Sepsis:

A Mechanism for Vasodilatation in the Kidney

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THE SYSTEMIC HEMODYNAMIC effects of severe sepsis reflect a hyperdynamic state characterized by an increased cardiac index, expanded blood volume, widened pulse pressure, expanded extracellular fluid volume and decreased peripheral vascular resistance.[3,20] The renal circulation is classically considered exempt from this hyperdynamic state and responds to sepsis with increased renal vascular resistance and decreased renal flow. Most estimates of renal plasma flow in septic patients, however, have been extrapolated from measurements of para-amino hippurate clearance (C_{PAH}) assuming a constant extraction ratio (E_{PAH}) of 0.91. In view of the many factors such as temperature,[7] liver disease,[8] and acute or chronic fluid loading,[1] which are known to alter E_{PAH}, this assumption must be regarded as highly speculative pending clinical confirmation in septic patients.

Recent clinical[17] and experimental observations[10] of renal function in the presence of sepsis cast some doubt on the concept that the renal circulation is truly exempt from this hyperdynamic state. Clinically,[17] we have identified in a significant number of severely septic patients a syndrome of "inappropriate polyuria" characterized by relatively high urine volumes which tend to deplete the required circulatory volume and lead to hypotension and renal failure if large intravenous fluid replacement is not provided. This syndrome is comparable to that seen in patients receiving phenoxybenzamine. Large volumes of intravenous fluid replacement maintain normal effective circulatory volume as measured by blood pressure and pulse and protect renal function as measured by glomerular filtration rate and effective renal plasma flow. Experimentally, Hermreck and Thal[10] reported an increase in true renal blood flow in dogs with septic hind limbs. This increase in renal blood flow was measured with an electromagnetic flowmeter and correlated directly with a concomitant increase in cardiac output.

The present study was designed to determine: 1) in dogs, the effect of a different septic preparation on renal vascular resistance, and 2) in man, the effect of severe sepsis on renal function and hemodynamics.

Methods

1. *Experimental Studies*

Renal vascular resistance in dogs was measured in an *in situ* isolated canine kidney[13] perfused at a constant rate intermittently with autologous blood, homologous control blood and homologous blood from septic dogs. Laparotomy and left nephrectomy were performed on 16 adult mongrel dogs under pentobarbital anesthesia (25 mg./Kg.) and controlled endotracheal ventilation. The dogs weighed between 15 and 23 Kg. The aorta above and below both renal arteries was dissected free and the intervening lumbar arteries were ligated and divided. The left renal artery was cannulated with a #320 polyethylene catheter for perfusion into the isolated aorto-renal segment (ARS). A second polyethylene catheter was passed retrograde into the ARS via the

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femoral artery and used to monitor continuous ARS pressure. Temporary occlusion with appropriately placed umbilical tapes allowed intermittent isolation of the ARS for purposes of perfusion. The carotid artery was cannulated and used to perfuse the ARS with autologous blood through an occlusive finger pump and to measure systemic pressure.[13] ARS perfusion pressure was maintained slightly above systemic pressure to minimize or eliminate interference from collateral circulation. Flow rates required to maintain this perfusion pressure averaged 103 ml./min. (range: 63–175 ml./min.) All dogs were heparinized (2 mg./Kg.) prior to initiating the perfusion.

The ARS was intermittently perfused with autologous blood from the recipient dog's own carotid artery until reliable baseline measurements were obtained. After equilibration, the ARS was alternately perfused through a three-way stop cock for 20 to 60-second periods with homologous blood obtained from the carotid arteries of both control and septic dogs. Flow rates were kept constant; thus, any change in ARS pressure reflected a change in renal vascular resistance. Following each perfusion with control or septic blood, the ARS was cleared by means of a short-term perfusion with balanced electrolyte solution prior to re-establishing baseline perfusion.

