Hemodynamic and Humoral Characteristics of Hypertension Induced by Prolonged Stellate Ganglion Stimulation in Conscious Dogs

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ABSTRACT

Recent evidence has suggested that cardiac factors may play a role in the evolution of arterial hypertension. To test the possibility that an increase in cardiac performance can lead to a sustained increase in systemic blood pressure, we electrically stimulated the left stellate ganglion of six conscious dogs continuously for a 7-day period and monitored cardiac output and arterial blood pressure. In all six dogs, stimulation elicited an abrupt rise in systemic blood pressure that was entirely due to a rise in cardiac output that lasted at least 6 hours. After 1 day of continuous stimulation, cardiac output returned to control values, but blood pressure remained elevated. After 7 days of stimulation, blood pressure was increased by an average of 25 mm Hg and peripheral resistance by 35 ± 4%. Measurements of blood volume, plasma renin activity, circulating catecholamines (three of the six dogs), and sodium balance showed that none of these factors could explain the development of this sustained hypertension. Pharmacologic blockade with phenoxybenzamine prevented in large part the rise in blood pressure in short-term stellate ganglion stimulations, whereas propranolol had very little effect on the pressor response, although it nearly abolished the increase in cardiac output. The data indicate that continuous stimulation of the stellate ganglion in conscious dogs leads to sustained rises in both blood pressure and peripheral resistance; these changes are apparently mediated by increased activity of the sympathetic nervous system.

KEY WORDS **cardiac output** **arterial blood pressure** **phenoxybenzamine** **propranolol** **catecholamines** **plasma volume** **heart rate** **sodium balance**

■ Recent studies in man and experimental animals have suggested the possibility that the heart plays an active role in the genesis of some types of hypertension. Early stages of the disease are often associated with an increased cardiac output in both man (1-3) and experimental animals (4-8). Although hypervolemia may account for some instances of increased cardiac output, an expanded blood volume has not been found in all cases (9, 10) and evidence for increased cardiac performance has been reported in some (11, 12). The possible importance of increased cardiac activity in the development of some types of hypertension has been frequently suggested by the clinical observation of a high incidence of hypertension in idiopathic hyperdynamic circulatory states (13-15) and the demonstration of increased cardioadrenergic drive in borderline hypertension (16).

Closely allied to these observations are the many reports of acute hypertension produced by stellate ganglion stimulation in animals. These studies, mostly performed in anesthetized dogs, demonstrate that electrical stimulation of either the right or the left ganglion increases cardiac output and raises arterial blood pressure (17-19). Rohse et al. (20) have shown that this pressor response can, under certain conditions, be maintained for several hours in the anesthetized dog. Freis (21) has suggested the term "cardioadrenergic hypertension," but there is no evidence that a sustained increase in arterial blood pressure can be produced by stellate ganglion stimulation in conscious animals. To determine whether hypertension can indeed evolve from a period of sustained increase in cardiac performance, we developed a method for prolonged stimulation of cardiac sympathetic fibers in conscious dogs and performed sequential hemodynamic, volume, and humoral studies during such stimulation.

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Methods

Animal Preparation.—Eight mongrel dogs of either sex were used for these experiments (body weight 21.7 ± 0.9 [SE] kg). Under sterile conditions they were equipped with an aortic electromagnetic flowmeter, and a stimulating electrode was placed around the left stellate ganglion through a thoracotomy at the third intercostal space. The flow transducer and the electrode cables were worked underneath the skin to the back of the neck and exteriorized through a skin button. At the same time a catheter was inserted into the aorta through an iliac artery to allow chronic recording of arterial blood pressure and blood sampling (7).

Stellate Ganglion Stimulation.—The electrode placed around the body of the stellate ganglion (Fig. 1) was a wrap-around electrode made of platinum embedded in Silastic (Medtronic Inc., model 7X120A-13). The sympathetic chain was cut below T3 to avoid stimulation of abdominal structures. All other branches and spinal connections of the stellate ganglion were left intact to avoid degeneration of the many preganglionic fibers that travel through it (22, 23) and also to keep its blood supply intact. The right stellate ganglion was left untouched.

Stimulation was provided by a constant-current battery-operated stimulator (Medtronic Inc., model SP 1432) that gave a biphasic output pulse. Tests with various loads (250–1000 ohms) showed that the current pulse remained constant up to amplitude settings of 15 mA, a level never attained in our study. The intensity, frequency, and duration of the pulses could be selected over a wide range. The stimulations performed ranged from 4.2 to 6 mA in intensity, the duration of each pulse was 5 msec, and the frequency was between 4 and 10 pulses/sec.

The intensity of the stimulation was determined in preliminary trials and was selected to give a clear initial response without eliciting discomfort in the dog. Although the dogs were aware of the stimulation and exhibited a slight tremor of the left front leg, they did not appear to suffer from even prolonged stimulations, as evidenced by their unchanged eating, drinking, and sleeping habits and by their constant body weights.

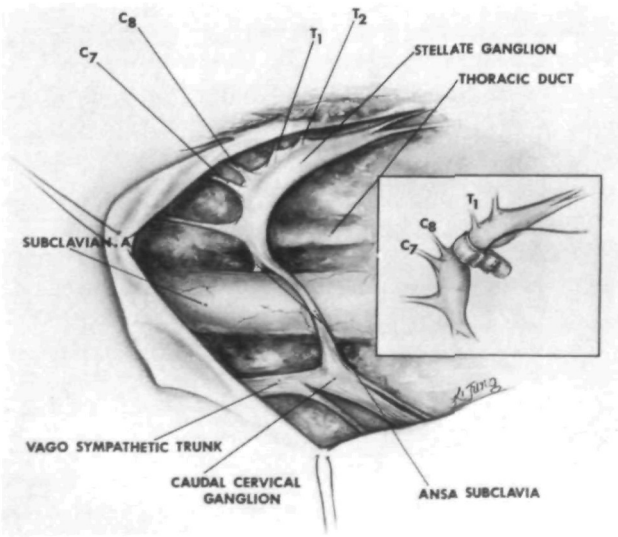

FIGURE 1

Placement of the electrode on the left stellate ganglion in the dog.

