Journal of Clinical Investigation
Vol. 46, No. 4, 1967

Comparison of Effects of Deoxycorticosterone and Dexamethasone on Cardiovascular Responses to Norepinephrine *

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Summary. **Cardiovascular responses to graded iv infusions of norepinephrine were observed in 24 dogs that had been treated for 1 week with either placebo, dexamethasone, or deoxycorticosterone. Eight dogs served as control and received daily iv injections of placebo; eight dogs received the mineralocorticoid, deoxycorticosterone; and eight received the glucocorticoid, dexamethasone. The three groups did not differ with respect to base-line hemodynamic variables either before administration of norepinephrine or after autonomic reflexes had been inhibited by ganglionic blockade. Comparisons of the three groups' hemodynamic responses to norepinephrine were made both before and after ganglionic blockade with the parallel line bioassay as a statistical test.**

Dogs given deoxycorticosterone had much greater increases in mean arterial pressure and peripheral resistance with norepinephrine than did dogs given dexamethasone or placebo. Dogs given dexamethasone had slightly greater increases in mean arterial pressure than did dogs given placebo; changes in peripheral resistance were similar in the two groups. The augmented response of mean arterial pressure was apparent only after ganglionic blockade in the dexamethasone group. The vascular effects of norepinephrine, therefore, were markedly augmented by treatment with doxycorticosterone and only slightly augmented by treatment with dexamethasone.

The effect of norepinephrine on mean right atrial pressure was augmented in both groups treated with steroid before hexamethonium but only in the group treated with dexamethasone after hexamethonium.

The results indicate that deoxycorticosterone and dexamethasone have different qualitative and quantitative effects on circulatory responses to norepinephrine.

Introduction

Corticosteroids that affect electrolyte metabolism and corticosteroids that affect carbohydrate metabolism may have different effects on cardiovascular responses to norepinephrine. Such differences could account for the seemingly contradictory observations that pressor responses to norepinephrine are augmented in animals or humans given mineralocorticoid (1–3) but not in humans treated with glucocorticoid (4). In this experiment dogs treated with a placebo, deoxycorticosterone (a mineralocorticoid), and dexametha-

* Submitted for publication July 15, 1966; accepted December 22, 1966.

Supported by research grants HE-02644 and HE-09835, Research Career Program Awards HE-K6-4626 and HE-K3-17013, and postdoctoral fellowship HE-28-749 from the National Heart Institute.

Presented in part at the Fiftieth Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April 15, 1966.

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sone (a glucocorticoid) were compared with respect to their circulatory responses to norepinephrine.

Methods

Twenty-four male mongrel dogs weighing 13.0 to 21.5 kg were studied. The first dog was given daily iv injections of placebo; the second, of dexamethasone; and the third, of deoxycorticosterone. This order of matching treatment and dogs was repeated until each of the three treatment groups (control, dexamethasone, and deoxycorticosterone) contained eight animals. All dogs were treated for 7 days. During this period they were caged in the same area and given identical rations. All had free access to water. Steroids were dissolved in distilled water and 20% ethanol for iv administration. Each dog was given 1 ml per kg per day. The placebo given to control dogs was the dilute ethanol solution without steroid. The dose of dexamethasone was 30 μg per kg on the first day and 10 μg per kg per day thereafter. The dose of deoxycorticosterone was 150 μg per kg on the first day and 50 μg per kg per day thereafter. Dogs were weighed and venous blood samples for hematocrit were obtained at the beginning and end of treatment. On the eighth day the animals were anesthetized with chloralose, 50 mg per kg, and urethane, 500 mg per kg, intubated, and ventilated with a Harvard respiratory pump. Decamethonium bromide, 0.15 mg per kg, was given initially and at intervals of 30 minutes to maintain muscle relaxation. Short, large bore plastic cannulas were inserted into both femoral arteries. One was connected to a Sanborn pressure transducer; the other was connected to the cuvette of a Gilford densitometer, which was in turn connected to an infusion–withdrawal pump. Another cannula was inserted into a femoral vein for iv administration of norepinephrine. A cardiac catheter was inserted into the other femoral vein and advanced until its tip was located in the right atrium. This catheter was connected to a Sanborn pressure transducer. Another cardiac catheter was inserted through the jugular vein and advanced until its tip was in the pulmonary artery. This catheter was connected to a modified Fox injection system and a reservoir of indocyanine green dye. Dye curves were obtained by drawing blood from the femoral artery through the densitometer after injection of dye into the pulmonary artery. Withdrawn blood was returned to the dog after each dye curve by reversing the motor on the withdrawal pump. Dye curves and blood pressures were recorded with a Sanborn direct writing oscillograph.

