Sustained Blood Pressure Elevation to Lower Body Compression in Pigs and Dogs

STEVO JULIUS, M.D., RAMIRO SANCHEZ, M.D., SAMUEL MALAYAN, PH.D.,
MICHAEL HAMLIN, MARY ELKINS, M.S.T.,
DAVID BRANT, M.S., AND DAVID F. BOHR, M.D.

SUMMARY Inflatable suits were constructed for lower body compression in pigs and dogs. The suit for pigs encompassed hindquarters and part of the abdomen, and the smaller suit for dogs compressed only the hindquarters, leaving free the abdominal cavity. In conscious, diazepam-pretreated pigs, the compression lasted 30 minutes; during that period the blood pressure increased 50/38 mm Hg over the baseline. In chloralose-anesthetized dogs, the compression was extended to 3 hours; the blood pressure increase was 44/53 mm Hg. Blood pressure fell to the baseline immediately after decompression in both animals. In both species the substantial blood pressure increase was due to an increase of vascular resistance; this did not induce the expected baroreceptor-mediated bradycardia. In dogs, the blood pressure increase was accompanied by a large increase of plasma norepinephrine (from 179 to 975 pg/ml). To test whether the increase of vascular resistance reflected the mechanical compression of the vessels under the suit, animals were pretreated with trimethaphan. In pigs the trimethaphan substantially decreased the vascular resistance and the blood pressure response. This indicated that a portion of the vasoconstriction occurred in areas outside the suit. Lower body compression is a new model to cause prolonged blood pressure elevation by noninvasive and nonpharmacologic means. The mechanism of the blood pressure elevation requires further investigation.

(Hypertension 4: 782-788, 1982)

KEY WORDS • cardiac output • hemodynamics • right atrial pressure • norepinephrine • vascular resistance • trimethaphan

A follow-up to our work on the role of cardiac receptors in the regulation of renin release,1 we searched for a practical way to translocate blood from the lower part of the body to the cardiopulmonary region. A suit for lower body compression of pigs was constructed. It soon became evident that external compression of the lower body induces a prolonged increase of blood pressure. This blood pressure elevation became the main focus of our research. A smaller suit that compresses only the hindquarters but not the abdomen of dogs was then constructed to further investigate this blood pressure response. Large and prolonged blood pressure elevations were also seen in dogs.

The hemodynamic characteristics of the sustained blood pressure response to the lower body compression in pigs and to hindquarter compression in dogs are the subject of this report.

From the Division of Hypertension, Department of Internal Medicine, and the Department of Physiology, University of Michigan Medical School, Ann Arbor, Michigan.

Supported in part by National Heart, Lung, and Blood Institute and National Institutes of Health Grants HL-21893 and HL-18575.

Address for reprints: Stevo Julius, M.D., Division of Hypertension, Box 48, R6669 Kresge Medical Research Building, University of Michigan Medical School, Ann Arbor, Michigan 48109.

Received June 9, 1981; revision accepted April 26, 1982.

Material and Methods

Pigs

Nine young male Yorkshire pigs weighing between 30 and 60 kg were used in this study. Aortic pressure was measured via a Herd-Barger catheter2 inserted in the thoracic part of the descending aorta, and central venous pressure was measured through a similar catheter with its tip placed at the confluence of the superior and inferior vena cavae. Both pressures were monitored by means of Statham strain gauges and recorded on a Grass polygraph. Relative cardiac output was measured with an electromagnetic flow probe (Zapeda Instruments, Seattle, Washington) surrounding the ascending aorta. Cardiac output was expressed as a fraction of the control value. All catheters and electrical leads were brought out through the left side and tied to a tygon-sheathed copper wire which was looped under the skin at the level of the eighth rib. The pigs were allowed to recover for at least 2 weeks after the surgical insertion of catheters and the flow probe. The suit for compression of the lower body encompassed the hindquarters and extended over the lower third of the abdomen.

