Laboratory Studies

Neurogenic Pressor Episodes Fail To Cause Hypertension, But Do Induce Cardiac Hypertrophy

Stevo Julius, Ying Li, David Brant, Lisa Krause, and Andrew J. Buda

Repeated neurogenic pressor episodes by hindquarter compression were elicited in nine experimental dogs. Conscious dogs underwent 6 hours of compression every day over a period of 9 weeks. The average mean blood pressure increase during the compression periods was 25 mm Hg, but after decompression the blood pressure promptly returned to baseline values. This blood pressure response was constant and did not change over the 9-week period. The blood pressure increase was associated with a significant increase of plasma norepinephrine values.

After validity of the model was established, echocardiographic measurements were performed at baseline and after 3, 6, and 9 weeks of compression in six experimental and six time-control dogs. Concentric left ventricular hypertrophy was already detectable at 3 weeks, and at the ninth week, the left ventricular mass was 28% above the baseline value. The left ventricular mass in time-control dogs remained unchanged over the same period of time. The time-left ventricular mass curves in experimental dogs were significantly different (by profile analysis), had different means (p<0.005), were not parallel (p<0.0006), and the overall group difference was highly significant (p<0.00001). Since left ventricular hypertrophy, a poor prognostic sign in clinical situations, can evolve before established hypertension, present therapeutic recommendations based on permanently elevated blood pressure values may not be entirely justified.

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Two notions are deeply engrained in the traditional thinking about hypertension. The first is that patients with hypertension undergo a phase of "labile" neurogenic hypertension 1 that eventually, through the cumulative effect of pressor episodes, leads to sustained hypertension. 2 Second is that labile blood pressure per se is an innocuous condition 3 and that target organ damage is a relatively late complication of sustained hypertension. This attitude largely determines the rather cautious "wait until the blood pressure is permanently elevated" approach to antihypertensive treatment. 4 However, practicing physicians increasingly recognize that some patients with even the mildest forms of hypertension already show signs of left ventricular hypertrophy and that such patients may require early treatment.

We developed a model to elicit repeated pressor episodes in dogs. 5,6 The following lines of evidence obtained in chloralose-anesthetized animals indicate that the blood pressure increase during compression is neurogenic: 1) blood pressure elevation is associated with increase of plasma norepinephrine and plasma renin as well as an acceleration of heart rate; 2) the increase of blood pressure, plasma norepinephrine, and renin are abolished by a low spinal anesthesia; 3) hemodynamically the blood pressure increase is due to an elevation of vascular resistance, and both high resistance and blood pressure are abolished with ganglionic blockade; and 4) the blood pressure response is not altered when the circulation to the hindquarter has been severed through ligation of the vena cava and the lower aorta. This, in turn, suggests that the afferents for the reflex originate in the hindquarters and proves that the response is not dependent on distant effects of the translocated blood or chemical effluents from the compressed area. Our results have been confirmed by Bradley and Hjemdahl 7 who linked the blood pressure response to enhanced neurogenic drive to the kidneys.

This model offers unique opportunities to study the effects of transient blood pressure elevation on
the average pressure and on the function or morphology of target organs. The present study will show: 1) that external compression of hindlimbs can be extended over a period of months to cause repeated pressor episodes in conscious animals; 2) that 6 hours of hypertension every day over a period of 9 weeks does not cause sustained hypertension; and 3) that, in the absence of sustained hypertension, the experimental animals developed concentric left ventricular hypertrophy.

Materials and Methods

Blood pressure studies were performed in nine mongrel dogs (one male and eight female). All dogs were adult and of stable weight. The average weight at the outset of the experiment was 23.4±0.07 kg and at the end was 23.8±0.24 kg (NS). Six additional dogs were used as a time-control group for echocardiographic studies.