Rate and depth of ventilation were adjusted at the beginning of the experiment so that the concentration of CO_2 in expired air was about 5% as measured with a Beckman CO_2 analyzer. The settings on the respiratory pump were not changed after the initial adjustments. The lungs, however, were hyperinflated every 30 minutes to prevent atelectasis. After the animal had been pre-

TABLE I

*Averages of base-line hemodynamic variables before infusion of norepinephrine**

Group	BPm		PR		CO		HR		SV		RAPm	
	Before C^6	After C^6	Before C^6	After C^6	Before C^6	After C^6	Before C^6	After C^6	Before C^6	After C^6	Before C^6	After C^6
	mm Hg		*U*		*L/min*		*beats/min*		*ml*		*mm Hg*	
Control	114.5 ±4.5	81.6 ±9.4	30.1 ±6.3	33.6 ±3.2	3.88 ±0.33	2.36 ±0.16	120.8 ±11.1	145.1 ±6.8	33.1 ±2.5	16.4 ±1.4	3.9 ±0.5	3.1 ±0.5
Dexamethasone	106.2 ±5.0	87.5 ±6.3	37.6 ±5.9	40.1 ±3.9	3.20 ±0.46	2.23 ±0.23	102.0 ± 7.2	146.7 ±8.7	30.7 ±2.8	15.7 ±2.3	3.7 ±0.4	2.7 ±0.4
Deoxycorticosterone	103.8 ±4.6	71.8 ±5.1	34.1 ±2.8	34.8 ±3.0	3.05 ±0.26	1.99 ±0.15	113.2 ± 7.1	131.0 ±4.9	27.1 ±1.9	15.3 ±1.1	4.0 ±0.7	4.0 ±1.3

* Each entry is the average of observations on eight dogs ± 1 SE. BPm = mean arterial pressure; PR = total peripheral resistance; CO = cardiac output; HR = heart rate; SV = stroke volume; RAPm = mean right atrial pressure. Before C^6 and after C^6 are before and after ganglionic blockade with hexamethonium.

TABLE II

*Analysis of variance of the data summarized in Table I**

Source of variation	df	BPm		PR		CO		HR		SV		RAPm	
		MS	F†	MS	F†	MS	F†	MS	F†	MS	F†	MS	F†
Groups	2	509.40	1.43	198.81	1.13	1.49	1.54	520.77	0.94	51.18	0.92	2.90	0.41
Ganglionic blockade (before C^6 vs. after C^6)	1	9,324.19	39.89‡	60.53	1.08	16.88	50.43‡	10,063.02	23.24‡	2,505.63	204.21‡	3.97	4.11
Groups × ganglionic blockade	2	250.56	1.07	7.95	0.14	0.36	1.07	792.02	1.83	24.84	2.02	1.06	1.10
Dogs within groups	21	355.34	1.52	175.78	3.14‡	0.97	2.90‡	555.95	1.28	55.81	4.55	7.10	7.35‡
Error	21	233.72		56.00		0.33		432.97				0.97	

* See footnote to Table I for abbreviations.

† F values for groups were calculated with the mean square for dogs within groups as divisor. All other F values were calculated with the mean square for error as divisor. Significant F values for ganglionic blockade (before C^6 vs. after C^6) indicate that base–line hemodynamic variables were altered significantly by C^6 administration. Nonsignificant F values for groups × ganglionic blockade interaction indicate that the effects of C^6 on base–line variables did not differ among groups. Nonsignificant F values for groups indicate that dogs treated with dexamethasone, deoxycorticosterone, or placebo did not differ significantly with respect to base–line hemodynamic variables (7).