At least 30 minutes before the experimental period, the penned pigs were tranquilized with diazepam (Valium), 10 mg/kg, to prevent combative behavior
against attempts to fit the suit. Sedate but fully conscious, they were strapped to a board, and the aortic flow probe was connected to the electromagnetic flowmeter. After hemodynamic variables had become stable, a 10-minute control period began. The compression suit was then inflated with nitrogen from a high-pressure tank to a pressure of 50 mm Hg. The desired degree of inflation was achieved in 5 seconds and maintained constant for a period of 30 minutes, after which the suit was unzipped and pulled off. Hemodynamic variables were monitored for another 10 minutes during the recovery phase.

Five pigs were subjected to ganglionic blockade after completion of the above protocol. Trimethaphan camsylate (trimethaphan), 0.15 mg/kg/min, was infused intravenously in a 5% dextrose solution. When hemodynamic variables had stabilized in a new steady state, the same protocol of the control experiment was repeated in the animals subjected to ganglionic blockade. Total peripheral resistance was derived by dividing mean arterial pressure by cardiac output. Both cardiac output and total peripheral resistance were expressed as a fraction of the control value. This was done by taking the mean of the 10 values recorded every minute for the 10 minutes of the control period and dividing all subsequent values by it.

The effectiveness of ganglionic blockade with trimethaphan was tested by administering 2 mg of phenylephrine (1% phenylephrine hydrochloride, Neo-Synephrine hydrochloride). If no reflex bradycardia occurred in response to an increase in arterial pressure of at least 50 mm Hg, the ganglionic blockade was assumed to be effective. All animals showed effective blockade by this criterion.

Dogs

Mongrel male and female dogs were anesthetized with chloralose in an initial bolus of 120 mg/kg followed by an infusion of 43 mg/kg/hr. An arterial catheter was placed at the root of the aorta. A venous catheter was passed into the right ventricle and then withdrawn and lodged in the right atrium.

Cardiac output was measured by dye dilution with indocyanine green. Arterial blood was withdrawn through a Gilford densitometer and later reinfused into the animal. The densitometer was calibrated against three known concentrations of dye added to an animal's blood. Plasma catecholamines were measured by a radioenzymatic method. Pressures were measured by a Statham strain gauge and recorded on a Brush polygraph. The hindquarters were compressed with an inflatable suit (Jobst Institute, Toledo, Ohio); when inflated, the suit did not cause abdominal compression (fig. 1).

Group A

Group A consisted of 11 experimental and five control dogs. Blood pressure was monitored continuously, and the baseline values were recorded 40 and 60 minutes after completion of surgical procedures. At 60 minutes, blood was withdrawn for hormonal measurements. The suit was then instantly inflated to a pressure 10 mm Hg below the animal's resting diastolic blood pressure. The compression was maintained for 3 hours in all animals, and then the suit was deflated for 10 minutes. The control dogs had an uninflated suit throughout the procedure. After the baseline measurements, hemodynamic and hormonal measurements were taken during 10, 60, 120, and 180 minutes of inflation.

Group B

Group B consisted of five dogs. Resting measurements were taken 30 minutes after surgery, and the suit was inflated for 30 minutes. After deflation of the suit, a search was started for the highest rate of infusion of trimethaphan that did not cause resting hypotension. This took between 30 and 120 minutes. The final dose ranged from 2 to 32 mg/kg/min in individual dogs. After the blood pressure on the last infusion rate of trimethaphan was stable for 10 minutes, the suit was inflated for 30 minutes. After that the suit was deflated and the trimethaphan infusion discontinued for 60 minutes. At that point a sequence of resting measurements and of 30-minute inflation was repeated.

Statistical Analysis

Student t test was used for comparison between groups. Paired t tests were used for within-group comparison. Where multiple comparisons within a group were needed, repeated measures analysis with simultaneous confidence intervals or a Bonferroni correction for repeated paired comparison was used.

