Vascular Responses to Norepinephrine in Adrenal Insufficiency.* (24782)

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A previous report from this laboratory indicated that there was no impairment in cardiovascular responses (force of cardiac contraction, arterial pressures) to intravenous norepinephrine in dogs 2-4 days after complete adrenalectomy(1). The results confirmed, in part, the pressor responses reported by Salmoiraghi and McCubbin(2), but were in conflict with those reported by Ramey, Goldstein and Levine(3). Possible reasons for these discrepancies were discussed previously(1). Ramey and Goldstein have summarized the literature on cardiovascular responses to sympathomimetic stimuli in adrenal insufficiency (4). The present study was undertaken in an attempt to determine more directly the *vascular* smooth muscle responses to norepinephrine in adrenal insufficiency.

Methods. Nine control dogs and 12 adrenalectomized dogs were studied; the adrenalectomized dogs were prepared by a 2 stage operation and were studied 3 days after complete adrenalectomy without having received any replacement therapy. All dogs were anesthetized with sodium pentobarbital and were heparinized to prevent coagulation. Femoral blood flow was measured with a Shipley-Wilson recording rotameter(5) inserted into one femoral artery. Femoral arterial pressure head was measured by a Statham pressure transducer connected to the distal limb of the rotameter; mean pressure was obtained by electrical integration. Flow and pressure were recorded simultaneously with a multichannel research recorder (Electronics for Medicine, Inc.). Femoral vascular resistance was calculated as the ratio of pressure (mmHg) to flow (ml/min). The rotameter was calibrated at the termination of each experiment with the animal's own blood. The pressure transducer was repeatedly calibrated against a mercury manometer and checked for linearity of response. Norepinephrine was injected *intra-arterially via* the distal limb of the rotameter; a series of graded doses (0.01, 0.05 and 0.10 μg/kg) was injected into each animal at the beginning of each experiment and, in the majority of animals, was repeated after a 2 hour waiting period under anesthesia. Five of the 9 control dogs and 6 of the 12 adrenalectomized dogs were given hydrocortisone sodium succinate (10 mg/kg i.v. expressed as free hydrocortisone) immediately after the first series of norepinephrine injections. Sodium and potassium in serum were determined by flame photometry; chloride was determined with an Aminco/Cotlove chloride titrator(6).

Results. At the time of the experiments the adrenalectomized dogs were all observed to be sluggish, weak and anorexic, and required approximately half the dose of anesthetic required by control dogs. Serum electrolytes were determined before and 3 days after complete adrenalectomy in 9 dogs, and exhibited classical and significant ($p<.01$ or .05) changes (-12 meq Na^+, -9 meq Cl^-, $+1.3$ meq K^+) of adrenal insufficiency. Hydrocortisone plasma levels were studied in 4 of the adrenalectomized dogs and were reported as zero in each case.†

Average initial pressure, flow, and resistance values for the femoral vascular bed are shown for 9 control and 12 adrenalectomized dogs in Table I. These values were deter-

TABLE I. Initial Values.

Measurement	Control (9)	Adrenalectomy (12)	"p"
Mean femoral B.P. (mm Hg)	122 ± 4.9*	77 ± 7.8*	<.01
Femoral blood flow (ml/min.)	25 ± 2.2	8 ± 1.6	"
Resistance (mm Hg/ml/min.)	5.23 ± 2.19	17.19 ± 4.69	<.05

* Mean ± S.E.

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† We are indebted to Dr. C. A. Papacostas for steroid determinations.

TABLE II. Responses to Norepinephrine.

Measurement	Dose, i.a. (μg/kg)	Control (9)	Adrenalectomy (12)
Change in mean femoral B.P. (mm Hg)	.01	+3.4 ± 1.0*	+1.3 ± .6*
	.05	+7.9 ± 1.0	+3.2 ± .8
	.10	+9.7 ± 1.8	+4.0 ± .9
Change in femoral blood flow (ml/min.)	.01	−11.6 ± 1.7	−3.9 ± 1.0
	.05	−15.6 ± 1.6	−4.9 ± 1.2
	.10	−16.4 ± 1.9	−6.7 ± 1.6
Change in resistance (mm Hg/ml/min.)	.01	+ 5.14 ± .82	+13.12 ± 4.61
	.05	+11.38 ± 2.51	+26.33 ± 11.93
	.10	+17.33 ± 4.51	+45.07 ± 18.06
% change in resistance	.01	+102 ± 17.4	+ 88 ± 13.5
	.05	+228 ± 43.5	+208 ± 48.0
	.10	+329 ± 78.8	+394 ± 107.4

* Mean ± S.E.

mined prior to first injection of norepinephrine.

Responses to graded intra-arterial doses of norepinephrine are shown in Table II. These responses were determined prior to the 2 hour waiting period, *i.e.*, before any of the animals received treatment. As indicated by the increases in resistance there was no impairment in *vascular* responses to norepinephrine in adrenalectomized animals. In fact, in terms of resistance units they appeared to be hyperresponsive, although statistically this was not significant ("p" $=>0.1$). In terms of percentage change there was clearly no significant difference ("p" $=>0.6$) between adrenalectomized and control animals.

