. We evaluated the effects of physical exercise for 12 weeks on forearm hemodynamics in untreated patients with mild essential hypertension who were divided randomly into an exercise group (n=10) and a control group (n=7). After 12 weeks, the forearm blood flow response to acetylcholine increased significantly, from 25.8 ± 9.8 to 32.3 ± 11.2 mL · min⁻¹ · 100 mL tissue⁻¹ ($P < 0.05$), in the exercise group but not in the control group. The increase in the forearm blood flow after isosorbide dinitrate was similar before and after 12 weeks of follow-up in both groups. The infusion of N^G-monomethyl-L-arginine abolished the exercise-induced enhancement of forearm vasorelaxation evoked by acetylcholine in the exercising group. In normotensive subjects also, long-term aerobic exercise augmented acetylcholine-stimulated nitric oxide release.

Conclusions—These findings suggest that long-term physical exercise improves endothelium-dependent vasorelaxation through an increase in the release of nitric oxide in normotensive as well as hypertensive subjects. (*Circulation*. 1999;100:1194-1202.)

Key Words: exercise ■ nitric oxide ■ acetylcholine ■ endothelium ■ hypertension

Several nonpharmacological interventions are recommended in the primary prevention of hypertension and other cardiovascular diseases.¹ However, the antihypertensive and antiatherogenic mechanisms of exercise have not been fully clarified.

In hypertensive patients, endothelium-dependent vascular relaxation has been reported to be impaired in coronary,² forearm,^{3,4} and renal arteries.⁵ Endothelial dysfunction may be involved in the development of atherosclerosis and may increase the risk of cardiovascular and cerebrovascular diseases. The beneficial effects of regular physical exercise on endothelial function has been shown in experimental animals^{6,7} and healthy young men.⁸ However, there is no information in patients with essential hypertension.

Thus, in the present study, to evaluate the effects of aerobic exercise on endothelial function, we measured the forearm vascular responses to vasoactive agents, such as acetylcholine, an endothelium-dependent vasodilator, and isosorbide dinitrate (ISDN), an endothelium-independent vasodilator before and after a 12-week exercise treatment.

Methods

Subjects

We studied 17 Japanese patients with mild untreated essential hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg) who had no habit of exercise (13 men and 4 women; mean age, 47 ± 10 years). Patients with a history of hypercholesterolemia, diabetes mellitus, or a smoking habit were excluded. Fifteen normotensive healthy subjects (systolic blood

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pressure <140 mm Hg and diastolic blood pressure <80 mm Hg) (12 men and 3 women; mean age, 44±7 years) were used to compare endothelium-dependent and -independent responses of forearm vasculature at baseline. The study protocol was approved by the ethical committee of the First Department of Internal Medicine of Hiroshima University. Informed consent for participation was obtained from all subjects.

Ten patients (7 men and 3 women; mean age, 49±10 years) were subjected to regular aerobic exercise. A 4-week run-in period was followed by a 12-week physical exercise period. Seven patients (6 men and 1 woman; mean age, 44±8 years) were subjected to 12 weeks of follow-up without any lifestyle modification. During the run-in period, subjects remained sedentary, and blood pressures were stable. The patients were divided randomly into the exercising group and control group.

In addition, the same protocol was performed in 12 normotensive subjects apart from the group that was used to compare vascular responses at baseline. The subjects were divided randomly into the exercising group (6 men and 1 woman; mean age, 27±4 years) and the control group (5 men; mean age, 28±5 years).

Aerobic Exercise

Subjects undertook 30 minutes of brisk walking 5 to 7 times per week for 12 weeks. Subjects were asked to record the exercise performed and were to maintain their original lifestyle and dietary habits, especially their intake of sodium, potassium, calories, and alcohol. We checked the exercise performance sheet and measured 24-hour urinary excretions of sodium and potassium every 4 weeks. In the preliminary study, the intensity of brisk walking ordered was equivalent to 52±9% of the maximum oxygen consumption (n=5).

Measurement of Forearm Blood Flow

Forearm blood flow (FBF) was measured with a mercury-filled Silastic strain-gauge plethysmograph (EC-5R, D.E. Hokanson, Inc) as previously described.^{3,9} Forearm vascular resistance (FVR) was calculated as the mean arterial pressure divided by FBF. FBF was calculated by 2 observers who did not know the exercise status of the subjects and results from the linear portions of the plethysmographic recordings. The intraobserver coefficient of variation was 3.0±1.8%.

Study Protocol

The forearm vascular responses to acetylcholine (Daiichi Pharmaceutical Co) and ISDN (Eisai Pharmaceutical Co) alone and after the infusion of N^G-monomethyl-L-arginine (L-NMMA, Sigma Chemical Co) were evaluated at the beginning and at the end of the 12-week period. The study began at 8:30 AM with the subjects in the fasting condition. A 23-gauge polyethylene catheter (Hakow Co) was inserted into the left brachial artery for the infusion of acetylcholine, ISDN, and L-NMMA and for the recording of arterial pressure with an AP-641G pressure transducer (Nihon Kohden Co) under local anesthesia (1% lidocaine). Another catheter was inserted into the left deep antecubital vein to obtain blood samples.