Collection of Hemodynamic Data.—The experiments were performed in an isolated room, and the dogs were housed in a pen equipped for continuous recording of hemodynamic variables without interference from the observer (24). An arterial pressure transducer was fixed at heart level into a fiber glass harness which fit over the dog's back and was held in place by a canvas bib. The cables from the pressure and electromagnetic flow transducers were brought to the top of the cage through a protective flexible tube.

Hemodynamic variables were recorded for 2–8 hours every day; they included aortic blood flow, arterial blood pressure (mean and pulsatile pressures were recorded alternately every day), and heart rate. Cardiac output was computed from the beat-to-beat integration of the aortic flow signal over 4-second periods as described previously (6). Control data were averaged from values obtained during the 3 days preceding the start of the stimulation. The periods used for calculation of the daily averages were only those at least 5 minutes long during which the dogs were lying down quietly, as ascertained by direct observation of the animals through a window and evidenced on the record by very stable arterial blood pressure, heart rate, and cardiac output.

For the short-term stimulations (see experimental protocol), one experimenter was present and the dogs were kept standing to avoid the hemodynamic effects of a possible postural change at the start of the stimulation. However, short-term experiments performed after phenoxybenzamine administration were conducted while the dogs were lying down.

Balance Studies.—The dog pen was designed so that urine could be collected; the daily urine volume and the urinary sodium and creatinine concentrations were measured. The amount of fluid and sodium ingested daily was also measured to calculate the daily balance, but the excretion of sodium in the feces was not considered; this omission undoubtedly accounts for the slight but significant positive sodium balance calculated during the control period in this study, since fecal excretion of sodium in dogs without diarrhea represents a small and relatively constant amount compared with urinary excretion (Liard, unpublished observations).

Other Measurements.—Plasma renin activity was measured by the radioimmunoassay technique for angiotensin I described by Haber et al. (25). Plasma catecholamines (total of epinephrine and norepinephrine) were determined by the ethylenediamine method as modified by Manger et al. (26). Plasma protein concentration was measured by the Biuret method, sodium and potassium concentrations were determined by flame photometry, osmolality by a freezing point depression osmometer, and hematocrit by microcentrifugation, thus obviating the need for correction for trapped plasma. Plasma volume was measured with Evans blue dye by back extrapolation to zero time from three samples obtained 15, 25, and 35 minutes after injection of the dye. All blood samples were obtained through the chronic arterial catheter before the dogs were fed; after centrifu-

gation of the sample the red cells were reinjected except when blood was drawn for catecholamine determinations.

Experimental Protocol.—Following a 2-week period of recovery from surgery, the dogs were placed in the recording pen, and sodium balance studies and recording sessions were started. Control blood samples were obtained several times during this period for the measurements described earlier; the last samples were drawn immediately before the start of the stimulation. Plasma volume was measured the day of the stimulation or the day before (27).

Two hours after the start of the stimulation and while hemodynamic measurements were being continuously collected, plasma volume was again determined and blood samples were drawn for determination of all of the variables measured during the control period. These measurements were repeated 1, 4, and 7 days after the start of the stimulation, and arterial blood pressure, cardiac output, and heart rate were recorded every day for at least 2 hours starting in the morning. The stimulator was turned off after 7 days; hemodynamic variables were measured during the 2 hours immediately following the end of the stimulation and then again on the first, third, and seventh days after stimulation had been stopped. Plasma volume was determined 3 days after the end of the stimulation, and the other blood indexes were obtained 1 and 3 days after the stimulation. The sodium balance studies were conducted throughout the period of stimulation and for the 3 following days. When hemodynamic data were not being recorded, the dogs were taken out of the harness but remained in the same cage and wore a jacket containing the stimulator. Six complete experiments were performed in six dogs. All changes reported for these prolonged stimulations refer to the control values obtained for the 3 days preceding the stimulation.

Effect of Adrenergic Blockade on the Acute Hemodynamic Changes Resulting from Stellate Ganglion Stimulation—In the six dogs previously subjected to a 7-day stimulation, 1 week or more after the end of the stimulation, and in two other similarly prepared dogs, 4.5-6-mA, 5-msec, 5- or 10-Hz stimulations were performed for 2-minute periods. This experiment was repeated several times in every dog for a total of 32 stimulations in eight dogs. Following a short-term stimulation, propranolol (2 mg/kg) or phenoxybenzamine (5 mg/kg) was given and the stimulation was repeated using the same parameters 10–15 minutes after propranolol administration or 1 hour after phenoxybenzamine administration. To assess the degree of alpha or beta blockade obtained, the effect of either norepinephrine (1.5 μg/kg) or isoproterenol (1 μg/kg) was determined before and after administration of the blocking agent. A total of 10 stimulations was performed in five dogs after propranolol administration, and a total of 12 stimulations was carried out in five dogs after phenoxybenzamine administration. None of the stimulations was performed within 7 days of a previous administration of phenoxybenzamine or within 24 hours of a previous administration of propranolol. All changes reported for these short-term stimulations refer to the control value obtained for the 30 seconds preceding the stimulation.

Statistical analysis of the data was performed using the method of paired variates (28). Changes were considered to be significant if the P value was less than 0.05.

Results

HEMODYNAMIC CHANGES IN RESPONSE TO 7 DAYS OF STIMULATION

The hemodynamic pattern observed during chronic stellate ganglion stimulation was characterized by an initial phase of increased mean arterial blood pressure, increased cardiac output, and normal peripheral resistance and later by elevated mean arterial blood pressure, normal or subnormal cardiac output, and increased peripheral resistance.

