Effects of Stress on Blood Pressure and Cardiac Pathology in Rats with Borderline Hypertension

JAMES E. LAWLER, PH.D., GREGORY F. BARKER, B.A., JOHN W. HUBBARD, B.S., AND ROBERT G. SCHAU, PH.D.

SUMMARY Repeated attempts to produce hypertension (HT) through psychological stress have failed to elevate blood pressure (BP) to levels seen in chronic, untreated essential HT in humans. In general, these studies have two characteristics in common: they utilize the normotensive animal, with no genetic history of HT, and they involve stressors to which animals readily adapt. The present study utilized offspring with one HT parent. The male F1 offspring of SHR X WKY had borderline HT (X ± SEM = 152.4 ± 1.34 mm Hg). With a conflict paradigm used as the stressor, experimental animals eventually developed severe HT (188.3 ± 2.70 mm Hg) compared to two non-stressed control groups (158.4 ± 2.31 mm Hg and 151.9 ± 2.25 mm Hg). After 15 weeks of stress for 2 hours daily, termination of conflict for 10 weeks did not reduce the HT in experimental animals. Subsequent analyses revealed that stressed animals, when compared to nonstressed controls, exhibited elevated heart-weight-to-body-weight ratios and significant cardiac pathology in the form of myofibrillar degeneration, accumulation of inflammatory cells, and fibrosis. The implications of using this model for the analysis of cardiovascular concomitants of stress-induced HT are discussed.

(Hypertension 3: 496-505, 1981)

KEY WORDS • stress-induced hypertension • cardiac pathology • borderline hypertensive rat • systolic blood pressure

THE decade of the 1970s revealed an increased interest in central nervous system (CNS) mechanisms that control blood pressure (BP).1-4 Numerous brain-stem structures, as well as the hypothalamus, have subsequently been implicated in some forms of experimental hypertension.2, 3, 4 Although these studies have demonstrated that the lesioning, stimulation, or chemical modification of numerous CNS structures can drastically alter BP levels, both acutely and chronically, extrapolating these findings to human essential hypertension (HT) has been viewed by many with skepticism. Nevertheless, the idea that a neurogenic trigger may exist for at least some cases of borderline HT has been expressed by Julius and Esler.9 Others have even gone further by suggesting that from 45% to 100% of all cases of essential HT are related to a primary or secondary neurogenic mechanism.10

One putative neurogenic trigger for essential HT in humans is psychological stress. Even a cursory review of the numerous studies done in this area reveals poor experimental design, inappropriate analysis, conflicting results, and biased reporting.11-18 One obvious difficulty in trying to determine if stress is related to essential HT is that the majority of these studies are necessarily post facto in nature. Whether chronic stress precedes HT with any greater regularity than it precedes normotension is an important question to ask, but a difficult one to investigate.

Many researchers have turned to the animal model in an attempt to determine if chronic stress leads to HT. For the most part, the results of these studies have been disappointing. Classical conditioning has been found ineffective in producing HT.14, 15 Operant procedures have also been disappointing.16, 17 Some success has been reported in mice subjected to psychosocial stress.18 However, animals did not maintain elevated BPs after experiencing less than 6 months of crowding. In any event, even animals subjected to 9 months of psychosocial stress failed to have mean systolic BPs outside the range many consider...
"borderline" hypertension (140-160 mm Hg). This moderate success with mice has not been replicated with psychosocial stress in rats. Other studies, utilizing cage motion, noise, and flashing lights, have similarly only produced borderline hypertension.

On the basis of this review, one may be led to any of three conclusions: 1) although neurogenic mechanisms may be important in some animal models of HT, psychological stress is not a sufficient stimulus to serve as a neurogenic trigger; 2) the paradigms used to stress animals have been inadequate tests of hypotheses linking psychological factors with HT; 3) the animal model utilized has been inappropriate. Since the first possibility represents the null hypothesis of this study, discussion will be addressed to the second and third points.

