

Protection Against Circulatory Collapse After Adrenalectomy by Splanchnic Neurectomy.* (30977)

ALLAN M. LEFER AND WILLIAM F. BURNETT† (Introduced by W. P. Anslow, Jr.)

Departments of Physiology and Surgery, University of Virginia School of Medicine, Charlottesville

Acute bilateral adrenalectomy in the dog results in a state of cardiovascular collapse. The time course and the hemodynamic pattern of this shock-like state have previously been characterized(1). This condition is manifested by a marked decline in arterial blood pressure, in myocardial contractility and in femoral blood flow. Heart rate is markedly increased. These hemodynamic alterations reach a maximum about 3 hours after removal of the second adrenal gland. Plasma catecholamines increase before the onset of these hemodynamic alterations, occurring just after removal of the first adrenal gland. Administration of appropriate doses of ganglionic blocking agents or of large amounts of cortisol prior to adrenalectomy prevent the occurrence of the cardiovascular collapse.

The general purpose of this study was to elucidate further the mechanism of the interrelationships between the adrenal cortex and the sympathetic nervous system with regard to the phenomenon of post-adrenalectomy cardiovascular collapse.

Methods. Male mongrel dogs 15.5 to 22.5 kg fed a diet of Purina dog chow and water *ad libitum* were anesthetized with 30 mg/kg pentobarbital injected intravenously. Three groups of dogs were used. Group I consisted of 7 dogs which received no prior treatment during the 14 days immediately preceding their adrenalectomy. Group II consisted of 4 dogs in which a sham splanchnic neurectomy was performed 14 days prior to adrenalectomy. Group III consisted of 10 dogs to which a bilateral splanchnic neurectomy was performed 14 days prior to use as experimental subjects. The one-stage bilateral splanchnic neurectomies were performed under sterile surgical technique, also using pento-

barbital anesthesia. The thoracic (greater) splanchnic nerves were approached by a midline abdominal incision through the diaphragm. The left and right greater splanchnic nerves were isolated and a one cm segment removed from each. Identification of the nerve was confirmed by tracing the nerve fibers to the adrenal gland.

The following hemodynamic variables were continuously recorded on an Offner Type R Dynograph: left ventricular contractile force (LVCF), mean arterial blood pressure (MABP), central venous pressure (CVP) and heart rate (HR). The details of these procedures have been described(1). LVCF was measured using a Sutfin-Lefer strain gauge arch sutured to the epicardial surface of the left ventricle(2). The segment of myocardium directly beneath the gauge was stretched 33% of its end-diastolic length. Blood samples were taken just before, and one hour after, adrenalectomy for hematocrit and plasma 17-hydroxycorticosteroid determinations. Adrenalectomy was accomplished through a flank incision on both sides. Plasma 17-hydroxycorticosteroids were determined by the Porter-Silber method(3). Hematocrits were corrected for plasma trapping according to the method of Chien and Gregerson(4).

Results. Sham and splanchnic neurectomized dogs and dogs which received no prior treatment had the same hemodynamic status at the time of the adrenalectomy. The sham splanchnic neurectomy (laparotomy and isolation of the splanchnic nerves) thus had no detectable effect on basal cardiovascular function. The splanchnic neurectomized dogs, on the other hand, exhibited a significantly lower mean arterial blood pressure from the untreated controls [134.0 ± 2.6 vs 117.1 ± 2.3 mm Hg ($P < 0.02$)]. This pressure decrease was not in the range of severe hypotension. The splanchnic neurectomized dogs exhibited essentially a normal level of circulatory function in all other variables measured (Table I).

* This investigation was supported by a grant from the Virginia Heart Assn. and by USPHS Research Grant HE-09924 from Nat. Heart Inst.

† Surgical Research Fellow.

TABLE I. Initial Hemodynamic Values for 3 Groups of Animals.

