THERE IS AN ABNORMAL cardiovascular response to exercise in hypertension. Exercise can be broadly divided into two types of which one is dynamic or endurance and the other is static or strength (6, 50, 52). These two types of exercise represent the two ends of the exercise spectrum and most physical activity is some combination of each type. Also each type of exercise can be of high, moderate, or low intensity (50). In dynamic or endurance exercise of a high intensity such as long distance running, there is a moderate increase in mean arterial pressure (MAP) due to a marked increase in systolic arterial pressure and a small increase or a decrease in diastolic arterial pressure. Heart rate is markedly increased, stroke volume is increased, and there is an increase in sympathetic efferent activity to the heart and blood vessels (52). In static or strength exercise, such as power lifting, there is a marked increase in MAP due to an increase in both systolic and diastolic arterial pressures. Also, there is a moderate increase in heart rate and little change in stroke volume. In general, the increase in sympathetic efferent activity is likely to be greater in static compared with dynamic exercise, but this would be dependent on the relative intensities of the exercise being performed.

In hypertensives there are greater increases in arterial pressure, heart rate, and sympathetic efferent activity in both types of exercise than in normotensive individuals (4, 5, 21). During dynamic exercise maximal oxygen uptake is lower in sedentary hypertensive patients than in sedentary normal controls (19, 43, 66). However, a more trained patient with hypertension may have a higher maximal oxygen uptake during dynamic exercise than a less trained normal subject (62).

The abnormal cardiovascular response to exercise in hypertension makes the patient more prone to have an untoward event (angina, myocardial infarction, or cerebrovascular accident) than a normal subject (56, 57). This poses a dilemma for
the patient and the doctor since exercise training that is carefully prescribed, monitored, and sometimes even supervised can cause an improvement in the hypertension (13, 16, 20, 36, 37, 65, 90).

Two neural factors have been shown to contribute significantly to this abnormal cardiovascular response to exercise. These are 1): the exercise pressor reflex (EPR) and 2) functional sympatholysis.

Exercise Pressor Reflex

Neural Pressor Reflex during exercise. The cardiovascular response to physical activity is rapidly and appropriately matched to the intensity of exercise (47). How this extremely fast and precise matching is achieved has intrigued physiologists for well over a hundred years. There were four early giants in the field whose research increased our understanding and directed our research in this area (48). They are Johan Johansson from Stockholm whose studies in 1893 were performed in rabbits and dogs (28), August Krogh and Johannes Lindhard from Copenhagen whose studies in 1913 and 1917 were performed in humans (39, 40), and Horace Smirk from Cairo and later New Zealand whose studies were also performed in humans (1–3). A more detailed presentation of these early studies has been published (48). From their work a hypothesis for the framework of the neural control of the circulation during exercise can be formulated (54).

Central control is a feed-forward mechanism originally called “cortical irradiation” in 1913 (40) and later termed Central Command in 1972 (22). This mechanism is widely accepted as a concept but the neural substrate for its operation has been elusive (93). In animals, stimulation of diencephalic and brain stem locomotor regions has been used as a surrogate, but this area is not the site of central command (7, 92). In humans, brain imaging and brain stimulation methodologies have been used to study this mechanism (7, 94). Areas of interest have included the insular cortex and the anterior cingulate cortex (94).

The peripheral control mechanism has been more widely studied (11, 12, 31, 32, 45, 49, 53) and was termed the exercise pressor reflex (EPR) in 1983 (51). Comprehensive review articles have been published on this mechanism (31, 32, 55, 75). These two mechanisms of neural control during exercise are not mutually exclusive but work in close concert with some overlap or redundancy.

Another input into the medullary cardiovascular control areas during exercise is the arterial baroreflex. The concomitant increase in blood pressure and heart rate was a dilemma without a good explanation for many years. It is now known that the arterial baroreflex is reset during exercise, remains operational, and modulates blood pressure and heart rate continuously (18, 29).

Exercise pressor reflex defined. The EPR has been primarily studied during static exercise. That large increases in blood pressure, with small increases in heart rate and cardiac output, occur during static contraction of the forearm muscles (handgrip) was shown by Lind et al. (44). Also the intensity of static exercise can be quantitated as the percentage of the maximal voluntary contraction (%MVC). This type of exercise is well suited for studying both central command and the EPR.

