Many factors have been proposed to contribute to the pressure, the mechanism remains elusive because the individual variability in their blood pressure response. In blood pressure; however, there is substantial interin-
teractive index (SI) by an intravenous glucose tolerance test,
of systemic SNS activity and determined the insulin sensi-
tivity contribute to the heterogeneous blood pressure response to aerobic exercise training, we used compartmental analysis of \[^{3}H\]\textit{norepinephrine} kinetics to determine the extravascular norepinephrine release rate (NE2) as an index of systemic SNS activity and determined the insulin sensitivity index (SI) by an intravenous glucose tolerance test, before and after 6 mo of aerobic exercise training, in 30 (63 ± 7 yr) hypertensive subjects. Maximal \(O_{2}\) consumption increased from 18.4 ± 0.7 to 20.8 ± 0.7 ml·kg\(^{-1}\)·min\(^{-1}\) (\(P = 0.02\)). The average mean arterial blood pressure (MABP) did not change (114 ± 2 vs. 114 ± 2 mmHg); however, there was a wide range of responses (−19 to +17 mmHg). The average NE2 did not change significantly (2.11 ± 0.02 vs. 2.11 ± 0.13 \(\mu g\)·min\(^{-1}\)·m\(^{-2}\)), but there was a significant positive linear relationship between the change in NE2 and the change in MABP (\(r = 0.38, P = 0.04\)). SI increased from 2.81 ± 0.37 to 3.71 ± 0.42 \(\mu U\) \(\times 10^{-4}\)·min\(^{-1}\)·ml\(^{-1}\) (\(P = 0.004\)). The relationship between the change in SI and the change in MABP was not statistically significant (\(r = −0.03, P = 0.89\)). When the changes in maximal \(O_{2}\) consumption, percent body fat, NE2, and SI were considered as predictors of the change in MABP, only NE2 was a significant independent predictor. Thus suppression of SNS activity may play a role in the reduction in MABP and account for a portion of the heterogeneity of the MABP response to aerobic exercise training in older hypertensive subjects.

nepinephrine; insulin sensitivity; aging

### Sympathetic activity and the heterogenous blood pressure response to exercise training in hypertensives

Michael D. Brown, Donald R. Dengel, Robert V. Hogikyan, and Mark A. Supiano. Sympathetic activity and the heterogenous blood pressure response to exercise training in hypertensives. *J Appl Physiol* 92: 1434–1442, 2002; 10.1152/japplphysiol.00477.2001.—To test whether changes in sympathetic nervous system (SNS) activity or insulin sensitivity contribute to the heterogeneous blood pressure response, we used compartmental analysis of \[^{3}H\]\textit{norepinephrine} kinetics to determine the extravascular norepinephrine release rate (NE2) as an index of systemic SNS activity and determined the insulin sensitivity index (SI) by an intravenous glucose tolerance test, before and after 6 mo of aerobic exercise training, in 30 (63 ± 7 yr) hypertensive subjects. Maximal \(O_{2}\) consumption increased from 18.4 ± 0.7 to 20.8 ± 0.7 ml·kg\(^{-1}\)·min\(^{-1}\) (\(P = 0.02\)). The average mean arterial blood pressure (MABP) did not change (114 ± 2 vs. 114 ± 2 mmHg); however, there was a wide range of responses (−19 to +17 mmHg). The average NE2 did not change significantly (2.11 ± 0.02 vs. 2.11 ± 0.13 \(\mu g\)·min\(^{-1}\)·m\(^{-2}\)), but there was a significant positive linear relationship between the change in NE2 and the change in MABP (\(r = 0.38, P = 0.04\)). SI increased from 2.81 ± 0.37 to 3.71 ± 0.42 \(\mu U\) \(\times 10^{-4}\)·min\(^{-1}\)·ml\(^{-1}\) (\(P = 0.004\)). The relationship between the change in SI and the change in MABP was not statistically significant (\(r = −0.03, P = 0.89\)). When the changes in maximal \(O_{2}\) consumption, percent body fat, NE2, and SI were considered as predictors of the change in MABP, only NE2 was a significant independent predictor. Thus suppression of SNS activity may play a role in the reduction in MABP and account for a portion of the heterogeneity of the MABP response to aerobic exercise training in older hypertensive subjects.

### Exercise training-induced changes in blood pressure

Two of which are changes in insulin sensitivity and sympathetic nervous system (SNS) activity (19, 22, 25, 27, 32). Impaired insulin sensitivity, or insulin resistance, is a common feature of hypertension and may affect blood pressure by altering renal sodium handling and SNS activity (44). There is evidence for heightened SNS activity during the development and maintenance of hypertension (9, 13, 31). Our laboratory has previously shown that, compared with older normotensive subjects, older hypertensive subjects tend to have heightened systemic SNS activity (50). Therefore, altered SNS activity may contribute to exercise training-induced changes in blood pressure in older hypertensive individuals. A number of studies in humans that have used different methods to assess the effects of aerobic exercise training on SNS activity have reported mixed results (8, 21, 24, 35, 39–41, 46, 47, 54), but very few have studied hypertensive individuals.