	LVCVF (g)	MABP (mm Hg)	HR (beats/min)	CVP (cm H ₂ O)
No prior treatment (7)	45.5 ± 2.4	134.0 ± 2.6	149.1 ± 3.4	+ .35 ± .6
Sham splanchnic neurectomy (4)	51.3 ± 3.8	132.0 ± 4.3	151.0 ± 4.2	+ .30 ± .5
Splanchnic neurectomy 14 days prior to adrenalectomy (10)	45.0 ± 3.3	117.1 ± 2.3	162.4 ± 5.7	-.56 ± .5

LVCVF = left ventricular contractile force. MABP = mean arterial blood pressure. HR = heart rate. CVP = central venous pressure.

All values are means ± S.E. taken just prior to adrenalectomy, after the chest had been closed.

Acute bilateral splanchnic neurectomy was also performed in 4 dogs. MABP declined from an average of 136.5 ± 8.2 mm Hg before neurectomy to a stable value of 92.0 ± 2.4 mm Hg, 2 hours after the nerves were cut.

Fig. 1 shows the time course of MABP changes in 2 typical experiments (a sham splanchnic neurectomized dog and a splanchnic neurectomized dog). Both dogs were bilaterally adrenalectomized (right adrenal removed 30 minutes after the left adrenal). The sham splanchnic neurectomized dog exhibited the usual steep decline in MABP which commenced soon after removal of the second adrenal. This typical decline in MABP to severe hypotensive levels occurred in all 4 sham splanchnic neurectomized dogs

and in all 7 dogs receiving no prior treatment. The time course of the MABP changes in the sham splanchnic neurectomized dog shown in Fig. 1 is virtually identical to the MABP changes observed in the group which received no prior treatment. MABP usually reached a stable minimal value 180 minutes after completion of the adrenalectomy. Although not shown in Fig. 1, MABP was recorded for an additional 60 minutes and the values obtained at 240 minutes post-adrenalectomy were essentially the same as those observed at 180 minutes post-adrenalectomy. The slight rise in MABP which occurs between removal of the left and right adrenals (30 to 60 minutes) was observed in 3 of the 4 sham splanchnic neurectomized dogs and in 5 of the 7 untreated dogs. This rise may be attributed to

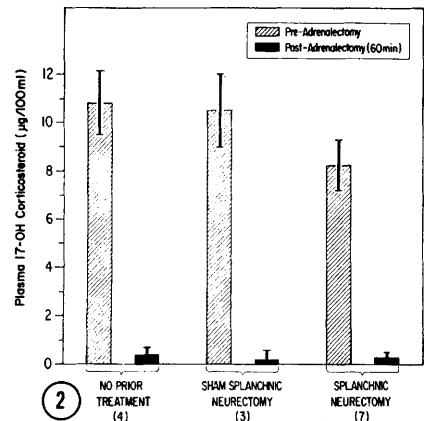
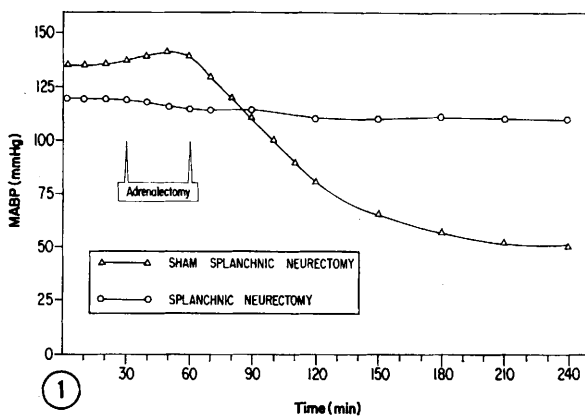


FIG. 1. Time course of changes in mean arterial blood pressure (MABP) in 2 typical experiments (splanchnic neurectomy (○—○) and sham splanchnic neurectomy (Δ—Δ)). The left adrenal gland was removed at first arrow, the right adrenal at second arrow. The splanchnic neurectomized dog had a slightly lower initial MABP but showed no significant decrease in MABP after adrenalectomy.

