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Distribution of Intrarenal Blood Flow During Bacterial Sepsis

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In contrast to hemorrhagic or cardiogenic shock, bacterial sepsis is often associated with hyperdynamic circulation, especially when hypotension is corrected by adequate volume administration [21]. Although renal blood flow (RBF) was historically felt to be depressed during sepsis, this confusion was due to inappropriate extrapolation from animal endotoxin shock models where the entire circulation was depressed [7]. In 1969, using a canine model of bacterial sepsis, Hermreck and Thal first documented significantly increased RBF in most dogs during sepsis [5]. Major contributions were then made by Lucas and associates, who extended this observation to patients in septic shock [11, 16, 18]. These authors reported that septic patients often exhibit polyuria which persists despite hypovolemia and hypotension and is therefore inappropriate [11, 18]. If unrecognized, this polyuria, combined with increased cardiac output, may be interpreted as evidence of volume overload and elicit the therapeutic response of fluid restriction. Unfortunately, such management often leads to renal failure and death, in contrast to patients in whom adequate volume is restored [18].

Since these observations were reported, several attempts have been made to define the mechanism of inappropriate polyuria [2, 6, 15]. The present study employed a canine bacterial sepsis model similar to that reported by Postel *et al.* in which live *Pseudomonas* organisms were infused into awake dogs [14]. Microspheres were used to investigate the possibility that changes in the intrarenal distribution of blood flow could account for the clinical observations noted above.

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METHODS

Fifteen female dogs (12–30 kg; mean, 19 ± 5 kg) were allowed free access to food and water until they were briefly anesthetized with intravenous thiamylal sodium (10 mg/kg). During this light anesthesia a transfemoral 7F side-hole cardiac catheter was positioned in the left ventricle by pressure recording. A transfemoral 18.5-gauge polyethylene catheter was placed in the abdominal aorta near the level of the renal arteries. A similar catheter was placed in the brachial artery for pressure recording. A Swan–Ganz thermodilution catheter was inserted into the pulmonary artery via the external jugular vein and a Foley catheter was inserted into the bladder. The incisions for catheter placement were closed and the dogs were allowed to recover completely from the anesthesia. When the animals were completely awake they were placed in an upright Pavlov stand for the remainder of the experiment. Mean arterial pressure and rectal temperature were continuously recorded on a Hewlett–Packard Series 8800 recorder. Cardiac output was measured intermittently by thermodilution using an Edwards Model 9500 computer. Urine output was collected at 15-min intervals and analyzed for creatinine and sodium concentration. Simultaneous serum samples for

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sodium, creatinine, white blood cell count, and hematocrit were obtained. After the animals were stable in the Pavlov stand, baseline data were collected for 60 min. At the end of this sampling period intrarenal blood flow distribution and total RBF were measured using a microsphere technique. Carbonized microspheres labeled with 141 Ce (15 ± 5 μm diameter in 20% dextran) were used (Nuclear Products, 3M Co.). Microspheres (400,000) were injected through the left ventricular catheter and flushed with 20 ml of heparinized saline over 10 sec. A blood reference sample was withdrawn simultaneously from the abdominal aortic catheter using a Harvard withdrawal pump at the rate of 20 ml/min for 1 min, beginning 5 sec before microsphere injection.

Following this determination, six control animals received an intravenous infusion of sterile BHI broth (Bacto brain–heart infusion, Difco Laboratories, Detroit, Michigan) at the rate of 0.5 ml/min for 90 min. This infusate was verified sterile by bacteriologic culture in each instance. Data were collected during this 90-min infusion period as described above. Immediately prior to termination of the infusion, intrarenal blood flow distribution was again measured using ^{85}Sr-labeled microspheres.