In addition, exercise training has been shown to improve aerobic capacity and lower body fat, each of which could also contribute to a reduction in blood pressure. It has been demonstrated that obesity, like insulin resistance, is associated with increased renal sodium reabsorption and heightened SNS activity, which could lead to elevated blood pressure (17). Maximal oxygen consumption (\(V_{O2}\) max) is the best overall index of cardiovascular (CV) fitness, and high \(V_{O2}\) max levels are associated with lower blood pressure (2, 8). Thus hypertensive individuals who are sedentary and moderately obese may lower their blood pressure through exercise training-induced reductions in the percentage of body fat and improvements in \(V_{O2}\) max.

Older hypertensive individuals are characterized by heightened systemic SNS activity, insulin resistance, obesity, and decreased aerobic capacity. Based on the above observations, reductions in systemic SNS activity may mediate a reduction in blood pressure independently, or it may exert its effects indirectly through changes in insulin resistance or obesity. The purpose of

---

Address for reprint requests and other correspondence: M. D. Brown, Dept. of Kinesiology, Univ. of Maryland, College Park, MD 20742-2611 (E-mail: mb166@umail.umd.edu).
the present investigation was to test the hypothesis that exercise training-induced changes in systemic SNS activity would be a significant predictor of changes in blood pressure, independent of changes in insulin sensitivity, the percentage of body fat, and VO\textsubscript{2}\text{max} in older hypertensive individuals.

**METHODS**

**Subject selection.** Informed consent was obtained from 30 older subjects with mild hypertension. The protocol was approved by the University of Michigan Institutional Review Board for Human Subjects Research. Subjects were screened before entry into the study with a medical history and physical examination, a complete blood count, routine chemistries, and a urinalysis. For subjects who were not taking antihypertensive medications, casual blood pressure was measured on three separate occasions over a 3-wk period using a standard mercury sphygmomanometer. Hypertensive subjects who were being treated with antihypertensive medications underwent a 4-wk washout period during which their medications were withdrawn. After 3–4 wk without medication, these subjects also had their casual blood pressure measured on three separate occasions over a 3-wk period using a standard mercury sphygmomanometer. In all subjects, three casual blood pressure measurements were obtained in the morning after 15 min of quiet seated rest. The blood pressure values obtained on each of the 3 days were averaged, and this became the study entry blood pressure value for each subject. Subjects then underwent a maximal graded exercise test (Bruce protocol) to screen for coronary heart disease. During this test, electrocardiogram, oxygen consumption (VO\textsubscript{2}), and carbon dioxide production (VCO\textsubscript{2}) were measured continuously. VO\textsubscript{2} and VCO\textsubscript{2} were measured using a Collins CPX/Plus Metabolic System. Individuals were excluded from the study if they had clinically significant medical illness such as cardiac, renal (serum creatinine >135 mmol/l), hepatic, or gastrointestinal disease; significant laboratory abnormalities; or a positive graded exercise test. Also excluded were individuals with a recent history of smoking or drug or alcohol abuse. The absence of diabetes mellitus, according to World Health Organization criteria (53), was confirmed in all subjects by a standard 75-g oral glucose tolerance test. Hypertension was defined as a seated systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg. All subjects were community dwelling and in good health, except for having mild hypertension.

**Study overview.** After a minimum of 3–6 wk without antihypertensive medications, subjects were placed on a controlled diet for 7 days. The diet at baseline and after exercise training was identical in carbohydrate (50–55%), fat (30–35%), protein (15–20%), and sodium (200 mmol/day) content. The University of Michigan General Clinical Research Center (GCRC) Metabolic Kitchen prepared all meals during the 7-day dietary period. Determination of 24-h urinary electrolyte excretion on the day before the study was used to assess dietary compliance. Subjects then underwent baseline assessments that included studies of systemic SNS activity and arterial \(\alpha\)-adrenergic responsiveness on day 6 of the diet and studies of insulin sensitivity on day 7 of the diet. These baseline assessments were followed by 6 mo of aerobic exercise training. Those subjects who initially had their antihypertensive medications withdrawn (\(n = 22\)) resumed their medication during the exercise training. These subjects then tapered and stopped using their medication during the 5th mo of exercise training. This procedure for medication withdrawal has been used successfully in our laboratory's previous studies (5, 7). At the end of the 6th mo of exercise training, subjects repeated the controlled diet, and final testing again occurred on days 6 and 7 of the diet. Subjects continued to train throughout the final testing period. All studies were performed 48 h after a training session to avoid the acute effects of exercise on blood pressure and SNS activity (36, 52).

**Study protocol.** All studies were performed at the GCRC beginning at 7:30 AM to control for any diurnal variation in norepinephrine (NE) metabolism (42) or arterial \(\alpha\)-adrenergic tone (37). Subjects were studied after a 12-h fasting period in the supine position in a quiet room maintained at a constant temperature of 23–25°C. Subjects abstained from the use of caffeine and other known modulators of catecholamine release and metabolism during the fasting period.

The percentage of body fat and body mass index were determined at baseline and after 6 mo of aerobic exercise training. Percent body fat was assessed by dual-energy X-ray absorptiometry (Lunar DFX-IQ, software version 4.1d, medium speed; Lunar Radiation, Madison, WI). Body mass index was determined as the body weight (kg) divided by the height squared (m\(^2\)).