The nine dogs were instrumented with a subcutaneous port (VAP Norfolk Medical Products, Inc., Skokie, Illinois) connected to the infrarenal abdominal aorta. When required, the intra-arterial blood pressures were monitored and blood pressure samples collected by inserting a "Huber" point needle into the port using sterile techniques. The pressures were measured with a Hewlett-Packard (Palo Alto, California) 1290C strain-gauge manometer connected to an 8805D signal conditioner, stored on magnetic tape, and later analyzed by a signal analysis data acquisition system that sampled the arterial pulse waveform at 250 samples/sec (Po-Ne-Mah, Inc., Storrs, Connecticut). The data acquisition system archived systolic pressure, diastolic pressure, mean pressure, and heart rate averages for every minute. These 1-minute values were then averaged every 10 minutes to obtain average period values.

It took, on the average, 3 weeks to train the animals to rest in the sling and another week for them to adjust to the compression with the suit (Jobst Institute, Toledo, Ohio). The suit encompassed the hindlimb and the gluteal region, but the abdomen was not compressed (Figures 1 and 2).

Trained animals were brought from the kennels to the laboratory every day to undergo a 3-hour compression in the morning and another 3 hours in the afternoon. The pressure in the suit was 30 mm Hg. In the early experiments, one animal developed a transient paresis (3 days) of a limb. The lesion was attributed to a crease in the poorly fitted suit. In later experiments, all dogs tolerated the procedure well and none showed signs of discomfort.

The daily 6-hour compression schedule was maintained for 9 weeks. At the end of each week the blood pressure was monitored 40 minutes before the compression, during the 3 hours of compression, and 40 minutes after deflation of the suit. Blood for determination of renin and catecholamines was drawn at the end of the rest, compression, and decompression periods.

FIGURE 1. Conscious dog in inflated pressure suit.

FIGURE 2. Another view of suit (not inflated) showing that abdominal cavity is free of suit.
TABLE 1. Average Blood Pressure Values 40 Minutes Before, During (3 Hours), and 40 Minutes After Compression

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>Compression</th>
<th>Decompression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>D</td>
<td>S</td>
</tr>
<tr>
<td>1</td>
<td>150±7</td>
<td>82±7</td>
<td>176±5</td>
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<tr>
<td>2</td>
<td>153±8</td>
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<td>155±7</td>
<td>84±3</td>
<td>183±8</td>
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<td>86±4</td>
<td>176±7</td>
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<td>183±6</td>
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<td>174±5</td>
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<td>175±4</td>
</tr>
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<td>142±5</td>
<td>79±4</td>
<td>175±6</td>
</tr>
<tr>
<td>9</td>
<td>166±14</td>
<td>86±6</td>
<td>177±10</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
S, systolic; D, diastolic

After the first three dogs proved that it was feasible to maintain pressor responses over a 9-week period, we assessed cardiac dimension by two-dimensional echocardiography in the remaining six dogs. Two-dimensional echocardiographic examinations (MK600, Advanced Technology Laboratories, Bellevue, Washington) were performed before the start of the compression period and at the end of the third, sixth, and ninth week of compression in six experimental animals. The echocardiographic measurements were all performed by the same observer (L.K.).

The dogs were placed on their right sides on an examination table that had a section removed to provide a window for transducer placement. The transducer was positioned from below, proximal to the area of maximal cardiac impulse. Short axis images were obtained at the midpapillary and mitral valve levels of the left ventricle. Long axis images were obtained with the transducer rotated until the longest length was visualized. During the echocardiographic examination the animals did not wear the compression suit.

Two-dimensional echocardiographic analysis was performed with the use of a Diasonics minicomputer-based video digitizing system, previously validated in our laboratory. End-diastolic frames were selected for analysis with the use of the cardiac wave in lead II as a marker of end diastole. Endocardial and epicardial borders for three consecutive beats during normal sinus rhythm, using the cross-sectional view at the papillary and mitral valve levels, were carefully traced directly from the video display onto a digitizing tablet. Left ventricular length was determined by measuring the length from apex to the mitral valve using the long axis view. Volumes were determined by Simpson's rule, and mass was calculated by subtracting epicardial volumes from endocardial volumes and multiplying the result by the specific gravity of myocardial muscle.

