Exercise Training Lowers Resting Renal But Not Cardiac Sympathetic Activity in Humans

Ian T. Meredith, Peter Friberg, Garry L. Jennings, Elizabeth M. Dewar, Virginia A. Fazio, Gavin W. Lambert, and Murray D. Esler

Endurance exercise training has previously been shown to reduce the plasma concentration of norepinephrine. Whether reduction in sympathetic activity is responsible for the blood pressure–lowering effects of exercise training is unknown. Using a radiotracer technique, we measured resting total, cardiac, and renal norepinephrine spillover to plasma in eight habitually sedentary healthy normotensive men (aged 36±3 years, mean±SEM) after 1 month of regular exercise and 1 month of sedentary activity, performed in a randomized order. One month of bicycle exercise 3 times/wk (40 minutes at 60–70% maximum work capacity) reduced resting blood pressure by 8/5 mm Hg (p<0.01) and increased maximum oxygen consumption by 15% (p<0.05). The fall in blood pressure was attributable to a 12.1% increase in total peripheral conductance. Total norepinephrine spillover to plasma was reduced by 24% from a mean of 438.8 ng/min (p<0.05). Renal norepinephrine spillover fell by an average of 41% from 169.4 ng/min with bicycle training (p<0.05), accounting for the majority (66%) of the fall in total norepinephrine spillover. Renal vascular conductance was increased by 10% (p<0.05), but this constituted only 18% of the increase in total peripheral conductance. There was no change in cardiac norepinephrine spillover. The reduction in resting sympathetic activity with regular endurance exercise is largely confined to the kidney. The magnitude of the fall in renal vascular resistance, however, is insufficient to directly account for the blood pressure–lowering effect of exercise, although other effects of inhibition of the renal sympathetic outflow may be important. (Hypertension 1991;18:575–582)
Fig. 1. Schematic design of the study shows the randomization, run in, and crossover phases. Open boxes represent 1-month intervals of either training or sedentary activity. Shaded boxes represent the investigation periods at the end of each month. This comprised 2 investigational days separated by 24 hours. Day 1 investigations included weight (Wt), 4-day dietary history (Diet), blood pressure (BP), heart rate (HR), cardiac output (CO), and maximum oxygen consumption (Vo2max). Day 2 investigations included measurements of total, cardiac, and renal norepinephrine spillover.

Methods

Eight normal healthy male subjects (aged 36±8 years; weight, 74±8 kg; mean±SD), participated in the study, which was performed with written informed consent and the approval of the Alfred Hospital Human Research Ethics Committee. The subjects, recruited from the community by advertisement, were all habitually sedentary and did not participate in regular sporting or vigorous leisuretime activities. Their ages ranged from 24 to 40 years with a mean of 36 years. After a 2-week run in period, half the subjects were randomly assigned to perform a training regimen for 1 month while the other half performed normal sedentary activities. At the end of the month, after 2 investigation days separated by 24 hours, the activity levels were reversed. Two further days of investigations after the second month completed the study (Figure 1). The training month involved 40 minutes of supervised exercise on an electronically braked bicycle ergometer (Ergomed 740, Siemens, FRG) in the laboratory three times per week for 4 weeks. Each 40-minute training interval began with a 5-minute "warm-up" (cycling with no added resistance) followed by 30 minutes at 60-70% of the previously determined maximum work capacity and ended with a 5-minute "cool-down" period. Heart rate was monitored using a Respironics Heart Rate Monitor, and the work was adjusted to maintain the heart rate during exercise within a range of 120-150 beats/min. During the sedentary month, the subjects performed 40 minutes of armchair reading in the same laboratory three times a week for the 4 weeks.

All the participants were screened by history, examination, and routine laboratory tests in the run in phase. Each subject completed the protocol without interruption and no subject received medication during the course of the study. Other than their prescribed level of physical activity, all other factors in their daily lives were kept as constant as possible. The potentially confounding effect of changes in subject body weight and dietary intake (particularly sodium intake) were monitored by measurement of body weight, 24-hour urine sodium excretion (for 1 day) and a 4-day diet diary at the end of each month of the study. A full dietary history was obtained from each participant by one of us (V.A.F.) during the course of the study.