**Measurement of VO\textsubscript{2}max.** A maximal exercise test was performed at baseline, after 3 mo, and again after 6 mo of aerobic exercise training. The initial treadmill speed was set to elicit 75% of each subject's VO\textsubscript{2}max measured during their screening treadmill test. The treadmill elevation was increased every 2 min until the subject was exhausted and could not continue. VO\textsubscript{2} and VCO\textsubscript{2} were measured continuously, and blood pressure and a 12-lead electrocardiogram were recorded every 3 min during the test. A true VO\textsubscript{2}max was considered to be attained if two of the following three criteria were achieved: 1) respiratory exchange ratio >1.10; 2) maximal heart rate >90% of age-predicted maximum (220 – age); and 3) a plateau in VO\textsubscript{2} (change in VO\textsubscript{2} <0.2 l/min).

**Aerobic exercise training protocol.** Exercise training consisted of three sessions per week of supervised treadmill walking for a total of 6 mo. The intensity and duration of exercise were progressively increased so that subjects completed 40 min per session at 70% of their heart rate reserve for the last 3 mo of training. Compliance with the training program was 91%; if a subject's attendance decreased <90%, his or her data were not included in the analyses. However, no subject met this threshold.

**\[^{3}H\]NE kinetics protocol.** The \[^{3}H\]NE kinetics protocol was performed as previously described (3). On day 6 of the controlled diet, a 20-gauge, 1.25-in. Insyte catheter was placed into the brachial artery of the nondominant arm and connected to a pressure transducer (Hewlett-Packard 1290A quartz transducer; Hewlett-Packard, Andover, MA). Intraarterial blood pressure was measured as previously described (3). Measurements were obtained while the subject was in the supine position, after a 20-min resting period. The average of readings obtained every 5 min during the \[^{3}H\]NE infusion was determined. An intravenous catheter was placed in the arm contralateral to the arterial catheter for infusion of \[^{3}H\]NE. The purity of each lot of radioisotope was determined by high-performance liquid chromatography, was identical for all studies, and exceeded 90%. Thirty minutes after insertion of the catheters, an infusion of tracer \[^{3}H\]NE (\(t\)-ring-2,5,6-\[^{3}H\]NE; specific activity 40–60 \(\mu\)Ci; New England Nuclear, Boston, MA) was given at a rate of \(~0.7\) \(\mu\)Ci/min for 60 min. Blood samples (10 ml) were obtained at 40, 50, and 60 min during the tracer \[^{3}H\]NE infusion. The tracer \[^{3}H\]NE infusion was then stopped, and samples were collected at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, and
20 min for the measurement of \(^{3}H\)NE concentration. Samples for endogenous catecholamine levels were obtained at 40, 50, and 60 min during the infusions and at 10 and 20 min during the decay period.

Arterial \(\alpha\)-adrenergic responsiveness protocol. After the tracer \(^{3}H\)NE infusion protocol, \(\alpha\)-adrenergic-receptor responsiveness was assessed by measuring forearm blood flow (FBF) using venous occlusion plethysmography during an intrabrachial artery infusion protocol, which we have previously described (20). After baseline FBF recordings, the effect of intra-arterial infusions of NE on FBF was determined. NE (Levophed bitartrate, Sterling Drug, New York, NY) was diluted in 5% dextrose to achieve stepwise increasing infusion doses of 0.00125, 0.005, 0.02, 0.08, and 0.24 \(\mu\)g·dl⁻¹·min⁻¹. Each NE dose was administered by an infusion pump (Harvard model 970T; Harvard Apparatus, South Natick, MA) for 4 min before FBF was recorded during the 5th min of each infusion. After the FBF measurement at the 0.24 \(\mu\)g·dl⁻¹·FADV⁻¹·min⁻¹ dose, the NE infusion was stopped. Mean arterial blood pressure (MABP) was determined just before each FBF measurement.

Frequently sampled intravenous glucose tolerance test. On day 7 of the controlled diet, at baseline, and after 6 mo of aerobic exercise training, subjects underwent a frequently sampled intravenous glucose tolerance test (FSIVGTT) to assess whole body insulin sensitivity, as previously described (6). The FSIVGTT included an injection of insulin (Humulin R, Eli Lilly, Indianapolis, IN) to augment the insulin response and enhance the precision of the estimates of insulin action (57). An intravenous catheter was inserted in a retrograde fashion into a dorsal hand vein, and the hand was placed in a thermostatically controlled (60°C) warming box to arterIALIZED venous samples for the measurement of glucose and insulin (57). An intravenous catheter was inserted into an antecubital vein of one arm for the injection of glucose and insulin. In the contralateral arm, a second intravenous catheter was inserted in a retrograde fashion into a dorsal hand vein, and the hand was placed in a thermostatically controlled (60°C) warming box to arterialized venous samples for the measurement of glucose and insulin (11). Both catheters were kept patent using a slow infusion of 0.45% saline (<0.5 ml/h). Twenty minutes after the placement of catheters, baseline blood samples were obtained, and blood pressure and heart rate were measured at 5-min intervals.