‡ $p < 0.01$.

pared, heparin,[1] 500 USP U per kg, was administered intravenously, and 50 ml of arterial blood was taken for calibration of the densitometer. L-Norepinephrine bitartrate in ascending doses of 0.06, 0.12, and 0.24 μg of base per kg per minute was infused intravenously during three consecutive 4-minute periods. Ten minutes after stopping norepinephrine each dog was given hexamethonium bromide, 5 mg of base per kg. Twenty minutes later the infusions of norepinephrine were repeated. Duplicate observations were made before any norepinehrine was administered and during the final 1½ minutes of each infusion.

Mean arterial and mean right atrial pressures were recorded by electronic damping of the output from the pressure transducers. Cardiac output was calculated from dye curves by the Stewart–Hamilton equations (6). There were 384 dye curves or 192 duplicate pairs. The average per cent difference between duplicate cardiac output determinations was 4.38% with a standard error of 0.28%. Total peripheral vascular resistance was calculated as the difference between mean arterial and mean right atrial pressures in millimeters Hg divided by cardiac output in liters per minute and expressed in arbitrary units. Heart rate was counted from the arterial pressure record.

The effects of control, deoxycorticosterone, and dexamethasone treatments on body weight and hematocrit were compared with analysis of variance (7). Analysis of variance also was used to compare the effects of these treatments on mean arterial pressure, cardiac output, mean right atrial pressure, total peripheral vascular resistance, heart rate, and stroke volume after anesthesia but before administration of norepinephrine (7). The effects of the three treatments on responses to norepinephrine (defined as the differences between observations made before and those made during norepinephrine infusions) were compared with a parallel line bioassay as a statistical test (8).

[1] The preservatives in the brand of heparin employed in these experiments do not interfere with optical characteristics of indocyanine green dye (5).

Results

Body weight and hematocrit

Small decreases in body weight were noted during the week of treatment. The decreases were similar in the three groups. Hematocrit did not change significantly.

Base–line hemodynamic observations (Tables I and II)

Observations were made on arterial and right atrial pressures, cardiac output, and heart rate before norepinephrine was infused. There were no significant differences among the three groups of dogs with respect to the base–line levels of these observed hemodynamic variables or the calculated values for base–line levels of derived variables. Administration of hexamethonium caused significant reductions in base–line values for mean arterial pressure, cardiac output, and stroke volume; there were significant increases in heart rate but no significant changes in peripheral resistance or right atrial pressure. Again there were no significant differences among the three groups with respect to these base–line levels.

Responses to norepinephrine (Tables III and IV, Figures 1 and 2)

Comparisons between control animals and animals given deoxycorticosterone. Before administration of hexamethonium, increases in mean ar-

