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The Effect of Splenectomy on Renal Function in Epinephrine-Induced Renal Failure (41116)

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Abstract. In previous studies, iv infusion of epinephrine (4 μg/kg/min) for 6 hr was shown to cause acute tubular necrosis in 75% of intact, but in only 13% of splenectomized dogs. The present study presents similar experiments in which renal function is studied. Epinephrine infusion in intact dogs was marked by sustained depression of renal blood flow, creatinine clearance, and urine flow. Decreases in renal function were less pronounced in splenectomized dogs, and generally showed a significant tendency to improve over the 6-hr infusion period. It was concluded that the tubular lesion in epinephrine-infused intact dogs results from a sustained decrement in renal perfusion. It is suggested that the protective effects of splenectomy may involve reduced blood coagulability or facilitated renal prostaglandin release, but the data thus far available are insufficient to affirm or deny these possibilities.

It has recently been shown that iv infusion of epinephrine (4 μg/kg/min) for 6 hr causes severe renal tubular lesions in intact dogs, while renal damage was infrequent and much less severe in acute (post 30 min) and chronic splenectomized (post 2–3 wks) dogs (1). Congestion and thrombosis in the renal microvasculature suggested that the mechanism of the renal lesion may be thrombotic in origin. It was not known, however, whether the lesions observed were the direct result of a "splenic factor," or whether the spleen merely potentiates the effects of another pathophysiological mechanism(s). The experiments of the present study were designed to provide additional data concerning the pathophysiology of epinephrine-induced acute renal failure and the protection afforded by prior splenectomy.

Materials and Methods. A total of 11 mongrel dogs, 6 intact, and 5 chronic splenectomy (3 wks postsplenectomy), were studied. All animals were anesthetized with sodium pentobarbital (30 mg/kg body wt). The left kidney was exposed and an electromagnetic blood flow meter probe was placed around the renal artery. The femoral artery, femoral vein, cephalic vein, and ureter were catheterized. Blood pressure from the femoral artery and abdominal vena cava via the femoral vein were monitored using resistance bridge transducers and a Grass polygraph. Renal blood flow was obtained using a Biotronex BL 613 electromagnetic blood flow meter. Each dog received a constant iv infusion of 0.9% saline containing sufficient creatinine to yield adequate plasma levels of this substance. Hourly urine collections were made in calibrated containers with midpoint arterial blood collections. Each experiment consisted of an initial 15-min collection period, after which sufficient epinephrine was added to the infusion to deliver 4 μg/kg/min. Six consecutive 1-hr collection periods were obtained, and the kidney was removed, decapsulated, and weighed. Renal tissue was collected and prepared for light and electronmicroscopy as previously described (1). Plasma and urine were analyzed for creatinine by the Jaffe reaction and osmolality using a Fiske osmometer. Plasma protein was measured by the biuret reaction.

For statistical purposes each of the variables were examined separately. The six hourly measurements made during epinephrine infusion were regarded as six levels of the time factor and the two groups,

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splenectomized and intact dogs, were regarded as two levels of the groups' factor. An unweighted means technique (2) was used to adjust for the difference in group sizes. An analysis of variance appropriate for a two-factor design with repeated measure on the time factor enabled the statistical testing of the following.

1. Differences between the two-group means averaged over the six times (Group Main Effect)
2. Differences among the 6 hr averaged over the two groups (Time Main Effect)
3. Difference between the patterns over time of the two groups (Time × Group Interaction)

Results. Mean values of renal blood flow (RBF), creatinine clearance (C_{cr}), urine flow, and osmolar clearance (C_{osm}) over the 6-hr infusion period are presented in Fig. 1. Urine flow and Ccr in splenectomized dogs differed significantly ($P < 0.05$) from those in intact dogs in terms of group main effect as well as group × time interaction. That is, the mean values as well as the patterns of the responses of these two parameters differed with respect to splenectomy. In contrast, RBF values differed in terms of group main effect only, while no significance was found for C_{osm}. It was also noted that the group main effect mean value of hematocrit in intact dogs (58%) was greater ($P < 0.01$) than that of the splenectomized group (46%), but no significant differences were noted for either arterial blood pressure or plasma protein concentration. A significant negative correlation ($r = -0.729$) was obtained when pooled creatinine clearance and hematocrit were compared, but creatinine clearance and plasma protein concentration appeared to be unrelated.