The procedure began with an intravenous push of 50% glucose (300 mg/kg) over 30 s, followed 20 min later by an injection of insulin (0.02 U/kg). Blood samples (3 ml) for glucose and insulin were collected into chilled tubes containing heparin sodium at standard time points for the 3 h after the administration of glucose. The tubes were stored temporarily on ice and centrifuged immediately at the end of each study. Plasma was stored at −80°C until assay. Plasma glucose was measured by the autoanalyzer glucose oxidase method, and insulin was measured by radioimmunoassay in the Core Laboratory of the University of Michigan Diabetes Research and Training Center. To avoid interassay variability, samples from each of the subject's two studies were analyzed together in the same assay. Insulin sensitivity index (SI) was calculated from the temporal pattern of glucose and insulin data throughout the FSIVGTT using the MINMOD program (1). SI is a measure of the effect of an increment in plasma insulin to enhance the fractional disappearance of glucose.

Plasma catecholamine analytic methods. Arterial blood samples were collected into chilled plastic tubes containing EGTA and reduced glutathione. The tubes were kept on ice until centrifugation at 4°C. Plasma samples were stored at −70°C until assayed. Plasma NE and epinephrine (Epi) were quantified by a single-isotope radioenzymatic assay, with all samples from a given subject analyzed in the same assay (10). The intra-assay coefficient of variation for NE in this assay is 5%. Alumina extraction of plasma samples and measurement of \(^{3}H\)NE levels were carried out as previously described (10, 33).

Data and statistical analysis. Compartmental analysis of \(^{3}H\)NE kinetics was performed using the previously described physiologically based minimal two-compartment model (30). Compartment 1 represents the intravascular plasma-containing space, whereas compartment 2 represents the extravascular space. The quantity of NE in each compartment (NE mass in the intravascular compartment and in the extravascular compartment), the rate of NE appearance into each compartment [into compartment 1 (R₁₂) and into compartment 2 (NE₂)], the NE metabolic clearance rate from compartment 1, the NE spillover fraction, and the volume of distribution of NE in compartment 1 were calculated from the two-compartment model as functions of the estimated transfer rate coefficients, as previously described (30).

Statistical analysis was performed using Statview 4.5 (Abacus Concepts, Berkeley, CA). Intra-arterial blood pressure obtained during the studies of SNS activity before and after exercise training was used in the statistical analyses. Differences between values at baseline and after aerobic exercise training were assessed with a t-test for paired comparisons, corrected for multiple comparisons using Scheffe's correction. Dose-response data for NE were analyzed by repeated-measures ANOVA as the percent change in FBF from the baseline value obtained before the first infusion of each drug to control for potential differences between groups in baseline FBF. ANOVA was used to determine whether the outcome variables changed differently when the subjects were grouped by gender, by use of antihypertensive medications, or, in the women, by use of hormone replacement therapy. The difference in values between baseline and after aerobic exercise training was calculated and used to determine relationships between variables of interest. Values are presented as means ± SE. A value of \(P < 0.05\) was selected to indicate statistical significance.

RESULTS

Subjects. Subject characteristics before and after 6 mo of aerobic exercise training are presented in Table 1. Thirty older (63 ± 7 yr) and moderately obese subjects (18 women, 12 men) with mild essential hypertension were studied. Seven of the eighteen women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>After Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>83.5 ± 1.5</td>
<td>82.3 ± 2.9</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>38.7 ± 1.5</td>
<td>37.2 ± 1.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.6 ± 0.7</td>
<td>24.3 ± 0.7</td>
</tr>
<tr>
<td>VO₂max, ml·kg⁻¹·min⁻¹</td>
<td>18.4 ± 0.7</td>
<td>20.8 ± 0.7*</td>
</tr>
<tr>
<td>SI • U × 10⁻⁴·min⁻¹·ml⁻¹</td>
<td>2.81 ± 0.37</td>
<td>3.71 ± 0.42*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>65 ± 2</td>
<td>64 ± 2</td>
</tr>
</tbody>
</table>

Intra-arterial BP, mmHg

| Systolic BP | 164 ± 2 | 165 ± 2 |
| Diastolic BP | 82 ± 1 | 82 ± 1 |
| Mean BP | 114 ± 2 | 114 ± 2 |

Values are means ± SE. VO₂max, maximal oxygen consumption; SI, insulin sensitivity index; BP, blood pressure. *P < 0.05, baseline vs. after exercise training.
were using hormone replacement therapy. The average attendance at the exercise sessions was 91%. There were no changes in body weight or the percentage of total body fat. VO\textsubscript{2}max increased by 13% ($P = 0.02$), indicating that there was an exercise training effect on CV fitness; however, resting heart rate was unchanged after exercise training. As a group, there were no significant differences in intra-arterial systolic blood pressure, diastolic pressure, or MABP after aerobic exercise training. When the study population was grouped based on gender or whether or not they were using antihypertensive medications ($n = 22$), there were no differences in the changes in intra-arterial systolic blood pressure, diastolic blood pressure, or MABP. There was substantial heterogeneity of the blood pressure response with the ranges of the change in systolic blood pressure, diastolic blood pressure, and MABP after exercise training, namely, $-24$ to $+23$, $-17$ to $+15$, and $-19$ to $+17$ mmHg, respectively.