Results

Systemic Hemodynamics

In both species there was a substantial increase in blood pressure. The increase in pigs after 30 minutes of compression was 50/38 mm Hg (fig. 2) and in dogs
Figure 2. Hemodynamic response to lower body compression in nine pigs. Cardiac output is measured by an aortic flowmeter, which was not calibrated; changes are therefore expressed as ratio to baseline values. Similarly, vascular resistance had to be expressed as a ratio change. Bars delineate standard error of the mean. Because of multiple and not independent observations, a repeated measures analysis with simultaneous confidence intervals for three time periods was used. The times were: 10-minute average baseline, average of 20–29 minutes with the pressure suit, and 10-minute average during decompression recovery. Asterisks show changes from baseline to inflation; daggers show changes from inflation to recovery. One symbol = p < 0.05, two = p < 0.01, and three = p < 0.001. No significant difference was found between baseline and recovery.

After 180 minutes of compression, 44/53 mm Hg (fig. 3). These blood pressure changes were highly significant. In both species the blood pressure elevation was due entirely to an increase of vascular resistance. In spite of the elevated blood pressure, bradycardia was absent in both species; at 180 minutes, the heart rate of the dogs was, in fact, increased. In pigs the mean central venous pressure initially increased but after 10 minutes started to decline. In dogs, compression with the small suit also caused only a transient increase of the right atrial pressure. Decompression caused an immediate fall of the blood pressure in both species. This fall of blood pressure in pigs was due to a fall in vascular resistance. Hemodynamic measurements on decompression in dogs were not available. The dogs were rechallenged after 10 minutes of decompression: again, the blood pressure promptly increased.

A time control group of animals was used in dog experiments. Increases of blood pressure and resistance occurred only in experimental animals; the blood pressure in control dogs tended to decrease with the passage of time.

During the period of compression in dogs (180 minutes), which was much longer than in pigs (30 minutes), the dogs’ blood pressure remained substantially elevated. The decrease in systolic blood pressure at 60 to 180 minutes was not significant, whereas the diastolic blood pressure remained consistently elevated during the whole experiment.

Ganglionic Blockade

In both species the ganglionic blockade substantially interfered with the blood pressure response. In pigs (fig. 4) a residual minor response was still observable, whereas in dogs (fig. 5), the blockade fully abolished the blood pressure increase. In both groups, trimethaphan did not cause resting hypotension before re-inflation, and thus, was not acting as a nonspecific hypo-
SUSTAINED BLOOD PRESSURE ELEVATION: Julius et al. 785

**Figure 3.** Hemodynamic response to hindquarter compression in dogs. The solid line represents the average in the experimental dog; the interrupted line is the average of five control dogs. The bars represent standard error of the mean. Significance of difference (by Student t test) between the groups is denoted by asterisks: *p < 0.05; **p < 0.02; ***p < 0.001. Changes within a group (by paired t test) are denoted by daggers. Since paired t test is not applicable to repeated measures, only the significance of difference between rest and 180 minutes of compression was tested. The exception is the right atrial pressure, which showed an initial transient rise. The significance by paired t test was measured at that point. The —40 point denotes 40 minutes after completion of surgery; the 0 point was 60 minutes after surgery. D = deflation; R = reinflation.