Nine experimental dogs received an infusion of live *Pseudomonas aeruginosa* organisms originally isolated from a dog manifesting clinical sepsis at the School of Veterinary Medicine, Michigan State University, East Lansing, Michigan and designated PSa_{EL}. This organism was maintained in BHI broth and stored at 4°C between experiments. Initially a culture of PSa_{EL} grown in BHI broth for 24 hr at 37°C was diluted with sterile 0.9% sodium chloride solution to provide varying concentrations of bacteria to test specific *in vivo* reactions. A standard inoculant was then selected which consisted of aliquots of undiluted 24-hr BHI broth cultures of PSa_{EL} which had an average concentration of 4.8 ($\pm$ 0.06) $\times$ 10^8 organisms/ml. These organisms were used within 90 min of preparation. Quantification of the challenge inoculum was performed by the following procedure: A 1-ml aliquot from the inoculant was serially diluted with sterile 0.9% sodium chloride solution and duplicate 0.5-ml aliquots from each dilution were spread onto blood agar plates. The resulting places were incubated overnight at 37°C and the colonies were counted. Bacteria were infused intravenously for 90 min in each experimental (septic) dog. Blood cultures (5 ml) were taken immediately prior to termination of the infusion and injected into 45 ml of Bectin–Dickinson tripticase soy broth. A 1-ml aliquot of each blood culture was serially diluted and duplicate 0.5-ml aliquots from each dilution were spread onto blood agar plates. The resulting plates were incubated overnight at 37°C and the colonies were counted.

Immediately prior to termination of the bacterial infusion, intrarenal distribution of blood flow was determined in septic dogs using ^{85}Sr microsperes. Approximately 1 hr later the animals were sacrificed and the kidneys were removed and fixed in 10% formalin solution. During the entire experiment fluid administration was restricted to 0.5 ml/min of D_5W or broth infusion.

Total RBF was calculated by the reference sample technique [1, 3]. Both entire kidneys from each animal plus the aortic reference blood samples were counted using a sodium iodide crystal scintillation detector. Samples were placed into plastic containers and rotated to eliminate geometric variance. The details of this calculation have been previously described [3].

Following isotope counting of the entire kidney, each kidney was divided in half coronally. Thin sections were taken in coronal fashion from three different areas of cortex of each half kidney. These blocks of cortex (approximately 4 mm thick $\times$ 10 mm wide) were then cut into four equal layers (from outer to inner cortex) and labeled as Layers 1 through 4. It was found that equal layers could be cut by hand after familiarity was obtained with this

technique. The six samples of each layer from each kidney were then pooled in preweighed air-tight vials and subsequently weighed prior to counting. Samples from both kidneys from each dog were counted separately as an index of variance. The sample vials of each cortical layer were then counted for both isotopes simultaneously using a lithium-drifted germanium detector. Using previously described calculations [3, 12], computer analysis resolved microsphere distribution into the percentage distribution of blood flow to each of the four cortical layers for each isotope. Using the correction for ellipsoidal geometry of the kidney, this distribution was then converted to percentage distribution to each of four equal volume cortical zones, labeled Zones 1 through 4 from the outer to inner cortex [12]. Zonal perfusion rate, or absolute blood flow to each zone, normalized for relative zone mass, was calculated [3]. The 30-min interval prior to microsphere injection was selected for comparison of hemodynamic, serum, and urine variables. Baseline and infusion values were compared using Student's two-tailed t test for paired data. Control and septic animals were also compared using Student's two-tailed t test for uncorrelated means. Kidney specimens from each animal were examined by light microscopy.

RESULTS

Quantitative blood cultures in septic dogs varied from 6.7×10^4 to 1.2×10^6 organisms/ml ($3.7 \pm 3.5 \times 10^5$, $\bar{x} \pm$ SD). Differences appeared to reflect individual dog variation, since the magnitude of bactermia was not correlated with changes in other measured variables.