A useful model to study the EPR was developed in cats in which central command is not involved and the arterial baroreflex can be abolished or controlled (11, 12, 45, 76). After a laminectomy, the ventral roots of the L7 and S1 spinal segments are sectioned and the peripheral ends are placed on electrodes. Stimulation of these electrodes produces contraction of the triceps surae muscle that in turn elicits a marked increase in blood pressure and a small increase in heart rate (12, 45). Sectioning of the corresponding dorsal roots abolishes the response, which proves that this is a reflex arising from afferents originating in the contracting skeletal muscle (12, 45). The EPR has also been extensively studied in humans (75).

There are four groups of afferent fibers in the dorsal roots that project from skeletal muscle and they have been classified by anatomical and electrophysiological properties (8, 9, 25, 26, 55). These are groups I and II, which are thickly myelinated, group III (Aδ), which is thinly myelinated, and group IV (C), which is unmyelinated. Both anodal and anesthetic blocks were employed to determine which fibers were responsible for the cardiovascular changes during muscle contraction (45). Conduction in the large myelinated fibers (groups I and II) was interrupted by a direct current anodal block, and conduction in the thinly myelinated group III (Aδ) and unmyelinated group IV (C) fibers was interrupted by an anesthetic (lidocaine) block. It was shown that the blockade of the thinly myelinated afferent fibers had no effect on the increased blood pressure and heart rate responses to induced exercise; however, the blockade of the thinly myelinated (Aδ) and unmyelinated (C) afferent fibers abolished the cardiovascular response to induced exercise (45). Thus the reflex was caused by activation of fine afferent fibers (i.e., group III and IV).

Next, it was important to characterize the response of the thinly myelinated group III (Aδ) and unmyelinated group IV (C) fibers to muscle contraction. Studies were again performed in cats and afferent fibers were identified in the dorsal root by their conduction velocity. It was found that group III fibers, which have a conduction velocity between 2.5 and 30.0 m/s, were predominantly activated by mechanical distortion in the contracting muscle (31–34, 46, 55). Also group IV (C) fibers, which have a conduction velocity of <2.5 m/s, were predominantly activated by metabolic byproducts in the contracting muscle (31–34, 46, 55). These fibers, which are activated by muscle contraction, are known as ergoreceptors. Also, it was discovered that some of the fibers found in the dorsal root were not activated by muscle contraction and only responded to noxious stimuli such as strong pinching of the triceps surae (34, 55). They are known as nociceptors.

A classification of the fine (small) group III and group IV afferent (sensory) fibers from muscle has been made. As stated, these afferents can be divided into two main categories. These are the ergoreceptors and the nociceptors. Nociceptors are high-threshold afferents that are activated by a noxious stimulus and are responsible for muscle pain including claudication. Ergoreceptors, on the other hand, are low-threshold afferents that are activated by muscle contraction. These afferents are of two types. Group III (Aδ) fibers are predominantly activated by mechanical deformation, which occurs when the contracting muscle develops tension and stimulates mechanoreceptors. Group IV (C) fibers are predominately activated by the products of muscle metabolism, which include, but are not limited to, H+, K+, ATP, diprotonated phosphate, prostaglan-
dins, and bradykinin (32). These products stimulate receptors that have been termed metaboreceptors. However, this classification is not black and white and has some exceptions. Mechanoreceptor sensitivity is altered by the metabolic products of muscle contraction and thus behave as metaboreceptors. Also metaboreceptors in rare cases are activated by muscle deformation.

The components of the exercise pressor reflex are shown in Fig. 1. Contracting skeletal muscle activates both the metaboreflex and the mechanoreflex. When the metabolically sensitive receptors are activated, they send impulses to the cardiovascular control areas in the medulla oblongata via predominately group IV (C) afferent fibers. The mechanically sensitive receptors are also activated by muscle contraction and they send impulses to cardiovascular control areas in the medulla via predominately group III (A-δ) afferent fibers. The cardiovascular control areas in the medulla that are involved include the nucleus tractus solitarius (NTS), rostral ventrolateral medulla (RVLM), and the caudal ventrolateral medulla (CVLM). Much work has been done to understand how these signals are processed in these areas and how sympathetic efferent fibers are activated to the heart and blood vessels. These neural mechanisms have been reviewed in several articles (14, 15, 78) and will not be discussed here. The increase in sympathetic efferent activity causes an increase in blood pressure, heart rate, and left ventricular contractility (11, 12, 31, 32, 45, 49, 53). Not shown in Fig. 1 is that a decrease in parasympathetic activity to the heart also occurs.