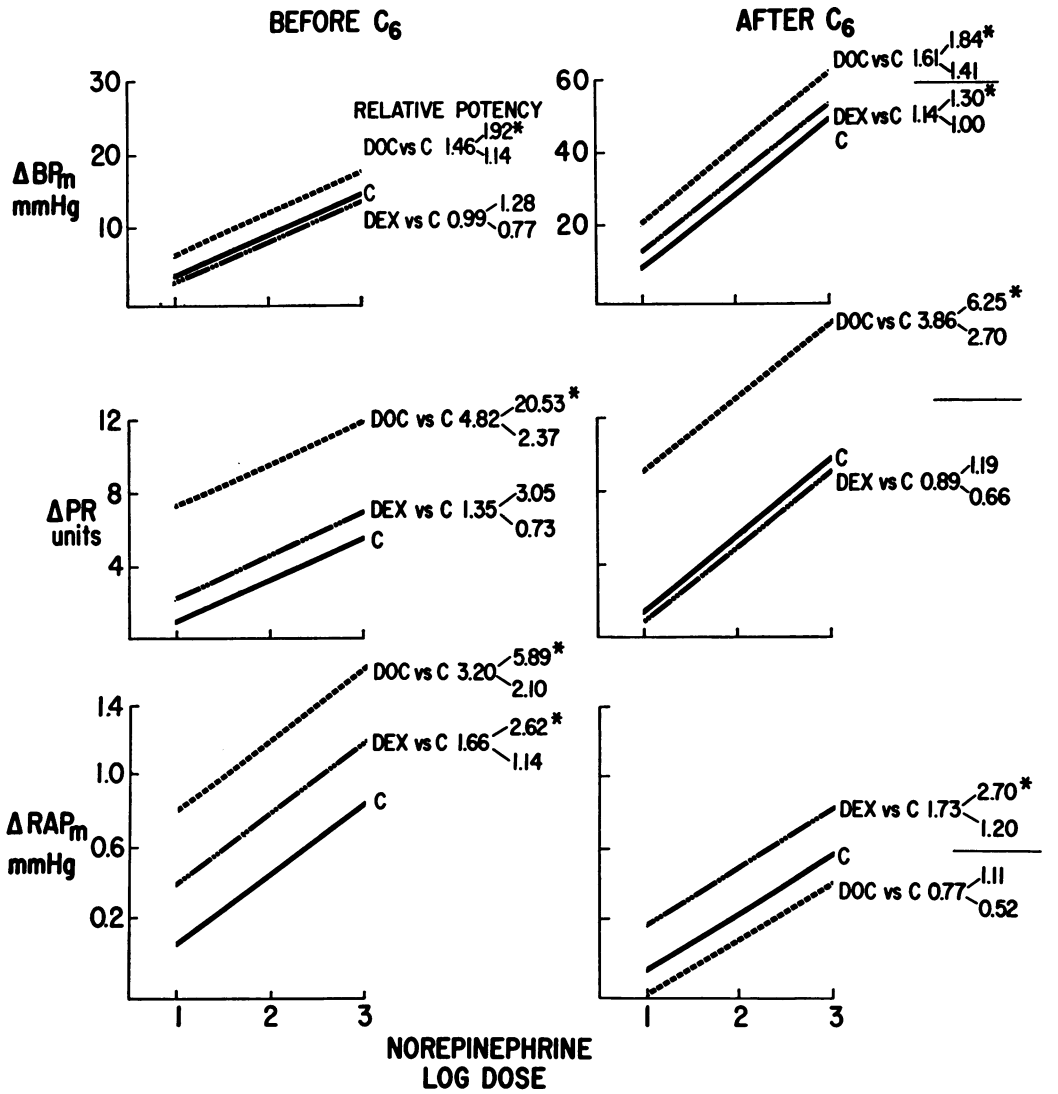

FIG. 1. DOSE-RESPONSE CURVES FOR MEAN ARTERIAL PRESSURE (ΔBP_M), TOTAL PERIPHERAL RESISTANCE (ΔPR), AND MEAN RIGHT ATRIAL PRESSURE (ΔRAP_M). C refers to data from control dogs treated with placebo; DEX refers to data from dogs treated with dexamethasone; DOC refers to data from dogs treated with deoxycorticosterone. Lines were drawn through the average level of response for each group of eight dogs with a regression coefficient calculated from the responses of the three groups considered together. Responses were compared by techniques of a parallel line bioassay (8). This was done by regarding norepinephrine in steroid-treated animals as the test preparation and norepinephrine in placebo-treated animals as the standard preparation. Relative potency (and 95% confidence limits) indicates the ratio (and limits for the ratio) of a dose of norepinephrine that gives a certain response in placebo-treated dogs to the dose that gives the same response in steroid-treated dogs. Responses of steroid-treated animals were considered significantly different from responses of placebo-treated animals if a ratio of one was not included within the 95% confidence interval. Such significantly different responses are indicated by asterisks. Responses of deoxycorticosterone-treated animals were considered significantly different from responses of dexamethasone-treated animals if the 95% confidence intervals did not overlap. Such significantly different responses are indicated by lines between 95% confidence limits. Before C_6 refers to data obtained before ganglionic blockade with hexamethonium. After C_6 refers to data obtained after ganglionic blockade. On the abscissa, the scale for the norepinephrine dose was calculated as $\log_3$ (actual dose $\times$ 33). Dose 1 corresponds to 0.06, dose 2 corresponds to 0.12, and dose 3 corresponds to 0.24 μg norepinephrine base per kg per minute.