The vast majority of studies utilizing psychological stress have involved stimuli to which an animal can readily adapt. For example, classical conditioning, where some neutral stimulus takes on aversive characteristics by being paired with an unconditioned stimulus (such as shock), produces only transient elevations in BP and heart rate. Longer duration effects can be produced by conditioning schedules that require active participation by the animals. Signalled avoidance, where an animal must make a response (such as pressing a bar) during some neutral stimulus (e.g., a tone) in order to avoid an aversive event, such as shock, is one such schedule; another is Sidman avoidance, which requires the animal to respond within a certain time period without any exteroceptive signal. However, dogs on a Sidman avoidance schedule have been found to maintain their elevated BPs for only a matter of days. In addition, we have found that normotensive rats subjected to daily sessions of Sidman avoidance for 12 weeks failed to develop any changes in BP.

A more potent stressor would seem to be one that would allow the animal a certain degree of control over its environment while still maintaining some degree of environmental aversiveness. One such stressor is known as avoidance-avoidance conflict. If cutaneous electric shock is used, it is also known as shock-shock conflict paradigm, in which the animal must make a response (e.g., a 1 KHz tone) in order to avoid an aversive event, such as shock. This is a Sidman avoidance conflict paradigm, in which the animal is shocked five times for failing to make a response, and once for making it. The animal was developed by mating the SHR with its normotensive control animal, the Wistar-Kyoto (WKY). Animals stressed daily for 15 weeks developed HT, ending the study with pressures near 190 mm Hg. We undertook the current study to determine if the stress-induced HT is permanent and if there are pathophysiological correlates of stress-induced HT.

**Methods**

The study utilized 18 F1 generation male offspring of female SHR and male WKY rats. Both inbred parent groups were purchased from Taconic Farms (Germantown, New York). Female SHRs were initially housed in a group to synchronize estrous and then individually with one male WKY for 14 days. All F1 generation offspring were born within 5 days of each other. At 4 weeks of age, all pups were weaned, and the females sacrificed. Offspring were housed three to a cage until they were 13 weeks of age. Subsequently, they were individually housed.

Starting at 8 weeks of age and continuing throughout the study, systolic BPs were determined once weekly in conscious animals using the tail-cuff method. Animals were placed in a rat holder with preheated baseplate (37°C) for 5 to 10 minutes before measurements were taken. A mean of three artifact-free tracings was taken as the BP for the week. At 14 weeks of age, the systolic BPs of all animals were between 145 and 160 mm Hg.

At the end of 14 weeks of age, the 18 animals were randomly assigned to three groups of six rats each: experimental (E), control for mild restraint (Cm), and control for maturation (Cn). The Cm and Cn animals were subsequently studied 2 hours daily, 5 days per week, for 15 weeks. Each E and Cn animal was placed each weekday in a plexiglass conditioning cage that contained a small (7.6 cm diameter) wheel at the front. One quarter turn of the wheel served as the response required of E animals.

Experimental animals were trained daily for 3 weeks to turn the wheel during the presentation of a 1 KHz tone. Each response postponed tone onset by 10
seconds. Failure to respond within 10 seconds resulted in the presentation of five brief (2-second), low-current (0.2-0.3 mA) shocks applied through surface electrodes attached to the rat's tail. Independent presentation of tones and shocks to, and recording of responses from, E animals was accomplished with a microprocessor-based system, utilizing a custom interface and software developed in our laboratory.

The six C_M animals were placed in similar conditioning cages each day. These animals heard the tones that were presented to E animals, but received no shocks. The 6 C_M animals were never placed in conditioning cages.

After being trained the six E animals were subjected to daily 2-hour conflict sessions for 12 weeks. In conflict, E animals were shocked as before for failing to make a response in the appropriate time interval. However, they were also shocked once for every response they made. That is, they were shocked five times for failing to make a response and once for making it. This procedure maintained a consistent level of responding in all E animals.

Systolic BP determinations were obtained once weekly in E and C_R animals a minimum of 2 hours following removal from the conditioning cages. The C_M animals had their BPs taken at approximately the same time of day, to control for circadian rhythm effects.

At the end of the 12-week conflict period for E animals, a 10-week recovery period ensued during which no animals were placed in the conditioning cages. However, weekly systolic BP determinations continued to be obtained.

