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Effects of Moderate Uremia on Cardiac Contractile Responses[1] (39058)

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We have previously reported results of studies on the hearts of rats with two types of uremia (1, 2): (1) severe acute uremia created by bilateral nephrectomy, and (2) moderate uremia created by 5/6 nephrectomy. In the former case hearts were studied 24 hr after nephrectomy and in the latter, 2 weeks after surgery.

When hearts of rats with severe acute uremia were studied in an isolated heart apparatus, their performance was the same as control hearts. Under the same conditions, hearts of rats with moderate uremia show enhanced contractile responses. On the other hand, hearts of acute uremic rats studied *in vivo* were found to have greater contractile responses to gradual aortic occlusion than did hearts of sham operated animals (2). The present investigation was designed to determined if hearts from animals prepared with 5/6 nephrectomy show the same increased responses *in vivo* that they do *in vitro*, and to study the time course of the effect of uremia on the heart.

Methods. Male Wistar rats weighing 250–300 g were anesthetized with ether, and 5/6 nephrectomy was performed taking care not to remove the adrenal glands (1). Sham operated rats were used as controls. For the 24 hr prior to study the rats were fasted but allowed to drink water. For the study, the rats were anesthetized with intraperitoneal pentobarbital (60 mg/kg). Respiration was controlled via a tracheostomy by a Harvard small animal respirator. To study cardiac performance complete aortic occlusion was produced in the open chest animal as described previously (2). Left ventricular pressure was measured by a 17 cm long PE catheter which punctured the apex of the left ventricle, and low and high gain tracings for systolic and diastolic pressures were recorded with an Electronics for Medicine VR6 multichannel recorder. Left ventricular dP/dt was recorded with an R/C differentiating circuit.

Pressures were measured during ventricular ejection and aortic constriction 20 and 24 min after the start of the experiment. Then propranolol 1.5 mg was injected into the left ventricle and pressure and dP/dt responses were measured at 27.5 and 30 min. This dose of propranolol was sufficient to block any effect of isoproterenol 3×10^{-6} *M* when administered directly into the ventricle. Developed LV systolic pressure (DLVSP) was calculated from the peak ventricular systolic pressure (PLVSP) minus the end-diastolic pressure (LVEDP). We have previously discussed the use of cardiac responses during complete aortic occlusion as a measure of contractile performance (2).

At the end of each experiment, blood was drawn from the heart for analysis of sodium, potassium, phosphate, calcium, creatinine and blood urea (2). The wet weight of the ventricles was measured and dry weight obtained by drying hearts at 150° F to a constant weight.

Statistical significance was evaluated by the *t* test.

Results and discussion. Table I shows the heart weights, body weights, serum urea, and creatinine values in sham and uremic animals 48 hr, 1 and 2 weeks after 5/6 nephrectomy. There were no significant differences in heart weights. Dry/wet heart ratios also were not different, suggesting that myocardial edema did not occur during the period of observation. Uremic animals gained weight less rapidly than sham animals after the surgery. Serum urea and creatinine were significantly higher in all surgically treated animals. Serum potassium, sodium, phosphate and calcium were not significantly different be-

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TABLE I. HEART AND BODY WEIGHT—BLOOD CHEMISTRIES IN UREMIC RATS[a].

	Wet heart weight (mg)		Dry heart weight (mg)		Body weight (g)		Serum Urea (mg/100 ml)		Creatinine (mg/100 ml)	
	S[b]	U	S	U	S	U	S	U	S	U
48 hr	697 ± 27 (6)	700 ± 49 (6)	161 ± 3 (6)	158 ± 4 (6)	239 ± 3 (6)	239 ± 3 (6)	13.9 ± 0.9 (11)	48.7 ± 3.9 (12)	0.42 ± 0.03 (11)	1.25 ± 0.09 (12)
	NS		NS		NS		$p < 0.001$		$p < 0.001$	
1 week	868 ± 24 (8)	783 ± 38 (6)	196 ± 8 (8)	177 ± 8 (6)	302 ± 18 (12)	264 ± 13 (11)	15.9 ± 0.8 (12)	44.2 ± 2.5 (11)	0.41 ± 0.06 (12)	1.02 ± 0.09 (11)
	NS		NS		NS		$p < 0.001$		$p < 0.001$	
2 weeks	826 ± 32 (8)	856 ± 46 (7)	191 ± 9 (8)	197 ± 8 (7)	303 ± 7 (8)	268 ± 6 (7)	21.5 ± 0.8 (8)	61.0 ± 5.1 (7)	0.55 ± 0.04 (8)	1.20 ± 0.12 (7)
	NS		NS		$p < 0.005$		$p < 0.001$		$p < 0.001$	

[a] Results are mean ± SE. Number of hearts are in parentheses.
[b] S = sham; U = uremic; NS = nonsignificant.

tween sham and uremic animals. Serum magnesium was 1.42 ± 0.05 mg/100 ml in sham and 1.88 ± 0.06 in uremics after 48 hr ($P < 0.01$) but magnesium levels were not significantly different at one or two weeks. We have previously noted elevated serum magnesium, potassium and phosphate in acute uremic animals (2).