A rat model to assess the EPR. The cat model for studying the exercise pressor reflex has been adapted to a smaller experimental animal (i.e., the rat) so that disease states can be studied (heart failure and hypertension) (81). In the rat, depressor responses to muscle contraction occur when the animal is anesthetized by inhalant or injectable anesthetics. To obtain a pressor response the rat is briefly anesthetized with inhalant anesthetics and a decerebration performed (81). Next a laminectomy is completed and the L4 and L5 spinal roots are isolated. The ventral roots are separated and sectioned. The peripheral ends are placed on stimulating electrodes. Now, as in the cat, electrical simulation causes a contraction of the triceps surae muscle and this results in an increased blood pressure and heart rate. Also, when the appropriate dorsal roots are sectioned, the cardiovascular response does not occur again showing the response is a reflex from the contracting muscle (81).

The spontaneously hypertensive rat (SHR) has been used in our studies with the Wistar-Kyoto (WKY) rat serving as the control (42, 60, 61). Typical characteristics of the EPR in our first study by Smith et al. (82) showed a mean resting arterial pressure of 89 ± 8 mmHg in the WKY and 149 ± 5 mmHg in the SHR, mean heart weight-to-body weight ratio was 3.2 ± 0.1 mg/g in the WKY and 3.7 ± 0.1 mg/g in the SHR. Both of these differences were significant at P < 0.05. Lung weight-to-body weight ratio was 6.7 ± 0.5 mg/g in WKY and 7.3 ± 0.04 mg/g in SHR, which was not statistically different (82). This would indicate no pulmonary edema or left-sided heart failure in the SHR. This is important since a rat model of left heart failure has an exaggerated EPR (80). In our following studies using this model, the rats had similar characteristics demonstrating an elevated blood pressure, left ventricular hypertrophy, and no evidence of left ventricular failure (42, 60, 61).

EPR in SHR animals. Smith et al. (82) showed that activation of the EPR caused greater increases in blood pressure and heart rate in SHR than in WKY. Mizuno (61) found similar changes and also recorded renal sympathetic neural activity. These effects of induced static exercise on arterial blood pressure (ABP) and integrated efferent renal sympathetic nerve activity (RSNA) in WKY and SHR are shown Fig. 2. Dynamic tracings from one rat in each group are shown in Fig. 2A. On the left side in green is the response in WKY. There is a small increase in both blood pressure and integrated renal sympathetic nerve activity. On the right side, the SHR animal shows greater increases in blood pressure and integrated renal sympathetic nerve activity than those seen in the WKY. The averaged data from 14 WKY and 39 SHR expressed as means ± SE are shown Fig. 2B. The change in MAP (ΔMAP) was greater in the SHR (39 ± 5 mmHg) than in the WKY (9 ± 2 mmHg) as were the changes in RSNA (ΔRSNA), which was 139 ± 14% in the SHR and 48 ± 8% in the WKY. These changes were all statistically significant (P value < 0.05).

Mechanoreflex in SHR animals. Muscle stretch has been used to selectively activate the mechanoreceptors in the triceps surae muscle (83). Leal et al. (42) have shown, using this perturbation, that the mechanoreflex is accentuated in SHR animals. Mizuno et al. (61) has also studied this perturbation in SHR and WKY rats and included recordings of RSNA. Results from this study are shown in Fig. 3. Averaged data expressed as means ± SE are from both WKY (n = 12) and SHR (n = 37) animals. The changes in MAP (30 ± 5 vs. 10 ± 3 mmHg), heart rate (8 ± 1 vs. 3 ± 1 beats/min), and RSNA (97 ± 12 vs. 35 ± 7%) were all greater in the SHR than in the WKY. These changes were all statistically significant (P value < 0.05). There was no difference in the tension development in the two groups, and it was about the same magnitude as that seen during muscle contraction.