Following this recovery, all animals were sacrificed and their hearts immediately removed, washed free of blood in isotonic saline, and weighed. The ventricles were separated from the atria and great vessels, cut into three transverse sections from apex to base, and immersed in 10% neutral buffered formalin. The tissue was embedded in paraffin using a Fisher automatic tissue processor. At least three sections (6 to 8µm) were taken from each area and stained with hematoxylin and eosin. The degree of fibrosis in each region was estimated using a point-counting technique. Tissues were observed through a grid consisting of 100 squares. The number of squares overlying fibrous tissue on three sections was noted, and taken as a percent of the total number of squares that covered the tissue. This percent was the fibrosis score. A double-blind procedure prevented matching slides with group assignment until all data were quantified.

Results

All BP data were subjected to parametric analyses of variance with appropriate conservative post hoc comparisons. The data consisted of three determinations per week for 27 weeks in 18 animals, or 1458 systolic BP values. Since all pathology data were based on one sample for each subject, or 18 data points, nonparametrics were consistently used. The particular tests utilized were those suggested by Siegel, except where noted.

Systolic Blood Pressure

Separate analyses were carried out for Weeks 13 through 29 (baseline, training, and conflict) and for Weeks 30 through 39 (recovery). Results of these analyses are depicted in figure 1. All three groups began the study with the same systolic BPs. During the weeks of conflict, E animals showed an increase in BP compared to either control group, ending the study with BPs over 187 mm Hg. An analysis of variance revealed significant (p < 0.0001) main effects of groups [F(2/15) = 37.06] and weeks [F(16/240) = 7.19] and a groups-by-weeks interaction [F(32/240) = 10.01].

Follow-up analyses (Tukey HSD) revealed that E animals had significantly (p < 0.01) elevated pressures compared to C_R animals from Weeks 21 through 29 and compared to C_M animals from Weeks 19 through 29. Restraint animals had higher pressures than C_M animals on all but 2 weeks from Weeks 19 through 29. These results are similar to those previously reported.

FIGURE 1. Mean (± SEM) systolic blood pressure (BP) across baseline (PRE), training (TRNG), conflict, and recovery (POST) weeks in experimental (E), mild restraint control (C_R), and maturation control (C_M) animals.
Analysis of the 10-week recovery period, depicted in the right portion of figure 1, revealed a significant ($p < 0.0001$) effect of groups $[F(2/15) = 93.67]$. Experimental animals maintained their elevated BPs throughout the recovery period. Restraint animals, on the other hand, reduced their pressures in the recovery period, so that they were not significantly different from maturation animals after the first 3 weeks.

**Pathology**

Figure 2 depicts the results of the data for mean ($\pm$ SEM) heart-weight-to-body-weight ratios in the three groups. Although the differences between groups are small, an orderly trend is discernible. A Kruskal-Wallis analysis of variance revealed a significant ($p < 0.05$) difference between the groups in the ratios of heart weight to body weight ($H = 6.22$, df = 2). Follow-up analyses (Wilcoxon composite-rank test, one-tailed) revealed that E animals had significantly elevated heart-weight-to-body-weight ratios compared to both $C_R$ ($p < 0.01$) and $C_M$ ($p < 0.05$) groups. There were no significant differences between $C_R$ and $C_M$ groups.

There was a greater frequency of experimental animals with pathologies greater than 15% compared to the other two groups. These data are summarized in table 1. Five of six E animals had pathologies greater than 15%, while only three $C_R$ and one $C_M$ animal had pathologies greater than 15%.

**Table 1. Number of Animals in Experimental (E), Restraint ($C_R$), and Maturation Groups ($C_M$) with Less Than or Greater Than 15% Cardiac Pathology**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>E</th>
<th>$C_R$</th>
<th>$C_M$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 15%</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 15%</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

**Figure 2.** Mean heart-weight-to-body-weight ratios ($\pm$ SEM) in experimental, restrained, and maturation groups.

**Figure 3.** Photomicrograph of a section through the left ventricle near the apex showing pathology localized near the endocardial surface of an E animal ($\times$ 150).
similar pathologies. Chi-square analysis of these results was significant at $p < 0.05$ ($\chi^2 = 5.32$, one-tailed). A Wilcoxon composite-rank test\(^7\) revealed a significant ($p < 0.05$) difference in the mean pathologies of E vs CM rats (19.1% vs 12.1% respectively).