After 30 minutes in the supine position, we measured basal FBF and arterial blood pressure. Then, the effects of the endothelium-dependent vasodilator acetylcholine and the endothelium-independent vasodilator ISDN on forearm hemodynamics were measured. Acetylcholine (7.5, 15, and 30 µg/min) and ISDN (0.75, 1.5, and 3.0 µg/min) were infused intra-arterially for 5 minutes at each dose. The FBF was measured during the last 2 minutes of the infusion. The infusions of acetylcholine and ISDN were carried out in a randomized fashion. Each study proceeded after the FBF returned to baseline.

After a 30-minute rest period, L-NMMA, an inhibitor of NO synthase, was infused intra-arterially at a dose of 8 µmol/min for 5 minutes, and acetylcholine and ISDN were administered.

No significant change was observed in arterial blood pressure or heart rate by intra-arterial infusion of either acetylcholine and ISDN alone and after L-NMMA infusion in any groups.

TABLE 1. Baseline Clinical Characteristics in the Normotensive Subjects and Hypertensive Patients

Variable	Normotensive (n=15)	Hypertensive (n=17)
Body weight, kg	64.1±11.2	64.2±13.1
Body mass index, kg/m ²	24.5±1.7	24.4±1.8
Systolic blood pressure, mm Hg	115.6±8.8	153.2±7.8*
Diastolic blood pressure, mm Hg	68.4±6.7	96.8±4.7*
Heart rate, bpm	69.3±6.2	71.9±7.9
Total cholesterol, mmol/L	5.01±0.69	5.03±0.72
Triglycerides, mmol/L	0.97±0.50	1.01±0.59
HDL cholesterol, mmol/L	1.43±0.26	1.36±0.24
LDL cholesterol, mmol/L	3.34±0.49	3.44±0.64
Serum glucose, mmol/L	4.8±0.5	4.9±0.8
Serum insulin, pmol/L	54.1±12.5	59.2±16.9
PRA, ng · L ⁻¹ · s ⁻¹	0.35±0.12	0.30±0.11
PAC, pg/mL	90.1±35.8	87.7±33.8
Plasma Ang II, pg/mL	18.8±11.1	24.6±13.2
Plasma norepinephrine, pmol/L	2.41±0.88	2.53±0.53
Plasma NOx, µmol/L	28.1±9.0	23.8±6.9
FBF, mL · min ⁻¹ · 100 mL tissue ⁻¹	4.6±1.2	4.5±1.3
FVR, mm Hg · mL ⁻¹ · min ⁻¹ · 100 mL tissue ⁻¹	18.3±4.0	25.5±3.6*

PRA indicates plasma renin activity; PAC, plasma aldosterone concentration; Ang II, angiotensin II; and NOx, nitrite/nitrate. All results are presented as the mean±SD.

**P*<0.05 vs normotensive.

Statistical Analysis

Results are presented as mean±SD. Values of *P*<0.05 are considered significant. Baseline parameters between the exercising group and the control group were compared by ANOVA with Bonferroni's test. Comparisons between before and after exercise with respect to changes in parameters were performed with adjusted means on an ANCOVA, with baseline data used as the covariates. Comparisons of dose-response curves of parameters during the infusion of drug were analyzed by ANOVA for repeated measures. Relationships between variables were determined by linear regression analysis. The data were processed by use of either the software package StatView IV (Brainpower) or Super ANOVA (Abacus Concepts).

Results

Clinical Characteristics

The systolic and diastolic blood pressures and FVR were significantly higher in the hypertensive patients than in the normotensive subjects. Other parameters were similar in the 2 groups (Table 1).

The responses of the FBF and FVR to acetylcholine were smaller in the hypertensive patients than in the normotensive subjects (Figure 1). The vasodilating effect of ISDN was similar in the 2 groups (Figure 1).

Effects of Aerobic Exercise on Baseline Clinical Characteristics and Endothelial Function in the Hypertensive Patients

The baseline values for parameters at week 0 were similar in the exercise and control groups (Table 2). In the exercising group, the frequency of aerobic exercise was 5.7±0.5 times per week. The urinary excretions of sodium and potassium