At the end of the experiments, all six animals that underwent echocardiographic measurements were killed to verify the echocardiographic measurements; the heart was carefully dissected to remove the epicardial fat and isolate the left ventricle, and the left ventricle was weighed by a person not aware of the echocardiographically calculated left ventricular mass. Six dogs were used as a time-control group for echocardiographic measurements. These dogs were not instrumented and were not killed at the end of the observation period. Echocardiographic measurements were performed at baseline and after 3, 6, and 9 weeks of observation. Since these dogs were not regularly brought in to the laboratory, they were used as a time-control group for the effects of aging, but could not be used to evaluate the effect of the laboratory setting on the left ventricular mass.

The protocol was reviewed and approved by the Institutional Review Board for use of animals in research. Student's t test for paired comparisons was used for statistical analysis within a group. A profile analysis was used to compare the time-cardiac size relation between experimental animals and the time-control group.

Results

The systolic and diastolic blood pressure averages before, during, and after compression in nine dogs are given in Table 1.

The blood pressure invariably increased in all dogs. The magnitude of the blood pressure response did not change across the 9-week period. All nine dogs showed a significant increase of plasma norepinephrine and heart rate. Since the main theme of the present study relates to the development of left ventricular hypertrophy, complete results for all variables are shown for the six dogs which underwent echocardiography. The blood pressure, plasma norepinephrine, and plasma renin responses in these six dogs were the same as for all nine dogs (six not significantly different from nine for blood pressure, norepinephrine, or plasma renin activity at 3, 6, and 9 weeks).

The large amount of data was reduced for clarity and statistical testing to the average of each 3-week period: early (first to third week), middle (fourth, fifth, and sixth week), and late (sixth through ninth
The mean blood pressure and heart rate responses during these periods are shown in Figure 3 for the six dogs who also had echocardiographic measurements. The mean blood pressure increase averaged 25 mm Hg and remained the same throughout the 9 weeks of the experiment. Decompression caused a prompt reduction of the blood pressure. The precompression baseline levels did not change throughout the experimental period. It was not technically feasible to assess the blood pressure outside of the laboratory. However, since the baseline blood pressure did not increase over the 9-week period and at 40 minutes after decompression the in-laboratory blood pressures fell to baseline levels, we speculate that the compression had no lasting effect on the blood pressure levels. The heart rate was more variable but was generally elevated during the compression and tended to mirror the blood pressure responses.

Figure 4 shows plasma norepinephrine and renin responses in the six dogs. Plasma norepinephrine increased during the compression and the increase became significant in the middle and late compression weeks. When norepinephrine responses of all nine animals were analyzed, the norepinephrine response became significant also in the third week ($p<0.025$). Upon decompression, the norepinephrine decreased and in the ninth week was significantly lower than during the compression. Plasma renin showed a similar trend as norepinephrine, but the response was more variable and did not reach significance. The renin response in these conscious dogs was less impressive than in anesthetized animals where, in addition to norepinephrine increase, we invariably elicited large increases of plasma renin levels. Analysis of renin responses in nine animals did not alter the conclusions reached on six dogs.

![Weekly 3 Hour AM Monitoring Averages](image)

**Weekly 3 Hour AM Monitoring Averages**

**FIGURE 3.** Mean blood pressure (MBP) (above) and heart rate (below) responses. Averages of each 3-week period (one measurement each week) are shown. Points at curve represent average of 10-minute intervals. Brackets are SEM.

**FIGURE 4.** Norepinephrine and renin responses to compression. $p$ value at end of compression depicts difference from baseline. $<p$ value at end of decompression period refers to changes from peak value during compression. These values have not been corrected for multiple comparisons. If Bonferroni correction is used, results are not significant.
The results of the echocardiographic assessment of the left ventricular wall mass are depicted in Figures 5, 6, and 7.

Figure 5 shows the correlation between the calculated left ventricular wall mass by echocardiography and the weight of the left ventricle at autopsy in six dogs. The remarkable congruency of the values attests to the validity of the echocardiographic studies performed in the study.

Figure 6 shows the percentage change of left ventricular wall mass from baseline in six experimental and six time-control dogs. Experimental dogs had significant changes in left ventricular wall mass already at 3 weeks. Thereafter the left ventricular wall mass increased further after 6 weeks and the increase appeared to level off at 9 weeks. No changes in left ventricular wall mass were observed in control dogs. Profile analysis indicated that the curves in experimental and control dogs were different (e.g., were not parallel \( p<0.0006 \)), had different means \( p<0.005 \), and the overall group difference was highly significant \( p<0.00001 \).