The control dogs received water *ad libitum* from the night prior to operation and cannulation of the carotid artery. The septic dogs were prepared by appendectomy without ligature within 24 hours prior to study. These dogs received no antibiotics but received intravenous balanced electrolyte solution to prevent dehydration. Approximately 60% of the dogs made septic by this method died within 24 hours and were thus not used. Hematocrit and serum osmolalities were monitored in the surviving septic dogs and the control dogs. Only those septic and control dogs with comparable hematocrits (± 3%) and serum osmolalities (± 5%) were included. All dogs with hematocrit levels below 35% and above 45% were excluded. After exclusion of either the dehydrated or hyperosmolar septic animals, a total of 16 ARS preparations were perfused and admissible for statistical evaluation. A total of 25 perfusions from 16 control dogs and 34 perfusions from 16 septic dogs were made into the ARS of 16 recipient animals.

2. *Clinical Studies*

Glomerular filtration rate and effective renal plasma flow were measured by clearances of inulin (C_{IN}) and para-amino hippurate (C_{PAH}) on 34 occasions in 22 severely septic patients with peritonitis due either to hollow viscus perforation or strangulation obstruction. Fifteen of these patients subsequently died and four developed renal failure. Para-amino hippurate extraction ratios (E_{PAH}) were calculated in six of these patients and these measurements were used to calculate true renal blood flow. Measurements of (C_{IN}), (C_{PAH}), and (E_{PAH}) were made during three consecutive 15-minute collection periods after a 45-minute equilibration period, following a bolus injection of inulin and para-amino hippurate calculated to achieve serum levels of 25 mg./100 ml. and 2 mg./100 ml. respectively. Throughout the equilibration and collection periods, a constant infusion of inulin and para-amino hippurate was maintained in order to keep the plasma levels constant. This technic follows the prescribed method of Homer Smith and has been previously reported by us.[17] All studies were made more than 72 hours after the initial operative procedure to minimize or eliminate the effects of anesthesia.

Measurements of (E_{PAH}) in the six severely septic patients were facilitated by placing under direct fluoroscopic control a custom-made #2 wide arc Odman-Ledein type catheter deeply into the right renal vein via a femoral vein. Careful gravity aspiration of blood from these catheters was performed to prevent mixture from inferior vena caval blood. The entire procedure in these six critically ill patients required the careful coordination of both the clinical and renal services along with the intensive care unit nursing personnel and the Department of Radiology. This careful coordination by all involved parties insured optimal patient care throughout the period of renal evaluation. The results of the renal function studies, along with the results of in-depth respiratory and cardiac studies, were used to monitor daily treatment part of which was supervised by the renal unit. All measurements were corrected to 1.73 M^2 surface area and reported as a percentage of the expected norm, which is 125 ± 25 ml./min. for C_{IN} and 650 ± 160 ml./min. for C_{PAH}.[17] Appropriate correlations to the cardiac output determined by cardiogreen dilution technic and total peripheral vascular resistance were made whenever possible.

Results

Experimental Studies

Renal vascular resistance as estimated by the change in ARS pressure while being perfused at a constant flow rate (Average = 103 ml./min.) decreased an average of 34 ± 7.3% SD (69 ± 7.5 ml./min. SD) during 25 perfusions with control blood and 53 ± 8.3% SD (51 ± 8.6 ml./min. SD) during 34 perfusions with septic blood when compared to the baseline perfusion with autologous blood. This decrease in total renal vascular resistance with septic blood over that with control blood in dogs with comparable hematocrits and

TABLE 1. *Effect of Sepsis on Renal Function*

Measurements Studied*	Results
Glomerular Filtration Rate—22 patients C_{IN}(ml./min.)	85 ± 30.3% S.D. (107 ± 38 ml./min. S.D.)
Effective Renal Plasma Flow—22 patients C_{PAH}(ml./min.)	73 ± 29.6 % S. D. (474 ± 192 ml./min. S.D.)
Extraction Ratio Para-amino hippurate in 6 patients E_{PAH} (%)	0.43 Range 0.04 to 0.62
True Renal Plasma Flow in 6 patients C_{PAH}/E_{PAH} in ml./min.	171% Range 51 to 276% (1238 ml./min. Range 364 to 2000 ml./min.)