**Effects of aerobic exercise training on plasma catecholamines and parameters of NE kinetics.** Arterial plasma NE and Epi levels and the estimated parameters of NE kinetics at baseline and after aerobic exercise training are provided in Table 2. There were no significant differences in values for arterial plasma NE or Epi or in any of the NE kinetic parameters after exercise training compared with baseline. There was substantial variability in the responses of catecholamines and NE kinetic parameters to exercise training. The ranges of the change in arterial plasma NE and Epi after exercise training were $-298$ to $+254$ and $-110$ to $+64$ pg/ml, respectively. The ranges of the change in NE\textsubscript{2} and R\textsubscript{12} were $-2.9$ to $+2.3$ and $-0.37$ to $+0.28$ pg·min\textsuperscript{-1}·m\textsuperscript{-2}, respectively. Because there was substantial variation in the responses of blood pressure and parameters of NE kinetics to exercise training, we determined the relationship between the change in MABP and the changes in NE\textsubscript{2} and R\textsubscript{12}, the indexes of systemic SNS activity. There was a significant linear-positive relationship between the change in NE\textsubscript{2} and the change in MABP with exercise training ($r = 0.38$, $P = 0.04$, Fig. 1). Of the 13 older hypertensive subjects whose MABP was lower after aerobic exercise training, NE\textsubscript{2} was also lower in 10 of these subjects. There was also a significant linear-positive relationship between the change in R\textsubscript{12} and the change in MABP ($r = 0.52$, $P = 0.003$, Fig. 1). Similarly, in 10 of the 13 subjects whose MABP was lower after exercise training, R\textsubscript{12} was also lower. The relationship between the change in arterial plasma NE levels and the change in MABP with exercise training was not statistically significant ($r = 0.24$, $P = 0.20$). There was no effect of gender or use of antihypertensive medications on the relationship between exercise, MABP, and plasma catecholamines or parameters of NE kinetics.

**Effects of aerobic exercise training on FBF responses to NE.** There was no significant difference in resting FBF ($3.6 \pm 0.2$ vs. $3.5 \pm 0.2$ ml·dl·FAV\textsuperscript{-1}·min\textsuperscript{-1}) after exercise training. To determine the effects of aerobic exercise training on α-adrenergic-receptor responsiveness, dose-response curves were constructed and analyzed as the percent change in FBF from the baseline.

### Table 2. Values for arterial plasma NE, Epi, and parameters of NE kinetics at baseline and after 6 mo of aerobic exercise training

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>After Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial NE, pg/ml</td>
<td>$326 \pm 18$</td>
<td>$323 \pm 17$</td>
</tr>
<tr>
<td>Arterial Epi, pg/ml</td>
<td>$66 \pm 6$</td>
<td>$61 \pm 6$</td>
</tr>
<tr>
<td>NE kinetics parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE\textsubscript{2}, pg·min\textsuperscript{-1}·m\textsuperscript{-2}</td>
<td>$2.11 \pm 0.15$</td>
<td>$1.99 \pm 0.13$</td>
</tr>
<tr>
<td>Q\textsubscript{1}, pg/m\textsuperscript{2}</td>
<td>$0.42 \pm 0.03$</td>
<td>$0.48 \pm 0.09$</td>
</tr>
<tr>
<td>Q\textsubscript{2}, pg/m\textsuperscript{2}</td>
<td>$47.05 \pm 3.53$</td>
<td>$44.63 \pm 3.36$</td>
</tr>
<tr>
<td>R\textsubscript{12}, pg·min\textsuperscript{-1}·m\textsuperscript{-2}</td>
<td>$0.40 \pm 0.02$</td>
<td>$0.39 \pm 0.02$</td>
</tr>
<tr>
<td>MCR, l·min\textsuperscript{-1}</td>
<td>$1.01 \pm 0.03$</td>
<td>$0.99 \pm 0.02$</td>
</tr>
<tr>
<td>V\textsubscript{D}, liters</td>
<td>$2.44 \pm 0.14$</td>
<td>$2.21 \pm 0.12$</td>
</tr>
<tr>
<td>NESF, %</td>
<td>$17 \pm 1$</td>
<td>$22 \pm 4$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE. NE, norepinephrine; Epi, epinephrine; NE\textsubscript{2}, rate of NE appearance into an extravascular compartment; Q\textsubscript{1} and Q\textsubscript{2}, mass of NE in compartments 1 and 2; R\textsubscript{12}, rate of NE appearance from the extravascular to the intravascular compartment; MCR, metabolic clearance rate; V\textsubscript{D}, volume of distribution; NESF, spillover fraction. Values for NE kinetics parameters were estimated using a minimal 2-compartment model of the kinetics and distribution of $[^{14}C]$NE. None of the values after exercise training was significantly different from baseline.