The pathologies seen in the 5 E, 3 CR, and 1 CM animals were confined to the left ventricular apex (fig. 3). These lesions consisted of myofibrillar degeneration (fig. 4), accumulation of inflammatory cells (fig. 5), and fibrosis (fig. 6). All figures are from experimental animals.

Finally, the relationship between stress-induced hypertension, heart-weight-to-body-weight ratios, and myocardial damage was assessed by intercorrelating these values for all 18 subjects. Table 2 presents the terminal BP readings, along with heart-to-body-weight ratios and pathology scores. Animals were ranked from highest to lowest on each variable. The difference between these ranks was obtained and squared, and was used to determine Spearman rho correlations. As can be seen, E animals tended to have low numbered ranks on all variables, indicating that high BP tended to be accompanied by elevated heart-to-body-weight ratios and pathology scores. The CM animals tended to have the lowest BP, with accompanying low scores on heart-to-body-weight ratios and pathology. These interrelationships were confirmed by statistical analyses. There was a significant correlation between pressures and heart-to-body-weight ratios of 0.70 ($p < 0.005$). Similarly, pressures were significantly correlated with pathology scores ($\rho = 0.54$, $p < 0.02$). However, there was no significant correlation between pathology scores and heart-to-body-weight ratios ($\rho = 0.29$, $p > 0.10$).

**Body Weight**

Analysis of variance was performed on weekly body weight data for E, CR, and CM animals. Significant main effects of weeks ($p < 0.0001$) and groups ($p < 0.02$) were found, as well as a groups-by-weeks interaction ($p < 0.0001$). Follow-up analyses (Tukey HSD) revealed that all animals had equivalent weights at the start of study (E = 342.7 g; CR = 350.2 g; CM = 339.7 g; $p > 0.38$). After the 3 weeks of training, however, a significant groups effect was found (E = 376.8 g; CR = 402.2 g; CM = 402.3 g; $p < 0.03$). This weight reduction was maintained throughout the conflict period (E = 426.7 g; CR = 458.7 g; CM = 460.8 g; $p < 0.02$ for Week 29).

During the 10-week follow-up period, however, there was a partial recovery of body weights in E

![Figure 4](http://hyper.ahajournals.org/)

**Figure 4.** Photomicrograph demonstrating myofibrillar degeneration in an E animal (× 400).
animals. By the time the animals were sacrificed, E
animals were only 3.8% lighter than C_M (E = 471.3 g; 
C_R = 487.8 g; C_M = 489.8 g). Analysis of variance
failed to demonstrate any group difference in body
weights at the end of study \( F(2/15) = 1.50, p > 0.10 \).

Behavior

Table 3 depicts the behavioral data for E animals
during the conflict weeks. The first column depicts the
number of responses made by E animals that resulted
in the presentation of a brief shock. Analysis of
variance revealed a significant \( p < 0.01 \) effect of
weeks \( F(11/55) = 2.64 \). During early conflict weeks,
when BP was low, animals were making between 2500
to 3200 responses per 2-hour session. Later, when BP
had become elevated, fewer responses were being
made (1900 to 2300).

The second column depicts the average number of
tones presented during each 2-hour session. There
appears to be an increasing trend across weeks. This
was confirmed by analysis of variance, which revealed
a significant \( p < 0.0001 \) effect of weeks \( F(11/55) = 5.82 \). Combining the information from Columns 1
and 2 showed that the animals made fewer responses,
yet more tones were presented, across conflict weeks.
Thus, the animals were becoming more efficient.
Perfect efficiency would result in one response for each
tone presented. Efficiency ratios (ER) for each week
are depicted in Column 4. These ratios were deter-
mined by dividing the tones presented by responses. A
high ratio shows improved efficiency. As can be seen,
during the early weeks when BP was low, the performance
was not very efficient \( ER = 0.152 \pm 0.013 \) for
the first 5 weeks of conflict). Later, as BP was ele-
vated, performance became more efficient \( ER =
0.220 \pm 0.016 \) for the last 5 weeks of conflict). This
represents a 45% improvement in the ER.