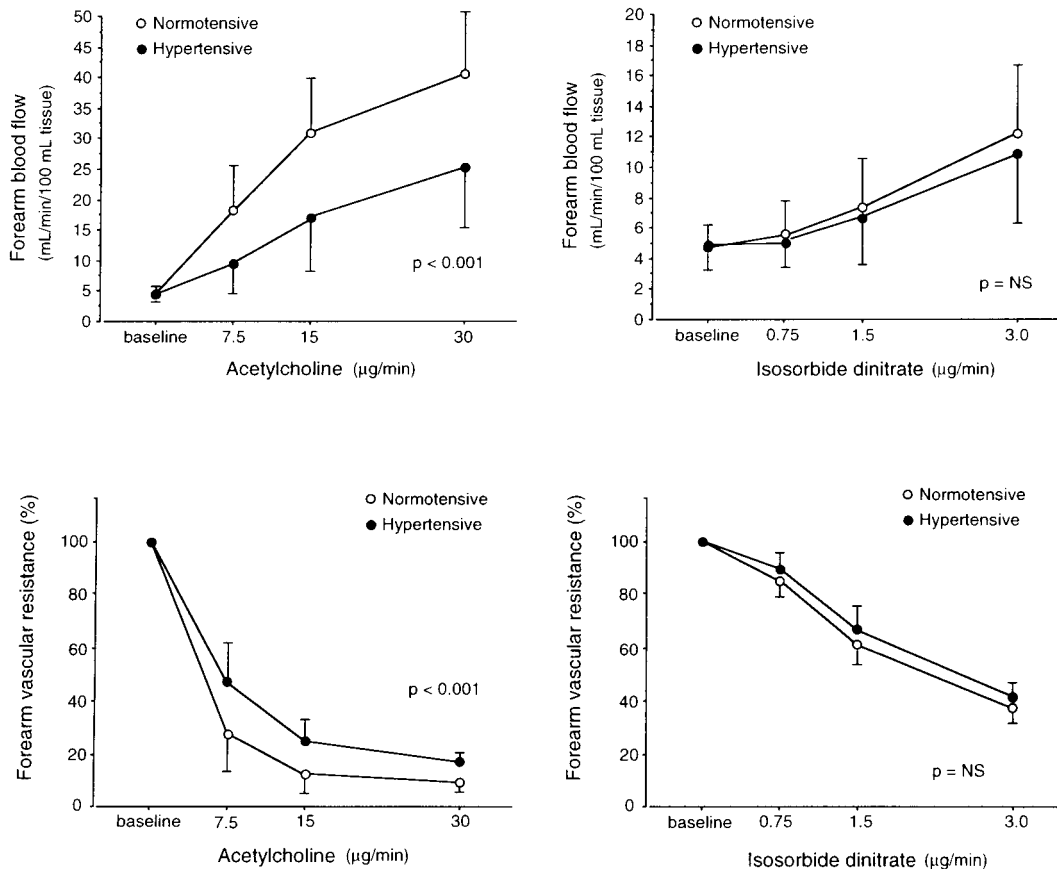


Figure 1. Effects of acetylcholine and ISDN on FBF and FVR in normotensive and hypertensive subjects.

were similar at 0 and 12 weeks and at each 4-week interval (data not shown) in both groups. The 12 weeks of aerobic exercise lowered the systolic and diastolic blood pressures, serum concentrations of total cholesterol and LDL cholesterol, plasma concentration of norepinephrine, and FVR and increased HDL cholesterol. Aerobic exercise did not affect the body weight, heart rate, basal FBF, or other parameters. In the control group, the baseline clinical characteristics were similar at 0 and 12 weeks of follow-up.

At baseline, these vasodilating effects of acetylcholine and ISDN were similar in the 2 groups.

The response of the FBF to the infusion of acetylcholine was increased significantly and that of FVR was decreased significantly by 12 weeks of exercise, but they were not altered by 12 weeks of follow-up in the control group (Figure 2).

The increase in the maximal FBF response to acetylcholine correlated significantly with the change in the ratio of total to HDL cholesterol ($r = -0.61$; $P < 0.05$) (Figure 3) and the decrease in LDL cholesterol ($r = -0.48$, $P < 0.05$) after 12 weeks. There was no significant correlation between the increase in the maximal FBF response and the change in mean blood pressure, norepinephrine concentration, or other parameters.

The increase in the FBF and the decrease in the FVR during the infusion of ISDN were similar at the beginning and end of the 12-week study period in both groups (Figure 4).

Effects of L-NMMA on the Forearm Vascular Response to Acetylcholine and ISDN in the Hypertensive Patients

L-NMMA significantly decreased basal FBF and significantly increased basal FVR in both the exercising group and the control group. The change in basal forearm vascular responses to L-NMMA was similar in both groups at the 0- and 12-week time points (Figures 5, 6, 9, and 10).

L-NMMA decreased the response to acetylcholine in both groups at both time points (Figures 2 and 5). L-NMMA abolished the enhanced response of forearm vasorelaxation to acetylcholine induced by 12 weeks of exercise in the exercising group (Figure 5). L-NMMA did not modify the response to ISDN at 0 and 12 weeks in either group (Figures 4 and 6).

Effects of Aerobic Exercise on Endothelial Function in the Normotensive Subjects

The 12 weeks of aerobic exercise lowered the serum LDL cholesterol (3.10 ± 0.56 to 2.71 ± 0.51 mmol/L, $P < 0.05$) and increased HDL cholesterol (1.38 ± 0.42 to 1.53 ± 0.44 mmol/L, $P < 0.05$). Aerobic exercise did not affect the blood pressure, body weight, heart rate, basal FBF, or other parameters. In the control group, the baseline clinical characteristics were similar at 0 and 12 weeks of follow-up.

At baseline, the vascular responses to acetylcholine and ISDN were similar in the 2 groups. The response of the FBF

TABLE 2. Baseline Clinical Characteristics Before and After 12 Weeks of Exercise in the Hypertensive Patients