* Glomerular filtration rate, effective renal plasma flow and true renal plasma flow are expressed as percentage of expected norm corrected to 1.73 M^2 surface area. Actual flow rates are in parentheses.

serum osmolalities was statistically significant ($p = 0.05$).

Clinical Studies

The (C_{IN}) and (C_{PAH}) averaged 85 ± 30.3% SD (107 ± 38 ml./min. SD) and 73 ± 29.6% SD (474 ± 192 ml./min. SD) of the expected norm for the 34 determinations in 22 severely septic patients (Table 1). (E_{PAH}) in the six patients with renal vein samples averaged 0.43 (range = 0.04 to 0.62) compared to an expected normal of 0.91. The two patients with nonoliguric renal failure had an average (C_{IN}) and (C_{PAH}) of 29% (35 ml./min.) and 16% (104 ml./min.) respectively of expected norm. The true renal plasma flow was measured in one of these patients and it was 2000 ml./min. or 276% of expected. Cardiac outputs measured by cardiogreen dilution technique within 36 hours of the renal hemodynamic studies in four patients with (E_{PAH}) measurements averaged 9.0 L/min. reflecting the hyperdynamic state of sepsis. The ratio of true renal blood flow to total cardiac output averaged 21% (range 16% to 26%) in these four patients (Table 2). This rise in true renal blood flow paralleled the increase in cardiac output.

Discussion

The classic concept that sepsis increases renal vascular resistance appears to be an extension of the misconception that sepsis causes increased total peripheral vascular resistance with decreased cardiac output.[11,15,16] This interpretation of the systemic and renal hemodynamic effects of sepsis is based primarily on animal studies where various artificial preparations were used to mimic clinical sepsis. Unfortunately, clinical sepsis is not a pure syndrome that can be reproduced by infusion of endotoxin or other bacterial products but is a complex physiologic response to a multiplicity of offending stimuli released from various bacteria with their appropriate toxins and several factors which have not yet been identified. The systemic vasodilatory effects of sepsis became documented only when investigation shifted from the experimental laboratory to the intensive care unit. These systemic hemodynamic studies were facilitated by the accurate measurements of true cardiac output which can be obtained by using the cardiogreen dilution technic. Accurate measurements of true renal blood flow have in the past been hampered by the difficulties inherent in obtaining uncontaminated renal vein samples when measuring para-amino hippurate clearance. This led to the frequent use of para-amino hippurate clear-

TABLE 2. *Sepsis and Renal Hemodynamics—Parameters Studied**

Patients	GFR (C_{IN})	ERPF (C_{PAH})	Extraction Ratio (E_{PAH})	TRPF ($C_{PAH}/(E_{PAH}$)	Renal Blood Flow Cardiac Output
1.	12% †(15 ml./min.)	12% (80 ml./min.)	4%	276% (2000 ml./min.)	19%
2.	136% (169 ml./min.)	135% (883 ml./min.)	62%	196% (1424 ml./min.)	23%
3.	97% (121 ml./min.)	106% (687 ml./min.)	48%	198% (1431 ml./min.)	26%
4.	114% (149 ml./min.)	79% (515 ml./min.)	45%	158% (1144 ml./min.)	—
5.	76% (95 ml./min.)	69% (448 ml./min.)	42%	147% (1066 ml./min.)	16%
6.	86% (107 ml./min.)	31% (207 ml./min.)	56%	51% (364 ml./min.)	—
Average	87% (109 ml./min.)	72% (470 ml./min.)	0.43	171% (1238 ml./min.)	21%

* GFR, ERPF and TRPF measurements are corrected to % of expected norm per 1.73 M^2.
† Actual flow rates are in parentheses.

ance as a measurement of renal plasma flow assuming a constant extraction ratio of 0.91. It is apparent from the present study that this assumption is invalid and previous clinical measurements of renal blood flow using this technic must be discounted. Clearance of para-amino hippurate must be regarded as only a measurement of effective renal plasma flow by which one measures plasma perfusing functioning nephrons.