Metaboreflex in SHR animals. It has been shown that the TRPV1 receptor is located in the group IV (C) afferents and that it plays a role in the metaboreflex of Sprague-Dawley rats (79). Additionally, hindlimb intra-arterial administration of capsaicin (a TRPV1 agonist) has been shown to elicit a significantly larger increase in blood pressure and heart rate in SHR compared with WKY rats (42). It is also known that capsazepine
blocks the TRPV1 receptor activity (79). To further examine the metaboreflex in SHR and WKY animals, ischemic contraction was used (60). This maneuver produces a marked stimulation of the metaboreflex. The results showing averaged data expressed as means ± SE of such a study are shown in Fig. 4A. Capsazepine causes a significantly greater decrease in MAP and RSNA in SHR than WKY animals. Thus the metaboreflex component of the EPR is enhanced in this animal model of hypertension (60).

To further demonstrate the enhanced metaboreflex in the SHR compared with the WKY, protein expression of the TRPV1 receptor in the dorsal root ganglion was measured (60) and is shown in Fig. 4B. This was accomplished by using a Western blot analysis to determine the densities of TRPV1-to-GAPDH ratios that were normalized to WKY samples (60). The WKY is shown in green and the SHR is shown in red. The TRPV1 expression was greater by 90 ± 27% in SHR compared with WKY (P < 0.05).

**EPR and exercise training.** Exercise training has been shown to be beneficial in hypertensive patients (13, 16, 20, 36, 37, 65). Since the EPR is enhanced in the SHR, the effect of exercise training in this condition was studied. Exercise training studies were performed in both WKY and SHR animals (58). Age-matched WKY and SHR animals were randomly divided into untrained (UT) and exercise trained (ET). The ET groups were housed with a running wheel and were allowed to exercise spontaneously. The animals trained for ~3 mo. The UT animals were housed without a wheel for the same period of time. Both before and after training, peak oxygen uptakes were determined in all four groups (WKYUT, WKYET, SHRUT, and SHRET). Peak oxygen uptake was significantly increased in the trained animals in each group (58).

The effects of exercise training on the EPR are shown in averaged data expressed as means ± SE in Fig. 5. Activation of the EPR caused greater increases in ΔMAP (53 ± 11 vs. 12 ± 5 mmHg) and ΔRSNA (145 ± 32 vs. 47 ± 15%) in SHRUT than in WKYUT at approximately the same amount of tension development. Also, exercise training significantly attenuated the ΔMAP (53 ± 11 vs. 19 ± 3 mmHg) and ΔRSNA (145 ± 32 vs. 57 ± 11%) responses in SHRET but not in WKYET (58).

**Functional Sympatholysis**

**Definition.** A second contributing neural factor to the abnormal cardiovascular response to exercise is functional sympatholysis. The term functional sympatholysis was introduced in a paper published in 1962 and was defined as the diminished vasoconstriction to increased sympathetic activity that occurs in working muscles during exercise (70). Earlier work had also suggested this concept (68, 69). A later study by Kjellmer in cats also concluded that vasoconstriction was reduced in exercising muscle (38).

However, all of these studies (38, 68–70) had relied on resistance changes when both pressure and flow were changing and where baseline flows varied widely. Because this was cause for concern, an experimental preparation was developed in dogs to perform pressure-flow curves under different conditions (70). A diagram of this preparation is shown in Fig. 6. Two dogs were utilized, with one serving as the experimental dog and the other as a donor dog. The femoral artery of the donor dog was connected to the femoral artery of the isolated leg in the experimental dog through a roller pump to control femoral artery flow. A recording rotameter (77) was used to measure blood flow and a transducer was utilized to measure perfusion pressure. Blood was returned from the isolated leg of the experimental dog to the donor dog by connecting the femoral veins through a blood reservoir that was used to replenish blood loss from blood donors. Both dogs were placed on ventilators. Arterial pressure was measured by a pressure gauge in the abdominal artery of the experimental dog. In addition, the common carotid arteries of the experimental dog were cannulated centrally, and the flow was directed to the reservoir of a Dale-Schuster pulsatile pump, which delivered the blood back distally into the common carotid arteries at a constant pressure. The pump was stopped to produce a low
carotid sinus pressure. To produce muscle contractions in the vascularly isolated perfused leg, needle electrodes were placed in the quadriceps muscle and connected to a stimulator which produced rhythmic dynamic contractions (30).