Variable	Exercising Group		Control Group	
	Before (0 week)	After (12 weeks)	Before (0 week)	After (12 weeks)
Body weight, kg	63.7±13.8	63.6±13.9	65.1±12.3	65.1±12.5
Body mass index, kg/m ²	24.3±1.8	24.2±1.8	24.5±1.7	24.5±1.7
Systolic blood pressure, mm Hg	151.6±7.0	144.3±6.9*†	155.6±8.9	155.1±9.2
Diastolic blood pressure, mm Hg	96.2±4.7	92.0±5.2*†	97.6±4.8	96.9±9.3
Heart rate, bpm	73.2±9.8	69.8±9.6	70.1±5.2	68.9±5.0
Total cholesterol, mmol/L	5.08±0.75	4.48±0.58*	4.98±0.69	4.96±0.71
Triglycerides, mmol/L	1.04±0.54	0.98±0.52	0.96±0.66	1.01±0.62
HDL cholesterol, mmol/L	1.33±0.21	1.49±0.31*	1.44±0.28	1.43±0.29
LDL cholesterol, mmol/L	3.52±0.67	2.78±0.56*	3.33±0.59	3.32±0.61
Serum glucose, mmol/L	4.9±0.9	4.7±0.8	4.8±0.6	4.8±0.6
Serum insulin, pmol/L	61.3±17.8	58.2±18.6	56.3±15.8	55.9±16.5
PRA, ng · L ⁻¹ s ⁻¹	0.29±0.12	0.24±0.18	0.31±0.09	0.30±0.12
PAC, pg/mL	86.2±41.2	80.1±38.6	89.8±23.3	90.1±24.6
Plasma Ang II, pg/mL	23.1±12.1	20.2±11.5	26.8±14.7	27.3±14.9
Plasma norepinephrine, pmol/L	2.66±0.57	1.87±0.72*	2.34±0.48	2.29±0.61
Plasma NOx, μmol/L	24.6±7.3	26.1±7.9	22.8±6.3	22.6±6.2
Urinary sodium excretion, mmol/d	148±40	136±45	128±42	126±38
Urinary potassium excretion, mmol/d	76±8	74±7	73±9	70±7
FBF, mL · min ⁻¹ · 100 mL tissue ⁻¹	4.5±1.2	4.7±1.3	4.6±1.4	4.5±1.3
FVR, mm Hg · mL ⁻¹ · min ⁻¹ · 100 mL tissue ⁻¹	25.6±3.2	23.2±2.8*	25.4±4.1	25.8±4.2

Abbreviations as in Table 1. All results are presented as mean±SD.

**P*<0.05 vs before (0 week), †*P*<0.05 vs control group (after).

to the infusion of acetylcholine was increased significantly and that of FVR was decreased significantly by 12 weeks of exercise, but they were not altered by 12 weeks of follow-up in the control group (Figure 7). The increase in the FBF and the decrease in the FVR during the infusion of ISDN were similar at the beginning and end of the 12-week study period in the exercising group and the control group (Figure 8). The intra-arterial infusion of L-NMMA decreased the response to acetylcholine in both groups at both time points. L-NMMA abolished the enhanced response of forearm vasorelaxation to acetylcholine induced by 12 weeks of exercise in the exercising group (Figure 9). L-NMMA did not modify the forearm vascular response to ISDN at 0 and 12 weeks in either group (Figure 10).

Discussion

These findings suggest that acetylcholine-induced vasodilation in forearm arteries was significantly blunted in patients with essential hypertension and that long-term mild physical exercise not only lowers blood pressure but also improves endothelium-dependent vasorelaxation in patients with mild essential hypertension through the increased release of NO. In addition, acetylcholine-stimulated NO release was augmented by long-term aerobic exercise in the normotensive subjects.

One possible mechanism by which long-term aerobic exercise augments acetylcholine-stimulated NO release is an increase in vascular shear stress resulting from increased

flow. Acute or chronic increases in shear stress patently stimulate the release of NO in isolated vessels¹⁰ and cultured cells.¹¹ Sessa et al¹² recently demonstrated that, in epicardial coronary arteries of dogs, the increase in shear stress for 10 days of treadmill exercise enhanced the expression of the vascular endothelial constitutive NO synthase gene, leading to acetylcholine-stimulated NO release. In addition, chronic increases in shear stress have been shown to lead to functional and histological alterations of vascular endothelium, resulting in enhanced vascular structure and function.¹³

In the present study, a 12-week aerobic exercise program raised HDL cholesterol but lowered total cholesterol and LDL cholesterol. These findings are consistent with previous studies of long-term exercise.^{1,8} Several lines of evidence have shown that there is a potent relationship between the total serum cholesterol level and the endothelium-dependent vascular response to acetylcholine in forearm circulation¹⁴ and that cholesterol-lowering and antioxidant therapy restored an impaired endothelium-dependent vasodilation.¹⁵ Oxidized LDL, LDL that has undergone oxidative modification, has been shown to interfere with the formation of NO¹⁶ and to directly inactivate NO.¹⁷ In the present study, there was a weak but significant correlation between the change in the ratio of total to HDL cholesterol and in LDL cholesterol and the increase in forearm vascular response to acetylcholine after exercise. Although we did not directly measure

