Arterial Baroreceptor Reflex Modulation of Sympathetic-Cardiovascular Adjustments to Heat Stress

Kevin C. Kregel, David G. Johnson, Charles M. Tipton, and Douglas R. Seals

The purpose of this study was to determine if the arterial baroreceptor reflexes modulate the sympathoexcitatatory responses to acute heat stress. To address this, arterial pressure, heart rate, mesenteric and renal blood flow velocity (Doppler flow probes), arterial plasma norepinephrine, and colonic temperature were measured before and during whole body heating (42°C ambient temperature) in groups of conscious, unrestrained rats with (sham) or without (sinoaortic deafferentation) intact arterial baroreceptor reflexes. Heating was stopped when a colonic temperature of 41°C was attained. Baseline levels of arterial pressure were similar in the two groups, whereas heart rate was elevated in deafferented versus sham-operated rats (p<0.01). The increases above baseline for both arterial pressure (73±4 vs. 27±2 mm Hg) and heart rate (127±10 vs. 33±5 beats/min) were threefold to fourfold greater at the end of heating in the deafferented versus the sham group (p<0.01). Declines in mesenteric and renal blood flow were similar in the two groups during heating; however, deafferented rats had greater increases in both mesenteric and renal vascular resistance (p<0.05). Plasma norepinephrine was elevated at baseline in deafferented versus sham rats and increased in both groups during heating (p<0.01). The magnitude of the increase in plasma norepinephrine from baseline to 41°C was fivefold greater in the deafferented versus the sham rats (p<0.01). Furthermore, deafferented rats reached a colonic temperature of 41°C much faster than the sham rats (38±6 vs. 94±13 minutes), resulting in a threefold greater heating rate (p<0.01). These findings indicate that the arterial baroreceptors modulate the arterial pressure, heart rate, and visceral vascular resistance responses to nonexertional heat stress in the conscious rat and suggest that this modulation is mediated, at least in part, via baroreceptor inhibition of central sympathetic outflow. Moreover, thermal tolerance during prolonged heat exposure is in part dependent on intact arterial baroreceptor reflexes. (Hypertension 1990;15:497-504)

Although it has some limitations, the rat has been frequently used as an experimental model to study mechanisms involved in thermoregulation during acute heat exposure in humans.1-3 This form of environmental stress elicits a highly coordinated pattern of autonomic-cardiovascular adjustments in an attempt to maintain internal body temperature within its normal homeostatic range.4 Animal studies indicate that a differentiated pattern of regional sympathetic vasomotor outflow5-7 and concurrent changes in blood flow8-10 are necessary components of the thermoregulatory adjustments to heat stress. For example, in the rat the stimulation of peripheral and central thermoreceptors by high ambient temperatures evokes increases in arterial pressure, heart rate, and vascular resistance in the viscera and decreases in vascular resistance in cutaneous regions.5 A preliminary report suggests that this hemodynamic pattern is associated with an augmented sympathetic neural outflow as indicated by elevations in plasma norepinephrine.11 However, in spite of these physiological adjustments, internal body temperature rises with continued thermal challenge, eventually resulting in heat stroke.1-3,12

In contrast to the sympathoexcitation-pressor effects of thermoreceptor activation, the arterial baroreceptors exert an inhibitory influence on sympathetic outflow that acts to buffer increases in...
arterial pressure produced during some forms of acute physical stress such as vigorous muscle contraction.\textsuperscript{13,14} Given this, one might hypothesize that the sympathetic-circulatory responses to acute heat stress might be exaggerated in the absence of arterial baroreceptor reflexes. Consistent with this postulate, brief thermal challenge in anesthetized cats after removal of the arterial baroreceptors caused an exaggerated increase in renal sympathetic nerve activity and a small pressor response not observed in animals with intact baroreceptors.\textsuperscript{5} However, it is not known whether the arterial baroreceptors play an important role in circulatory control or in thermal tolerance during heat stress in conscious animals.