Blood Pressure and Heart Rate Measurements

Resting blood pressure was measured using a random zero sphygmomanometer (Hawkesley Instruments, England) by a trained observer who was unaware of whether the subject was in the training or sedentary month. Blood pressure and heart rate measurements were taken on three occasions in the run in phase and at the end of each month on the first of the 2 investigation days, 48 hours after the last session of exercise. Supine and erect blood pressure and heart rate were recorded after the subjects had been lying down for 25 minutes and standing for 5 minutes before the subjects were involved in any of the day's prescribed activities. In each position, three blood pressure measurements, each at least 3 minutes apart, were taken and then averaged.

Hemodynamic and Work Capacity Measurements

Twice during the run in phase and on the first investigation day at the end of each month, maximum work capacity and maximum oxygen consumption (Vo2max) were measured during a "sprint" exercise test. The exercise test was performed on a Siemens-Elema bicycle ergometer, commencing at zero workrate. Each minute the workload was increased 20 W until any further increase was prevented by fatigue. Oxygen consumption was measured by methods previously described and validated by our laboratory.

Supine cardiac output was measured by the "Indirect Fick" method using mixed venous PCO2 measured by a carbon dioxide rebreathing method described previously, which in our laboratory gives similar results to the thermodilution technique with a standard error for a single measurement of ±6%.

Vascular Conductance

To assess the contribution of the regional vascular beds, particularly the kidney, to the fall in total peripheral resistance, it was more convenient to assess changes in conductance units (flow/pressure, ml/min/mm Hg), since total peripheral conductance is the simple arithmetic sum of its regional compo-
Total peripheral and renal vascular conductance was calculated as:

\[
\text{Total peripheral conductance} = \frac{\text{Cardiac output}}{(\text{MAP} - \text{RAP})}
\]

Renal vascular conductance:

\[
\text{Renal blood flow} = \frac{\text{MAP} - \text{RAP}}{(\text{MAP} - \text{RAP})}
\]

where MAP denotes mean arterial pressure and RAP denotes right atrial pressure. Renal blood flow was calculated from the whole body clearance of para-aminohippurate (PAH), as described below.

**Total and Selective Regional Sympathetic Measurements**

Measurements of total, cardiac, and renal norepinephrine spillover to plasma were made on the second investigation day at the end of each month, 48 hours after the last sedentary or training period. All subjects were studied at rest in the supine position 2 hours after eating a standardized light breakfast (supplied by our institution). Tea, coffee, and alcohol were withheld for a minimum of 12 hours before the study.

Measurements were made after insertion of arterial and venous catheters. A 21-gauge cannula was inserted percutaneously into a brachial artery while the subject was under local anesthesia along with a 23-gauge peripheral intravenous line for infusion of tritiated NE (0.70 μCi/min Levo-[7-3H] norepinephrine, New England Nuclear, Boston, Mass., specific activity 14–20 Ci/mmol) and PAH. An 8.5 F percutaneous introducing sheath (Arrow International) was inserted into either antecubital vein for introduction of the coronary sinus and Cournand renal vein catheter. Tritiated NE was infused for 60 minutes to establish steady-state plasma concentration before sampling.

The coronary sinus, renal vein, and their corresponding arterial blood samples were transferred immediately to ice-cold tubes containing reduced glutathione (5 ml blood for endogenous NE estimation) and lithium heparin (10 ml for [3H]NE estimation). Coronary sinus, renal vein, and their corresponding arterial blood samples were transferred immediately to ice-cold tubes containing reduced glutathione (5 ml blood for endogenous NE estimation) and lithium heparin (10 ml for [3H]NE estimation). On completion of the study, samples were centrifuged at 4°C and plasma separated for storage at −70°C until assayed. Endogenous plasma NE concentration was measured by the method of Peuler and Johnson and plasma tritiated NE by liquid scintillation counting after extraction with alumina, as previously described.

**Coronary sinus plasma flow.** A 7 F coronary sinus thermodilution catheter, (Webster Laboratories, type CCS-7U-90B) interfaced with a Webster CF-300 Flowmeter was used to measure coronary sinus blood flow. Catheterization of the coronary sinus was performed under fluoroscopic control, correct positioning of the catheter 2–3 cm from the coronary sinus orifice (downstream to the Great Cardiac Vein) was verified by infusion of 2–5 ml contrast media (Omnipaque, Winthrop Laboratories). Coronary sinus blood flow was determined immediately after blood sampling by a minimum of 2 thermodilution measurements using rapid infusions of room temperature 5% dextrose until equilibrium was reached. Coronary sinus plasma flow was calculated from coronary sinus blood flow and the hematocrit.