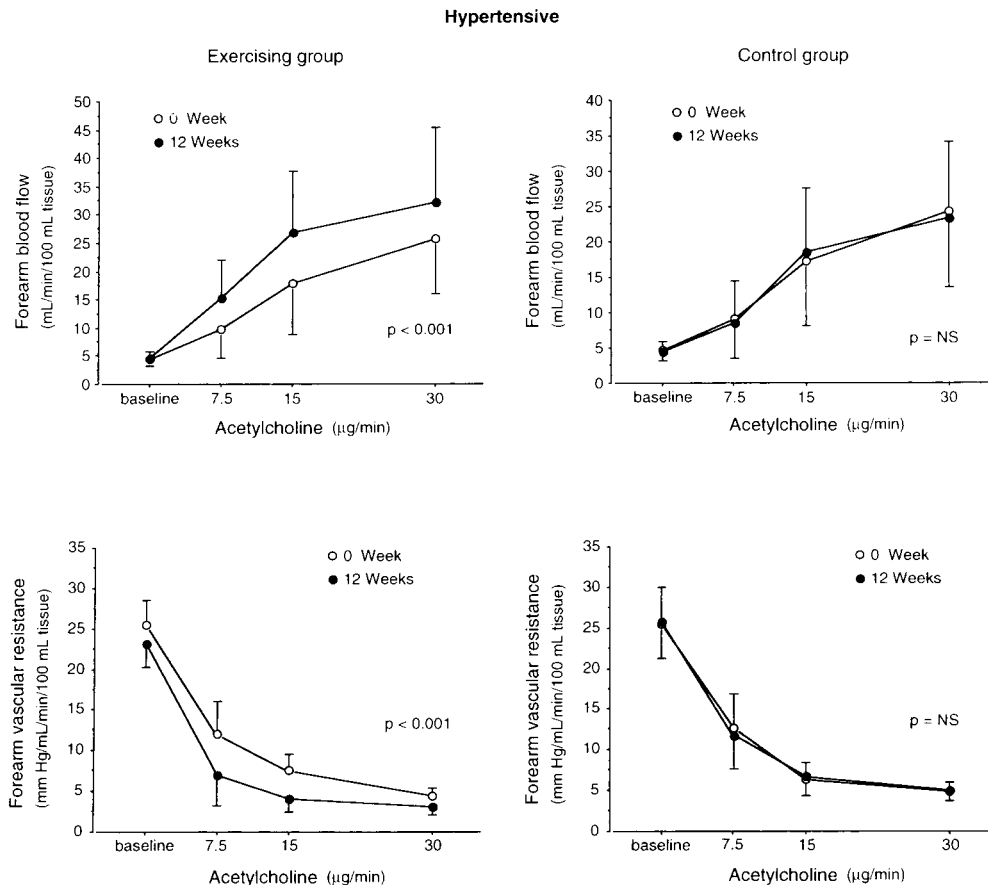


Figure 2. Effects of acetylcholine on FBF and FVR before and after 12 weeks of exercise in exercising group and control group in hypertensive patients.

oxidized LDL, the exercise-induced reduction in cholesterol, including lowered oxidized LDL, may, at least in part, contribute to the augmented forearm vascular response to acetylcholine.

Daily aerobic exercise significantly lowered the systolic blood pressure by 7 mm Hg and the diastolic blood pressure by 4 mm Hg. One could raise the possibility that the reduced blood pressure caused by exercise improved endothelial dysfunction in essential hypertension. It is controversial whether lowered blood pressure improves endothelial dys-

function in the forearm circulation of patients with essential hypertension.^{18,19} In the present study, there was no significant correlation between exercise-induced reduction in blood pressure and the increase in forearm vascular response to acetylcholine after exercise. In addition, aerobic exercise augmented endothelium-dependent vasodilation but did not alter blood pressure in the normotensive subjects. Therefore, the reduction in blood pressure may not contribute to the improved response of forearm vasculature to acetylcholine and the increase in NO release.

It is well known that there is an interaction between NO and norepinephrine, one of the vasoconstricting factors and an index of the sympathetic nervous system.²⁰ There is a possibility that regular exercise plays an important role in protecting the endothelium through the reduction in norepinephrine, leading to augmented acetylcholine-stimulated NO release. In the present study, long-term aerobic exercise significantly reduced plasma norepinephrine concentration. However, the decrease in norepinephrine did not correlate with the increase in the forearm vascular response to acetylcholine after exercise.

In conclusion, it is clinically important that walking, a safe form of daily exercise, not only can lower blood pressure but also may improve endothelial function in essential hypertensive patients. The improved acetylcholine-induced NO release by long-term aerobic exercise was not specific for patients with essential hypertension.

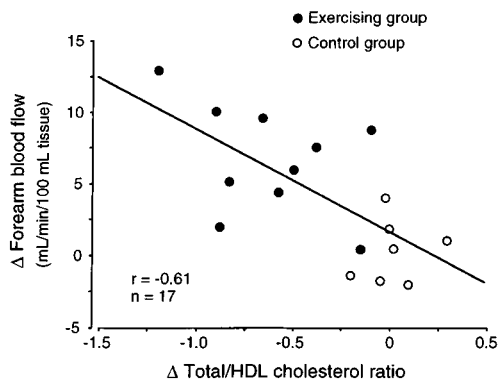


Figure 3. Relationship between change in ratio of total cholesterol to HDL cholesterol (Δ total/HDL cholesterol ratio; x axis) and increase in maximal FBF response to acetylcholine (Δ FBF; y axis) after exercise in hypertensive patients.