TABLE III

Responses to norepinephrine before

Norepinephrine	ΔBPm			ΔPR			ΔCO		
	C	DEX	DOC	C	DEX	DOC	C	DEX	DOC
	mm Hg			*U*			*L/min*		
0.06 μg/kg/min									
Before C^6	3.6±1.4	2.4±0.8	5.2±1.6	2.3±1.1	2.4±1.5	4.5±1.7	−0.23±0.15	−0.20±0.09	−0.18±0.09
After C^6	11.2±3.0	14.3±1.5	20.9±4.1	2.4±1.8	1.5±1.3	7.9±1.9	0.17±0.06	0.27±0.04	0.10±0.03
0.12 μg/kg/min									
Before C^6	8.6±1.4	8.0±1.4	10.6±1.9	3.9±2.6	4.3±2.6	10.0±2.6	−0.28±0.26	−0.16±0.17	−0.40±0.10
After C^6	26.8±3.6	29.1±0.7	38.1±6.8	4.5±2.1	3.7±2.0	13.4±2.3	0.46±0.08	0.48±0.06	0.29±0.07
0.24 μg/kg/min									
Before C^6	12.9±2.4	14.6±1.7	18.9±3.4	4.1±2.9	7.2±3.3	14.3±3.6	−0.18±0.32	−0.33±0.29	−0.44±0.11
After C^6	45.8±4.8	51.5±4.7	64.0±7.5	9.1±2.4	8.8±2.8	17.8±3.6	0.66±0.17	0.70±0.10	0.53±0.07

* Each entry is the average of observations on eight dogs ± 1 SE. Δ = response or the difference between the levels observed before and during an infusion of norepinephrine. C = control group of dogs, which received placebo; DEX = group of dogs that received dexamethasone; DOC = group of dogs that received deoxycorticosterone. See footnote to Table I for other abbreviations.

terial pressure and peripheral resistance with infusions of norepinephrine were greater in dogs given deoxycortisterone. These dogs also had greater increases in mean right atrial pressure and greater decreases in heart rate. Changes in cardiac output and stroke volume in animals treated with deoxycorticosterone did not differ significantly from the changes observed in control animals.

After administration of hexamethonium, increases in mean arterial pressure and peripheral resistance were greater in dogs treated with deoxycorticosterone. These dogs also had smaller increases in cardiac output and greater decreases in heart rate. There were no significant differences between the two groups with respect to changes in mean right atrial pressure and stroke volume.

Comparisons between control animals and animals given dexamethasone. Before hexamethonium increases in mean right atrial pressure with infusions of norepinephrine were greater in dogs given dexamethasone. The two groups did not differ significantly with respect to changes in mean arterial pressure, peripheral resistance, cardiac output, heart rate, or stroke volume.

After administration of hexamethonium, increases in mean arterial pressure, stroke volume, and mean right atrial pressure were greater in dogs given dexamethasone. These dogs also had significantly greater decreases in heart rate. The two groups did not differ significantly with respect to changes in peripheral resistance and cardiac output.

Comparisons between animals given deoxycorticosterone and animals given dexamethasone. Before hexamethonium the responses to norepinephrine in dogs treated with deoxycorticosterone did not differ significantly from responses in dogs given dexamethasone.

After administration of hexamethonium, increases in mean arterial pressure and peripheral resistance were greater in animals given deoxycorticosterone. Increases in mean right atrial pressure were greater in animals given dexamethasone. The two groups did not differ significantly with respect to changes in cardiac output, heart rate, or stroke volume. It should be pointed out, however, that increases in cardiac output in dogs given dexamethasone exceeded the increases in dogs given deoxycorticosterone by a margin that bordered on significance.

Discussion

Deoxycorticosterone has a pronounced effect on electrolyte metabolism and almost no effect on carbohydrate metabolism. In contrast, dexamethasone has virtually no effect on electrolyte metabolism and a very potent effect on carbohydrate metabolism (9). The doses of these two steroids were chosen so that mineralocorticoid effects of deoxycorticosterone and glucocorticoid effects of dexamethasone were equivalent to corresponding effects of 0.3 mg per day of 9α-fluorohydrocortisone in a human subject of average size (9). Subjects given this dose of 9α-fluorohydrocortisone for 1 week had augmented forearm vascular responses to norepinephrine (10).