Pressure-flow curves were generated by changing flow with the roller pump from 25 ml/min to above 100 ml/min during rest and to 150 ml/min during exercise. At selected values of flow, perfusion pressure was measured. This maneuver was performed during four conditions (70): 1) resting leg with normal carotid sinus pressure; 2) resting leg with low carotid sinus pressure (a baroreflex stimulus to increase sympathetic activity); 3) exercising leg with normal carotid sinus pressure; and 4) exercising leg with low carotid sinus pressure (a baroreflex stimulus to increase sympathetic activity).

An example of these pressure-flow curves is shown in Fig. 7 (70). In Fig. 7, mean arterial blood pressure (MBP, in mmHg) is on the y-axis and perfused leg blood flow (ml/min) is on the x-axis. The resting values with normal carotid sinus pressure are the open green circles connected by a green line. The resting values with low carotid sinus pressure are the closed green circles. They are all above and to the left of the green line, which shows vasoconstriction. The exercising values with normal carotid sinus pressure are the open red triangles and they are also connected by a red line. The exercising values with low carotid sinus pressure are the closed red triangles and they are located along the same red line. Unlike the resting condition, this finding indicates that no vasoconstriction occurred in the isolated vasculature during exercise with a baroreflex-induced stimulus to increase sympathetic activity (70).

All four curves have a flow value of 100 ml/min. During rest with a low carotid sinus pressure this flow requires a perfusion pressure of ~230 mmHg and during rest with a normal carotid

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Fig. 3. Effect of muscle stretch on ΔMAP, ΔRSNA, ΔHR, and change in tension development in WKY and SHR. Average data expressed as means ± SE. *P < 0.05 compared with WKY. Adapted from Mizuno et al. (61).

Fig. 4. A: MAP and RSNA responses to ischemic muscle contraction before (dark circles) and after (light circles) capsazpine. B: protein expression of the TRPV1 receptor in the dorsal root ganglia of WKY and SHR. Average data expressed as means ± SE. *P < 0.05 compared with WKY. Republished from Mizuno et al. with permission (60).
sinus pressure it requires a perfusion pressure of ~180 mmHg (70). This observation clearly indicates vasoconstriction during a baroreflex stimulus to increase sympathetic activity. During exercise with either a normal or a low carotid sinus pressure, only a perfusion pressure of ~125 mmHg is required to achieve this same flow. This observation shows that there is marked vasodilation during exercise and that this vasodilation is not affected by a baroreflex stimulus to increase sympathetic activity.

In retrospect it was a mistake to only publish one of our best studies that showed complete abolition of vasoconstriction during exercise. Most of the studies simply showed that the shift up and to the left during a baroreflex stimulus to increase sympathetic activity was much smaller during exercise than it was during rest, indicating that at least some vasoconstriction remained during muscle contraction; although much less than that seen during resting conditions. This percent change in the movement of the curve is similar to using the percent change in conductance (70), which will be discussed later.

The concept of functional sympatholysis has had a very stormy history and was rarely mentioned from 1962 to 1994 (32 years). Since the first published studies used changes in resistance to evaluate vasoconstriction or vasodilation, it was stated that the concept was a "mathematical artifact" (41, 64, 86). This reasoning suggested that basing one’s interpretation on calculated resistance changes would lead to erroneous conclusions and that calculation of conductance would correct this error (41, 64, 87). However, the statement ignored the pressure-flow curves in the 1962 paper, which did not depend on the calculation of resistance or conductance and which clearly showed an attenuated vasoconstrictor response to experimentally increased sympathetic activity during muscular exercise (70).

![Fig. 5. Effect of exercise training on the EPR. UT, untrained. ET, exercise trained. *P < 0.05 compared with WKY<sub>UT</sub>. †P < 0.05 compared with SH<sub>UT</sub>. From Mizuno et al. (58).](http://ajpregu.physiology.org/)

![Fig. 6. Preparation in dogs for studying functional sympatholysis. For description see text.](http://ajpregu.physiology.org/)
The so-called “mathematical artifact” was restudied by Thomas, Hansen, and Victor in 1994 (86). They performed a study in rats and conclusions were based on conductance calculations. Using changes in conductance, they found that functional sympatholysis occurred and that it was more prominent in glycolytic (gastrocnemius) than in oxidative (soleus) skeletal muscle. However, there were still doubters because pressure and flow were both changing and the baseline flows (rest vs. exercise) were markedly different (87).