Hypertensive

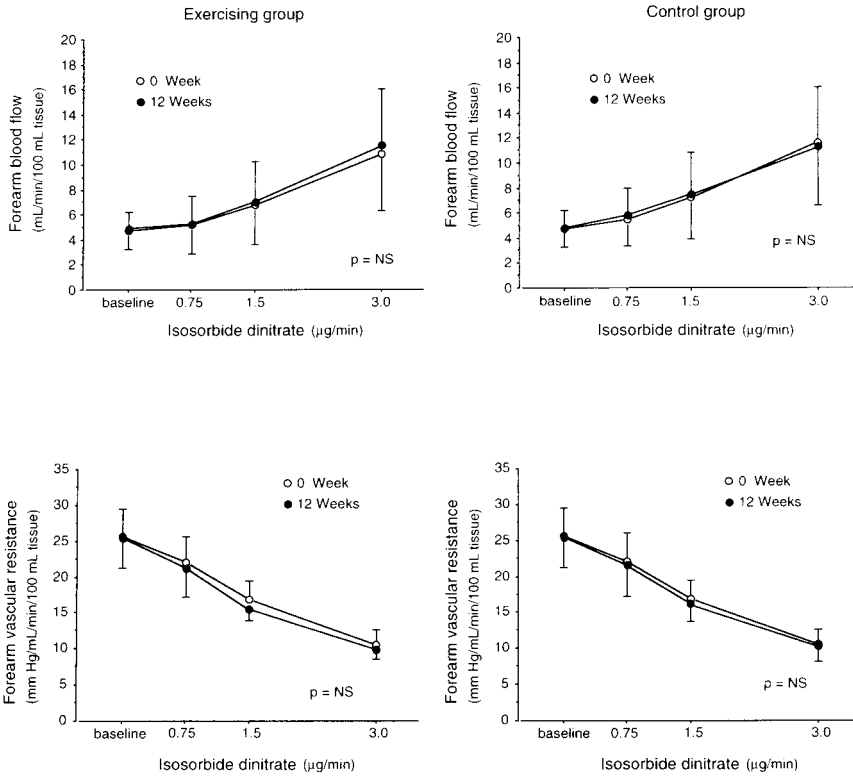


Figure 4. Effects of ISDN on FBF and FVR before and after 12 weeks of exercise in exercising group and control group in hypertensive patients.

Hypertensive

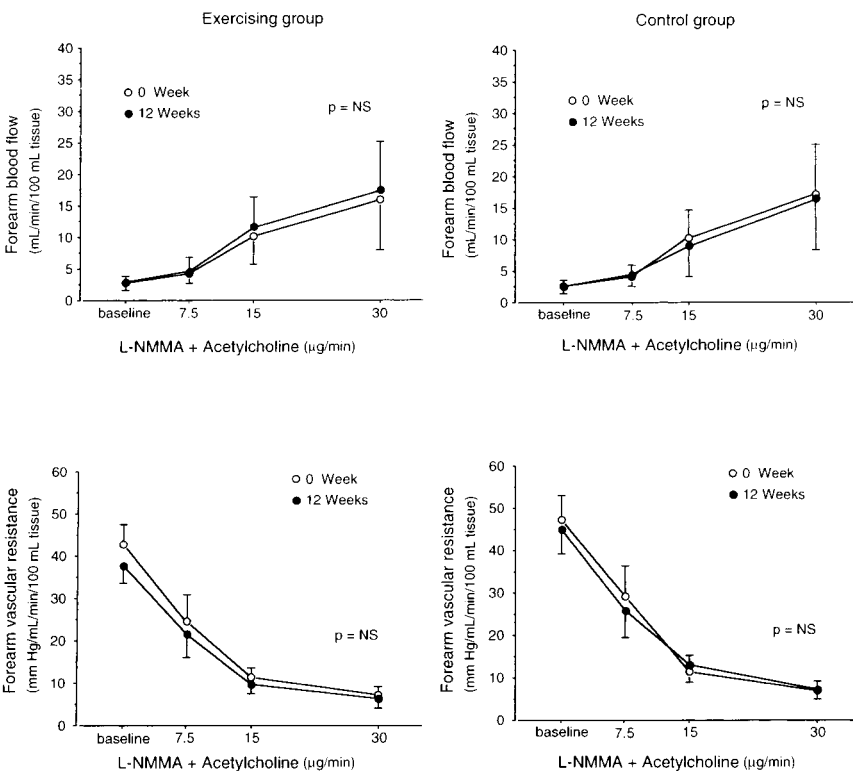


Figure 5. Effects of acetylcholine before and after L-NMMA on FBF and FVR before and after 12 weeks of exercise in exercising group and control group in hypertensive patients.