Column 3 depicts the average number of times the E
animal failed to make a response during the tone.
Each of these failures led to five inescapable shocks.
There appears to be a trend downward in the number
of failures across conflict weeks. This was confirmed
by analysis of variance \( F(11/55) = 9.85, p < 0.0001 \).

Another indication of improved performance across
conflict weeks is the percentage of tones that resulted
in failures to avoid five shocks. A high percentage
represents poor performance; a low score, good per-
formance. Failure percentages are depicted in Column
5. As can be seen, early weeks had higher failure
percentages than later weeks.

**Figure 5.** Photomicrograph demonstrating the accumulation of inflammatory cells in an E animal \((\times 400)\).

<table>
<thead>
<tr>
<th>Subject</th>
<th>BP (mm Hg)</th>
<th>Rank</th>
<th>Hrt/bdy wt (x 10^3)</th>
<th>Rank</th>
<th>Pathology (%)</th>
<th>Rank</th>
</tr>
</thead>
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<tr>
<td>E1</td>
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<td>3</td>
<td>0.3553</td>
<td>9</td>
<td>23.81</td>
<td>4</td>
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<tr>
<td>2</td>
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<td>4</td>
<td>0.3747</td>
<td>4</td>
<td>8.70</td>
<td>15</td>
</tr>
<tr>
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<td>0.3633</td>
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<td>20.00</td>
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</tr>
<tr>
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<td>13.73</td>
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<tr>
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</tr>
<tr>
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<td>0.3763</td>
<td>3</td>
<td>13.93</td>
<td>11.5</td>
</tr>
</tbody>
</table>

\( \rho = 0.70 \) (BP & hrt/bdy wt) \( \rho = 0.54 \) (BP & pathology) \( \rho = 0.29 \) (pathology & hrt/bdy wt)

Rankings were used to determine intercorrelations (Spearman rho).

FIGURE 6. Photomicrograph demonstrating fibrosis in an E animal (x 400).
Subject has remained controversial at least in part because of the impracticality of long-term (several decades) studies in humans and the impossibility of the controlled long-term manipulation of stress factors. This has led many investigators to the animal model, in which chronic well-controlled environmental manipulations of a psychological nature are possible. Despite numerous attempts, the majority of studies has failed to produce sustained HT. In fact, recent reviews have emphasized the paucity of data relating stress to hypertension. However, previous studies may have been an inadequate test of the hypothesis that stress may serve as a trigger for HT, since they involved both stressors to which animals readily adapt and animals that are apparently not very susceptible to stress-induced HT.

In the present study we sought to maximize the probability of producing stress-induced HT by using a conflict paradigm on a genetic strain of rats that developed systolic BP in the borderline hypertensive range. Daily sessions of conflict in the animals eventually produced pressures approaching 190 mm Hg. Termination of conflict for 10 weeks revealed that these BP elevations were sustained, and that the stress-induced hemodynamic overload of the heart produces significant alterations in cardiac morphology. These changes, which include ventricular hypertrophy and fibrous replacement of muscular tissue, are correlated with the severity and duration of the hemodynamic stress. Since the effects of hemodynamic overload appear to be restricted to the left ventricle, our significant group differences were probably attenuated to some extent by using whole hearts. Left ventricular weights would probably have shown even greater differences between groups than was apparent utilizing whole hearts.

In addition to studies that demonstrate that hypertension is a response to sustained HT, other studies show a certain degree of independence between HT and hypertrophy. For example, peripheral sympathectomy in young SHRs prevents the development of HT, but not hypertrophy. Similar effects are seen with antihypertensive agents like hydralazine and minoxidil. In addition, hypertrophy is evident in the SHR even in the prehypertensive stage.