**Renal plasma flow.** Renal plasma flow was estimated from the whole body clearance of PAH. Standard curves relating optical density to the concentration of PAH were constructed using each subject’s plasma. The concentrations of PAH in duplicate arterial and renal vein samples were determined from these curves, and the arterial concentration at steady state was used to calculate total body clearance. Renal plasma flow was derived from total...
clearance corrected for renal fractional extraction of PAH. Plasma flow was converted to blood flow using each subject's hematocrit.

**Statistical Analysis**

Analysis of the effects of training on resting hemodynamics and oxygen consumption was performed using two-way analysis of variance. Results are expressed as mean±SED. The comparative effects of 1 month of regular exercise with 1 month of sedentary activity on total and regional NE spillover and clearance for each subject were analyzed by paired t test. Regional organ blood flow and vascular conductance changes were also analyzed by paired t test. A value of p<0.05 was considered statistically significant.

**Results**

One month of bicycle ergometer exercise 3 times/wk reduced resting supine blood pressure on average by 8±3/5±2 mm Hg (mean difference±SED) from 117/72 to 109/67 mm Hg (p<0.01). Blood pressure measured in the erect position was similarly affected. The fall in blood pressure was independent of the order in which the training and sedentary phases were performed. Training reduced resting heart rate by 8±2 beats/min (p<0.001) and increased VO2max by 15% from 35.5 to 40.8 ml/kg/min (mean increase 5.3±0.9 ml/kg/min, p<0.05) (Figure 2).

Concomitant with the fall in blood pressure, cardiac output rose 5%, by 0.3±0.1 l/min (p<0.001), and stroke volume increased 20% or 18±4 ml with training (p<0.001). Total peripheral resistance was reduced by an average 12% or 1.6±0.3 mm Hg/l/min (p<0.001) (Figure 2). Total peripheral conductance was increased 12.1% or 9.1±2.1 ml/min/mm Hg (p<0.001) (Table 1). This was associated with a 10.2% increase in renal vascular conductance (1.7±0.7 ml/min/mm Hg) but no change in coronary vascular conductance. The rise in renal vascular conductance was equivalent to 18.7% of the increase in total peripheral conductance.

Arterial plasma NE concentration was on average reduced by 21% or 48.5±18.4 pg/ml (p<0.05), while plasma epinephrine remained unchanged with 1 month of training (Figure 3). The reduction in plasma NE was entirely due to a 24% reduction in total NE spillover to plasma (p<0.05), since training did not alter total clearance of NE from plasma. Total NE spillover to plasma was reduced by 105.9±33.0 ng/min with 1 month of training (p<0.05) (Table 2).

Renal NE spillover to plasma was reduced 41%, from 169.4 to 100.6 ng/min with training while cardiac NE spillover was unaffected (Figure 4, Table 2). Renal and cardiac extraction of [3H]NE were unchanged with training. The fall in renal NE spillover was disproportionate to the reduction in total NE spillover to plasma, accounting for 66% of the total reduction in NE spillover to plasma (Figure 4).

The fall in blood pressure, total and renal NE spillover to plasma with training were not the result of a change in subject body weight (74.0 kg and 74.4 kg, SED 0.47 kg, mean weights before and after training, respectively) or other potentially confounding variables. Dietary sodium intake, as assessed by 4-day diet diary and 24-hour urinary sodium excretion in each phase of the study, remained unchanged (159 mmol/day and 172 mmol/day, SED 19 mmol/day, mean urinary excretion rates before and after training, respectively). Estimates of daily alcohol consumption and the percentage of total and polyunsaturated fat intake also remained stable throughout the study.