![Fig. 1. Linear regression plots showing the relationship between the changes (delta) in rate of norepinephrine appearance into an extravascular compartment (NE\textsubscript{2}; A) and rate of norepinephrine appearance from the extravascular to the intravascular compartment (R\textsubscript{12}; B) and mean arterial blood pressure with 6 mo of aerobic exercise training.](http://jap.physiology.org/)
value obtained before the infusion of NE to control for potential differences in baseline FBF. Complete studies of FBF responses to intrabrachial artery NE infusion were not obtained in two subjects because of failure of the arterial line. Before and after exercise training, the five doses of NE elicited significant decreases in FBF. Exercise training had no effect on FBF responses to NE (ANOVA, \( P = 0.44 \)). The FBF responses to NE data were also analyzed based on whether a subject’s MABP was reduced (responder) or not reduced (nonresponder) after exercise training. We found no significant differences in FBF responses to NE (\( P = 0.25 \)) between the responders and nonresponders. The results were similar when the analysis was conducted with subjects grouped on the basis of gender and antihypertensive medication status.

Effects of aerobic exercise training on insulin sensitivity. \( S_I \), as assessed using the glucose and insulin data from the FSIVGTT and the Bergman Minimal Model, increased significantly from 2.81 to 3.71 \( \mu U \times 10^{-4} \text{min}^{-1} \text{ml}^{-1} \) (\( P = 0.004 \)) after aerobic exercise training. The range of the changes in \( S_I \) with exercise training was from −1.59 to +7.00 \( \mu U \times 10^{-4} \text{min}^{-1} \text{ml}^{-1} \). The relationship between the change in \( S_I \) and the change in MABP was not statistically significant (\( r = -0.03, P = 0.89 \)). The change in \( S_I \) was also not related to the change in \( NE_2 \) (\( r = 0.21, P = 0.27 \)). Again, the results were similar when the analysis was conducted with subjects grouped on the basis of gender and antihypertensive medication status.

To determine the extent to which changes in the independent variables (differences in \( V_O_{2 \text{ max}} \), percent body fat, \( NE_2 \), and \( S_I \)) contributed to the change in MABP with aerobic exercise training, we performed a stepwise linear regression analysis. The analysis revealed that, when changes in \( V_O_{2 \text{ max}} \) (\( r = -0.25, P = 0.19 \)), percent body fat (\( r = 0.11, P = 0.56 \)), \( NE_2 \), and \( S_I \) were considered as possible predictors of the change in MABP, only \( NE_2 \) emerged as the single, independent predictor (\( r = 0.38, P = 0.04 \)), accounting for 14% of the variance in the change in MABP.

**DISCUSSION**

In this study of older hypertensive subjects, there was no significant overall effect of aerobic exercise training on intra-arterial blood pressure; however, there was a wide range of blood pressure responses. We found the change in \( NE_2 \) to be the only significant independent predictor of the change in MABP and, as such, significantly contributed to the heterogeneity of the MABP response to 6 mo of aerobic exercise training. Other proposed mechanisms for the exercise training-induced reduction in blood pressure, such as changes in insulin sensitivity, \( V_O_{2 \text{ max}} \), and percent body fat, were not related to the MABP response to aerobic exercise training.

Nonpharmacological interventions, including exercise training, continue to be emphasized by the US National Heart, Lung, and Blood Institute Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, report number VI, for the treatment of essential hypertension (34). In our laboratory’s recent review, we showed that ~75% of hypertensive subjects significantly reduced their systolic and diastolic blood pressure with aerobic exercise training (16). In the present study, just 30% of the subjects achieved a reduction in their intra-arterial blood pressure with aerobic exercise training. The training stimulus was sufficient to cause a significant 13% increase in \( V_O_{2 \text{ max}} \), which indicates that there were adaptations of the CV system. This increase in \( V_O_{2 \text{ max}} \) is comparable to the 14–16% increases observed in our laboratory’s previous studies (5, 7). Thus the low percentage of subjects who reduced their blood pressure cannot be explained by a suboptimal training stimulus. Aging per se is associated with heightened SNS activity (45, 51), and there is evidence for SNS activation during the development and maintenance of hypertension (9, 13, 31). Supiano et al. (50) previously showed that the extravascular NE release rate, \( NE_2 \), tended to be higher in older hypertensive (2.23 \( \mu g \cdot \text{min}^{-1} \cdot \text{m}^{-2} \)) compared with older normotensive (1.64 \( \mu g \cdot \text{min}^{-1} \cdot \text{m}^{-2} \)) humans. Grassi et al. (14) used microneurography and similarly found that hypertension in older individuals was associated with SNS activation. It has been proposed that a reduction in the level of SNS activity may be associated with the exercise training-induced reduction in blood pressure. This is plausible, especially in older hypertensive subjects, because they are likely to have heightened systemic SNS activity. Aerobic exercise training could elicit adaptations in the adrenergic system, because the SNS is activated during each bout of exercise, and repeated activation of the SNS could result in an attenuation of resting SNS activity.