In 2002, two papers, which were parallel studies in humans and dogs, were published together and they clearly established the concept of functional sympatholysis (73, 89). Both of these studies evaluated the vasoconstrictor effect of increased sympathetic activity by calculating the percent reduction in vascular conductance (85, 87, 88), which is similar to the percent leftward movement of pressure-flow curves as discussed earlier.

\[
\% \text{Reduction in Conductance} = \frac{\text{Final Conductance} - \text{Initial Conductance}}{\text{Initial Conductance}} \times 100
\]

In these studies, the percent change in conductance was used because of the different baselines of resting and exercising blood flow values. Also these two studies (73, 89) recognized the power of using pressure flow curves to evaluate vasoconstrictor activity and gave credit to the 1962 paper (70).

In the human study, dynamic forearm contractions were used as the exercise condition, and in the dog study, running on a treadmill was used as the exercise condition (73, 89). In both studies, increased sympathetic activity was produced by tyramine infusion, which elicited endogenous release of norepinephrine. In both of these studies the magnitude of vasoconstriction, when evaluated as the percent change in conductance, was much less in exercising muscle than it was in resting muscle. Thus these combined findings supported the existence of functional sympatholysis beyond any reasonable doubt and it is a concept that is now generally accepted. In the times since these two studies were published, other papers have supported the concept of functional sympatholysis (17, 24, 35, 95).

Functional sympatholysis is an important component of the integrated cardiovascular response to exercise as was recently pointed out in a review article by Thomas (84). Also, Saltin and Mortensen (74) discussed “the crucial significance of functional sympatholysis for achieving a blood flow that matches the energy demand of human skeletal muscle”.

Proposed mechanisms. Even though the concept of functional sympatholysis is now accepted, the responsible mechanisms are not proven. Two mechanisms have been proposed to explain this phenomenon. During exercise there is increased efferent sympathetic activity to the blood vessels in both resting and exercising skeletal muscle (23). In resting muscle, the nerve impulses cause release of the neurotransmitter norepinephrine (NE), which activates the \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptors causing vasoconstriction (71). In exercising muscle, as in resting muscle, the increased nerve impulses cause release of NE. However, the actions of NE on \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptor are opposed. One proposed mechanism for this opposition is that nitric oxide synthase (NOS) is activated in the contracting muscle and releases nitric oxide (NO), which acts on vascular smooth muscle or endothelial cells to oppose the activation of \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptors by NE and thereby attenuates the vasoconstriction (10, 88). A second proposed mechanism is that ATP, released from both muscle and deoxygenated hemoglobin, activates the purinergic receptor \( P_2 \), and may act on vascular smooth muscle or endothelial cells to attenuate the vasoconstriction (63, 72). Early work in both rats, dogs, and humans strongly supports the NO hypothesis. However, more recent work in humans supports the ATP hypothesis. Clearly more work in humans is needed to resolve this controversy.

Hypertensive animals and the effect of exercise training. In 2006, Zhao et al. (96) studied the magnitude of functional sympatholysis in rats made hypertensive by either chronic angiotensin II infusion or by a nonoccluding unilateral renal artery stenosis. They measured percent change in conductance for their evaluation of the degree of vasoconstriction. Functional sympatholysis was impaired in both models of hypertension. In addition, Jendzjowsky and Delorey (27) showed that exercise training in normal Sprague-Dawley rats enhanced functional sympatholysis, and they also used percent change in conductance. Based on these reports, a paper published in 2014 by Mizuno et al. (59) asked two questions. First, was functional sympatholysis impaired in an animal model of essential hypertension (i.e., the SHR rat)? Second, if it were, could it be improved by exercise training? Again exercise training was performed by voluntary wheel running and evaluated by determining peak oxygen consumption as described previously.

The experimental preparation used by Mizuno and colleagues was that of Thomas, Hansen, and Victor (86) and is shown in Fig. 8. Arterial pressure was measured in the lower aorta. Stimulating electrodes were placed on the lumbar sympathetic chain to experimentally increase sympathetic efferent activity. A Doppler flow probe was placed around the femoral artery. Simulated exercise was produced by inducing contraction of the triceps surae muscles using stimulating electrodes placed on the tibial nerve (motor). The triceps surae muscle was attached via the calcaneal tendon to a force transducer to measure muscle tension.