Figure 2 illustrates the hemodynamic changes during the first 2 hours of stimulation in one dog; mean arterial blood pressure, pulse pressure, and cardiac output were all increased above control values, although the initial changes after 5 minutes were larger than those measured after 2 hours of stimulation. The pattern was the same for all six dogs (Table 1); pressure and output were significantly increased after 120 minutes of stimulation, but the changes were not as pronounced as those after 5 minutes of stimulation. Peripheral resistance did not change significantly during this period, although heart rate was returning toward its control value. Over the following hours and days (Fig. 3), cardiac output, which was significantly elevated after 6 hours of stimulation, returned to its control value after 1 day. The apparent decrease below the control value during the following days was not statistically significant. In marked contrast to this normalization of cardiac output, mean arterial blood pressure remained significantly elevated during the whole period of the stimulation, with an average increase on the seventh day of 22.7 ± 4.3 (SE) mm Hg. By then, total peripheral resistance, which was still within the control range after 6 hours, had reached a value 35% above control.

The heart rate was still slightly increased after 6 hours of stimulation (+5.8 ± 2.2 beats/min), but it then decreased below control (not significantly) from the first day after the start of stimulation until the end of stimulation. Pulse pressure remained significantly elevated during the whole stimulation period (+16.7 ± 6.0 mm Hg after 1 day, +20.8 ± 8.0 mm Hg after 7 days). Peak aortic blood flow was significantly increased after 1 day (+20.5 ± 7.4 ml/sec), but it then decreased to a value not significantly different from control.

When the stimulation was ended after 7 days, the mean arterial blood pressure decreased rapidly

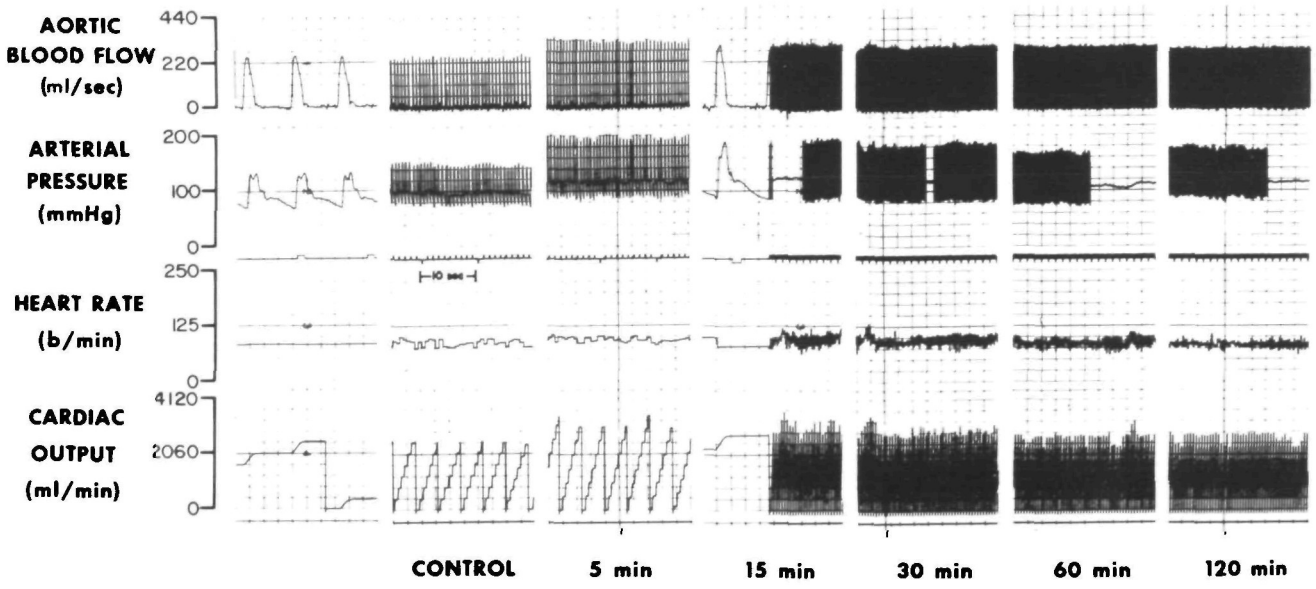

FIGURE 2

Lasting increases in both arterial blood pressure and cardiac output during a 2-hour electrical stimulation of the left stellate ganglion in a conscious dog.

(Table 2) over 15 minutes to a value not significantly different from the prestimulation control level; this initial decrease was accompanied by a decrease in both cardiac output and peripheral resistance. Then mean arterial blood pressure increased somewhat again; it was significantly higher than the prestimulation value 2 hours later (Table 2, Fig. 3). During this period, total peripheral resistance was not significantly different from the value measured before the end of the stimulation, and a significant decrease in cardiac output accounted for almost all of the decrease in mean arterial blood pressure. As shown in Table 2, pulse pressure decreased rapidly to its prestimulation value, although heart rate and peak aortic blood flow did not change significantly during the first 2 hours following the end of the stimulation. On the day following the end of the stimulation there was almost complete normalization of mean arterial blood pressure in all six dogs (Fig. 3). In three dogs, this normalization of mean arterial blood pressure was associated with a return of total peripheral resistance to the control level (mean difference from prestimulation value +0.73 ± 0.82 mm Hg $[ml/min]^{-1} \times 10^3$), whereas in the other three dogs peripheral resistance was still significantly increased (+9.53 ± 1.52 mm Hg $[ml/min]^{-1} \times 10^3$) and cardiac output was still significantly decreased.