Cardiac index did not change significantly from baseline to infusion periods in either control or septic dogs (Table 1). Furthermore, no statistical difference was noted between control and septic animals during baseline or infusion. Mean arterial pressure did not change significantly in control animals. Septic animals, however, demonstrated significant hypotension during bacterial infusion, which was significantly lower than control animals (Table 1). Heart rate was statistically equivalent in control and

TABLE 1

		Baseline	Infusion	p Value
Cardiac index (l/min/m²)	Control	3.6 ± 0.2[a]	3.3 ± 0.3	NS
	Septic	3.4 ± 0.1	3.0 ± 0.2	NS
Mean arterial pressure (mm Hg)	Control	140 ± 5	** 145 ± 5	NS
	Septic	138 ± 5	** 122 ± 6	<0.02
Heart rate (bpm)	Control	143 ± 11	135 ± 11	NS
	Septic	135 ± 6	133 ± 8	NS
Rectal temperature (°C)	Control	40.3 ± 0.2	* 40.3 ± 0.2	NS
	Septic	40.4 ± 0.2	* 41.1 ± 0.3	<0.02
Renal blood flow[b] (ml/min)	Control	226 ± 20	220 ± 25	NS
	Septic	280 ± 37	308 ± 25	NS
Renal blood flow/per gram (ml/min/g)	Control	5.15 ± 0.33	4.97 ± 0.41	NS
	Septic	5.52 ± 0.74	6.09 ± 0.52	NS

[a] Mean ± SEM.

[b] Renal blood flow is expressed as the mean value of right and left kidneys.

* $p < 0.05$, control vs septic animals.

** $p < 0.01$, control vs septic animals.

TABLE 2

		Baseline	Infusion	p Value
White blood cell count (cells/mm^3)	Control	13,000 ± 2,600[a]	** 16,600 ± 3,500	<0.03
	Septic	13,000 ± 1,400	** 3,900 ± 500	<0.0001
Hemocrit (vol%)	Control	42.8 ± 2.6	* 39.2 ± 2.6	NS
	Septic	43.1 ± 1.7	* 47.3 ± 1.6	<0.03
Urine output (ml/min)[b]	Control	0.34 ± 0.18	* 0.39 ± 0.22	NS
	Septic	0.42 ± 0.15	* 0.90 ± 0.19	<0.03
Creatinine clearance (ml/min)[b]	Control	73 ± 14	83 ± 6	NS
	Septic	82 ± 13	93 ± 14	NS
Sodium excretion (μeq/min)[b]	Control	13 ± 6	25 ± 11	NS
	Septic	38 ± 11	104 ± 36	<0.04

[a] Mean ± SEM.

[b] Urine output, creatinine clearance, and sodium excretion expressed as the sum of both kidneys, i.e., total animal values.

* $p < 0.05$, control vs septic animals.

** $p < 0.001$, control vs septic animals.

septic animals and did not change during infusion (Table 1). While rectal temperature did not change in control animals during sterile broth infusion, septic dogs demonstrated pyrexia (40.4–41.1°C) which was also significantly greater than control animals (Table 1). White blood cell count increased slightly but significantly in control animals during sterile broth infusion (Table 2). Septic animals, however, demonstrated a marked leukopenia (13,000–3,900 cells/mm^3) during bacterial infusion (Table 2). Control animals showed no change in hematocrit during infusion. Septic dogs, however, showed significant hemoconcentration during bacterial infusion, which was statistically greater than for control animals (Table 2).

Urine output in control animals did not change significantly during sterile broth infusion (0.3–0.4 ml/min) (Table 2). Septic dogs, however, showed a greater than 100% increase in urine output during bacterial infusion ($p < 0.03$) (Table 2). Thus, during the 90-min bacterial infusion, when all animals were receiving 0.5 ml/min of BHI broth, septic dogs demonstrated polyuria at nearly twice the rate of fluid infusion. Creatinine clearance in both septic and control animals did not change significantly during infusion (Table 2). Baseline sodium excretion was not statistically different between control and septic groups. There was no significant increase in sodium excretion during infusion in control animals (Table 2). Septic animals, however, showed a significant increase in sodium excretion (38–104 μq/min) during bacterial infusion (Table 2).

Baseline RBF in control animals was 226 ml/min and did not change significantly during sterile broth infusion (Table 1). Septic animals demonstrated a mean baseline RBF of 280 ml/min, which was not statistically greater than control animals. RBF increased to 308 ml/min during bacterial infusion. This change, however, was not statistically significant (Table 1).