FIG. 2. Effect of acute adrenalectomy on plasma 17-hydroxycorticosteroid concentrations in dogs receiving no prior treatment, in dogs in which a splanchnic neurectomy was performed, and in sham splanchnic neurectomized dogs. Bar heights are mean values with standard errors of the mean indicated. All groups showed similar initial values. Steroid levels fell to extremely low values 60 min after adrenalectomy in all groups.

TABLE II. Hemodynamic Changes Following Acute Adrenalectomy.

	LVCF	MABP	HR	CVP
	— % of control —		Δ in beats/min	Δ in cm H ₂ O
No prior treatment (7)	47.3 ± 3.9	40.2 ± 2.9	+31.5 ± 7.1	+ .2 ± .6
Sham splanchnic neurectomy (4)	49.8 ± 2.0	41.0 ± 1.5	+30.8 ± 7.9	+ .3 ± .5
Splanchnic neurectomy 14 days prior to adrenalectomy (10)	92.2 ± 2.3	87.0 ± 2.8	+ 2.4 ± 5.4	+ .7 ± .5

LVCF = left ventricular contractile force. MABP = mean arterial blood pressure. HR = heart rate. CVP = central venous pressure.

All values are means ± S.E., using pre-adrenalectomy (0 time) and 180 minutes post-adrenalectomy as the two reference points.

release of endogenous catecholamines in response to surgical trauma. The MABP of the typical splanchnic neurectomized dog shown in Fig. 1 did not significantly decline at any time during the experiment. This lack of change in MABP was a consistent finding in all 10 dogs subjected to splanchnic neurectomy.

Table II shows a summary of the hemodynamic changes after acute adrenalectomy in all 3 groups of dogs. No significant changes in LVCF, MABP, HR or CVP in the splanchnic neurectomized dogs occurred 180 minutes post-adrenalectomy. These values (splanchnic neurectomized dogs) can be compared to the large decreases in LVCF and MABP, and the large increase in HR observed in the untreated and the sham splanchnic neurectomized groups ($P < 0.001$). No significant differences existed in any hemodynamic value between the sham neurectomy and untreated dogs. CVP did not significantly change after adrenalectomy in any of the 3 groups. In 4 acutely splanchnic neurectomized dogs, bilateral adrenalectomy resulted in the development of circulatory collapse comparable to that seen in the sham neurectomized dogs. MABP decreased from 92.0 ± 2.4 mm Hg to 41.8 ± 3.1 mm Hg ($P < 0.001$) 90 minutes after adrenalectomy.

Fig. 2 gives the concentrations of plasma 17-hydroxycorticosteroids before and after adrenalectomy in all 3 groups of animals. A rapid decline in plasma corticosteroid levels developed within one hour after adrenalectomy in all 3 groups.

There were no significant changes in hematocrit 60 minutes after adrenalectomy in any of the 3 groups.

Discussion. These data confirm the earlier

finding(1) that acute bilateral adrenalectomy results in a state of circulatory collapse. This collapse starts shortly after completion of adrenalectomy, reaches a peak 3 hours later, and occurs at a time when plasma corticosteroids have virtually disappeared, but presumably while the sympathetic nervous system exhibits increased activity. Levine and Goldstein(5) have cited considerable evidence which shows that the cardiovascular collapse seen in adrenalectomized animals is not due to the external insult (or stress) but rather to the "increased levels of elicited epinephrines acting on a glucocorticoid-deficient vasculature." The data presented here support this concept.

Kleinberg *et al*(6) showed that spinal anesthesia or sectioning of the spinal cord at the level of the first or second thoracic segment protected against circulatory failure resulting from intestinal stripping and bilateral adrenalectomy. These workers concluded that trauma to visceral afferent elements in the splanchnic area leads to an intense stimulation of the vessels in that region presumably *via* activation of the medullary vasomotor center. The present study supports this concept.