**Discussion**

In this study we sought to examine the effects of endurance exercise training on regional sympathetic outflows and therefore chose an exercise training regimen previously shown to reduce blood pressure, total peripheral resistance, and plasma NE concentration in both normotensive and hypertensive patients. The magnitude of the effects of bicycle ergometer exercise 3 times/wk on resting blood pressure, heart rate, and maximum oxygen consumption observed were similar to those previously reported. Training resulted in a 21% reduction in plasma NE.
TABLE 1. Total and Regional Hemodynamic Adjustments With Exercise Training

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sedentary phase</th>
<th>Trained phase</th>
<th>SED</th>
<th>% Change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>88</td>
<td>81</td>
<td>2</td>
<td>-7</td>
<td>0.001</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>9</td>
<td>8</td>
<td>2</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.9</td>
<td>6.2</td>
<td>0.1</td>
<td>+5</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68</td>
<td>60</td>
<td>2</td>
<td>-11</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>87</td>
<td>105</td>
<td>4</td>
<td>+20</td>
<td>0.001</td>
</tr>
<tr>
<td>TPC (ml/min/mm Hg)</td>
<td>75.0</td>
<td>84.1</td>
<td>2.1</td>
<td>+12.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>1,290</td>
<td>1,330</td>
<td>60</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>RVC (ml/min/mm Hg)</td>
<td>16.5</td>
<td>18.2</td>
<td>0.7</td>
<td>+10.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Coronary sinus flow (ml/min)</td>
<td>162</td>
<td>157</td>
<td>6</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>CVC (ml/min/mm Hg)</td>
<td>2.1</td>
<td>2.1</td>
<td>0.1</td>
<td>...</td>
<td>NS</td>
</tr>
</tbody>
</table>

SED: standard error of the difference; TPC, total peripheral conductance; RVC, renal vascular conductance; CVC, estimated coronary vascular conductance.

Data are expressed as mean; SED refers to the standard error of the difference. Concentration. This was due to a reduction in total NE spillover to plasma. Plasma NE clearance, the other major determinant of plasma NE concentration, remained unchanged.

The major new finding in this study relates to the differential effects of endurance exercise training on cardiac and renal sympathetic nervous outflows. Training selectively lowered resting renal but not cardiac NE spillover. The former was due to a reduction in renal NE release suggesting reduced nerve firing rates, since the rate of NE escape or spillover into the renal veins is largely proportional to the rate of renal sympathetic nerve firing. Other possible mechanisms for a lower renal NE spillover, such as a reduction in flow-dependent NE washout or altered renal extraction of NE, can be excluded because renal plasma flow tended to increase marginally with training, and tritiated NE extraction, indicative of neuronal NE uptake, remained unchanged. Cardiac NE spillover to plasma is also proportional to the rate of cardiac sympathetic nerve firing under conditions where neuronal reuptake of NE is unaffected. Since cardiac extraction of \([\text{H}]\text{NE}\) was unchanged and coronary sinus plasma flow remained constant, the absence of any change in cardiac NE spillover suggests cardiac sympathetic nerve firing rates were also unchanged. It should perhaps be pointed out, however, that we have measured only the principal neurotransmitter of the sympathetic nerves, norepinephrine, and the influence of exercise training on release of possible cotransmitters such as neuropeptide-Y and epinephrine and their potential role in the observed hemodynamic changes remain undetermined.

The fall in resting renal sympathetic nerve activity accounted for two thirds of the reduction in total body noradrenaline spillover with training indicating a preferential effect of endurance exercise training on renal sympathetic activity. The remaining one
third of the reduction in total noradrenaline spillover occurred in regional sympathetic outflows other than the kidney, possibly in skeletal muscle and splanchnic sympathetic outflows. In humans, a reduction in muscle sympathetic nerve activity has been observed in the short term after acute exercise, and in the spontaneously hypertensive rat, a more sustained reduction in splanchnic sympathetic nerve activity has been observed in a model of acute endurance exercise. Whether these findings persist after long-term endurance exercise training has not been established.

The issue to be resolved is whether the reduction in renal sympathetic activity could be responsible for the hemodynamic changes observed with exercise training in these normotensive subjects. If this is so, then it is not simply due to an increase in renal vascular conductance consequent on withdrawal of efferent sympathetic vasoconstrictor activity. The increase in renal vascular conductance is insufficient to account for more than a fifth of the observed rise in total peripheral conductance. Training-induced falls in blood pressure and total peripheral resistance could, however, be effected through modification of other regulatory functions of the renal sympathetic nerves.