TABLE III
*and after ganglionic blockade**

ΔHR			ΔSV			ΔRAPm		
C	DEX	DOC	C	DEX	DOC	C	DEX	DOC
beats/min			*ml*			*mm Hg*		
−12.3± 4.1	−12.1±2.8	−17.3±1.8	1.5±1.1	2.3±0.9	3.0±1.1	0.0±0.2	0.4±0.1	0.7±0.2
1.6± 4.3	− 5.9±2.7	− 4.4±3.6	1.1±0.8	2.7±0.4	1.3±0.5	0.0±0.0	0.1±0.1	−0.2±0.2
−21.0± 6.6	−18.6±4.5	−30.5±2.7	4.0±2.0	5.5±1.1	4.9±1.7	0.5±0.2	0.8±0.2	1.1±0.4
− 3.2± 8.0	−14.2±3.5	− 9.5±7.1	3.8±1.4	5.6±0.9	4.1±0.9	0.2±0.1	0.4±0.1	0.1±0.1
−33.4±10.2	−29.4±7.3	−40.1±4.2	9.9±2.7	8.8±1.2	8.6±2.2	0.9±0.4	1.1±0.3	1.8±1.6
−14.6±11.0	−27.6±3.4	−27.9±8.0	7.8±1.5	10.5±1.7	9.9±1.5	0.5±0.1	1.0±0.3	0.4±0.4

The three groups of dogs did not differ significantly with respect to their base–line hemodynamic variables or their responses to ganglionic blockade. The altered responses to norepinephrine, therefore, cannot be attributed to differences in base–line vasomotor activity.

Data from the experiment reported here indicate that dogs given deoxycorticosterone had greatly augmented vascular responses to norepinephrine. This was deduced from changes in the relationship between calculated peripheral vascular resistance and mean arterial pressure during administration of norepinephrine. These animals had greater increases in resistance, i.e., greater vasoconstriction, against greater increases in transmural pressure than did either control dogs or dogs given dexamethasone. The vascular effects of norepinephrine also were augmented in dogs given dexamethasone because the vasoconstriction was similar to that in control dogs

TABLE IV
*Analysis of variance of the data summarized in Table III**

Source of variation		df	ΔBPm		ΔPR		ΔCO		ΔHR		ΔSV		ΔRAPm	
			MS	F†	MS	F†	MS	F†	MS	F†	MS	F†	MS	F†
Doses		8												
Groups	Before C⁶	2	83.43	1.38	259.40	2.28	96,299.38	0.13	561.72	1.01	1.04	0.02	3.36	1.91
	After C⁶		1,091.26	2.45	521.99	4.58‡	192,255.38	1.71	746.00	1.01	24.82	1.04	0.94	1.02
Regression	Before C⁶	1	1,645.02	126.58§	358.07	21.42§	152,889.19	1.87	5,002.08	58.25§	558.29	85.35§	9.45	56.76§
	After C⁶		17,595.02	508.31§	753.67	92.48§	2,442,165.19	90.72§	5,043.00	44.97§	719.20	193.22§	5.33	56.26§
Parallelism	Before C⁶	2	20.02	1.54	65.92	3.94‡	103,475.44	1.27	33.15	0.39	8.38	1.28	0.23	1.40
	After C⁶		77.65	2.24	11.83	1.45	4,071.94	0.15	57.25	0.51	3.71	1.00	0.20	2.14
Quadratic	Before C⁶	1	4.34	0.33	1.38	0.08	5,712.84	0.07	8.03	0.09	13.02	1.99	0.01	0.05
	After C⁶		171.17	4.95‡	8.12	1.00	122.84	0.005	272.25	2.43	16.81	4.52‡	0.09	0.95
Difference of quadratic	Before C⁶	2	4.38	0.34	2.46	0.15	56,681.46	0.73	25.55	0.03	3.52	0.54	0.04	0.22
	After C⁶		9.67	0.28	6.30	0.77	5,655.55	0.21	25.75	0.23	1.19	0.32	0.06	0.61
Dogs within groups	Before C⁶	21	60.42	5.64§	113.91	6.81§	763,316.05	9.35§	557.14	6.49§	52.06	7.96§	1.76	10.56§
	After C⁶		444.89	12.85§	114.05	13.99§	112,671.86	4.19§	741.06	6.61§	23.77	6.39§	0.92	9.74§
Error	Before C⁶	42	12.99		16.71		81,663.44		85.87		6.54		0.17	
	After C⁶		34.62		8.51		26,920.10		112.14		3.72		0.09	