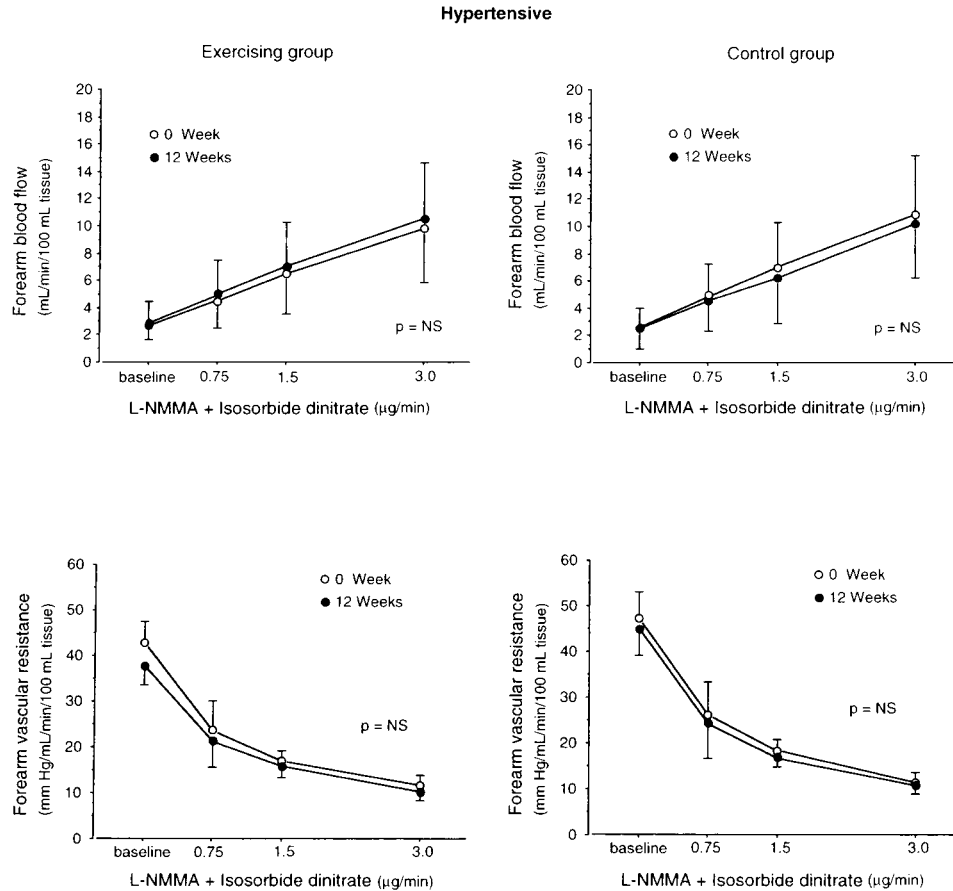


Figure 6. Effects of ISDN before and after L-NMMA on FBF and FVR before and after 12 weeks of exercise in exercising group and control group in hypertensive patients.

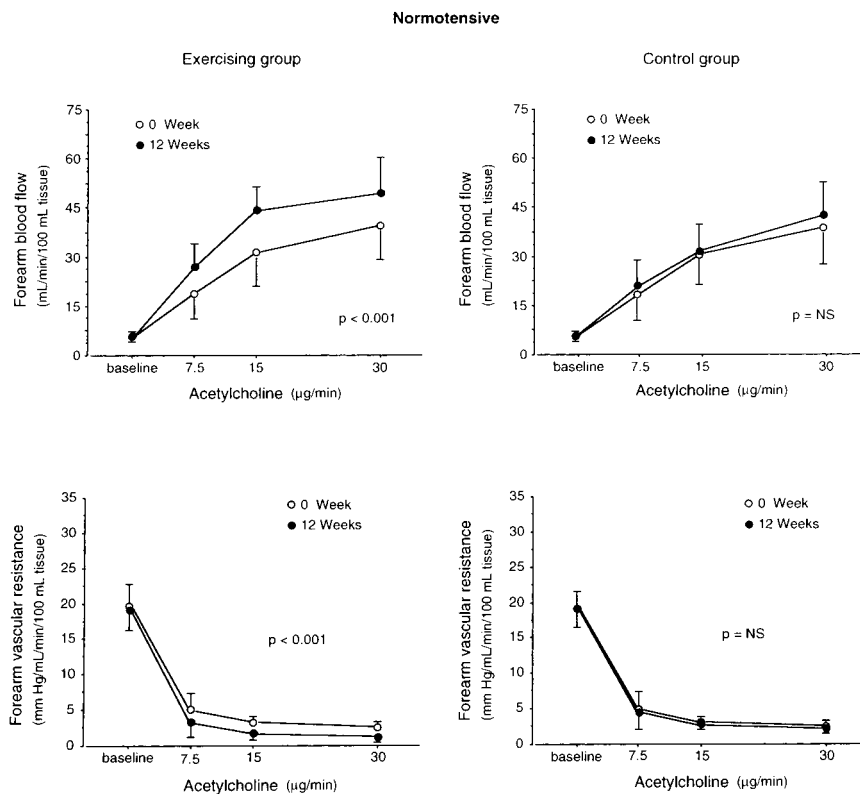


Figure 7. Effects of acetylcholine on FBF and FVR before and after 12 weeks of exercise in exercising group and control group in normotensive subjects.

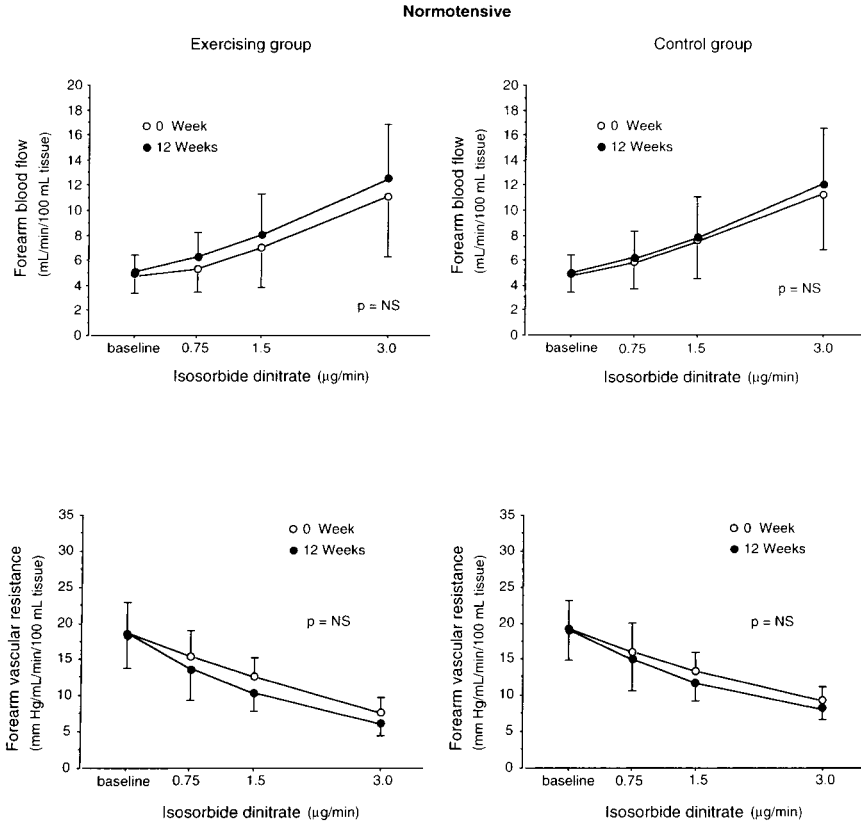


Figure 8. Effects of ISDN on FBF and FVR before and after 12 weeks of exercise in exercising group and control group in normotensive subjects.