We found that, of the 13 older hypertensive subjects whose MABP was lower after aerobic exercise training, 10 of these subjects also reduced their \( NE_2 \) and \( R_{12} \). Thus the rate of NE release into an inaccessible extravascular compartment and the \( R_{12} \) were reduced in those subjects who also reduced their MABP, as illustrated by the significant relationships between the changes in \( NE_2 \) and \( R_{12} \) and the change in MABP with aerobic exercise training. The relationship between the change in \( NE_2 \) and the change in MABP with aerobic exercise training is particularly important, because this measure is a more proximate estimate of systemic SNS activity than arterial plasma NE levels (49). Before the aerobic exercise training program, the group’s average \( NE_2 \) value was 2.11 ± 0.15 \( \mu g \cdot \text{min}^{-1} \cdot \text{m}^{-2} \), which is comparable to the heightened SNS activity that our laboratory previously found in older hypertensive subjects (50). Our results suggest that a reduction in SNS activity may be one mechanism whereby aerobic exercise training reduces blood pressure in older hypertensive individuals and, as such, may play a role in the heterogeneity of blood pressure response to aerobic exercise training in this population.

Improvements in \( V_O_{2 \text{ max}} \), percent body fat, and insulin sensitivity are often observed after aerobic exer-
Exercise training. In the present study and similar to most studies, there was a wide range in the exercise training responses of these factors, which also may have contributed to the heterogeneity of the blood pressure response with aerobic exercise training. In the present study, the group’s average $S_1$ before exercise training was $2.81 \pm 0.37 \mu U \times 10^{-4} \cdot min^{-1} \cdot ml^{-1}$, which would be considered insulin resistant ($S_1 < 3.0$) as defined by Bergman (1). However, after 6 mo of aerobic exercise training, the group’s average $S_1$ significantly increased to $3.71 \pm 0.42 \mu U \times 10^{-4} \cdot min^{-1} \cdot ml^{-1}$. All studies after the 6 mo of exercise training, including the studies of insulin sensitivity, were performed 48 h after an exercise training session. King et al. (23) found that insulin action remained high after 5 consecutive days of aerobic exercise in moderately trained subjects. Costill et al. (4) previous showed that consecutive days of exercise caused a cumulative depleting effect on muscle glycogen stores. In the present study, exercise training occurred on 3 nonconsecutive days per week. It is likely that, in the present study, muscle glycogen was not depleted to the same extent as in the study by King et al. (23). Thus it is probable that only a small portion, at most, of the increase in insulin sensitivity was due to the last exercise training session. $\dot{V}O_2_{\text{max}}$ increased significantly by 13% in the present study, and the percentage of body fat was lower after exercise training, but the difference did not reach statistical significance. However, despite improvements in insulin sensitivity and $\dot{V}O_2_{\text{max}}$ after aerobic exercise training, neither of these two factors was an independent predictor of the change in blood pressure. We found that only the change in systemic SNS activity, as measured by NE$_2$ and R$_{12}$, was related to the change in blood pressure with aerobic exercise training.

The present study is the first to use a minimal two-compartment model analysis to estimate the rate of entry of NE into an extravascular compartment that is not accessible through blood sampling before and after aerobic exercise training in older hypertensive subjects. Simply, the compartmental analysis provides an estimate of the rate of NE release at the nerve terminals. The results of previous studies that measured plasma NE levels before and after exercise training in hypertensive individuals have been mixed (8, 24, 55). This may be because the extent to which plasma NE levels provide an index of SNS activity may vary, because the plasma NE levels indirectly reflect the rate of NE released at the nerve terminals (49). In the present study, there was no overall significant change in plasma NE and Epi levels or any of the other NE kinetic parameters after aerobic exercise training. There was no significant association identified between the change in MABP and the change in plasma NE levels. However, both two-compartmental model indexes of systemic SNS activity (NE$_2$ and R$_{12}$) were significantly related to the change in MABP. This suggests that the reduction in MABP that occurs after aerobic exercise training in some older hypertensive subjects is accompanied by suppression of resting systemic SNS activity.

Other studies have employed different techniques to assess the effects of exercise training on SNS activity. Results from studies in normotensive subjects using the microneurographic approach have not been consistent (35, 47). However, the durations of these exercise training programs have been relatively short, with the study by Sheldahl et al. (47) being the longest, lasting just 3 mo. Several studies have used the noncompartmental isotope dilution technique to determine the effects of exercise training on NE kinetics (21, 39–41, 46, 54). The primary outcome measure with this technique is NE spillover, which represents the small fraction of NE released from the nerve terminals that appears in the circulation (49). The majority of these studies investigated the effects of exercise training on resting metabolic rate (39, 40, 54), and none of the studies assessed NE spillover in hypertensive individuals. In cross-sectional and exercise training studies, Poehlman et al. found that resting levels of NE spillover were increased in active older subjects (59–76 yr) compared with inactive older and active and inactive younger subjects (18–36 yr) (41) and that NE spillover was higher in older normotensive subjects after exercise training (39, 40). Two studies reported that exercise training decreased NE spillover (21, 54). In a study by Jennings et al. (21), a decrease in NE spillover with exercise training was associated with a reduction in blood pressure in young, healthy subjects. More recently, Tremblay et al. (54) found that resting NE spillover was reduced in young normal men after exercise training. Again, none of these investigations studied older hypertensive subjects.