* See footnote to Table III.
† F for groups was calculated with the mean square for dogs within groups as divisor. All other F values were calculated with the mean square for error as divisor. Significant F values for regression and nonsignificant F values for parallelism indicate that the chief requirements for a parallel line bioassy are satisfied (8).
‡ $p < 0.05$.
§ $p < 0.01$.

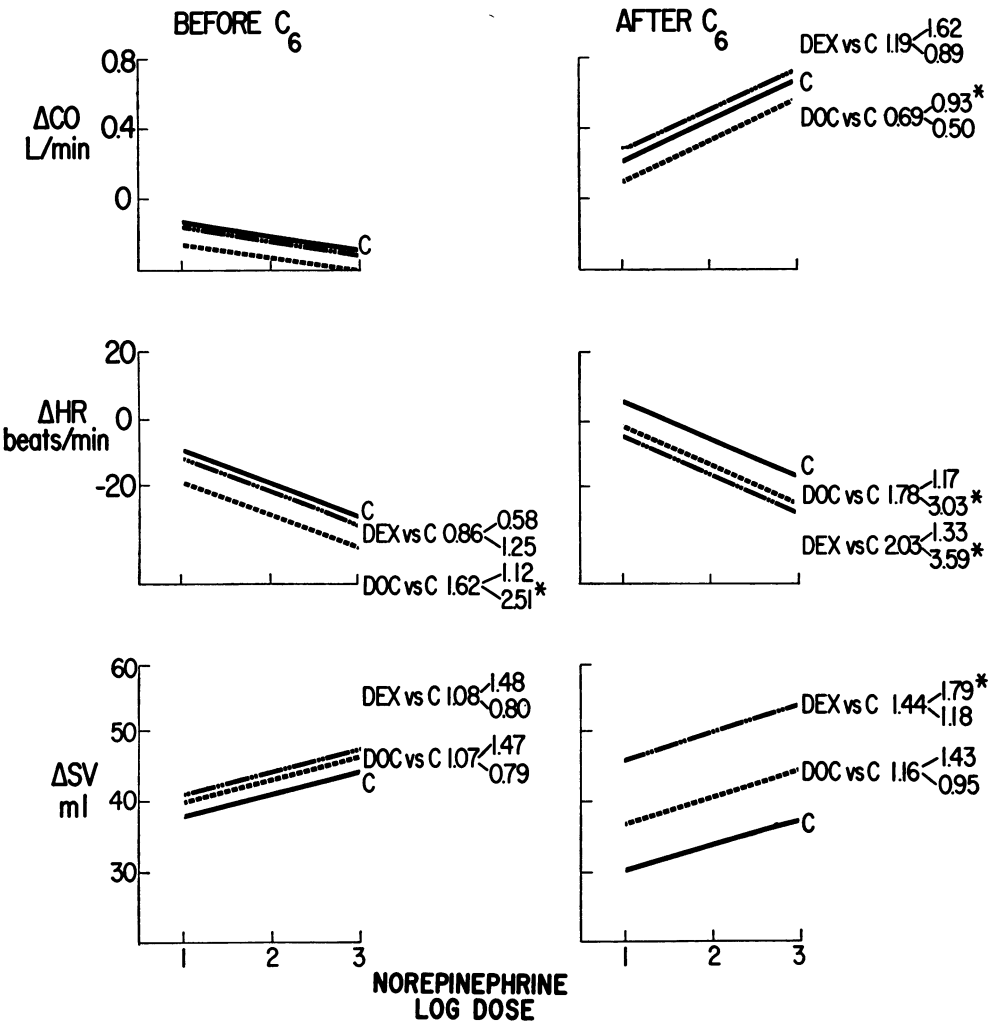

FIG. 2. DOSE-RESPONSE CURVES FOR CARDIAC OUTPUT (ΔCO), HEART RATE (ΔHR), AND STROKE VOLUME (ΔSV). See legend for Figure 1. Before C_6, cardiac output did not change with administration of norepinephrine; the requirements for the bioassay were not satisfied and relative potency was not calculated. Note that the limits for relative potency in the panels for heart rate are inverted. Thus, before C_6, dogs given deoxycorticosterone had the greatest cardiac slowing in response to norepinephrine.