Table III shows responses to a second series of intra-arterial injections of norepinephrine after a 2 hour waiting period. As indicated in the table, one of the control groups and the adrenalectomized group had received intravenous hydrocortisone 2 hours before the norepinephrine injections. Qualitatively, responses for all 3 groups were similar to those observed prior to the 2 hour waiting period and prior to steroid treatment (Table II). Quantitatively, vascular responses, as indicated by increases in resistance, were greater in some of the animals, including untreated controls, after the 2 hour waiting period than before.

Discussion. Using femoral vascular resistance as an index, and interpreting an increase in resistance as indicating vasoconstriction, we conclude that there was no impairment in vascular responses to norepinephrine in the adrenalectomized animals used in this study. These results are in agreement with those of Brown and Remington(7) who found no impairment in femoral vascular responses to norepinephrine in adrenal insufficiency, using conductance as an index. However, these investigators injected norepinephrine *intravenously* whereas we injected *intra-arterially*. In our experience vascular responses to intravenous doses of norepinephrine are difficult to interpret. As pointed out by Brown and Remington(7) there is a diphasic change in resistance

TABLE III. Responses to Norepinephrine after Two Hour Wait.

Measurement	Dose, i.a. (μg/kg)	Control (4) (untreated)	Control (5) (hydrocortisone)	Adrenalectomy (6) (hydrocortisone)
Change in mean femoral B.P. (mm Hg)	.01	+ 1.0 ± 1.0*	+2.2 ± 1.7*	.0 ± .0*
	.05	+ 7.8 ± 2.6	+5.4 ± 1.8	+1.7 ± .8
	.10	+11.8 ± 2.4	+7.0 ± 1.7	+5.3 ± .9
Change in femoral blood flow (ml/min.)	.01	− 9.6 ± 3.2	− 6.7 ± 2.0	−2.8 ± .4
	.05	−11.4 ± 2.6	−11.8 ± 2.4	−3.2 ± .5
	.10	− 8.8 ± 2.0	−13.7 ± 3.3	−6.7 ± 2.3
Change in resistance (mm Hg/ml/min.)	.01	+15.05 ± 9.8	+ 9.36 ± 2.6	+14.47 ± 5.70
	.05	+43.30 ± 33.3	+20.30 ± 2.9	+52.82 ± 33.71
	.10	+46.13 ± 30.5	+31.52 ± 9.8	+66.18 ± 32.81

* Mean ± S.E.

(or its reciprocal conductance) in response to intravenous norepinephrine. There is first a decrease in femoral vascular resistance; this is then followed by an increase in resistance, believed due to the vasoconstrictor action of the drug on the femoral vessels. Brown and Remington(7) attribute the initial fall in resistance to passive distention of the vessels as a result of the rise in central arterial pressure. We suggest that an additional factor may be baroreceptor reflexes activated by the rise in pressure, and operating to produce reflex vasodilation. We have, in this investigation, avoided intravenous injections in favor of intra-arterial injections of doses estimated beforehand to produce little or no systemic pressor effect. Response to intra-arterial injections is monophasic, resistance being increased. Our results suggest that there may be impairment in *pressor* responses of the adrenalectomized animals to *threshold* doses of norepinephrine which is not apparent with higher doses(1). This suggestion is supported by previous findings by Remington and coworkers(8). However, analysis of the responses to threshold stimuli is also subject to greater influence from measurement errors, errors resulting from spontaneous pressure changes, etc.

The lower blood pressure and femoral blood flow values, and the higher femoral resistance values present initially in the adrenalectomized animals are in accordance with the results of Brown and Remington(7) and Wyman, Fulton and Shulman(9).

Summary. Femoral vascular resistance as calculated from pressure/flow ratios was used as an index of vascular responsiveness to norepinephrine in control and adrenalectomized dogs. As indicated by changes produced by small *intra-arterial* doses of norepinephrine, there was no impairment in vascular responses of adrenalectomized animals when compared to controls.

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Absorption of Chimyl Alcohol in Man.* (24783)

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Metabolism of glyceryl ethers has received scant attention, although their distribution in nature is widespread(1,2). Since their discovery in 1922 by Tsujimoto and Toyama, these compounds have been noted as major components of non-saponifiable fraction of many marine oils(3) and are found also in mammalian species, even in human atheromata(4). They are alpha-glyceryl ethers of long-chain fatty alcohols; the ether bond is resistant to alkaline hydrolysis. When the ether linkage is made with oleyl alcohol, the glyceryl ether is called selachyl alcohol; with stearoyl alcohol-batyl alcohol; with palmitoyl alcohol - chimyl alcohol. When the other 2 hydroxyl groups of glycerol are esterified with

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