Table II shows the mechanical responses of the hearts in these experiments. The results shown are those recorded 24 min after completion of the installation of the catheters and 2.5 min after the injection of propranolol. Left ventricular performance improved with time after surgery in both sham and uremic animals, suggesting that surgery *per se* had some effect on cardiac function. However, the only significant differences between sham and uremic were observed after 48 hr. At that time, when the serum urea was only 43% as high as that observed 24 hr after bilateral nephrectomy (2), baseline performance during ejection was not different between hearts of uremic and sham animals. However, significantly greater responses in left ventricular systolic pressure and maximum dp/dt during aortic occlusion were observed in uremic than in sham animals. After propranolol, hearts of uremic animals maintained higher heart rates than sham, and the increased responses of pressure and dp/dt in hearts of uremic rats persisted. There were no differences in left ventricular end-diastolic pressures between sham and uremic animals that could have accounted for the increased responses to afterload. We had previously shown in the 24-hr postnephrectomy animals that both baseline performance and responses to aortic occlusion were higher in the uremic animals both before and after administration of propranolol (2). Therefore, some vestiges of this increased contractile responsiveness persists for at least 48 hr in rats with less profound uremia.

One or two weeks after surgery, all differences between the cardiac responses of sham and uremic rats had disappeared, even though the degree of azotemia was similar to that observed at 48 hr.

The series of investigations was begun initially to test the hypothesis that heart function may be depressed in uremia (1, 2). The present results are consistent with our previous reports that contrary to that hypothesis, hearts of uremic rats either have normal or increased reserve capacity to respond to various interventions with increased myocardial performance.

The findings *in vivo* at 24 (2) and 48 hr after the onset of uremia, suggest that there is some aspect of the acute uremic state that permits the heart to respond with increased contractile performance. Since enhanced performance was not observed when hearts of acute uremic rats were perfused *in vitro* with nonuremic perfusion medium (1), the findings *in vivo* are most likely due to a blood borne factor or factors that are not blocked by β-adrenergic block agents.

The loss of these increased responses *in vivo* with time is of interest in that increased contractile and external work responses were previously observed when hearts of similar rats were perfused *in vitro* in the absence of uremic blood. This suggests that there are compounds in chronic uremic blood that may be inhibitory to the heart, and mask the

TABLE II. MECHANICAL FUNCTION IN HEARTS OF UREMIC RATS.[a]

	Number of Hearts		Ejection				Isovolumic			
			Control		Propranolol		Control		Propranolol	
	S[b]	U[b]	S	U	S	U	S	U	S	U
					Heart Rate (BPM)					
48 hr	7	10	238 ±11	229 ±10	167 ±5	182 ±8[e]	244 ±10	231 ±11	165 ±5	182 ±9[d]
7 days	8	7	283 ±14	271 ±13	223 ±12	211 ±9	281 ±16	280 ±14	223 ±13	211 ±8
14 days	8	6	293 ±11	267 ±12	203 ±10	180 ±7	290 ±10	268 ±13	203 ±11	181 ±7
					DLVSP (mm Hg)					
48 hr	7	10	63 ±6	66 ±7	52 ±8	57 ±5	168 ±9	209 ±10[h]	122 ±13	156 ±7[g]
7 days	8	7	86 ±7	82 ±5	78 ±4	66 ±8[d]	197 ±7	211 ±8	169 ±8	172 ±10
14 days	8	6	104 ±5	106 ±13	87 ±6	89 ±8	204 ±3	222 ±17	169 ±7	185 ±19
					Max dP/dt (mm Hg/sec)					
48 hr	7	10	2010 ±240	2520 ±260[d]	1360 ±230	1840 ±180[d]	4240 ±510	5460 ±310[f]	2410 ±340	3210 ±220[e]
7 days	8	7	3970 ±280	3880 ±290	3160 ±430	2370 ±350[d]	5080 ±381	5030 ±358	3570 ±390	3220 ±260
14 days	8	6	5380 ±510	4910 ±750	3730 ±480	3590 ±580	7790 ±490	7780 ±1190	5160 ±380	5240 ±940
					EDP (mm Hg)					
48 hr	7	10	2.1 ±0.5	2.2 ±0.4	2.7 ±0.3	2.7 ±0.4	14.1 ±3.8	9.3 ±1.7[c]	10.6 ±7.0	11.0 ±1.4
7 days	8	7	2.0 ±0.4	3.1 ±0.6	3.0 ±0.5	2.7 ±0.4	11.4 ±2.3	16.3 ±2.6[d]	15.3 ±1.2	11.9 ±1.1[d]
14 days	8	6	2.8 ±0.4	3.3 ±0.6	3.7 ±0.3	3.2 ±0.5	17.3 ±1.6	17.0 ±3.3	14.0 ±1.6	12.0 ±1.1

[a] Results are mean ± SE.

[b] S = sham; U = uremic; EDP = end-diastolic pressure; DLVSP = developed left ventricular systolic pressure.

[c] $0.2 < P < 0.25$.

[d] $0.1 < P < 0.2$.

[e] $0.05 < P < 0.1$.

[f] $P < 0.05$.

[g] $P < 0.025$.

[h] $P < 0.02$.

increased intrinsic cardiac reserve we had previously demonstrated (1). This is consistent with our demonstration that a combination of uremic compounds exerts a depressant effect on cardiac function (3), and it is possible that such a combination, plus other nitrogenous compounds accumulate slowly during uremia.

The present studies do not elucidate specific mechanisms but point toward direct studies of the effects of uremic blood or serum on cardiac function. It is possible that in the early stage of uremia the serum will have a positive inotropic effect, whereas later a negative inotropic effect will be observed.

In summary, uremia of 2 weeks duration does not appear to be associated with gross

cardiac depression. At two weeks there may be a net depressant effect of uremic serum which hides an increase in intrinsic contractile reserve. On the other hand, in the initial phases of uremia, increased contractile reserve is observed, and that increased reserve appears to be due to factors that are extrinsic to the myocardium.

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