TABLE 1

Changes in Mean Arterial Blood Pressure (MABP), Cardiac Output (C.O.), Total Peripheral Resistance (TPR), Heart Rate (HR), Pulse Pressure (PP), and Peak Aortic Blood Flow (PABF) during the First 2 Hours of Left Stellate Ganglion Stimulation in Conscious Dogs (N = 6)

		Change from control value (minutes)				
	Control	5	15	30	60	120
MABP (mm Hg)	88.5 ± 3.6	+44.0 ± 2.5*	+30.7 ± 2.8*	+24.2 ± 2.8*	+19.8 ± 4.1*	+17.0 ± 4.0*
C.O. (ml/min)	2681 ± 261	+1330 ± 112*	+1191 ± 130*	+697 ± 120*	+506 ± 125*	+550 ± 86*
TPR (mm Hg $[ml/min]^{-1} \times 10^3$)	34.9 ± 4.0	−0.57 ± 1.37	−3.15 ± 2.09	+0.48 ± 1.23	+1.67 ± 1.58	−0.38 ± 2.09
HR (beats/min)	68.0 ± 5.7	+46.2 ± 10.7*	+33.8 ± 10.5*	+18.7 ± 6.0*	+10.2 ± 2.2*	+16.7 ± 6.4*
PP (mm Hg)	75.8 ± 7.8	+32.5 ± 5.7*	+25.8 ± 8.5*	+20.0 ± 7.6*	+19.2 ± 9.1	+13.3 ± 7.6
PABF (ml/sec)	213.5 ± 17.5	+44.2 ± 17.0*	+36.3 ± 16.9*	+30.0 ± 17.9	+30.5 ± 11.9*	+18.8 ± 10.3

Values are means ± SE.

* Change from the control value was significantly different from 0.

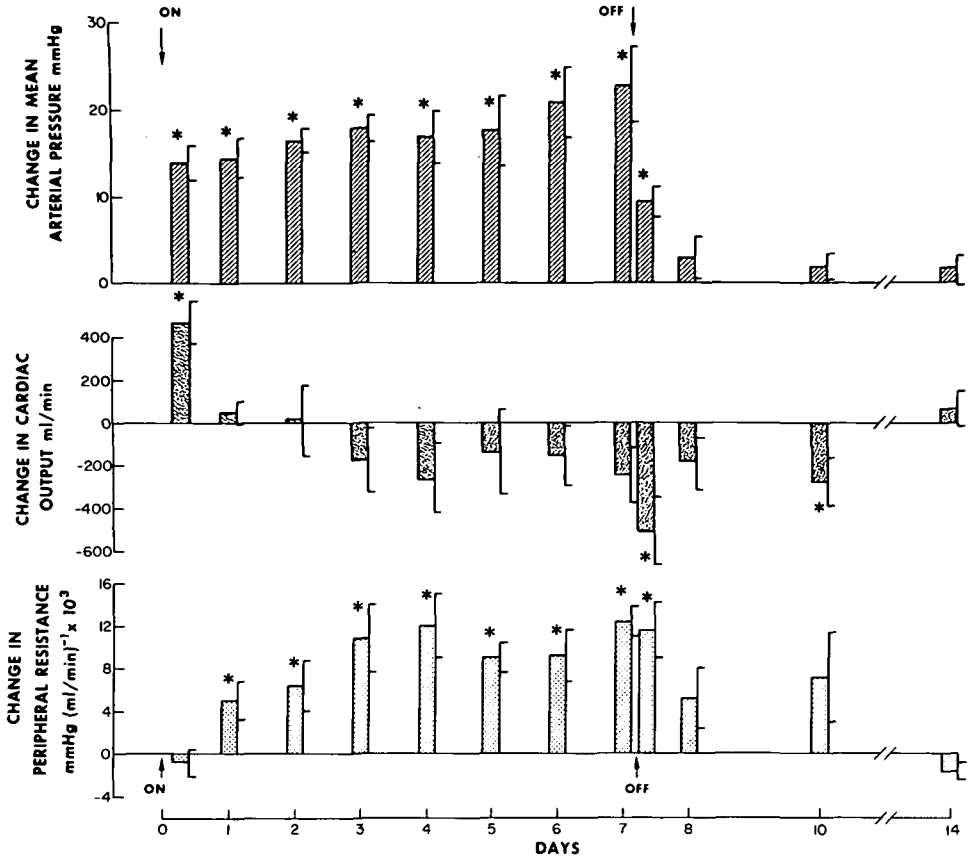

FIGURE 3

Changes ± SE in mean arterial blood pressure, cardiac output, and peripheral resistance in six dogs between 6 hours (ON) *and 7 days of continuous left stellate ganglion stimulation* (OFF) *and 2 hours and 1, 3, and 7 days following discontinuation of the stimulation. An asterisk indicates a significant change ($P < 0.05$) from the prestimulation values listed in Table 1.*

Despite these hemodynamic differences, the two groups of dogs did not show behavioral differences during stimulation; they had very similar changes in cardiac output and peripheral resistance after 7 days of stimulation. The third day after the end of the stimulation, two dogs still exhibited a high total peripheral resistance and a low cardiac output, whereas 7 days after the end of the stimulation all hemodynamic parameters had returned to their prestimulation values. In summary, the return of

TABLE 2

Hemodynamic Changes during the 2 Hours following the End of a Continuous, 7-Day Period of Stellate Ganglion Stimulation in Conscious Dogs

	Value before end of stimulation (control)	Change from value before end of stimulation (minutes)				
		5	15	30	60	120
MABP (mm Hg)	111.2 ± 4.6	−9.0 ± 5.6	−19.3 ± 3.6*	−16.7 ± 5.3*	−15.5 ± 4.7*	−13.4 ± 4.2*
C.O. (ml/min)	2432 ± 172	−68.5 ± 80.8	−177.3 ± 65.7*	−301.0 ± 93.7*	−186.7 ± 64.8*	−261.8 ± 98.7*
TPR (mm Hg [ml/min]$^{-1}$ × 10^3)	47.2 ± 4.5	−3.3 ± 2.8	−4.9 ± 1.7*	−1.0 ± 2.0	−3.8 ± 3.0	−0.9 ± 3.6
HR (beats/min)	62.2 ± 4.8	+2.8 ± 4.1	−2.3 ± 2.8	−3.3 ± 3.9	−0.7 ± 3.0	+2.3 ± 3.8
PP (mm Hg)	96.6 ± 7.1	−10.8 ± 6.0	−13.8 ± 5.6	−15.8 ± 5.4*	−17.5 ± 5.4*	−20.4 ± 6.3*
PABF (ml/sec)	213.8 ± 23.9	−7.7 ± 5.7	−5.8 ± 3.7*	−4.7 ± 3.1	−4.7 ± 3.3	−14.5 ± 7.9

Values are means ± SE. See Table 1 for definition of abbreviations.