**Discussion**

To our knowledge, this is the first description of a prolonged and substantial blood pressure increase induced by physical, noninvasive means in animals. There are reports of blood pressure increases in response to lower body compression in humans. Bondurant et al.  used a single chamber antigravitational suit enclosing the lower abdomen and legs. After 2 minutes there was a 20/20 mm Hg increase in intraarterial blood pressure. Similar results were also reported by...
FIGURE 4. Hemodynamic responses to lower body compression before and during ganglionic blockade with 0.15 mg/kg/min of trimethaphan in five pigs. The baselines before and during Arfonad administration were compared with a paired t-test with Bonferroni correction for repeated measures and were not different. With the same test, the arterial pressure during the compression period was significantly reduced with trimethaphan (*p < 0.05 for the whole period of compression). Decompression recovery periods were not significantly different. Additionally, changes during each period separately, e.g., before and during trimethaphan, were tested with a multiple measures test comparing baseline, compression period and decompression recovery period, as in figure 3. Daggers = baseline vs compression; asterisks = compression vs decompression. Note that the blood pressure and vascular resistance were significantly elevated over the baseline before trimethaphan, but not so during trimethaphan. However, decompression induced significant decreases of blood pressure and vascular resistance before and after trimethaphan.
Shubrooks et al.⁵ found an increase of vascular resistance with lower body compression in humans and believed that it reflected the mechanical compression of the vasculature under the suit. The increase of vascular resistance in our experiment cannot be entirely explained by mechanical compression with the suit. In pigs trimethaphan infusion did not alter the baseline vascular resistance, but prevented a substantial proportion of the increase of the vascular resistance during the lower body compression. This decrease of the resistance must have occurred in the areas outside of the suit, as it is hard to visualize how local vasodilation under the suit could offset the effect of mechanical compression. Central venous pressure changes during the compression were similar before and after ganglionic blockade, as were the cardiac output changes. This speaks against an influence of trimethaphan on the resistance to the venous return or on cardiac function in pigs. However, response to trimethaphan is dose-dependent, and at higher doses the blood pressure decrease can reflect a fall in cardiac output. Consequently, we cannot exclude that the total abolition of the blood pressure response with larger doses of trimethaphan in dogs may have been in part due to a cardiodepressant action of trimethaphan.

Trimethaphan experiments in pigs suggest that more than 50% of the vascular resistance increase was not secondary to a mechanical decrease of the vascular resistance under the compression suit. The nature of this increase requires further elucidation. However, we believe that our experiments provide indirect support for the notion that a part of the increase of resistance and blood pressure in these experiments is neurogenic. In addition to the effect of ganglionic blockade on the resistance response to the compression, there are two additional lines of evidence that suggest a neurogenic component. First, there is an absence of bradycardia in spite of a substantial blood pressure increase. If the blood pressure increase were mechan-  
al, the expected compensatory response would be an increased baroreceptor-mediated inhibition of the sinus node. This lack of baroreceptor response to the blood pressure elevation resembles other physiologic conditions such as isometric exercise⁶ and emotional elevation of blood pressure⁷ where the blood pressure increase reflects a central nervous sympathetic activation. Second, there is an increase of plasma norepinephrine, although we realize that plasma norepinephrine levels depend also on reuptake and clearance and cannot automatically be equated with an increased sympathetic tone.

The blood pressure response to lower body compression while rapid was not instantaneous (fig. 2). Reflex responses are usually faster than the increase observed in our experiments. This might speak against a neurogenic origin for the observed response, but it is well recognized that locally released substances play an important role in the reflex increases of blood pressure after dynamic exercise⁸,⁹ and after isometric exercise.¹⁰ The compression with the suit impedes the blood flow to the lower extremities. This could cause a
slow accumulation of locally released substances, which initiated the reflex pressor response.

The purpose of this paper is to report a new way of eliciting substantial and prolonged blood pressure elevation in animals. At the present time the mechanism of this blood pressure elevation remains speculative. In the past almost every new model of blood pressure elevation stimulated subsequent work to elucidate its pathophysiology, frequently adding important information to the general literature on blood pressure regulation. We hope that the present model, with its ability to alter blood pressure at will without surgery, will be a useful tool in the study of cardiac function, morphologic and biochemical myocardial changes, and the viability of damaged myocardium. In our laboratory we plan further studies to determine whether this potent, prolonged pressor response may be neurogenic.

References
Sustained blood pressure elevation to lower body compression in pigs and dogs.
S Julius, R Sanchez, S Malayan, M Hamlin, M Elkins, D Brant and D F Bohr

Hypertension. 1982;4:782-788
doi: 10.1161/01.HYP.4.6.782

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/4/6/782

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/