Hermreck and Thal[10] were the first to document a decrease in renal vascular resistance in septic animals. They used an electromagnetic flowmeter to measure flow through the renal artery in dogs with septic limbs. Using the same animal model for sepsis[18] we found a significant decrease in effective renal plasma flow but no decrease in true renal plasma flow. The extraction of para-amino hippurate in these animals was significantly reduced in comparison to control dogs. Thal postulated that increased renal blood flow in this preparation was due to the release of vasoactive agents such as endogenous pyrogens.[5] This concept is supported by the decrease in renal vascular resistance seen in the isolated aorto-renal segment when being perfused at a constant flow with blood from a septic animal. Clinical support of this concept has been limited previously to the study of renal hemodynamics following pyrogen,[4,12] or bradykinin[6] administration in human volunteers. These patients developed renal hyperemia with increased true renal blood flow and sodium excretion. The present study demonstrates that the kidney does share in this hyperdynamic state in critically ill septic patients.

The mechanism whereby renal vascular resistance is decreased in septic patients is uncertain. The hyperdynamic state seen clinically with massive sepsis is not accompanied by a similar increase in oxygen consumption,[2,20] so that systemic shunting seems likely. Such shunting is either physiologic whereby red blood cells passing through capillaries of septic areas are not releasing oxygen, or else anatomic in which pre-capillary arteriovenous communications allow the blood to bypass the cells. A similar phenomenon apparently is operative within the kidney. This may result from a redistribution of blood flow decreasing cortical flow while the medullary flow increases.[14] Such a redistribution could result in selected tubules exceeding their transport maximum for secreting para-amino hippurate. The effect of specific factors such as drugs, acidosis, or fever, upon the efficiency of the transport mechanism of these perfused tubules, however, is unknown. Alternatively, the blood may be perfusing the tubules evenly but the cells may not transport the para-amino hippurate as a result of injury to the transport mechanism. Regardless of which mechanism is active, extraction of para-amino hippurate is decreased while true renal blood flow increases in proportion to the increase in cardiac output.

The hyperdynamic renal circulation may explain the "inappropriate polyuria" which has been observed in many of these patients.[17] These patients may excrete from 200 to 500 cc. urine per hour at the expense of the circulatory volume resulting in hypotension if intravenous fluid replacement is not provided. This polyuria may reflect the increased solute[4] and sodium excretion[4] seen with renal hyperemia in man following pyrogen administration. Alternatively, pre-glomerular arterial venous shunting may increase renal venuole pressure sufficiently to impair sodium reabsorption. Certainly the anatomic and physiologic mechanisms of renal hyperemia in sepsis needs to be further clarified. Currently we are exploring the role of osmolar clearance, sodium reabsorption and renal venous pressure in comparable septic patients. Pending better understanding of renal hyperemia in sepsis, clinicians should anticipate inappropriately high urine excretion in septic patients. Fluid and electrolyte replacement in such patients is facilitated by close monitoring of urinary sodium concentration which, if inordinately low, reflects effective hypovolemia even when actual measurements of blood volume and central venous pressure are elevated.

Summary

The effects of sepsis on renal hemodynamics were studied: 1) Experimentally in dogs, by constant flow perfusions of both control and septic blood into an *in situ* isolated aorto-renal segment (ARS) in which a change in pressure reflects a change in renal vascular resistance (RVR) and 2) Clinically, by serial measurements of para-amino hippurate (ERPF) and Inulin clearance (GFR) in 22 septic patients and para-amino hippurate extraction ratio (E_{PAH}) in six critical septic patients.

Experimentally, RVR in the ARS decreased an average of 34% with control blood and 53% with septic blood. Clinically, GFR and ERPF averaged 85% and 73% of expected norm in 22 patients and E_{PAH} averaged 0.43 in six patients. Total renal blood flow averaged 171% of expected norm in six patients and 21% of cardiac output in four patients. The possible etiology and clinical implications of this renal hyperemia in septic patients are discussed.