* Change from the control value was significantly different from 0.

mean arterial blood pressure to its control value was rapid, although not immediate, and the general pattern was one of an initial decrease in cardiac output with a progressive return of peripheral resistance toward control with a very variable time course from one dog to the other.

VOLUME AND HUMORAL CHANGES IN RESPONSE TO CHRONIC STIMULATION

Table 3 summarizes the results for volume and humoral changes and shows that both plasma and blood volume decreased somewhat during the stimulation of the left stellate ganglion, although plasma protein concentration increased slightly. Plasma renin activity exhibited a small increase during stimulation, but statistical significance was reached only on the seventh day (Table 3). The control values for plasma sodium concentration (144.3 ± 1.7 mEq/liter), potassium concentration (3.86 ± 0.10 mEq/liter), and osmolality (2.982 ± 1.6 mosmoles/kg) were unchanged throughout the experiment.

In addition to these measurements, plasma catecholamine concentrations were determined in three dogs (Table 3); they did not change significantly during the stimulation or the poststimulation period. These three dogs did not differ significantly from the other three with respect to the changes in mean arterial blood pressure and total peripheral resistance induced by stellate stimulation.

After stimulation was discontinued, both plasma volume and total blood volume increased by 5.0 ± 1.2 ml/kg and 5.7 ± 2.1 ml/kg, respectively, relative to their values on the last day of the stimulation and reached values slightly, but not significantly, lower than the prestimulation control levels. Plasma protein concentration returned to its control value. After cessation of stimulation plasma renin activity fell to levels not significantly different from prestimulation values. The levels recorded 1 and 3 days after stimulation had been stopped were significantly lower than those obtained on the seventh day of stimulation. Plasma electrolytes and osmolality remained unchanged.

BALANCE STUDIES AND CREATININE CLEARANCE

For the period preceding the stimulation (average 6 days), the daily sodium balance in the six dogs averaged +0.54 ± 0.17 mEq/kg; this value was established for each of the six dogs by dividing the cumulative sodium balance for the control period by the number of days. The daily sodium balance did not change significantly following stimulation of the left stellate ganglion either during the first day or for any other day during the stimulation period. However, there was significant sodium retention on the first day following the end of the stimulation with a sodium balance of +2.04 ± 0.30 mEq/kg, compared with +0.56 ± 0.39 mEq/kg for the 2 days preceding the end of stimulation. Then, during the second and third poststimulation days, the daily sodium balance was again similar to the value obtained during the control period.

As an index of fluid balance, we calculated the difference between water intake and urinary volume; it did not change during or following stellate ganglion stimulation.

During the prestimulation period, an average endogenous creatinine clearance was calculated from the daily values for each dog; the mean value for the six dogs was 3.0 ± 0.39 ml/kg min^{-1}. Following stimulation of the stellate ganglion, that value tended to decrease the first day and then to increase toward the end of the stimulation period, but none of these changes was statistically significant.

ADRENERGIC BLOCKADE EXPERIMENTS DURING SHORT-TERM STIMULATION

To obtain more information on the nature of the changes in peripheral resistance measured during

TABLE 3

Plasma Volume (PV), Hematocrit (HT), Blood Volume (BV), Plasma Protein Concentration (PPC), Plasma Catecholamine Concentration (PCC), and Plasma Renin Activity (PRA) Changes Induced by Prolonged Stellate Ganglion Stimulation in Conscious Dogs

	N	Control before stimulation	Changes from prestimulation value			
			2 hours	1 day	4 days	7 days
PV (ml/kg)	6	59.1 ± 3.9	−1.9 ± 1.4	−1.7 ± 1.3	−3.2 ± 1.2*	−5.3 ± 1.9*
HT (%)	6	38.7 ± 1.0	−2.2 ± 0.6*	−1.9 ± 1.0	−0.5 ± 1.3	−0.3 ± 1.6
BV (ml/kg)	6	96.1 ± 4.1	−6.2 ± 1.7*	−5.4 ± 1.8*	−5.5 ± 1.7*	−8.8 ± 2.9*
PPC (g/100 ml)	6	6.30 ± 0.25	−0.08 ± 0.07	+0.14 ± 0.19	+0.19 ± 0.07*	+0.44 ± 0.19*
PCC (μg/liter)	3	1.8 ± 0.6	−0.4 ± 0.3	−0.4 ± 0.4	−0.6 ± 0.4	−0.2 ± 0.8
PRA (ng/ml $hour^{-1}$)	6	0.91 ± 0.26	+0.59 ± 0.37	+0.25 ± 0.27	+0.54 ± 0.48	+0.61 ± 0.11*

Values are means ± SE. N = number of dogs tested.

* Change was significantly different from 0.

the chronic stellate stimulation, pharmacologic blockade of alpha or beta receptors was induced in the same six dogs previously subjected to the 7-day stimulation (at least 7 days after the end of the stimulation) and in two more dogs. The hemodynamic results of the 2-minute stellate stimulations are summarized in Figure 4. As previously described in anesthetized animals (19), cardiac output and arterial blood pressure increased immediately in the untreated group. There was a small, but significant, fall in peripheral resistance for the first 20 seconds followed by a progressive rise to a value significantly above control in the last minute of stimulation. Heart rate increased significantly with the maximum increase (45.2 ± 6.8 beats/min) occurring 10–20 seconds after the start of the stimulation. Pulse pressure increased markedly from 72.4 ± 2.3 mm Hg to 125.1 ± 5.5 mm Hg during the last 30 seconds of stimulation, and so did peak aortic blood flow.