whereas transmural pressure was greater. The magnitude of the augmentation, however, was much less than that seen with deoxycorticosterone. These results suggest that the mineralocorticoid activity of 9α-fluorohydrocortisone was primarily responsible for augmenting vascular responses to norepinephrine in the earlier experiments (10).

It has been suggested that mineralocorticoids cause intracellular accumulation of sodium and depletion of potassium, reducing transcellular gradients for these cations (11–14). Reductions in these gradients are thought to be associated with augmented responsiveness to contractile stimuli (14–16).

Dexamethasone was associated with slight potentiation of the vascular effects of norepinephrine and did not block these effects as some observers have suggested (17). It is interesting that this potentiation was apparent only after ganglionic blockade. Reflex changes in the circulation may have obscured potentiation when autonomic pathways were intact.

These results in animals given dexamethasone are consistent with results from *in vitro* experiments in which spiral strips of rabbit aorta responded to norepinephrine with larger contractions when glucocorticoids were added to the bath (18). The reasons for this potentiation remain conjectural.

Before hexamethonium norepinephrine produced decreases in heart rate that were greater in dogs treated with deoxycorticosterone than in dogs treated with placebo. This probably was the result of greater increases in mean arterial pressure causing greater stimulation of baroreceptor reflexes.

After hexamethonium norepinephrine caused bradycardia in all three groups of dogs. The bradycardia was directly related to increases in blood pressure, suggesting incomplete vagal blockade by hexamethonium. Vagal ganglia are reported to be the least sensitive of all autonomic ganglia to the blocking action of hexamethonium (19). It is interesting that, after hexamethonium, heart rate decreased more in dogs treated with deoxycorticosterone than in dogs treated with placebo. This probably occurred because the enhanced pressor response caused greater stimulation of incompletely blocked baroreceptor reflexes. The bradycardia caused by norepinephrine after hexamethonium in dogs given dexamethasone is more difficult to explain because decreases in heart rate were proportionately greater than increases in mean arterial pressure. It is possible that dexamethasone potentiated the reflex effects of norepinephrine. It is also possible that greater increments in stroke volume provided a greater stimulus to the baroreceptors.

Before hexamethonium norepinephrine produced increases in mean right atrial pressure that were greater in animals treated with deoxycorticosterone and dexamethasone than in control animals. These enhanced responses could have resulted from greater venoconstriction with norepinephrine or from normal venoconstriction in the presence of a greater blood volume (20, 21). Deoxycorticosterone augmented arterial responses to norepinephrine; it might be expected to have a similar effect on venous responses. It is interesting that forearm venous responses to norepinephrine are potentiated by treatment with 9α-fluorohydrocortisone (22) and that increases in blood volume occur with administration of glucocorticoids (23).

After hexamethonium the effects of norepinephrine on mean right atrial pressure were greater in dogs treated with dexamethasone than in control dogs, but not greater in animals treated with deoxycorticosterone. In the latter group, preceding infusions of norepinephrine may have caused relatively greater constriction in postcapillary than in precapillary resistance vessels (24, 25). This could have led to greater capillary filtration, a reduction in intravascular volume, and a diminished response of right atrial pressure. The constrictor effect of norepinephrine on postcapillary resistance vessels probably was less pronounced in dogs treated with dexamethasone. In these animals the primary factor responsible for a greater increase in mean right atrial pressure could have been a greater blood volume.

Acknowledgments

We wish to thank Paul Leaverton, Ph.D., and John Krall of the Biostatistics Section, Department of Preventive Medicine, University of Iowa, for their help in developing the computer programs for statistical analysis of the data resulting from these experiments.

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