Figure 7 shows the trend of three indexes of cardiac size over time as well as the values for endocardial and epicardial volumes in six experimental dogs. Endocardial volume remained stable and the epicardial volume increased, demonstrating that repeated pressor episodes elicit concentric left ventricular hypertrophy.

The present study does not permit conclusions as to which component, blood pressure elevation or sympathetic activation, contributes to left ventricular hypertrophy. Neither the average blood pressure nor the plasma norepinephrine level correlated significantly to the left ventricular mass in this small number of experimental animals.

Discussion

Lack of Sustained Hypertension

The origin of the premise that hypertension evolves through a series of repeated pressor episodes, the cumulative effect of which lead to hypertension, can be traced to the report by Robinson.
and Brucer\textsuperscript{1} that suggests the existence of a labile phase before the development of established hypertension. Later research with 24-hour blood pressure monitoring\textsuperscript{11} and blood pressure self-determination by the subjects\textsuperscript{12} failed to uncover a phase of increased blood pressure variability in early stages of hypertension. Physiologically, the concept of transition from repeated pressor episodes to established hypertension finds strong support in Folkow's work on the role of vascular hypertrophy as an amplifying mechanism.\textsuperscript{2} However, animal experiments by and large failed to document transition from labile or reoccurring hypertension to a permanent elevation of the blood pressure.\textsuperscript{13-16} In the present study we induced larger blood pressure elevations and sustained them over a longer period of time than in previous negative studies, but have nevertheless failed to induce permanent hypertension. This negative finding calls for some further comment.

Recently, Anderson et al\textsuperscript{17} demonstrated that repeated pressor episodes in dogs by themselves are unable to induce hypertension. However, when these dogs were given a rather high sodium intake, repeated pressor episodes did induce prolonged but reversible hypertension. This experiment establishes the important principle that under certain circumstances repeated pressor episodes may cause prolonged blood pressure elevation. We also recognize that our dogs had not been selected for their genetic tendency to hypertension and that a subgroup prone to hypertension may have responded differently. Nevertheless, our data do suggest that rather large and prolonged pressor episodes, under normal circumstances, are not likely to cause sustained hypertension. These findings provide no support for the suggestion that pressor response to such maneuvers as exercise, cold pressor test, or mental arithmetic may predict the development of future hypertension. Even if these responses were representative of the daily blood pressure variability, and there is evidence that they are not,\textsuperscript{18,19} the daily blood pressure variability is a few orders of magnitude less than what has been described in our experiments. It is hard to visualize how these small pressor episodes, even over an individual's lifetime, could "by summation" or cumulative effect lead to sustained hypertension.

**Cardiac Hypertrophy**

Presence of cardiac hypertrophy is an important clinical feature in human hypertension since left ventricular hypertrophy, independent of blood pressure, is a strong predictor of cardiovascular mortality.\textsuperscript{20} It is generally thought that left ventricular hypertrophy is a late consequence of hypertension. This opinion is based on the linear relation between blood pressure and left ventricular hypertrophy in the general population as well as the age-related increase of cardiac hypertrophy in such populations. However, the literature suggests that changes in cardiac function\textsuperscript{21} and morphology\textsuperscript{22} may be already present in the earliest forms of hypertension. The blood pressure elevations in our experiment, though transient, certainly are not trivial and exceed naturally occurring pressor episodes. Nevertheless, the experiments provide the first confirmation that transient pressor episodes without sustained hypertension cause cardiac hypertrophy. It remains to be seen in future experiments whether smaller blood pressure elevations elicited more frequently, but over a longer period of time, will cause measurable cardiac hypertrophy.