Following phenoxybenzamine administration (5 mg/kg), the pressor response to an injection of norepinephrine (1.5 μg/kg) was reduced by 77% (Table 4); the decrease in cardiac output was significantly smaller. Propranolol (2 mg/kg) prevented almost completely the effect of isoproterenol (1 μg/kg) on cardiac output, heart rate, pulse pressure, and peak aortic blood flow (Table 4). The effects of stellate ganglion stimulation following these doses of the beta-receptor and the alpha-receptor blocker are summarized in Figure 4. After propranolol administration, the most striking feature was the unimpeded rise in mean arterial blood pressure with stellate stimulation even though the increase in cardiac output was only 11% of that measured in the untreated dogs; thus, the rise in pressure was related to a change in peripheral resistance. Cardiac acceleration was significantly inhibited by propranolol, but the maximum increase in heart rate (10–20 seconds after the start of the stimulation) was still 20.6 ± 3.1 beats/min. Propranolol prevented to a large extent the increase in pulse pressure with stimulation and actually reversed the effect on peak aortic blood flow, which decreased significantly during stimulation.

Alpha-receptor blockade by phenoxybenzamine did not alter the initial increase in cardiac output seen in the untreated group, but this increase was not as well sustained in the treated dogs and during the second minute of stimulation was significantly smaller than that in the untreated dogs. However, despite this large initial increase in cardiac output, the rise in mean arterial blood pressure was significantly smaller than that in the untreated group due

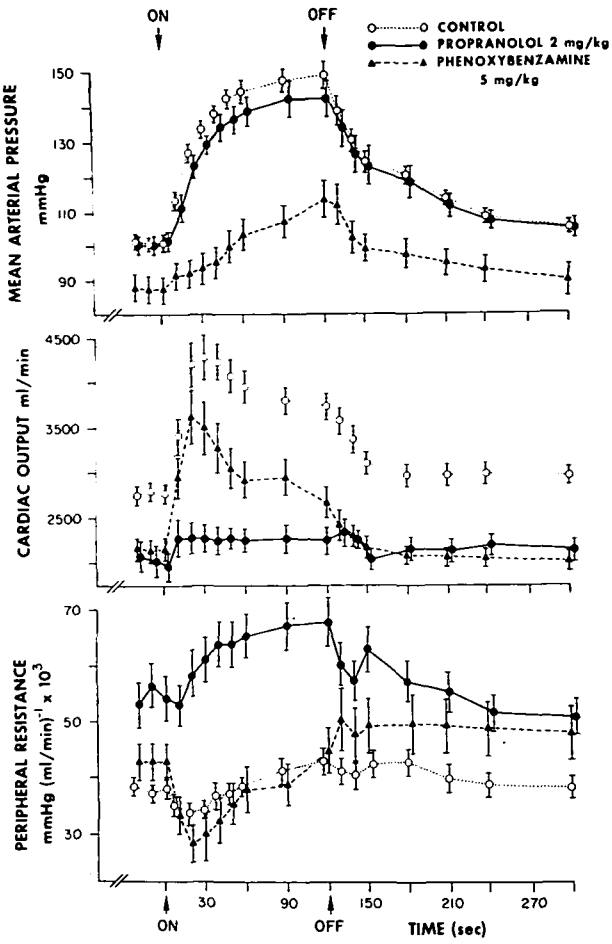

FIGURE 4

Mean arterial blood pressure, cardiac output, and peripheral resistance for 30 seconds before, during, and 3 minutes after a stellate ganglion stimulation 2 minutes in duration in conscious dogs that were untreated (32 experiments), given propranolol (10 experiments), or given phenoxybenzamine (12 experiments). Each point represents the mean ± SE for a period of 10 seconds for the 30 seconds preceding and the 60 seconds following the start of the stimulation and for the 30 seconds following the end of the stimulation or for a period of 30 seconds or 1 minute for the second minute of stimulation and for the second and third minute after discontinuation of the stimulation.

to a pronounced fall in peripheral resistance. The maximum increase in mean arterial blood pressure measured during the last 30 seconds of stimulation was 25.4 ± 6.4 mm Hg in the phenoxybenzamine-treated group (N = 12) compared with 50.3 ± 4.4 mm Hg (N = 32) in the untreated dogs. Cardiac acceleration was initially greater under alpha blockade than it was in control dogs; the maximum increase reached 86.7 ± 9.8 beats/min 10–20 seconds after the start of the stimulation. Later on, however, the changes in rate were not significantly different from those observed in the untreated group. The increase in pulse pressure was not as pronounced under alpha blockade as it was in the

TABLE 4

Peak Hemodynamic Changes Induced by Norepinephrine before and after Phenoxybenzamine (5 mg/kg) and by Isoproterenol before and after Propranolol (2 mg/kg) Administration

		Before antagonist					After antagonist					
	N	MABP (mm Hg)	C.O. (ml/min)	TPR (mm Hg [ml/min]$^{-1}$ × 10^3)	HR (beats/min)	PP (mm Hg)	PABF (ml/sec)	MABP (mm Hg)	C.O. (ml/min)	TPR (mm Hg [ml/min]$^{-1}$ × 10^3)	HR (beats/min)	PP (mm Hg)	PABF (ml/sec)
Norepinephrine (1.5 μg/kg)	5	+33.3 ± 4.1	−837 ± 170	+35.9 ± 5.1	−25.5 ± 8.3	+24.7 ±3.3	−19.3 ± 11.0	+7.8 ± 1.9*	−311 ± 86*	+13.8 ± 3.8*	−10.0 ± 4.5	+10.0 ± 3.6*	+4.0 ± 7.4*
Isoproterenol (1 μg/kg)	5	−22.8 ± 3.7	+1917 ± 293	−30.1 ± 4.1	+101.4 ± 17.6	+61.0 ± 17.3	+124.6 ± 9.5	−4.8 ± 1.4*	+194 ± 42*	−8.6 ± 1.8*	+8.2 ± 1.9*	+1.0 ± 1.0*	+11.6 ± 2.2*

Values are means ± SE. N = number of dogs tested. See Table 1 for definition of other abbreviations.
* Peak change induced by the agonist (norepinephrine or isoproterenol) was significantly changed by the specific alpha or beta antagonist used.

untreated group, but it was larger than that in the propranolol-treated dogs.