In addition to influencing renal blood flow and glomerular filtration rate through changes in renal vascular resistance, the renal sympathetic nerves regulate the release of renin and directly influence tubular sodium and water reabsorption. The latter functions, renin release and sodium reabsorption, can be influenced by changes in efferent renal sympathetic nerve activity insufficient to alter renal vascular resistance, renal blood flow, and glomerular filtration rate. Renal vein concentrations of renin, prostaglandins, or other vasoactive substances were not measured in the present study. However, previous work from our laboratory demonstrated plasma renin activity to be reduced in healthy sedentary subjects after an identical 1-month, 3 times/wk bicycle exercise training regimen. The fall in plasma renin occurred only in those subjects who had a fall in total body NE spillover to plasma. Lower plasma renin activity has also been observed in cross-sectional studies comparing athletes with their untrained counterparts, and in longitudinal studies of physical training. Recently, Hespel et al found plasma renin activity was inversely related to the increase in work capacity induced by 4 months of endurance exercise training. Despite these observations a causal link between reduced renal sympathetic activity, suppression of the renin-angiotensin system, and reduction of total peripheral resistance with endurance exercise training remains to be established.

The alternative possibility is that the reduction in renal sympathetic nerve activity is a consequence rather than the cause of the hemodynamic adaptations to regular exercise. The inhibition of renal sympathetic nerve activity may simply be a reflex response to an increase in cardiopulmonary baroreceptor afferent input with training. In healthy subjects total blood volume is generally thought to increase with training, primarily due to an increase in plasma volume, although a recent study in patients with essential hypertension found otherwise. Cardiac chamber volumes also increase with endurance training in echocardiographic studies, consistent with an increase in central blood volume. The resultant rise in cardiopulmonary or "central" blood volume would be anticipated to increase cardiopulmonary baroreceptor afferent input that would in turn inhibit efferent renal sympathetic nerve activity with little effect on cardiac sympathetic outflow.

It is interesting that resting cardiac sympathetic activity appeared unchanged by a training regimen that reduced heart rate and blood pressure, increased resting cardiac output, and reduced overall and renal sympathetic activity. The rise in resting cardiac output, which resulted from an increase in stroke volume, may not be neurally mediated. Cardiac output is determined primarily by the metabolic demands of the tissues. In our previous study, we observed a small but significant rise in resting oxygen consumption that may account for the rise in resting cardiac output. The resting bradycardia induced by training is generally considered to result in part from alterations in both cardiac parasympathetic and sympathetic nerve activity. The development of a significant bradycardia without evidence of a reduction in cardiac sympathetic nerve activity suggests that training may induce bradycardia through vagal and nonautonomic mechanisms, in particular a reduction in intrinsic heart rate (evidence reviewed in References 35 and 36). Recent work in our laboratory using total autonomic blockade to assess arterial baroreceptor function in humans after training also showed a reduction in intrinsic heart rate to be the major factor in the training-induced bradycardia. Our findings do not exclude the possibility that attenuation of cardiac sympathetic activity may have been more obvious under conditions that potently increase cardiac...
sympathetic nerve firing such as mental arithmetic testing or graded isotonic exercise. The finding that training did not reduce cardiac sympathetic activity is also pertinent to exercise rehabilitation of patients with coronary heart disease and congestive heart failure. A reduction in cardiac sympathetic activity through regular exercise has been thought to be an important mechanism for reducing myocardial oxygen demand and thus provided a rationale for the use of exercise training in preventing recurrent angina, and perhaps arrhythmias, in the postmyocardial infarction and heart failure populations.

In conclusion, endurance exercise training preferentially reduces renal and not cardiac sympathetic activity in normotensive subjects. The fall in renal sympathetic nerve activity accounted for two thirds of the reduction in total body norepinephrine spillover with training but was associated with only a comparatively small increase in renal vascular conductance. If the reduction in renal sympathetic nerve activity is causally related to the fall in blood pressure and total peripheral resistance with exercise training, then it is likely to be through mechanisms other than simply a reduction in renal vascular resistance.

References


**KEY WORDS** • exercise • blood pressure • norepinephrine • kinetics • catecholamines • sympathetic nervous system
Exercise training lowers resting renal but not cardiac sympathetic activity in humans.
I T Meredith, P Friberg, G L Jennings, E M Dewar, V A Fazio, G W Lambert and M D Esler

Hypertension. 1991;18:575-582
doi: 10.1161/01.HYP.18.5.575

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/18/5/575

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/