References

1. Biglieri, E. G. and Forsham, P. H.: Studies on the Expanded Extracellular Fluid and the Responses to Various Stimuli in Primary Aldosteronism. Am. J. Med., 30:564, 1961.
2. Clowes, Jr., G. H. A., Vucinic, M. and Weidner, M. G.: Circulatory and Metabolic Alterations Associated with Survival or Death in Peritonitis. Ann. Surg., 163:866, 1966.

3. Cohn, J. D., Greenspan, M., Goldstein, C. R., Gudwin, A. L., Siegel, J. H. and Del Guercio, L. R. M.: Arteriovenous Shunting in High Cardiac Output Shock Syndromes. Surg. Gynecol. Obstet., **127**:282, 1968.
4. Combos, E. A., Lee, T. H., Solinas, J. and Mitrovic, M.: Renal Response to Pyrogen in Normotensive and Hypertensive Man. Circulation, **36**:555, 1967.
5. Cooper, K. E.: Mechanisms of Action of Pyrogens. Fed. Proc., **22**:721, 1963.
6. Gill, Jr., J. R., Melmon, K. L., Gillespie, Jr., L. and Bartter, F. C.: Bradykinin and Renal Function in Normal Man: Effects of Adrenergic Blockade. Am. J. Physiol., **209**:844, 1965.
7. Gillenwater, J. Y., Frohlick, E. D. and Keller, A. D.: Differential Effects of Heat on Splenic and Renal Vascular Beds. Am. J. Physiol., **207**:133, 1964.
8. Gordon, M. E.: The Acute Effects of Abdominal Paracentesis in Laennec's Cirrhosis upon Changes in Electrolytes and Water, Renal Function and Hemodynamics. Am. J. Gastroenterol., **33**:15, 1960.
9. Hahn, H. H., Char, D. C., Postel, W. B. and Wood, W. B.: Studies on the Pathogenesis of Fever XV. The Production of Endogenous Pyrogen by Peritoneal Macrophages. J. Exptl. Med., **126**:385, 1967.
10. Hermreck, A. S. and Thal, A. P.: Mechanisms for the High Circulatory Requirements in Sepsis and Septic Shock. Ann. Surg., **170**:677, 1969.
11. Hinshaw, L. B., Emerson, Jr., T. E. and Reins, D. A.: Cardiovascular Responses of the Primate in Endotoxin Shock. Am. J. Physiol., **210**:335, 1966.
12. Lathem, W.: The Urinary Excretion of Sodium and Potassium During the Pyrogenic Reaction in Man. J. Clin. Invest., **35**:947, 1956.
13. Lucas, C. E. and Read, R. C.: Red Cell Crenation and the Renal Hemodynamic Effect of Mannitol. Surgery, **59**:408, 1966.
14. McNay, J. L. and Abe, Y.: Redistribution of Cortical Blood Flow During Renal Vasodilatation in Dogs. Circ. Res., **27**: 1023, 1970.
15. Priano, L. L., Wilson, R. D. and Traber, D. L.: Cardiorespiratory Alterations in Unanesthetized Dogs Due to Gram-negative Bacterial Endotoxin. Am. J. Physiol., **220**: 705, 1971.
16. Reddin, J. L., Starzecki, B. and Spink, W. W.: Comparative Hemodynamic and Humoral Responses of Puppies and Adult Dogs to Endotoxin. Am. J. Physiol., **210**:540, 1966.
17. Rosenberg, I. K., Gupta, S. L., Lucas, C. E., Khan, A. A. and Rosenberg, B. F.: Renal Insufficiency After Sepsis and Trauma: A Prospective Functional and Ultrastructual Analysis. Arch. Surg., **103**:175, 1971.
18. Sankaran, S., Rosenberg, I. K. and Lucas, C. E.: Unpublished data.
19. Webster, M. E. and Gilmore, J. P.: Influence of Kallidin-10 on Renal Function. Am. J. Physiol., **206**:714, 1964.
20. Wilson, R. F., Thal, A. P., Kindling, P. H., Grifka, T. and Ackerman, E.: Hemodynamic Measurements in Septic Shock. Arch. Surg., **91**:121, 1965.