Discussion

These experiments demonstrated that a prolonged elevation of mean arterial blood pressure could be produced by continuous stimulation of the left stellate ganglion in conscious dogs. However, this model differed in some respects from what was expected. Instead of being due to increased cardiac output and associated with signs of hyperkinetic circulation, such as increased heart rate, the sustained increase in blood pressure was characterized from the very first day by a normal or subnormal cardiac output and an increased peripheral resistance, with some slowing of heart rate. An important question concerns the mechanisms by which a hyperkinetic circulation (first 6 hours) developed into the hemodynamic pattern just described. It could be that the transient increase in cardiac output was the trigger for the subsequent changes in peripheral resistance. In fact, a sequence of events in accord with this hypothesis has been observed in several forms of experimental hypertension (4–8), and the suggestion has been made repeatedly that these changes in peripheral resistance are due to total body autoregulation. This concept states that an unwarranted increase in blood flow to the tissues consequent to an increase in cardiac output will lead to vasoconstriction and structural changes in the vascular wall that return flow to a level in accord with the metabolic needs of the tissues. In our experiments, however, several findings indicate that this mechanism may not be the whole explanation for the observed increase in peripheral resistance. We found (Fig. 4) that increases in both arterial blood pressure and peripheral resistance can occur even if changes in cardiac output are markedly depressed. Conversely, blockade with phenoxybenzamine prevents to a larger extent the rise in arterial blood pressure without interfering initially with the increase in cardiac output. Moreover, the reduction in cardiac output to normal or subnormal levels is at variance with accepted norms of autoregulation; the latter would predict a small residual increase in cardiac output during the steady-state phase. The rapidity of the changes in peripheral resistance observed in our experiments cannot be taken as an argument against autoregulation, which has been shown to occur very rapidly by Granger et al. (29).

We feel that other mechanisms might also play an important role in the increase in peripheral resistance observed in our experiments. The most likely appears to be the stimulation of afferent

fibers from the heart eliciting the same type of peripheral vascular responses that have been described by Peterson and Brown (30) and by Malliani et al. (31). These afferent fibers travel through the stellate ganglion before they reach the spinal cord through the dorsal roots. The nature of the pressor response observed in these chronic stimulations would then be that of a reflex increase in sympathetic tone. Indirect evidence for such an increase is the maintenance of a normal sodium excretion by the kidney despite the higher perfusion pressure and also the decrease in plasma volume in the absence of a significant change in external fluid balance, indicating an altered repartition of fluid between plasma and extravascular volumes possibly consequent to venoconstriction. A similar reduction of the ratio of plasma to interstitial fluid volume has been described by Tarazi et al. (32) in essential hypertension and tentatively related to venoconstriction. Venoconstriction has also been suggested as an important factor in the central redistribution of circulating blood volume and the increased cardiac output found in both experimental renal hypertension (6) and some forms of human hypertension (12, 33). However, it has recently been shown that electrical stimulation of the stellate ganglia (34) or their removal (35) in dogs leads to changes in the activity of atrial receptors which are known to contribute to the control of blood volume by venous mechanisms (36). It is likely therefore that the plasma volume changes measured in the present experiments are of complex origin.

The normal concentration of catecholamines indicates that the increase in peripheral resistance was not the result of an overflow of catecholamines from the stimulated heart or the adrenal glands. Increased plasma renin activity probably was not responsible for the rise in peripheral resistance, since the changes measured were very small. Other explanations for the increased peripheral resistance in dogs subjected to chronic stellate stimulation include the stimulation of sympathetic fibers innervating structures other than the heart and also unspecific effects of spread of current to other nerves. The similarity of the acute changes with and without anesthesia (37) indicates that pain was not the cause of the initial hypertension. Its possible role at a later stage was assumed to be small or nonexistent, because no evidence was found that pain actually occurred in these experiments.

In conclusion, we have shown that a sustained increase in mean arterial blood pressure results from prolonged stimulation of the left stellate ganglion in conscious dogs. Although increased cardiac performance was followed by sustained hypertension, the rise in arterial blood pressure may well have been the result of a different mechanism, possibly the stimulation of a pressor reflex.