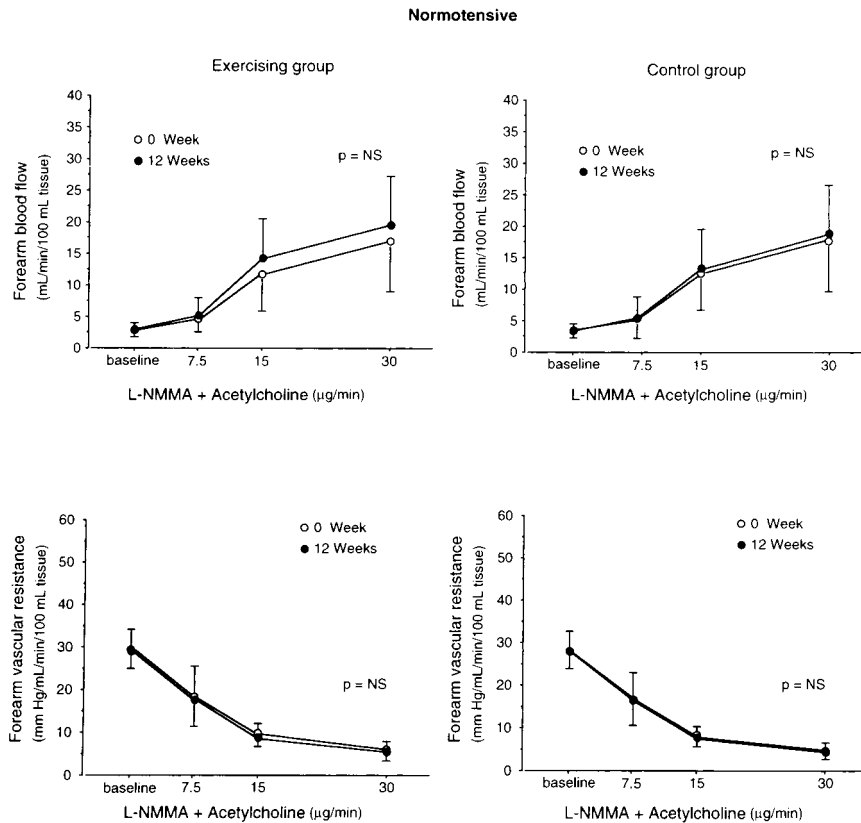


Figure 9. Effects of acetylcholine before and after L-NMMA on FBF and FVR before and after 12 weeks of exercise in exercising group and control group in normotensive patients.

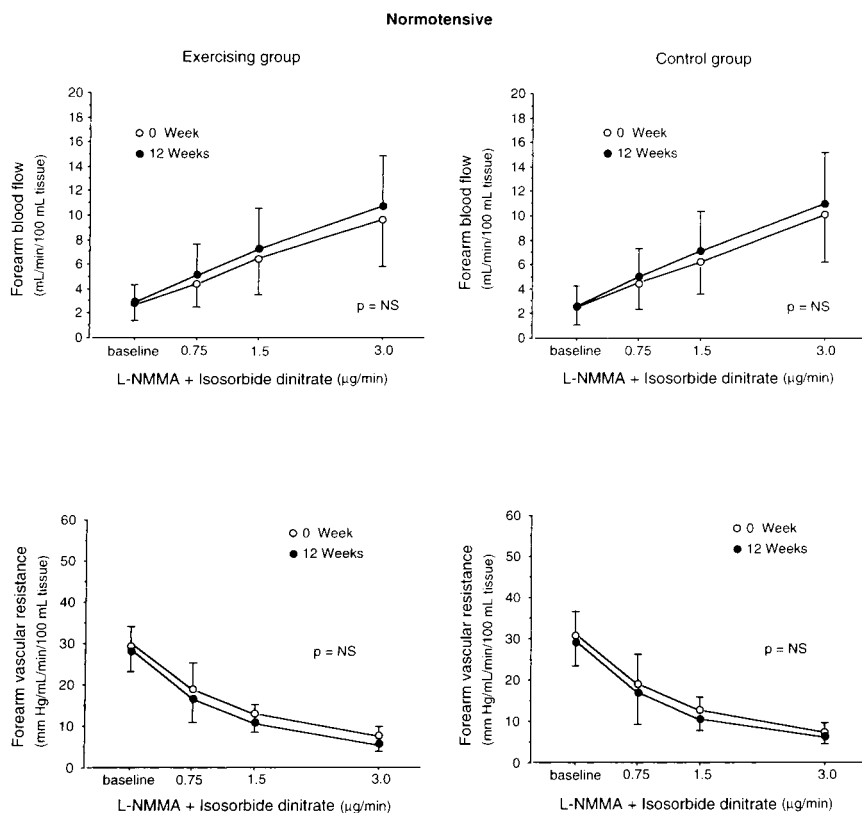


Figure 10. Effects of ISDN before and after L-NMMA on FBF and FVR before and after 12 weeks of exercise in exercising group and control group in normotensive subjects.

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