Therefore, the purpose of this study was threefold. First, we wanted to determine if the magnitudes of the increases in arterial pressure, heart rate, and visceral vascular resistance during heat stress were exaggerated in animals without intact arterial baroreceptors. Second, we wanted to determine whether these augmented circulatory responses (if observed) were associated with increased sympathetic neural activation as reflected by greater heat-induced elevations in plasma norepinephrine concentrations. Finally, we wanted to determine whether thermal tolerance (as indicated by the rate of increase in internal body temperature) was reduced in the absence of intact arterial baroreceptor reflexes. To answer these questions, we measured the cardiovascular, plasma norepinephrine, and thermal responses to nonexertional heat stress (42°C ambient temperature) in groups of conscious, unrestrained rats with and without intact arterial baroreceptor reflexes.

Methods

Animals

Adult male Sprague-Dawley rats (n=47) (Harlan Sprague Dawley, Inc., Indianapolis, Indiana) that weighed 260–320 g were used in these experiments. Rats were housed in temperature-controlled quarters with a 12-hour light/dark cycle and provided standard rat chow and water ad libitum. Before surgery, rats were familiarized to a colonic probe and the environmental chamber used during testing.

Surgery and Instrumentation

Rats were initially anesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and acepromazine maleate (1.2 mg/kg). Atropine sulfate was also administered (1 mg/kg i.p.) at this time. Bilateral sinoaortic deafferentation (SAD) was performed according to a procedure described by Krieger.\textsuperscript{15} After a 3.0 cm midline incision was made on the ventral surface of the neck, the carotid arteries were isolated and carefully separated from the vagus nerves with the aid of a dissecting microscope. The SAD was accomplished by cutting the superior laryngeal nerves near the vagi and the aortic depressor nerves and removing the superior cervical ganglia.

Each carotid sinus was deafferented by stripping the bifurcation of extraneous fibers and adventitia. Phenol (10% in 95% ethanol) was then applied to the internal, external, and common carotid arteries, and the incision was closed. The completeness of the SAD was evaluated in these rats by determining the bradycardia elicited by a 40–50 mm Hg increase in arterial pressure produced by an intravenous injection of phenylephrine (3–5 μg/kg). Only those rats that exhibited a change in heart rate of less than 20 beats/min were included in the SAD group. To further test the completeness of the SAD, nitroprusside (50 μg/kg i.v.) was injected into an additional six animals (three SAD, three sham) to determine the degree of tachycardia elicited by a 35–50 mm Hg decrease in mean arterial pressure. Heart rate increased 50–60 beats/min above baseline in the sham rats, but only 10–15 beats/min in the SAD rats. A sham surgery in a second group of rats involved a midline incision of the neck and a bilateral resection of the sternohyoideus muscle.

For some experiments, miniaturized Doppler flow probes (Crystal Biotech, Hopkinton, Massachusetts) were implanted before SAD surgery. After a midline laparotomy was performed, 4 mm segments of the superior mesenteric or left renal arteries were carefully isolated. Doppler flow probes were then placed on each isolated vessel for long-term measurement of blood flow as described elsewhere.\textsuperscript{16,17} The wire leads were tunneled beneath the skin, exteriorized at the back of the neck, and soldered to an electronic receptacle (Microtech, GF-6, Boothwyn, Pennsylvania). The receptacle was secured to the skull with screws and cranioplast cement. Rats were given 5–6 days to recover.

One day before testing, catheters were inserted into: 1) the right common carotid artery for determination of arterial pressure and heart rate and for blood withdrawal and 2) into the right jugular vein for drug infusion. These catheters were exteriorized at the back of the neck, filled with heparinized saline (200 units/ml), and sealed.

Measurements

The arterial catheter was connected to a pressure transducer (model P23Db, Statham Instr. Division, Gould Inc., Oxnard, California) and mean arterial pressure, obtained from a filtered pulsatile signal, and heart rate, obtained from a tachometer (9857B, SensorMedics, Anaheim, California), were monitored continuously (R-611 Dynograph, Beckman Instrs., Inc., Fullerton, California). To determine regional blood flow velocities, an ultraminiature plug connected the headpiece receptacle containing the flow probe wires to a pulsed Doppler flowmeter (The University of Iowa Bioengineering Resource Facility, Iowa City, Iowa) via soldered wire cables. Blood velocity (in kHz Doppler shift) is directly proportional to absolute blood flow\textsuperscript{18} and, therefore, the Doppler technique provides a relative measure of changes in flow. Because arterial pressure was mea-
sured concurrently with flow, vascular resistance could be calculated by dividing mean arterial pressure by the mean velocity signal. Blood flow velocities and estimated vascular resistances were expressed as percent changes from control values. Colonic temperature was measured from a thermistor probe (Yellow Springs Instr. Co., Yellow Springs, Ohio) inserted 6–7 cm into the colon. A thermistor probe was also attached to the ventral surface of the tail to monitor tail-skin temperature.