Three groups of rats were studied: 1) untrained WKY (WKY\text{UT}), 2) untrained SHR (SHR\text{ut}), and 3) trained SHR.
The WKY animals were not trained because it had already been shown that functional sympatholysis could be improved in normal rats in the Jendzjowsky and Delorey study (27). The percent change in femoral vascular conductance was used to determine the magnitude of vasoconstriction and the data are shown in Fig. 9. Dynamic tracings are shown in Fig. 9A and mean data in Fig. 9B. The data under resting conditions are shown in green and during exercise in red. In panel A, lumbar nerve stimulation at 5 Hz is shown by the black bar. The decrease in vascular conductance at rest is greater in WKYUT than in SHRUT. Exercise training enhanced functional sympatholysis in an individual SHR animal depicted in Fig. 9 (SHRET#1). A second individual SHR animal depicted in Fig. 9 (SHRET#2) demonstrated complete abolishment of vasoconstriction during exercise. The journal would not allow us to publish this latter finding because it did not represent the mean data reported. However, it confirmed the 1962 pressure-flow curves which showed this same total abolition of vasoconstriction (70). The averaged data expressed as means ± SE are shown in Fig. 9B (59). The decrease in percent change in conductance during exercise was less in SHRUT than WKYUT. With exercise training, the SHRET demonstrated an enhancement of functional sympatholysis.

The magnitude of functional sympatholysis can be expressed as follows:

\[
\text{Magnitude of Sympatholysis} = \frac{\% \text{Change of Vascular Conductance During Contraction}}{\% \text{Change of Vascular Conductance During Rest}}
\]

This value expressed as mean ± SE is shown Fig. 10A (59). The magnitude of sympatholysis is less in SHRUT than in WKYUT. The magnitude in SHRUT is more than that in SHRUT. There is no difference in the values between WKYUT and SHRUT.

Next, the mechanism of the change in functional sympatholysis was studied by giving \(N^G\text{-nitro-L-arginine methyl ester (L-NAME)}\) (an NOS inhibitor) to all three groups to determine if NO was involved (59). The results of this study are shown as means ± SE in Fig. 10B. The data in red are under control conditions and the data in blue were collected after giving L-NAME systemically. The magnitude of sympatholysis in WKYUT was less after L-NAME. The magnitude was the same in the SHRUT. Most interestingly, the magnitude of sympatholysis was much less after L-NAME in the SHRET. This shows that the training-induced improvements in functional sympatholysis in SHR were dependent on a NO mechanism (59).

**Human Hypertension.** Vongpatanasin et al. (91) have studied functional sympatholysis in normal subjects and in patients with hypertension. The preparation used in this study is shown in Fig. 11. Systolic and diastolic arterial pressures were determined by an automatic sphygmomanometer and heart rate was derived from an electrocardiogram. Forearm blood flow was measured by Doppler ultrasound and forearm muscle oxygenation by near infrared (NIR) spectroscopy. Muscle sympathetic nerve activity (MSNA) was measured from an electrode placed...
in the peroneal nerve. Intermittent hand grip contraction was performed at 30% maximal voluntary contraction (MVC) every 3 s. A tourniquet was placed on the upper arm for blood flow occlusion of 3 min to determine the total labile signal (TLS) to calibrate the NIR signal. Lower body negative pressure (LBNP) of $-20 \text{ mmHg}$ was used to unload the low pressure (cardiopulmonary) baroreceptors to experimentally increase sympathetic neural activity.