This study does not determine with certainty whether the circulatory collapse seen after adrenalectomy is due to a cardiac defect or to failure of the peripheral vasculature. However, the uniform lack of changes in central venous pressure in the groups which did exhibit circulatory collapse argues against cardiac failure as a major precipitating factor.

Protection by chronic splanchnic neurectomy could be attributed to one or more of the following factors: (1) delayed disappearance of plasma corticosteroids, (2) interrup-

tion of sympathetic reflex arcs, (3) some circulatory adjustment making the animal less sensitive to hormonal deficiency.

All groups of animals clearly exhibited very low plasma corticosteroid concentrations 60 minutes after completion of adrenalectomy. Cortisol(7), corticosterone(8) and aldosterone (9), have biological half-times of about 30 minutes in the dog. Therefore, one would expect that in 60 minutes the 17-hydroxycorticosteroids would have, at most, a concentration of 2 $\mu\text{g}/100$ ml. In view of the fact that the concentrations found at 60 minutes in these experiments are considerably lower than the minimal expected value, it would appear that a more rapid rate of disappearance of these steroids occurs. Splanchnic nerve section did not significantly alter pre-adrenalectomy plasma corticosteroid levels. Therefore, delayed disappearance of corticosteroids is not the mechanism of protection afforded by splanchnic neurectomy.

Interruption of sympathetic reflex arcs may involve either afferent or efferent pathways. The ability of chronic splanchnic neurectomy to protect might conceivably be explained by interruption of efferent pathways, however, acute splanchnic neurectomy does not protect and the efferent pathways are blocked equally well as in chronic neurectomy. On the other hand, interruption of afferent pathways may be the explanation of the protective action of chronic splanchnic neurectomy. If this is so, the question arises as to why acute splanchnic neurectomy fails to protect. The answer to this question may conceivably be attributable to stimulation of the cut central ends of the splanchnic nerve fibers in acute splanchnic neurectomy. This stimulation might not occur in chronic neurectomy since the cut fibers presumably will have healed in the 14 days between neurectomy and adrenalectomy. Irritation to the cut central ends of the rami innervating the adrenals could also take place in adrenalectomy alone, although the number of fibers so involved is considerably fewer than in splanchnic neurectomy. Whether or not the number of afferent fibers so stimulated in acute adrenalectomy is sufficient to bring about a sympathetic response of the same

magnitude as in acute neurectomy is debatable. The data do not permit one to select exclusively one or the other possibility or even to state whether the protection is explained by interruption of either pathway or both. However, the question of whether interruption of afferent or efferent fibers is responsible for the protection in chronic neurectomy is not important, since we are dealing here with circulatory reflexes, interruption of the arc of which at any point will abolish the reflex.

As to the third possibility—circulatory adjustment—we believe it to be a distinct possibility for the following reasons: two hours after acute neurectomy MABP is 92.0 ± 2.4 mm Hg whereas 2 weeks later MABP is 117.1 ± 2.3 mm Hg. These 2 values are significantly different ($P < 0.01$). It is obvious, therefore, that some circulatory adjustment has occurred in the 14 intervening days. The mechanism of this circulatory adjustment is unknown but may be due to reflexes involving sympathetic pathways or may be due simply to metabolic adjustments or to changes in the physiologic properties of vascular smooth muscle.

Splanchnic nerve section or sympathectomy has been reported to protect against circulatory collapse induced by a variety of other techniques. Sympathectomy has been reported to protect against hemorrhagic shock in dogs(10) and splanchnic denervation against endotoxin shock in dogs and rabbits (11). In addition, deafferentation of the dog hind limb protects against mortality in experimental traumatic shock following muscle injury(12). It is also known that humans with Addison's disease can suddenly lapse into circulatory collapse(13). These individuals have been shown to exhibit an exaggerated depressor response to acetyl-beta-methylcholine indicative of hyperactivity of the autonomic nervous system. All these findings can be interpreted to indicate that increased sympathetic activity can be deleterious and probably contributes to the development of a variety of types of shock.