**Plasma Norepinephrine Analysis**

Arterial blood samples (0.6 ml) for plasma norepinephrine measurement were collected and centrifuged at 4°C. The plasma was then stored at −80°C until analyzed. Norepinephrine concentration was determined radioenzymatically according to the technique described by Henry and Bowsher. Plasma epinephrine cannot be determined by this technique.

**Acute Heating Protocol**

On the day of an experiment, after attachment of colonic and tail-skin thermistors, rats were connected to the flowmeter by wire cables and to the pressure transducer by polyethylene tubing, then placed in an enclosed Plexiglas treadmill at an ambient temperature of 23–25°C for 60 minutes. During this time heart rate, arterial pressure, and body temperatures stabilized. The heating protocol consisted of exposure to an ambient temperature of 42°C, achieved by directing a constant air current into the treadmill with a commercially available heating source. Experiments were terminated when a colonic temperature of 41°C was achieved.

**Series I.** The purpose of the first series of experiments was to determine the cardiovascular, regional vascular resistance, and thermal responses to environmental heating in rats with and without intact arterial baroreceptor reflexes. Heart rate, arterial pressure, and colonic and tail-skin temperatures were measured continuously throughout the control and heating periods in all rats (n=25). Additionally, some of these rats (n=16) were instrumented with Doppler flow probes, permitting continuous monitoring of regional flow velocities.

**Series II.** The second series of experiments was designed to determine whether the cardiovascular responses observed during acute heating were associated with sympathetic neural activation. In eight sham and eight SAD rats, blood samples were withdrawn from the carotid artery catheter during the control period and when colonic temperatures of 39.5°C and 41.0°C were attained during the heating period for subsequent determination of plasma norepinephrine concentrations. Each withdrawal was followed by an infusion of an identical volume of blood from a donor rat. Heart rate, arterial pressure, and colonic and tail-skin temperatures were again measured before and during heating to ensure that the thermal-cardiovascular responses to heat challenge were similar to those observed in the first series.

**Data Analysis**

Significant changes in the dependent variables from control during heating within each group and differences in the magnitudes or rates of the changes between the SAD and sham groups were determined using an analysis of variance for repeated measures designs. Post hoc comparisons were made using Scheffe’s test. The relations between heart rate and arterial pressure compared with plasma norepinephrine were assessed with linear regression analysis. Differences were considered significant at the p<0.05 level.

**Results**

**Series I**

**Baseline levels.** Although control arterial pressure fluctuated more during the baseline period in the SAD rats, the average level of arterial pressure before heating was not different in the two groups. In contrast, heart rate during this period was elevated in the SAD compared with the sham-operated rats.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Series I</th>
<th>Series II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>288±5</td>
<td>286±6</td>
</tr>
<tr>
<td>Baseline MAP (mm Hg)</td>
<td>123±4</td>
<td>126±6</td>
</tr>
<tr>
<td>MAP at Tc=41°C (mm Hg)</td>
<td>150±4</td>
<td>189±4*</td>
</tr>
<tr>
<td>Baseline HR (beats/min)</td>
<td>390±7</td>
<td>421±11†</td>
</tr>
<tr>
<td>HR at Tc=41°C (beats/min)</td>
<td>433±7</td>
<td>550±6*</td>
</tr>
<tr>
<td>Baseline Tc (°C)</td>
<td>38.1±0.1</td>
<td>37.9±0.1</td>
</tr>
<tr>
<td>Baseline Ts (°C)</td>
<td>27.6±0.4</td>
<td>27.5±0.4</td>
</tr>
</tbody>
</table>

Data are mean±SEM for 12 sham-operated and 13 sinoaortic-deafferented (SAD) rats in series I and for eight sham and eight SAD rats in series II. MAP, mean arterial blood pressure; Tc, colonic temperature; HR, heart rate; Ts, tail-skin temperature.