In the present study, a lack of association between exercise training-induced changes in $\dot{V}O_2_{\text{max}}$, body fat percentage, or insulin sensitivity and exercise training-induced changes in the blood pressure suggests that these factors were not major contributors to the heterogeneity of the blood pressure response. It is possible that improvements in CV fitness ($\dot{V}O_2_{\text{max}}$) with aerobic exercise training could lead to aerobic exercise training-induced reductions in blood pressure mediated indirectly through various blood-pressure-regulating mechanisms. Similarly, aerobic exercise training-induced improvements in insulin sensitivity may affect the blood pressure response through alterations in insulin effects on renal sodium handling and SNS activity (44). However, in the present study, we did not find a significant relationship between the change in $\dot{V}O_2_{\text{max}}$ and $S_1$ and the change in NE$_2$ or R$_{12}$ with aerobic exercise training.

It is possible that aerobic exercise training does not alter systemic SNS activity but that it reduces vascular $\alpha$-adrenergic-receptor responsiveness, resulting in decreased peripheral vascular resistance. If exercise training reduced systemic levels of SNS activity, systemic $\alpha$-adrenergic responsiveness would upregulate. Therefore, we assessed $\alpha$-adrenergic responsiveness in the forearm by determining FBF responses to graded doses of intra-arterial NE before and after aerobic exercise training. FBF responses to NE were unchanged after exercise training. To our knowledge, the
only other study to assess the effects of exercise training on \(\alpha\)-adrenergic receptor responsiveness in hypertension was performed on hypertensive male Fisher-344 rats (26). In this study, exercise training enhanced myocardial \(\alpha_1\)-adrenergic-receptor responsiveness to phenylephrine. Because there were no changes identified in arterial \(\alpha\)-adrenergic responsiveness after aerobic exercise training in the present study, changes in MABP could not be attributed to changes in arterial \(\alpha\)-adrenergic responsiveness.

It is possible that some antihypertensive medications, as well as estrogen replacement, may affect aerobic exercise training-induced changes in CV function and SNS activity (12, 18, 38, 48, 56). Therefore, we also analyzed the data with the subjects grouped on the basis of gender, use of antihypertensive medications, and, in the women, whether or not they were using hormone replacement therapy. Based on these subject grouping variables, we did not find any differences in the changes in the outcome variables with aerobic exercise training. Thus in the present study, gender, antihypertensive medication, or hormone use appeared not to contribute to the heterogeneity of the change in blood pressure with aerobic exercise training.

A limitation of the present study is that the method used to assess SNS activity measures systemic and not organ-specific SNS activity. Because the SNS is activated in an organ-specific and not a systemic manner, it is possible that SNS activity was changed to a greater or lesser degree in various organs. In the present study, we were not able to discern whether changes in the SNS activity of specific organs occurred. It is also possible that, because of a lack of a control group, there may have been an order effect, particularly because of the invasive methods used to assess systemic SNS activity. However, using an 8-wk placebo-controlled, double-blind, randomized hypertension medication intervention, our laboratory previously showed that NE\(_2\) was unchanged (29). Therefore, in the present study, it is unlikely that an order effect or the lack of a control group affected the results. Approximately 30\% of the subjects in the present study lowered their blood pressure. This is in contrast to the 75\% of hypertensive subjects who reduce their blood pressure with aerobic exercise training that our laboratory previously reported (16). In the present study, we used an intra-arterial pressure transducer to measure blood pressure in the supine position. Nearly all of the previous studies used sphygmomanometry measures while subjects were in the seated position. Thus our results may not be directly comparable to studies that have employed indirect cuff measures in sitting or upright positions. It is also possible that individual genetic differences contributed to the heterogeneous blood pressure responses to aerobic exercise training. Recently, Hagberg et al. (15) and Rankinen et al. (43) found that common gene variants identified individuals who lowered their blood pressure the most with exercise training. Thus gene variations among individuals may account for a greater amount of heterogeneity in the blood pressure response to aerobic exercise training than systemic SNS activity.

In summary, the present study is the first to employ two-compartmental modeling of NE kinetics to study the effect of aerobic exercise training in older hypertensive individuals. This is especially important because older hypertensive subjects have been shown to have heightened SNS activity compared with their normotensive peers. We found that 6 mo of aerobic exercise training in older hypertensive subjects caused a wide range of blood pressure responses such that there was not a significant change in the group’s average resting, supine intra-arterial MABP. However, the change in systemic extravascular NE release rate significantly contributed to the heterogeneity of the MABP response to aerobic exercise training, whereas changes in VO\(_2\)\(_{\text{max}}\), percent body fat, and insulin sensitivity did not. These findings suggest that suppression of SNS activity may contribute to the reduction in MABP and account for a portion of the heterogeneity in the blood pressure response to aerobic exercise training in older hypertensive subjects.

The authors acknowledge the important contributions of many individuals to this study: Kathy Jarvenpaa and the General Clinical Research Center (GCRC) nursing staff; Connie Adaire and the GCRC diettian staff; and Marla Smith and Eric Leindecker for technical support.

This study was supported by National Institute on Aging Research Scientist Development Award in Aging Grant KO1 AG-0072301 (to D. R. Dengel); Department of Veterans Affairs Geriatric Research; Education and Clinical Center and Medical Research Service at Ann Arbor, University of Michigan; Claude D. Pepper Older Americans Independence Center (Grant AG-08808); and University of Michigan GCRC (Grant RR-00042).

Portions of this work were presented at the National Meeting of the American Federation for Medical Research in 1997.

REFERENCES