The phenomenon of post-adrenalectomy circulatory collapse appears to be a result of the summated responses to two simul-

taneous events, both of which are necessary for the phenomenon to occur. These two events are adrenal insufficiency (markedly reduced circulating concentrations of corticosteroids) and reflex sympathetic hyperactivity. Prevention of either event from occurring will protect against circulatory collapse.

Summary. Bilateral splanchnic neurectomy prevented the occurrence of circulatory collapse in dogs following acute bilateral adrenalectomy. Sham splanchnic neurectomy was not effective in this regard. The mechanism of this protective effect is not by delaying the disappearance of the corticosteroids, but rather by preventing hyperactivity of the sympathetic nervous system in the face of adrenal insufficiency.

The capable technical assistance of Thomas F. Inge, Jr. is gratefully acknowledged. The authors also wish to thank Dr. Julian I. Kitay, Endocrine Laboratory, Univ. of Virginia School of Medicine for steroid analyses.

1. Lefer, A. M., Lintz, E. M., Proc. Soc. Exp. Biol. and Med., 1965, v118, 1009.

2. Sutfin, D. C., Lefer, A. M., Med. Electron. Biol. Eng., 1963, v1, 371.

3. Silber, R. H., Porter, C. C., J. Biol. Chem., 1954, v210, 923.

4. Chien, S., Gregerson, M. I., In: Physical Techniques in Biological Research, Academic Press, 1962, v4, 1.

5. Levine, R., Goldstein, M. S., In: Handbuch der Experimentellen Pharmakologie, Springer-Verlag 1964, Part 2, 1.

6. Kleinberg, W., Remington, J. W., Drill, V. A., Swingle, W. W., Am. J. Physiol., 1942, v137, 362.

7. Hechter, O., Frank, E., Caspi, E., Frank, H., Endocrinology, 1957, v60, 705.

8. Willoughby, H. W., Chen, C., Freeman, S., *ibid.*, 1959, v65, 539.

9. Ayers, C. R., Davis, J. O., Lieberman, F., Carpenter, C. C., Berman, M., J. Clin. Invest., 1962, v41, 884.

10. Freeman, N. E., Shaffer, S. A., Schecter, A. E., Holling, H. E., *ibid.*, 1938, v17, 359.

11. Fine, J., Am. J. Surg., 1964, v107, 723.

12. Wang, S. C., Am. J. Physiol., 1947, v148, 547.

13. Perera, G. A., J. Am. Med. Assn., 1945, v128, 1018.

Received November 15, 1965. P.S.E.B.M., 1966, v121.

Effect of Coconut Oil on Serum Lipids of Normal and of Thyroidectomized Dogs.* (30978)

FRANCISCO GRANDE AND ALVIN SCHULTZ

Jay Phillips Research Laboratory, Mount Sinai Hospital and Departments of Physiological Hygiene and Medicine, University of Minnesota, Minneapolis

The occurrence of elevated serum cholesterol levels in human hypothyroidism has long been known. Thyroidectomy has been repeatedly reported to cause elevation of the serum lipids in the dog(1-4), but there is no information about the effect of dietary fat on the serum lipids of thyroidectomized dogs.

In the course of studies on the effects of dietary fat on the serum lipids of the dog it was observed that thyroidectomized dogs responded to the addition of saturated fat to the diet, in the form of coconut oil, with

greater increases of serum cholesterol concentration than normal animals. These observations are described here.

Methods. Male adult mongrel dogs were kept on a commercial low-fat dog food† which by analysis had a fat content of 1.6% (approximately 4% of the total caloric value), for at least one month before the beginning of the experiments.

The experimental diet consisted of a mixture of 80% of the low-fat diet and 20% of coconut oil. Approximately 40% of the total caloric value of this diet was provided

* Supported by Research Grant HE 09897 from Nat. Heart Inst., John A. Hartford Foundation, Inc., New York, and Mount Sinai Hospital Research Fund.

† Kibbies, Morton Dog Food Co., Minneapolis, Minn.