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References

1. Widimsky J, Fejfarova MH, Fejfar Z: Changes of cardiac output in hypertensive disease. Cardiologia 31:381-389, 1957
2. Lund-Johansen P: Hemodynamic pattern in essential hypertension at rest and during muscular exercise. Acta Med Scand 181(suppl 482):9-101, 1967
3. Frohlich ED, Tarazi RC, Dustan HP: Re-examination of the hemodynamics of hypertension. Am J Med Sci 257:9-23, 1969
4. Ledingham JM, Cohen RD: Changes in extracellular fluid volume and cardiac output during the development of experimental renal hypertension. Can Med Assoc J 90:292-294, 1964
5. Bianchi G, Tenconi LT, Lucca R: Effect in the conscious dog of constriction of the renal artery to a sole remaining kidney on haemodynamics, sodium balance, body fluid volumes, plasma renin concentration and pressor responsiveness to angiotensin. Cli Sci 38:741-766, 1970
6. Ferrario CM, Page IH, McCubbin JW: Increased cardiac output as a contributory factor in experimental renal hypertension. Circ Res 27:799-810, 1970
7. Ferrario CM: Contribution of cardiac output and peripheral resistance to experimental renal hypertension. Am J Physiol 226:711-717, 1974
8. Coleman TG, Guyton AC: Hypertension caused by salt loading in the dog: III. Onset transients of cardiac output and other circulatory variables. Circ Res 25:153-160, 1969
9. Tarazi RC, Dustan HP, Frohlich ED, Gifford RW Jr, Hoffman GC: Plasma volume and chronic hypertension: Relationship to arterial pressure levels in different hypertensive diseases. Arch Intern Med 125:835-842, 1970
10. Julius S, Pascual AV, Reilly K, London R: Abnormalities of plasma volume in borderline hypertension. Arch Intern Med 127:116-119, 1971
11. Hawthorne EW, Hinds JE, Crawford WJ, Tearney RJ: Left ventricular myocardial contractility during the first week of renal hypertension in conscious instrumented dogs. Circ Res 34(suppl I):I-223-234, 1974
12. Tarazi RC, Ibrahim MM, Dustan HP, Ferrario CM: Cardiac factors in hypertension. Circ Res 34(suppl I):I-213-221, 1974
13. Gorlin R: Hyperkinetic heart syndrome. JAMA 182:823-829, 1962
14. Gottsegen G, Okos G, Romoda T: Essential circulatory hyperkinesis. Am J Cardiol 10:785-791, 1962
15. Dustan HP, Tarazi RC: Etat circulatoire hyperdynamique beta-adrenergique. Rev Med 2:115-121, 1973
16. Ibrahim MM, Tarazi RC, Dustan HP, Bravo EL: Cardioadrenergic factor in hypertension. Am Heart J 88:724-732, 1974
17. Shipley RE, Gregg DE: Cardiac response to stimulation of

the stellate ganglia and cardiac nerves. Am J Physiol **143**:396-401, 1945
18. ANZOLA J, RUSHMER RF: Cardiac responses to sympathetic stimulation. Circ Res **4**:302-307, 1956
19. SARNOFF SJ, BROCKMAN SK, GILMORE JP, LINDEN RJ, MITCHELL JH: Regulation of ventricular contraction: Influence of cardiac sympathetic and vagal nerve stimulation on atrial and ventricular dynamics. Circ Res **8**:1108-1122, 1960
20. ROHSE WG, KAYE M, RANDALL WC: Prolonged pressor effects of selective stimulation of the stellate ganglion. Circ Res **5**:144-148, 1957
21. FREIS ED: Hemodynamics of hypertension. Physiol Rev **40**:27-54, 1960
22. WACKSMAN J, FARR WC, GRUPP G: Localization of the cardiac sympathetic synapses in the dog. Proc Soc Exp Biol Med **131**:336-339, 1969
23. WECHSLER JS, PACE JB, GOLDBERG JM, RANDALL WC: Location of synaptic connections in canine sympathetic cardiac innervation. Am J Physiol **217**:1789-1794, 1969
24. COWLEY AW JR, LIARD JF, GUYTON AC: Role of the baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circ Res **32**:564-576, 1973
25. HABER E, KOERNER T, PAGE LB, KLIMAN B, PURNODE A: Application of a radioimmunoassay for angiotensin I to the physiological measurements of plasma renin activity in normal human subjects. J Clin Endocrinol Metab **29**:1349-1355, 1969
26. MANGER WM, STEINSLAND OS, NAHAS GG, WAKIM KG, DUFTON S: Comparison of improved fluorometric methods used to quantitate plasma catecholamines. Clin Chem **15**:1101-1123, 1969
27. LIARD JF, COWLEY AW, MCCAA RE, MCCAA CS, GUYTON AC: Renin aldosterone, body fluid volumes and the baroreceptor reflex in the development and reversal of Goldblatt hypertension in conscious dogs. Circ Res **34**:549-560, 1974
28. ALDER HL, ROESSLER EB: Introduction to Probability and Statistics. San Francisco, Freeman, 1960, p 129
29. GRANGER HJ, GUYTON AC: Autoregulation of the total systemic circulation following destruction of the central nervous system in the dog. Circ Res **25**:379-388, 1969
30. PETERSON DF, BROWN AM: Pressor reflexes produced by stimulation of the afferent fibers in the cardiac sympathetic nerves of the cat. Circ Res **28**:605-610, 1971
31. MALLIANI A, PARKS M, TUCKETT RP, BROWN AM: Reflex increases in heart rate elicited by the stimulation of afferent cardiac sympathetic nerve fibers in the cat. Circ Res **32**:9-14, 1973
32. TARAZI RC, DUSTAN HP, FROHLICH ED: Relation of plasma to interstitial fluid volume in essential hypertension. Circulation **40**:357-365, 1969
33. ULRYCH M, FROHLICH ED, TARAZI RC, DUSTAN HP, PAGE IH: Cardiac output and distribution of blood volume in central and peripheral circulations in hypertensive and normotensive man. Br Heart J **31**:570-574, 1969
34. ZUCKER IH, GILMORE JP: Evidence for an indirect sympathetic control of atrial stretch receptor discharge in the dog. Circ Res **34**:441-446, 1974
35. FERRARIO CM, MCCUBBIN JW: Reduction in sensitivity of atrial receptors following sympathectomy. *In* The Nervous System in Arterial Hypertension, edited by S Julius and M Esler. Springfield, Ill., Charles C Thomas, 1975
36. GAUER OH, HENRY JP: Circulatory basis of fluid volume control. Physiol Rev **43**:423-481, 1963
37. LIARD JF, TARAZI RC, FERRARIO CM: Hemodynamic effects of stellate ganglion stimulation in conscious dogs. *In* The Nervous System in Arterial Hypertension, edited by S Julius and M Esler. Springfield, Ill., Charles C Thomas, 1975