Classic clinical\textsuperscript{23} and epidemiological\textsuperscript{3} studies suggest that average blood pressure and not the variability of the blood pressure are the most important predictors of cardiovascular damage. Recent human studies raise some interesting questions. Devereux et al\textsuperscript{24} found that blood pressure at work is the strongest predictor of left ventricular hypertrophy seen in people whose work does not require physical effort. It was speculated that this relation may not so much reflect the blood pressure elevation as the behaviorally induced sympathetic activation
underlying these pressor episodes. Recently Parati et al. correlated blood pressure variability with target organ damage. In this cross-sectional study the observed association may have been primary (e.g., increased blood pressure variability caused target organ damage or secondary vascular damage may have elicited insufficient baroreceptor buffering and thereby caused more blood pressure variability). In both instances, however, the increased blood pressure variability would be associated with bursts of sympathetic hyperactivity. In the present study, significant elevations of plasma norepinephrine occurred during the pressor episodes and the model, therefore, approximates the naturally occurring pressor episodes.

In recent editorials we pointed out that all existing antihypertensive drugs affect the average blood pressure, but do not decrease the blood pressure variability. Should it be subsequently proven that blood pressure variability contributes to left ventricular hypertrophy in the mildest forms of hypertension, the clinical practice of nonintervention in such patients may have to be reexamined, and a search for drugs capable of controlling blood pressure variability may be warranted.

Usefulness of the Model

We hope that some unique features of this new model will appeal to other investigators. The method permits induction of long-lasting, repeated neurogenic pressor episodes and thereby supplies a new tool to investigate the effects of these episodes on the cardiovascular system. Previous models to cause labile hypertension had numerous shortcomings. Such invasive procedures as stimulation of the defense area or the stellate ganglion can be extended only over relatively short periods of time. Removal of arterial baroreceptors or central destruction of the nuclei of the solitary tractus can cause labile blood pressure where periods of hypertension are offset by periods of hypotension, and the average blood pressure is only minimally elevated. Operant conditioning, as described by Anderson et al. is the most promising approach to induce short bursts of blood pressure elevation. However, the method requires a high level of experimental sophistication, the blood pressure responses are smaller and the pressor schedules shorter than with hindquarter compression. The question of whether repeated pressor episodes can lead to sustained hypertension is of major conceptual interest. Hindquarter compression seems to be an ideal method to study this question.

In the present study concentric cardiac hypertrophy ensued after 3 weeks of daily pressor episodes. The pressor episodes have been associated with consistent increases in plasma norepinephrine levels. It has been suggested that sympathetic stimulation may be an independent trophic factor for the development of cardiac and vascular hypertrophy. Some of the arguments stem from studies with regression of cardiac hypertrophy and have been lucidly reviewed in a recent article. Drugs that reduce the blood pressure level, but simultaneously cause sympathetic activation, do not elicit regression of existing cardiac hypertrophy. Vascular hypertrophy does not develop in denervated vessels. Norepinephrine stimulates the growth of cardiac myocytes and α receptors appear to be involved in the response. Since, during hindquarter compression, the development of left ventricular hypertrophy is associated with transient sympathetically mediated blood pressure increases, it would be of interest to separate the relative contributions of blood pressure elevation and of sympathetic activation on cardiac hypertrophy. From previous studies we know that hindquarter compression elicits the same magnitude of blood pressure increase if the animals are pretreated with β-adrenergic blockade. It may therefore be possible in the future to protect the heart and separate trophic β-adrenergic effects from the effect of blood pressure elevation per se.

The length and the frequency of pressor episodes can be varied, which offers the opportunity to study the dose–response relation and possibly the threshold of blood pressure elevation versus cardiac hypertrophy. By inducing repeated rapid increases of blood pressure, the method permits studying the earliest cardiac biochemical and molecular events that may precede cardiac hypertrophy.

Finally, the model permits future investigation of many interesting topics related to cardiac hypertrophy. Is there evidence for cardiac "hyperfunction" in early hypertrophy? At which stage of hypertrophy is there evidence of cardiac dysfunction? Is early cardiac hypertrophy associated with changes in cardiac compliance? What is the histology and morphology of cardiac hypertrophy in this model?

Our observations are preliminary and in essence demonstrate the feasibility of the model. We sincerely hope that the large potential of this model will be realized and used in further studies by other investigators.

References


Key Words: echocardiography • hypertrophy • transient hypertension • sympathetic tone • norepinephrine
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