TECHNICAL NOTE

Norepinephrine-induced acute renal failure: A reversible ischemic model of acute renal failure

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Several studies have shown that acute renal failure (ARF) can be produced in the dog by infusing norepinephrine (NE) into a renal artery [1, 2]. In these studies the injury appeared to be confined to the infused kidney, with no changes occurring in systemic hemodynamics or in the function of the contralateral kidney. The hemodynamic changes noted in the infused kidney were comparable to those seen in human ARF. A major criticism of these studies, however, is that the renal failure was not shown to be reversible, as it typically is in man. In the present study, we have reexamined the NE-induced model of ARF in the dog with the particular purpose of finding a set condition which would cause ARF and yet allow recovery of renal function within a period of time comparable to that usually seen in the human disease.

Methods

Protocol 1: Two-hour vs. 40-min infusion of norepinephrine into one renal artery of intact dogs. In this set of preliminary studies, two groups (each consisting of four dogs) were studied. The studies were performed under pentobarbital anesthesia (20 to 30 mg/kg of body wt, i.v.). An angiographic catheter (7–8 French) was introduced into a femoral artery and guided, under fluoroscopic control, into one renal artery. Using small flushes of dilute contrast medium, the catheter was positioned carefully to avoid obstruction of renal blood flow. Once the catheter was in place, NE was infused into the renal artery at a rate of 0.75 μg/kg/min. In the first group of four dogs, the NE infusion was given for 2 hr. In the second group, the infusion was given for only 40 min. The dogs were then allowed to recover from anes-

thesia and were again given their standard diet. Eight weeks later, the animals were again anesthetized and prepared for acute clearance studies. Through bilateral flank incisions, the renal veins and ureters were cannulated. Clearances of inulin as an index of glomerular filtration rate (GFR) and para-aminohippurate (PAH) were measured by standard techniques. Renal blood flow (RBF) was calculated from the PAH clearance with correction for extraction. In kidneys with no urine formation, RBF was measured with an electromagnetic flow probe. Creatinine was measured with an autoanalyzer (Technicon). Plasma renin activity was measured by radioimmunoassay [3]. Plasma and urine osmolality measurements were done with an osmometer (Advanced Instruments).

Protocol 2: Effect of 40-min infusion of norepinephrine into the renal arteries of previously uninephrectomized dogs. In this second set of studies, one kidney was removed 2 to 3 weeks before the experiments started, and then the remaining kidney received a 40-min infusion of NE (0.75 μg/kg/min) through the renal artery. At the time of the NE infusion and at frequent intervals thereafter, the animals were weighed. Blood and urine samples were obtained at the same intervals. These samples were obtained while the dogs were conscious and after they had fasted overnight. Creatinine and osmolality were measured in both plasma and urine. Plasma renin activity (PRA) was also measured at the same time.

Statistical analysis was performed by analysis of variance using Dunnett's method for multiple comparisons with the control [4]. Student's t test was used for single comparisons. A P value of < 0.05 was considered statistically significant. All data are expressed as the mean $\pm$ SEM.

Results

Protocol 1: Effects of 2-hr vs. 40-min infusion of norepinephrine into one renal artery of intact dog. The data from protocol 1 is presented in Table 1. Renal weight, GFR, and RBF were all significantly lower at the end of 8 weeks in the infused kidney of dogs which had received a 2-hr intrarenal infusion of NE than they were in those which had received only a 40-min infusion. There was no difference in the mean weights of the contralateral kidneys from the two groups. The relative renal sizes at 8 weeks for the 2-hr vs. 40-minute infusion are shown in Figure 1.

Protocol 2: Effects of 40-min infusion of norepinephrine into the renal arteries of previously unine-

Table 1. Protocol 1: Kidney weight, GFR, and renal blood flow 8 weeks after a 2-hr or 40-min intrarenal infusion of norepinephrine (0.75 μg/kg/min)[a]

	2-hr norepinephrine infusion		40-min norepinephrine infusion
Kidney wt, g			
Infused	15.8 $\pm$ 1.5	$P < 0.005$	50.2 $\pm$ 6.1
Contralateral	53.9 $\pm$ 7.3	NS	52.2 $\pm$ 3.5
GFR, *ml/min*			
Infused	1.3 $\pm$ 1.3	$P < 0.01$	24.3 $\pm$ 5.9
Contralateral	N.D.		40.2 $\pm$ 4.9
Renal blood flow, *ml/min*			
Infused	10 $\pm$ 0	$P < 0.05$	209 $\pm$ 67
Contralateral	N.D.		274 $\pm$ 55

N.D. = Not done

phrectomized dogs. Two of the nine animals in this group became anuric and died within 2 weeks. The remaining seven dogs survived the 8-week period of the study. In the seven surviving animals, oliguria

Fig. 1. *Infused kidney 8 weeks following 40-min (left) or 2-hr (right) intrarenal norepinephrine infusion.* A wedge section for histologic purposes was removed from the right kidney prior to this photograph.

was not a feature of the ARF. Three hours after the NE infusion, urine flow had almost doubled from 0.51 ± 0.19 to 0.99 ± 0.28 ml/min. For the next 8 weeks, urine flow remained at or above control values. The plasma creatinine concentration, however, began to rise within 3 hours of the NE infusion and reached its peak at 7 days. It then began to fall until it was only slightly above the control value at 56 days (Fig. 2). Clearance of inulin fell from a control value of 55.5 ± 5.7 ml/min to a low value of 10.7 ± 2.9 ml/min ($P < 0.01$) 24 hr after the infusion. Eight weeks after the infusion, the inulin clearance had returned to 27.3 ± 5.4 ml/min.