Distribution of intrarenal blood flow was analyzed for both right and left kidneys in all animals. There was no statistically significant difference between right and left kidneys. Therefore, the mean of right and left kidney values was utilized. Uncorrected distribution of blood flow (Layers 1–4) and corrected distribution of blood flow

TABLE 3

PERCENTAGE DISTRIBUTION OF INTRARENAL BLOOD FLOW

		Baseline	Infusion	p Value
Layer 1	Control	28.8 ± 1.6[a]	30.0 ± 2.5	NS
	Septic	30.4 ± 1.8	26.4 ± 1.4	<0.007
Layer 2	Control	31.7 ± 1.1	28.0 ± 1.3	<0.04
	Septic	29.9 ± 0.9	26.3 ± 0.9	<0.002
Layer 3	Control	23.8 ± 0.7	22.8 ± 1.3	NS
	Septic	23.4 ± 0.8	23.9 ± 0.8	NS
Layer 4	Control	15.2 ± 1.2	19.3 ± 2.5	NS
	Septic	16.2 ± 1.5	23.4 ± 1.5	<0.0001
Zone 1	Control	37.3 ± 1.6	39.1 ± 2.6	NS
	Septic	39.3 ± 1.8	36.1 ± 1.5	<0.05
Zone 2	Control	34.0 ± 0.9	29.8 ± 1.0	<0.004
	Septic	31.7 ± 0.9	29.2 ± 0.8	<0.005
Zone 3	Control	19.7 ± 0.6	19.2 ± 1.3	NS
	Septic	19.3 ± 0.9	20.6 ± 0.8	NS
Zone 4	Control	9.0 ± 0.8	11.5 ± 1.8	NS
	Septic	9.7 ± 1.0	14.4 ± 1.2	<0.0002

[a] Mean ± SEM.

(Zones 1–4) showed a gradual decrease in percentage from Zone 1 (outer cortex) to Zone 4 (juxtamedullary cortex) (Table 3). No significant difference in distribution was noted during baseline between control and septic animals. During sterile broth infusion there was a statistically significant decrease in the percentage distribution of blood flow to Zone 2 in control animals, while Zones 1, 3, and 4 were unchanged (Table 3 and Fig. 1). In addition to a similarly decreased blood flow distribution to Zone 2, septic animals demonstrated a significantly decreased distribution of blood flow to outer cortical Zone 1 (39.3–36.1%). Furthermore, percentage distribution to juxtamedullary Zone 4 increased from 9.7 to 14.4% ($p < 0.0002$) (Table 3 and Fig. 2). Differences in blood flow distribution between control and septic animals are shown in Fig. 3.

The only significant change in absolute

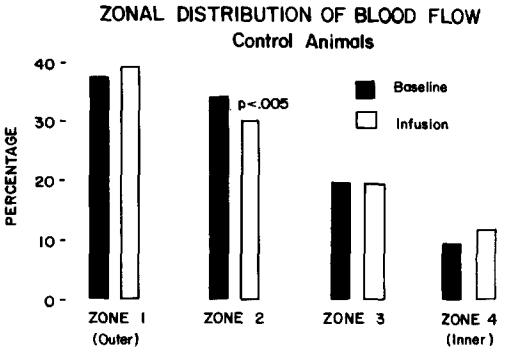

FIG. 1. Percentage distribution of intrarenal blood flow to each of four equal volume cortical zones in control animals.

zonal perfusion was a significant increase to juxtamedullary Zone 4 of septic animals during bacterial infusion (4.5–6.9 ml/min/g) (Table 4, Figs. 4 and 5). This was statistically different from control animals (Fig. 6).