†p<0.05 vs. sham group; *p<0.01 vs. sham group.
Colonic temperature rose progressively during the initial 20–30 minutes of heating in both groups until a level of approximately 40°C was attained (Figure 1). The colonic temperature of the sham rats plateaued at this level for the next 50–60 minutes before a final rapid increase to 41°C. In contrast, the SAD rats did not demonstrate this plateau period but instead exhibited a linear rise in colonic temperature from the onset of heating until 41°C was attained. The length of time to reach a colonic temperature of 41°C was markedly reduced in rats without intact baroreceptor reflexes compared with sham rats (38±6 vs. 94±13 minutes, p<0.01) (Figure 1). The corresponding rate of rise of colonic temperature was 150% greater in the SAD versus the sham rats (0.10±0.01° vs. 0.04±0.01° C/min, p<0.01).

Series II

Baseline levels. Plasma norepinephrine concentrations were markedly elevated in SAD compared with sham rats before heating (1.03±0.15 vs. 0.31±0.04 ng/ml, p<0.01) (Figure 4). As in series I, baseline mean arterial pressure and colonic and tail-skin temperatures were similar for both groups, whereas baseline heart rate was elevated in SAD compared with sham rats (p<0.05) (Table 1).

Responses to heating. Acute heating again produced baroreceptor-dependent changes, for SAD and sham rats, respectively, in mean arterial pressure (79±5 vs. 26±2 mm Hg), heart rate (140±12 vs. 24±7 beats/min), time to target colonic temperature (34±3 vs. 100±13 minutes), and heating rate (0.09±0.01° vs. 0.03±0.01° C/min) (all p<0.01). The differences were similar to those observed between the two groups in series I.
Plasma norepinephrine was increased in both groups at colonic temperatures of 39.5°C and 41°C during heating compared with baseline (p<0.01) (Figure 4). Within each group, plasma norepinephrine levels were significantly greater at a colonic temperature of 41°C compared with the value at a colonic temperature of 39.5°C (p<0.01). However, the magnitude of the rise in plasma norepinephrine from baseline levels during heating was threefold to fivefold greater in the SAD rats at colonic temperatures of 39.5°C (1.94±0.15 vs. 0.53±0.07 ng/ml) and 41°C (5.93±0.85 vs. 1.24±0.26 ng/ml) (p<0.01).

Discussion

The major findings of this study are: 1) the arterial baroreceptors modulate the arterial pressure, heart rate, and visceral vasoconstrictor responses to non-exertional heat stress in the conscious rat; 2) these modulatory effects appear to be mediated, at least in part, through baroreceptor inhibition of central sympathetic outflow; and 3) thermal tolerance during prolonged heat exposure is in part dependent on intact arterial baroreceptor reflexes.

Arterial Baroreceptor Modulation of Circulatory Adjustments to Acute Heat Stress

One might postulate that the arterial baroreceptors would antagonize the pressor response to heating-induced thermoreceptor stimulation through their modulatory influences on heart rate (cardiac output) and regional vascular resistance. However, there is little or no experimental support for this postulate, especially in the conscious animal.

Ninomiya and Fujita observed a small pressor response to peripheral heating in anesthetized, baroreceptor-denervated cats, whereas arterial pressure did not increase in baroreceptor reflex-intact controls. Simon and Riedel reported that arterial pressure "homeostasis" was reduced in anesthetized, baroreceptor-denervated rabbits during spinal cord heating, but the exact effect on arterial pressure was not clear. It has also been reported that elimination of both arterial and cardiopulmonary baroreceptor reflexes does not alter the regional vascular resistance responses to central heating in anesthetized dogs. None of these studies provided any clear insight as to the influence of baroreceptor denervation on the control of heart rate under these conditions.

In contrast to these previous investigations, the present study used a quite different experimental approach to reexamine this question, using prolonged, whole body heating of conscious, unre-
Arterial Baroreceptor Modulation of Sympathetic Nervous System Activity During Heat Exposure

Heat-induced stimulation of central and peripheral thermoreceptors elicits pronounced, yet differentiated, sympathetic nervous system activation. Selective heating of either the spinal cord or skin causes increased sympathetic discharge to the intestines and kidneys but complete inhibition of neural outflow to cutaneous regions in anesthetized rabbits and cats. Recent evidence also suggests that whole body heating evokes pronounced increases in plasma norepinephrine in anesthetized rats. In humans during whole body heating at rest, plasma norepinephrine increases in parallel with the rise in internal body temperature; the plasma norepinephrine response is also directly related to increases in heart rate and splanchnic vascular resistance. 