The depression in renal tubular function, as assessed by the urine to plasma (U/P) ratio of creatinine, was maximal 3 hours after the NE infusion (206 ± 51 to 11 ± 3, $P < 0.01$) and returned to 95 ± 25, 8 weeks after the infusion (Fig. 2). Similarly, the U/P osmolality fell from a control value of 4.4 ± 0.4 to a low value of 1.4 ± 0.1 ($P < 0.01$) 3 hr after the NE infusion and returned to 2.9 ± 0.6 8 weeks after the infusion.

Three hours after the infusion, PRA was elevated from 10.8 ± 3.7 to 24.4 ± 4.8 ng/ml/hr, $P < 0.01$, but at 24 hr and on subsequent days, PRA was not different from controls. Since the renin values at 3 hours were obtained during anesthesia and the later ones were not, the effect of anesthesia alone on PRA was examined in a second group of animals. PRA values obtained before and 3 hours after pentobarbital anesthesia in nine uninephrectomized, but otherwise healthy dogs, revealed no significant changes (2.5 ± 0.8 to 1.6 ± 0.3 ng/ml/hr, $P = $ NS).

At no time during the postinfusion period did the mean weights of the animals differ significantly from control.

Discussion

Two recent studies describe the characteristics of an ischemic model of ARF induced by the unilateral infusion of NE into a renal artery of the dog [1, 2]. When animals were studied 48 hr after the infusion, RBF had returned to 60% of control values, and GFR was unmeasurably low [2]. These hemodynamic abnormalities are similar to those noted in patients with ARF [5]. ARF in man, however, typically undergoes spontaneous remission, and this feature was not evaluated in these initial investigations with the NE-induced model in the dog.

In the present study, we found that the dose of NE previously used (0.75 µg/kg/min for 2 hr) caused renal failure which was not spontaneously reversible. GFR did not return, and the kidney was found to

be severely shrunken at the end of 8 weeks (Fig. 1). When the NE was infused for only 40 min, however, the ARF which followed was much more like that seen in man. Its mortality rate was 22%, well within the range of 10 to 50% commonly noted in man. The severe impairment of GFR and the lesser reduction in RBF during the early course of the disorder also conformed to the familiar pattern seen in the human disorder. Similarly, the impaired renal concentrating ability in the early stages of our experiments was comparable to what occurs during a similar period of time in human ARF. Most important, however, GFR and renal concentrating ability returned toward normal within the course of the study.

It is also noteworthy that high PRA was observed early in the course of the renal failure in our study, as it has in man [7]. The return of PRA to control values after 24 hr of ARF in our study, however, suggests that elevated PRA are not necessary in the mainte-
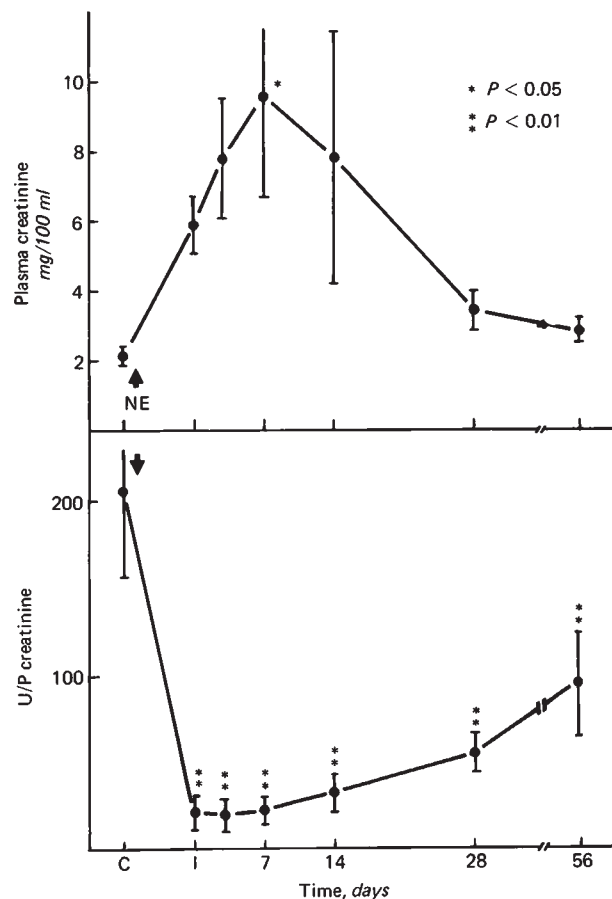

Fig. 2. *Effect of 40-min norepinephrine infusion on plasma creatinine (top) and urine to plasma ratio (U/P) of creatinine (bottom). Arrow indicates timing of norepinephrine (NE) infusion. Data are plotted as mean ± SEM.*

nance of ARF in this model. This observation is consistent with that of Baehler, Kotchen, and Ott [8].

Summary. The present study has defined conditions whereby a reversible form of ischemia-induced ARF can be produced in the dog. Unlike previous studies [9–11] which examined the acute phase of NE-induced ARF, this study demonstrates the feasibility of using the model for the longitudinal study of ARF. Such a model may be useful in studying the pathologic and physiologic changes which occur during different phases of ARF. Perhaps most important, this model should also provide a setting in which treatment measures, either prophylactic or therapeutic for ARF, can be examined.

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