When septic dogs were considered individually, six dogs each had increased RBF ("Group 1"), while three dogs each had decreased RBF ("Group 2"). High cardiac index was not correlated with high RBF in these dogs. Furthermore, no other variable allowed separation into these groups. Baseline mean RBF in Group 2 was significantly higher than both control and Group 1 animals (Table 5). Group 1 dogs showed a significantly increased RBF during infusion when compared to control animals. Thus, dogs responded to bacterial infusion with increased RBF compared to control animals,

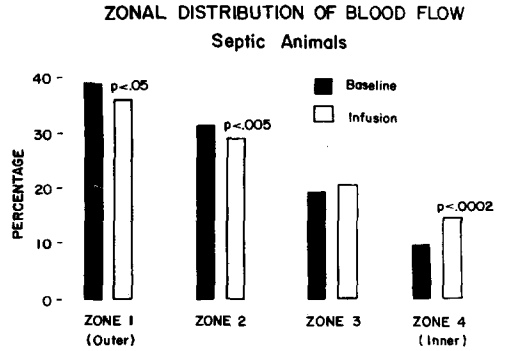

FIG. 2. Percentage distribution of intrarenal blood flow to each of four equal volume cortical zones in septic animals.

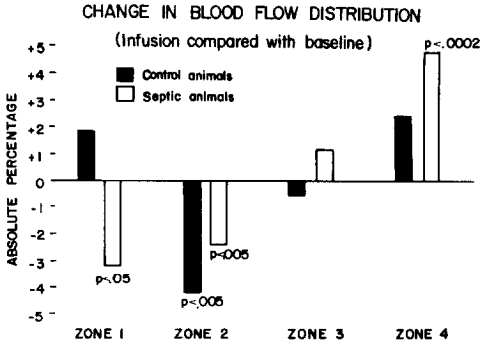

FIG. 3. Change in the percentage ditribution of zonal blood flow from baseline to infusion. Expressed in absolute percentage units changed for both control and septic animals.

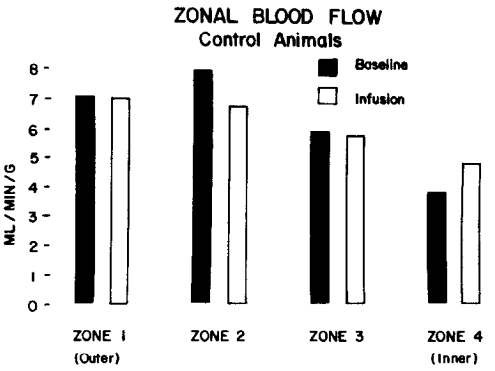

FIG. 4. Zonal perfusion in septic animals. Absolute blood flow rate per gram of tissue in each cortical zone.

unless they began the experiment with an already elevated RBF.

Intrarenal distribution of blood flow was also analyzed in these two subgroups of septic dogs. Both Group 1 and Group 2 animals showed the same pattern of redistribution to the juxtamedullary cortex as did septic dogs as a whole (Table 5). Increased total RBF during bacterial infusion in Group 1 was associated with increased zonal perfusion only to the juxtamedullary cortex (Table 5). Decreased total RBF in Group 2 during bacterial infusion was associated with decreased zonal perfusion of the outer cortex (Zones 1, 2, and 3) but unchanged juxtamedullary perfusion (Table 5).

Pathological examination of the kidneys revealed that microspheres were uniformly found in the distal capillary loops of glomeruli. Only occasionally were two microspheres lodged together and never more than two microspheres were seen together in one vessel. No microspheres were observed within the medulla. Control animals had histologically normal kidneys with the presence of microspheres as noted above. Septic animals showed mild degenerative changes in epithelial cells of the entire tubular portion of the nephron. Numerous polymorphonuclear leucocytes were seen within the capillary lumen of glomeruli. No difference was noted between outer cortical and juxtamedullary glomeruli. No fibrin thrombi were seen.

TABLE 4

		Baseline	Infusion	p Value
Zone 1 perfusion (ml/min/g)	Control	7.1 ± 0.6[a]	7.1 ± 0.6	NS
	Septic	8.0 ± 1.0	8.3 ± 1.0	NS
Zone 2 perfusion (ml/min/g)	Control	8.0 ± 0.6	6.8 ± 0.6	NS
	Septic	8.0 ± 1.1	8.1 ± 0.8	NS
Zone 3 perfusion (ml/min/g)	Control	5.9 ± 0.4	5.7 ± 0.8	NS
	Septic	6.3 ± 1.0	7.2 ± 0.5	NS
Zone 4 perfusion (ml/min/g)	Control	3.8 ± 0.4	* 4.9 ± 0.9	NS
	Septic	4.5 ± 0.9	* 6.9 ± 0.3	<0.03

[a] Mean ± SEM.