Do the arterial baroreceptors modulate central sympathetic outflow during acute heat exposure? Ninomiya and Fujita reported that arterial baroreceptor denervation resulted in an exaggerated increase in renal sympathetic nerve activity during heating in anesthetized cats but did not alter the inhibition of cutaneous nerve activity. However, anesthetized, baroreceptor-denervated dogs demonstrated increases in sympathetic discharge to visceral regions during heating that were similar to those observed in control animals; heat-induced inhibition of cutaneous sympathetic activity was also similar in dogs with and without intact arterial baroreceptor reflexes. Thus, the little available data from previous studies on anesthetized animals fail to provide any consistent insight regarding this question.

In the present study, we readdressed this issue in the conscious rat using the magnitude of the increase in plasma norepinephrine as a gross index of changes in general sympathetic neural activation elicited by whole body heating. We found that plasma norepinephrine increased in a time- and core temperature-dependent manner in both intact baroreceptor reflex and baroreceptor-denervated animals, indicating elevated central sympathetic outflow. However, the magnitude of the increase in plasma norepinephrine from baseline levels was roughly fivefold greater in the SAD rats compared with controls at a colonic temperature of 41°C (Figure 5). Although the limitations of using plasma norepinephrine as a quantitative measure of postganglionic sympathetic nerve discharge are widely recognized, nevertheless, our findings provide strong experimental support for the postulate that the arterial baroreceptors exert a striking modulatory influence on sympathetic neural activation during prolonged heat exposure in the conscious rat.

Was the removal of this modulatory effect of the arterial baroreceptors and the consequent augmentation in sympathetic outflow the mechanism responsible for the greater increases in arterial pressure, heart rate, and visceral vascular resistance in the SAD animals during whole body heating? In the present study, we did not perform pharmacological experiments with ganglionic blocking agents or autonomic receptor antagonists, and thus, cannot definitively answer this question with our data. However, the fact that the pressor, tachycardic, and visceral vasconstrictor responses to heating are primarily mediated by the sympathetic nervous system, taken together with the more pronounced increases in plasma norepinephrine we observed in the baroreceptor-denergated animals, suggests that the exaggerated circulatory adjustments to whole body heating in the SAD rats may have been mediated, at least in part, by a greater sympathetic neural activation. This postulate is further supported by the strong, direct correlations between the magnitude of the increase in plasma norepinephrine and the cor-

![Figure 5. Scatterplots showing relation between changes in plasma norepinephrine (PNE) concentration and corresponding changes in mean arterial pressure (MAP) (top panel: y=0.01x+23.455) and heart rate (HR) (bottom panel: y=0.023x+16.993) during acute heat stress in sham (n=8) and sinoaortic-deafferented (SAD) (n=8) rats.](http://hyper.ahajournals.org)
responding increases in mean arterial pressure and heart rate during heating in the present study (Figure 5). In addition, circulating norepinephrine can become a vasoconstrictor hormone at levels in excess of 1.8 ng/ml. Therefore, in the present study, the extremely high levels of circulating plasma norepinephrine measured in the SAD rats at the end of the heating period could have produced vasoconstriction and tachycardia separate from direct, neurally mediated influences. It is also possible that the greater increases in mesenteric and renal vascular resistance in the SAD rats during heating were, to some extent, an autoregulatory adjustment to maintain a particular level of blood flow in response to the greater arterial pressure in this group. However, it is clear that these augmented vascular resistance responses cannot be solely attributed to autoregulation, because blood flow would likely have remained at baseline levels and not fallen in response to heating (see Figure 3).

Role of Arterial Baroreceptors in Thermal Tolerance

Acute exposure to heat elicits a heart rate-mediated increase in cardiac output in humans. This increase in cardiac output is directed primarily to the skin circulation as both skeletal muscle and visceral blood flow decrease. During nonexertional (external) heating in which the ambient temperature is greater than the internal body temperature, the augmented skin blood flow will cause more heat to be absorbed from the environment unless there is a corresponding increase in evaporative heat loss.