It was not the purpose of the present study to examine the time course of the development of HT and hypertrophy, so we cannot state whether stress-induced hypertrophy preceded or followed HT. However, the high correlation between the degree of HT and the degree of hypertrophy suggests that hypertension was a response to HT. It would be difficult to envision a physiological mechanism that would tightly link HT and hypertrophy if the latter preceded the development of HT. On the other hand, if the degree of hypertrophy were a response to the degree of HT, one might expect a close correspondence between them.

Our study did not contain a control for "shock alone." Implicit in the concern for a shock-alone control is the assumption that one can easily separate the psychological components of an environmental stressor from the physical components. The usual shock-alone control is the "yoked" control. Yoked animals receive the same frequency, duration, and distribution of shocks as experimental animals. However, their responses are of no consequence in determining whether shock occurs. Far from being a control for shock alone, we contend that there is a large psychological component to the yoked control, which is especially prevalent in the shock-shock conflict paradigm.

Let us compare three schedules from the point of view of the yoked animal. In signalled avoidance, a tone sounds to warn the experimental animal that if a response is not made within some time frame (e.g., 10 seconds), shock will occur. The yoked animal in signalled avoidance learns the opposite of what it is supposed to learn. In other words, it has a "safe" period. It also learns that shock only comes on after the tone has...
been on for a number of seconds. Thus, although the animal does not have control over shock, it is able to predict it.

In Sidman avoidance, there is no warning signal. The experimental animal learns that a response must be made before a certain time period has elapsed (e.g., 10 seconds) or else shock is received. Thus, there is no tone to signal the yoked animal whether it is in a "safe" period. Nevertheless, the yoked animal still has a "safe" period. Once a shock occurs, another cannot be given for at least 10 seconds. Thus, shock itself serves as the safety signal.

The yoked animal on conflict has no "safe" period. It not only gets shocked each time a certain interval passes without a response from the experimental animal, but it also gets shocked each time the experimental animal responds. Since the yoked animal cannot know when this is, there is no "safe" period. Thus, the yoked animal on conflict can neither control nor predict the presentation of shock. The controllability and predictability of aversive events have been shown to be potent psychological variables. While little physiological work has been done, there is some evidence to suggest that yoked animals, especially yoked conflict animals, are indeed subjected to substantial psychological stress. Yoked animals on Sidman avoidance show no change in BP, while yoked conflict animals show a significant elevation in BP. If shock levels are severe, however, and if sessions are long (8 hours or more), yoked animals will ulcerate more (on conflict) and even die from bradyarrhythmia (on Sidman avoidance) more frequently than experimental animals.

A better shock-only control would seem to be one that provides completely predictable shock. Thus, the shock control animal would receive the same frequency and duration of shocks as the experimental subject, but all shocks would be preceded by a brief tone (e.g., 2 seconds long). Recent data suggest that there are problems with this control as well, since animals receiving the most predictable shock had higher BP than those receiving the least predictable shock.

Thus, a totally predictable shock also seems psychologically aversive. We conclude that at present there is no adequate control for shock alone when using a conflict paradigm.

Although there seems to be no appropriate shock only control, we do have evidence that shock frequency does not account for the BP elevation. As E animals were becoming more hypertensive, the number of shocks was actually decreasing. Comparison of the first 2 weeks of conflict with the last 2 shows that the BP increased 17.7% while the number of shocks received decreased 36%. There was also an inverse relationship between responses made and BP, ruling out an exercise-induced pressor response.

Stress-induced HT studies that have been moderately successful have utilized environmental stressors which the animal cannot readily ignore. Multiple sensory stimuli, psychosocial stress, and conflict have been most successful in eliciting relatively large, sustained pressor responses. The present study demonstrated that conflict in the rat with one hypertensive parent produces severe HT with concomitant pathophysiological changes in the myocardium. Not only is BP higher than that in studies previously reported, but even the magnitude of the BP elevation is greater in these animals than in normotensive rats subjected to conflict (37 vs 20 mm Hg respectively). The consistency and degree of HT produced in these animals (see table 2) should allow for the investigation of various physiological mechanisms, such as CNS, ANS, renal, neuroendocrine and hemodynamic, which are suspected of triggering and sustaining HT in humans.

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Hypertension. 1981;3:496-505
doi: 10.1161/01.HYP.3.4.496

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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