* $p < 0.03$, control vs septic animals.

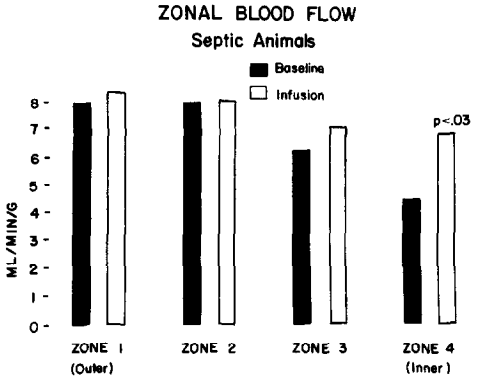

FIG. 5. Zonal perfusion in septic animals. Absolute blood flow rate per gram of tissue in each cortical zone.

DISCUSSION

A *Pseudomonas* strain with demonstrated virulence in dogs was used in this study. Quantitative blood cultures (4.8×10^4 org/ml) were comparable to lethal bacteremic levels reported by Postel *et al.* ($4-6 \times 10^4$ organisms/ml) [14]. Other measurements were similar in these two studies with the exception of temperature. The hypothermia noted by Postel *et al.* may have been due to pentobarbital suppression of the pyrexic response or to differences in the strain of *Pseudomonas* employed.

Cardiac output in some septic animals was clearly increased during bacterial infusion. Mean cardiac index for all dogs, however, did not significantly change. It has generally been observed that hyperdynamic circulation is seen only in the presence of adequate fluid resuscitation [21]. In the present model, fluid input was necessarily restricted to demonstrate "inappropriate" polyuria. Had blood pressure been maintained in these dogs by fluid administration, mean cardiac output would probably have increased, as noted by others [15].

There appear to be two different responses to bacterial sepsis. While most patients respond with high cardiac output, others respond with low cardiac output and usually succumb to this insult [21]. Twenty percent of hindlimb sepsis dogs were termed "nonresponders" by Hermreck *et al.* because they failed to increase their cardiac output [5]. Hinshaw *et al.* described two distinct responses in dogs receiving live *E. coli* [7]. Group 1 dogs responded with increases in cardiac output, renal blood flow, and urine output, and a gradual decrease in blood pressure. Group 2 dogs showed an abrupt decrease in blood pressure with decreased cardiac output, renal blood flow, and urine output. Group 2 dogs had a baseline RBF of 4.3 ml/min/g compared to 3.7 ml/min/g in Group 1. This agrees with observations in the present study that animals responding to bacterial infusion with decreased RBF (Group 2) had a higher baseline RBF than animals responding with increased RBF (Group 1). In analyzing zonal perfusion (Table 5), it is clear that Groups 1 and 2 differed at baseline due to increased perfusion of the outer cortex in Group 2. The etiology of this variation in baseline RBF was not determined in this study. Differences in response to bacterial sepsis are multifactorial and have not been delineated. Nevertheless, these differences did not alter the influence of bacterial infusion upon increased juxtamedullary blood flow.

Inappropriate polyuria has been documented in both patients and dogs during bacterial sepsis [6, 11, 16]. Endotoxin administration, in contrast, produces markedly decreased renal blood flow and oliguria [7]. In this study, diuresis persisted during bacterial infusion despite fluid restriction. In the presence of hypotension and hemoconcentration, this represents an "inappro-

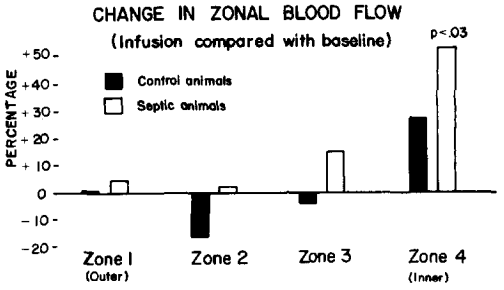

FIG. 6. Change in zonal perfusion from baseline to infusion. Expressed as percentage change for both control and septic animals.