In the study, 13 hypertensive patients and 15 normotensive matched controls were used. The dynamic data from one representative individual in each group is shown in Fig. 12A. The top trace in green is from a normotensive subject and the bottom trace in red is from a hypertensive patient. $\Delta \text{HbO}_2 + \text{MbO}_2$ represents alterations in muscle oxygenation and is a surrogate for blood flow during steady-state oxygen consumption. MSNA is muscle sympathetic nerve activity. Forearm blood flow is not shown. In the normotensive subject, LBNP during rest caused a large decrease in muscle oxygenation, which indicates marked vasoconstriction. Handgrip caused a small increase in MSNA. LBNP during exercise caused only a small decrease in muscle oxygenation, which indicated little vasoconstriction (i.e., functional sympatholysis). As described, occlusion of the upper arm for 3 min produced the TLS necessary to calibrate the NIR signal used to assess muscle oxygenation. In the hypertensive patient, LBNP at rest also caused a large decrease in muscle oxygenation (vasoconstriction). Handgrip now caused a marked increase in MSNA at the start of exercise, which was different from the normotensive subject. Also LBNP during exercise still caused a large decrease in muscle oxygenation (vasoconstriction still present). Thus this provided evidence that functional sympatholysis was markedly impaired in the hypertensive patient.

Average data expressed as means ± SE, including changes in forearm blood flow, are shown in Fig. 12B. On the left side of Fig. 12B are the normotensive subjects in green and on the right side are the hypertensive patients in red. $\Delta \text{HbO}_2 + \text{MbO}_2$ (% TLS) is the change in oxygenation as a percentage of the TLS. $\Delta \text{FBF}$ (%) is the percent change in forearm blood flow, and $\Delta \text{MSNA}$ is the percent change in muscle sympathetic activity (% total activity). In the normotensive subjects, there is a decrease in oxygenation and blood flow during rest; however, there is little change in these values during exercise, which is characteristic of functional sympatholysis. The change in muscle sympathetic activity was the same. In the hypertensive patients, there is a decrease in oxygenation and blood flow during rest, and there is also a decrease in both of these...

Fig. 10. Magnitude of functional sympatholysis. A: control data. B: effect of $N^\omega$-nitro-L-arginine methyl ester (l-NAME). From Mizuno et al. (59).

Fig. 11. Preparation in humans for studying functional sympatholysis. For description see text. Published with permission.
values during exercise. This demonstrates a marked impairment of functional sympatholysis. In this study it is also of interest that treatment with irbesartan, an angiotensin receptor blocker, restored functional sympatholysis in the hypertensive patients, whereas, chlorthalidone, a thiazide-type diuretic, had no effect (91).

In a second study by this group of a similar cohort of hypertensive patients, functional sympatholysis was likewise markedly impaired (67). In these patients, treatment with a B1-adrenergic receptor blocker nebivolol (which also has NO-potentiating vasodilatory effects), reversed the impairments in functional sympatholysis. However, metoprolol, a B1-adrenergic receptor blocker that does not cause vasodilation had no effect. These findings suggest that the NO produced by contracting muscle plays a role in mediating functional sympatholysis in humans. The data further suggests that NO may be released by vascular endothelial cells (67). More studies are needed to better understand these mechanisms.

Exercise training in humans. Complementing the evidence discussed previously from animal investigations, a study has been performed to determine if exercise training improves functional sympatholysis as well as reduces α-adrenergic responsiveness in patients with hypertension (62). Hypertensive patients and age-matched, normotensive control subjects received 8 wk of dynamic exercise training. Surprisingly, there was no evidence that functional sympatholysis was compromised in the vasculature of the legs of the hypertensive patients before training as it is in the forearms. That being said, the investigation did find that exercise training reduced α-adrenergic responsiveness and enhanced functional sympatholysis in both normotensive subjects and hypertensive patients (62).

Conclusions

In normal humans and animals, the exercise pressor reflex and functional sympatholysis play important roles in the integrated response to exercise so that the increase in blood flow to the contracting muscle is adequate to meet its greater metabolic demands.
In hypertension an enhanced exercise pressor reflex and an impaired functional sympatholysis set up a positive feedback circuit, which causes a progressively greater decrease in the blood flow to the exercising muscle. Thus these two neural factors are largely responsible for the abnormal cardiovascular responses to exercise in this condition.

In hypertension, exercise training decreases the enhanced exercise pressor reflex including the abnormal function of both of its components (i.e., mechanoreflex and metaboreflex) and improves the impairment in functional sympatholysis. Both of these changes improve the muscle blood flow to the active muscle during exercise and can cause a more normal cardiovascular response to physical activity in hypertension.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

J.H.M. drafted manuscript; J.H.M. edited and revised manuscript; J.H.M. approved final version of manuscript.

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