With this background, why was thermal tolerance in the present study (as indicated by the rate of increase in core temperature) reduced almost threefold in the SAD rats compared with the controls? Although no experiments were performed to specifically address this question, we advance the following hypothesis based on our data. First, the threefold to fourfold greater increase in heart rate in the SAD versus sham-operated rats during heating suggests that a much greater increase in cardiac output occurred in the baroreceptor-denervated animals. The equivalent decreases in blood flow in the mesenteric and renal arteries in the SAD and sham rats suggest that this greater cardiac output was not directed to the viscera but instead to either skeletal muscle or skin. Although we cannot rule out a greater increase in skeletal muscle flow in the SAD versus sham rats, the fact that muscle blood flow decreases and skin flow increases during whole body heating suggests that the "extra" cardiac output was directed to the skin. Furthermore, as there is an abrupt, complete inhibition of sympathetic nerve traffic to skin in both the baroreceptor reflex-intact and the baroreceptor-denervated states, the much greater increase in arterial (systemic perfusion) pressure in the SAD rats likely resulted in a more pronounced increase in cutaneous blood flow compared with the control animals. Presumably, this exaggerated increase in skin flow caused a proportionately greater increase in heat conductance to the core and a faster rate of rise in internal body temperature. Thus, it is likely that the arterial baroreceptors influence thermal tolerance during nonexertional, environmental heating in the conscious rat indirectly via their modulatory effects on the arterial pressure and cardiac output responses to this stress.

Baseline Conditions

In the present study, baseline heart rate and plasma norepinephrine concentrations were elevated in the SAD rats compared with their sham controls, whereas arterial pressure was not different in the two groups. Our observations are generally consistent with the results of previous investigations in which these variables were measured over a similar time period after surgery. Thus, our surgical interruption of arterial baroreceptor reflex afferent pathways produced qualitatively similar effects on general sympathetic neural outflow, heart rate, and arterial pressure as those reported previously.

Generalizations to Humans

It is difficult to generalize the present findings in rats to humans, in part because of the differences in heat dissipation mechanisms that exist between the two species. For example, because rats do not sweat, their primary means of heat dissipation are through conduction, convection, and radiation of heat from the tail to the environment. This limits their capacity for dissipating heat and was primarily responsible for the pronounced increase in internal body temperature that occurred with heating in the present study. Under similar environmental conditions in the human (i.e., hot and dry), although increased skin blood flow will cause heat to be absorbed by the body, the additional ability to dissipate a large amount of heat by evaporation of sweat would contribute to a greater heat tolerance (i.e., slower rate of heating) than is found in the rat. However, in hot, humid conditions, when the ambient temperature is elevated above the body's core temperature and heat loss through evaporation is severely reduced, heat will be gained from the environment in both humans and the rat. Therefore, the rat is most tenable as a model to study thermoregulatory responses to nonexertional heating in humans in conditions of high environmental water vapor pressure (i.e., high humidity).

In the present study, mild to moderate hyperthermia (i.e., colonic temperature <39°C) generally produced a very small, transient hypotension in conscious rats. As colonic temperature increased above this level, a moderate pressor response was generated. Under comparable conditions, a larger depressor response is produced in humans during the initial stages of hyperthermia, most likely due to the very large cutaneous vascular bed that is perfused compared with the rat (i.e., greater decrease in skin vascular resistance).
In nonexertionally heated humans, arterial pressure appears to return toward baseline levels as colonic temperature approaches 39°C. As hyperthermia progresses, it is possible that, as observed in the rat, a pressor response is also evoked in humans before the circulatory collapse accompanying heat stroke. However, there is no experimental data on this period of more severe hyperthermia, as the inherent risk of thermal injury in humans precludes the application of a stress that would produce a colonic temperature in this range. During this hypertensive phase in the rat (and possibly in humans), our data indicate that the baroreceptors oppose the pressor response in a fashion analogous to that which occurs during vigorous muscle contractions in both conscious and anesthetized laboratory animals.13,14

Acknowledgments

We thank Lisa Clayton-Bare for graphical assistance, Colleen Chapin for technical assistance, and Marilyn Kramer for secretarial assistance in preparing the manuscript.

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Hypertension. 1990;15:497-504
doi: 10.1161/01.HYP.15.5.497

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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