TABLE 5

		Baseline	Infusion	p Value
Total renal blood flow (ml/min)	Group 1[a]	*217 ± 28[b]	321 ± 30	<0.04
	Group 2[c]	407 ± 17	††283 ± 51	NS
	Control	†226 ± 20	220 ± 25	NS
Zone 1 distribution (%)	Group 1	40.7 ± 2.0	37.3 ± 1.5	NS
	Group 2	36.7 ± 3.5	33.7 ± 3.5	<0.02
Zone 2 distribution (%)	Group 1	31.0 ± 1.2	29.0 ± 1.2	<0.05
	Group 2	33.0 ± 1.0	30.0 ± 0.9	NS
Zone 3 distribution (%)	Group 1	19.0 ± 1.2	20.3 ± 1.1	NS
	Group 2	20.0 ± 1.0	21.0 ± 1.5	NS
Zone 4 distribution (%)	Group 1	9.5 ± 0.9	13.5 ± 1.1	<0.01
	Group 2	10.0 ± 3.0	16.3 ± 3.0	<0.02
Zone 1 perfusion (ml/min/g)	Group 1	*6.4 ± 0.7	8.9 ± 1.2	NS
	Group 2	11.1 ± 1.7	7.2 ± 1.8	<0.05
Zone 2 perfusion (ml/min/g)	Group 1	***5.9 ± 0.5	8.4 ± 1.0	NS
	Group 2	12.2 ± 0.8	7.6 ± 1.5	NS
Zone 3 perfusion (ml/min/g)	Group 1	**4.6 ± 0.6	7.5 ± 0.7	<0.02
	Group 2	9.6 ± 1.0	6.6 ± 0.7	NS
Zone 4 perfusion (ml/min/g)	Group 1	3.3 ± 0.7	6.8 ± 0.4	<0.003
	Group 2	6.7 ± 2.0	7.1 ± 0.3	NS

[a] Group 1: $n = 6$, septic animals with increased RBF.
[b] Mean ± SEM.
[c] Group 2: $n = 3$, septic animals with decreased RBF.
* $p < 0.02$, Group 1 vs Group 2, baseline.
** $p < 0.002$, Group 1 vs Group 2, baseline.
*** $p < 0.001$, Group 1 vs Group 2, baseline.
† $p < 0.03$, Group 2 vs Control, baseline.
†† $p < 0.001$, Group 1 vs Control, infusion.

priate polyuria." An intriguing hypothesis to explain this phenomenon is redistribution of renal blood flow to the juxtamedullary cortex. The presence of a high medullary concentration gradient is a major determinant of urine volume by means of the countercurrent mechanism of Henle's loop [4, 10]. Medullary blood flow is derived from efferent arterioles of juxtamedullary glomeruli [10]. Since microspheres will not pass through glomeruli to the medulla, juxtamedullary cortical flow (Zone 4) is used as a measure of medullary flow [12, 16, 17, 19]. Increased medullary blood flow will diminish (or wash out) the medullary concentration gradient [4, 10]. Lowering this medullary interstitial concentration decreases water reabsorption in Henle's loop and in collecting tubules so that water diuresis results [4, 10]. In this situation the effect of ADH is blunted, since increased collecting tubule permeability cannot result in water reabsorption without a concentration gradient [4]. Clinically, Lucas *et al.* found that ADH administration did not affect inappropriate polyuria [2, 11]. Hermreck *et al.* found in dogs with septic hindlimbs that ADH did decrease diuresis [6]. However, this administered dose of ADH has been criticized as probably causing renal vasoconstriction with decreased urine output on this basis [11].