Light and electronmicroscopic examina-

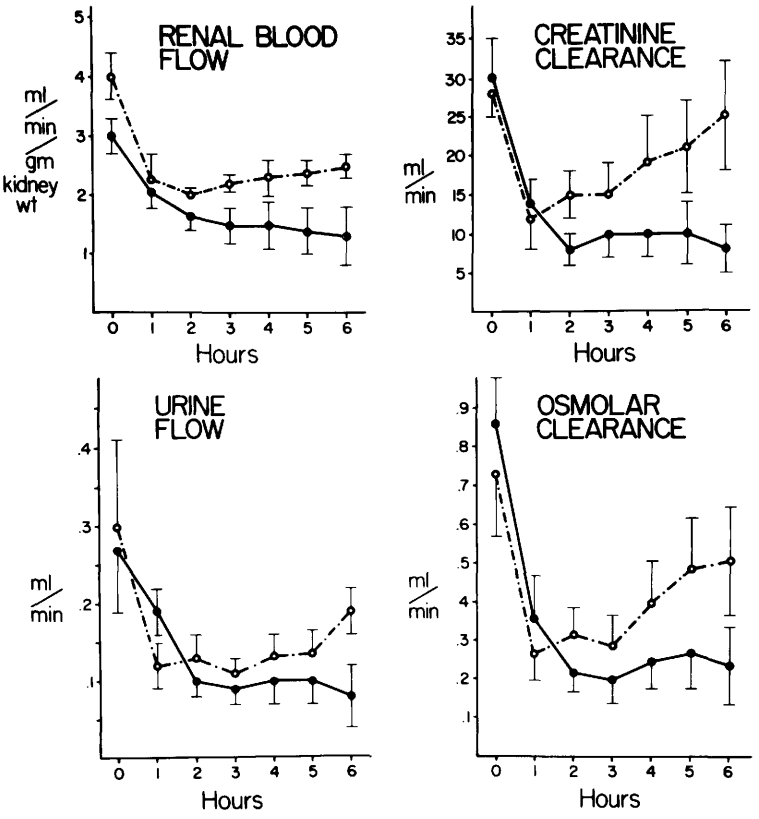

FIG. 1. Changes in renal function during 6 hr of iv epinephrine infusion in six intact (solid line) and five splenectomized (broken line) dogs. Means and standard errors are shown.

tion of the kidneys of the present study was conducted to confirm our previous observations (1). As before, glomerular and tubular necrosis with severe mitochondrial changes were found primarily in intact dogs, while kidneys from splenectomized dogs appeared essentially normal.

Discussion. The experiments of the present study demonstrate that the protective effect of splenectomy against epinephrine induced ATN may be due, in part, to improved RBF, C_{cr}, and urine flow in the asplenic animal. Progressive deterioration (or persistent depression) of renal function during epinephrine infusion is associated with the presence of splenic tissue in much the same way as are histopathologic changes (1). In our previous study (1) it was suggested that erythrocytes, leukocytes, and platelets released from the contracting spleen might lead to capillary stasis. This effect, together with epinephrine-induced increases in blood coagulability, could produce thrombosis and damage. The highly significant negative correlation between C_{cr} and Hct found in the present study suggests the differences in RBF and C_{cr} in splenectomized animals may be related to blood viscosity changes. Other factors, including release of clotting factors from the spleen (3), are probably involved, since splenectomy is protective against ATN even though it is performed after inducing splenic contraction (1). This observation is significant, since the renal lesion in this canine model is similar to that seen in man (1, 4), yet the human spleen is greatly limited in red cell storage capacity. Intravascular fibrin deposits in epinephrine-infused intact dogs (1) suggest that coagulopathy similar to that described by Whitaker *et al.* (5) may play a role in ATN. Intrarenal release of vasodilator substances may also be a significant factor in epinephrine-induced ATL. McGiff *et al.* (6) have shown that continuous infusion of norepinephrine causes the release of prostaglandin-like material that opposes the catecholamine effects. The result was a rapid recovery of renal function in spite of continued norepinephrine infusion. Prostaglandin synthesis also appears to mediate return of renal blood flow during acute episodes of hypovolemia (7). Thus, it is likely that prostaglandin synthesis is involved in catecholamine-induced renal failure, but the possible modulating effect of splenic tissue on prostaglandin-mediated systems is unknown. The mitochondrial changes observed in intact dogs (1) suggest a severe ischemic process, and have been considered by others as a sign of irreversible organ damage (8). Absence of these changes in splenectomized dogs suggests that improved perfusion, as observed in the present study, may be an important determinant of tissue survival in this model. Thus, it is likely that the overall decrement in renal function in intact epinephrine-infused dogs follows from the combined effects of increased blood viscosity, epithelial cell damage and necrosis, and alteration of renal prostaglandin synthesis. Even so, the mechanisms which mediate these renal responses to epinephrine infusion in intact and splenectomized dogs remain to be determined.

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