Increased blood flow to juxtamedullary glomeruli may in itself cause natriuresis [4]. Increased perfusion of these nephrons with unchanged GFR implies a decreased

filtration fraction. This results in lower peritubular osmotic pressure and less proximal tubular sodium reabsorption, leading to natriuresis [19]. An alternative mechanism proposed by Earley *et al.* is that decreased medullary hypertonicity leads to decreased water movement out of the permeable descending limb of Henle's loop [4]. A large volume of tubular fluid with the same amount but a lower concentration of sodium would thus reach the ascending limb. Since sodium reabsorption proceeds to a minimal concentration, a larger volume of fluid and an increased total amount of sodium would be delivered beyond Henle's loop, resulting in both natriuresis and diuresis [4].

Although redistribution of blood flow can explain polyuria and natriuresis during sepsis, many other factors, including aldosterone, ADH, renal perfusion pressure, catecholamines, renin–angiotensin, and prostaglandins may also contribute to this phenomenon. This study has not excluded these factors nor has it proven that redistribution of blood flow is responsible for the polyuria and natriuresis observed.

Ravikant and Lucas reported that renal blood flow distribution was unchanged in septic piglets using a microsphere technique [15]. Their technique of counting radioactivity in the medulla as an index of medullary blood flow, however, is subject to criticism. Since medullary blood flow derives from efferent arterioles of juxtamedullary glomeruli, no radioactivity should be found in the medulla when microspheres are injected [12, 19]. Thus, the conclusion that medullary blood flow does not change was not supported by appropriate measurements. In the clinical setting, Cortez *et al.* reported no change in the distribution of intrarenal blood flow in two septic patients using ^{133}Xenon clearance [2]. Recently, the use of xenon clearance for determining renal blood flow distribution has been criticized [3, 10, 19, 20]. In animal models, opposite results have been reported utilizing xenon clearance and microspheres [10, 19]. The validity of microsphere determination of renal blood flow distribution has been discussed extensively elsewhere and it is generally accepted to be the most accurate current technique [10, 12, 19]. In the absence of valid laboratory confirmation using microsphere techniques, the conclusion that renal blood flow does not redistribute during clinical sepsis seems ill-advised when based on xenon clearance measurements.

In the present study, decreased arterial pressure and increased or unchanged renal blood flow implied vasodilatation or decreased renal resistance. It is interesting that nearly all manipulations resulting in decreased renal resistance evoke redistribution of blood flow to the juxtamedullary cortex [10]. These include saline diuresis [20], hemorrhagic hypotension [17], and infusion of bradykinin [13], acetylcholine [13], and prostaglandin E. [8]. Unless total renal blood flow decreases markedly, as in hemorrhagic hypotension, these factors were all associated with diuresis and natriuresis [10]. Thus, the association of increased juxtamedullary blood flow with natriuresis and diuresis during renal vasodilation is not unique to this study.

The clinical application of these results awaits further delineation of the causes of renal blood flow redistribution. It is known that prostaglandin E infusion causes renal vasodilation with increased juxtamedullary blood flow [8] and, further, that indomethacin administration diverts blood flow away from the inner cortex, presumably by inhibiting prostaglandin synthesis [9]. It is possible that pharmacologic manipulation of intrarenal blood flow, perhaps by prostaglandin inhibition, might theraputically affect the inappropriate polyuria of sepsis.

SUMMARY

Inappropriate polyuria during bacterial sepsis represents a poorly understood clinical entity. This study employed live *Pseudomonas aeruginosa* infusion to simulate

this disorder in awake dogs. Intrarenal blood flow distribution was measured using radioactively labeled microspheres. Hypotension, leucopenia, hemoconcentration, pyrexia, polyuria, and natriuresis were produced. Most dogs showed increased total renal blood flow. Redistribution of renal blood flow away from the outer cortex toward the juxtamedullary cortex, as well as increased absolute perfusion of the juxtamedullary cortex, occurred. Washout of the medullary interstitial concentration gradient by increased blood flow can explain the observed diuresis. These results support but do not prove a causal relationship between redistributed intrarenal blood flow and polyuria during bacterial sepsis.

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