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NEPHROLOGY FORUM

Pathophysiology of pre-renal azotemia

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CASE PRESENTATION

An 18-year-old white male was admitted to the hospital for a lung transplant. This high school senior has no family history of lung disease and currently lives at home.

The patient had had seizures on day 2 after birth and has moderate cerebral palsy and well-controlled asthma. He was well until approximately one year prior to admission, when he fainted while lifting weights. Dyspnea, weakness, and light-headedness developed over the next three months. Primary pulmonary hypertension, diagnosed approximately seven months prior to this admission, worsened rapidly approximately two months later. The patient successfully underwent lung transplantation.

After the transplant, he received glucocorticoids, cyclosporine, and approximately 50–75 g/day of amino acids. He had been mildly hyperglycemic. On postoperative day 14, he received an additional 1 g of methylprednisolone for presumed transplant rejection. He received no blood transfusion. From days 3 through 11, the BUN and serum creatinine concentrations increased in parallel, from 22 mg/dl and 1.1 mg/dl to 123 mg/dl and 3.2 mg/dl, respectively. Thereafter, the cyclosporine level was reduced, and the serum creatinine declined somewhat. The BUN continued to rise, however. The serum sodium concentration decreased from 140 mEq/liter to 129 mEq/liter between day 3 and day 9, then increased gradually to 150 mEq/liter on day 15. Urine output ranged from 1 to 4 liters/day, but was fixed around 2 liters/day from days 9 through 14. Serial determinations of body weight were made on different scales and correlated poorly with intake and output (Table 1). Azotemia prompted a nephrology consultation on postoperative day 15.

On examination, the patient was awake and alert. Although intubated, he complained of thirst. The blood pressure was 103/64 mmHg; heart rate, 114 beats/min; the heart was in sinus rhythm; and the central venous pressure was 6 cm. Oxygen saturation was 96%. The skin and mucous membranes were dry. No edema was present. He had no signs of gastrointestinal bleeding.

Table 1 displays the pertinent clinical and laboratory values for this patient. In addition, the serum albumin was 2.4 g/dl. A 2 liter, 24-hour urine collection contained 30 g of urea nitrogen and 14 mEq/liter of chloride. The urine osmolarity on another spot sample was 650 mOsm/kg. The plasma osmolality was 360 mOsm/kg. The fractional excretion of urea was approximately 25%. Based on the rate of rise of the BUN and the amount of urea being excreted, the protein catabolic rate was estimated to be approximately 200 g/day.

On the basis of the physical exam, the patient was thought to be volume depleted. The high urine osmolarity and low fractional excretion of urea indicated the presence of endogenous ADH. The rising serum sodium suggested the loss of electrolyte-free water. The urine urea content indicated that despite the low fractional excretion of urea, 75% of the total urine output (1.5 liters/day) was obligated to the excretion of urea. All other things being equal (even the patient's inability to concentrate the urine above 650 mOsm/kg), if the protein catabolic rate were reduced to 60 g/day and the patient were placed in zero nitrogen balance, the urine output would have decreased to 875 ml/day. If the decrease in excretory burden and cessation of diuretics would allow for more efficient concentration of the urine, then the volume would decrease further. The consulting nephrologist recommended that the patient be given hypotonic saline to restore effective extracellular volume and to facilitate excretion of urea. This fluid infusion promptly reduced both the BUN and serum creatinine and corrected the hypernatremia.

DISCUSSION

DR. ROLAND C. BLANTZ (*Professor of Medicine and Head, Division of Nephrology, Hypertension and Bioengineering Institute, University of California, and Veterans Affairs Medical Center, San Diego, California, USA*): This case is characterized by a progressive elevation in BUN concurrent with a more modest increase in serum creatinine concentration and a tendency to both hypernatremia and hyperosmolarity. When first seen by the nephrologist, the patient appeared to be volume depleted; this impression was supported by the physical findings and laboratory data.

The clinical syndrome of pre-renal or functional renal failure is characterized by intact renal parenchymal function but renal hypoperfusion and typically is accompanied by a high ratio of BUN to serum creatinine and a low urine volume. These features arise as consequences of elevated levels of antidiuretic hormone (ADH), which increase reabsorption of both water and urea [1]. The present case is an instance of pre-renal failure that deviates from this paradigm because the urine volume was not low.

Homer Smith demonstrated 40 years ago that urea clearance is not a constant function of glomerular filtration rate (GFR) [2]. Urea back-diffuses into the papillary interstitium under the influence of antidiuretic hormone. The fraction of the tubular content that back-diffuses varies inversely with flow in the collecting duct. In the absence of ADH and in the presence of high urine

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Table 1. Patient's clinical and laboratory data

POD	Na *mEq/liter*	Weight *kg*	Urine output *cc/24 hrs*	Hct *%*	Glucose *mg/dl*	BUN *mg/dl*	Creat *mg/dl*	CsA[a] *ng/ml*
1	145	—	1635	40.0	224	18	1.1	218
2	139	72.5	1985	38.9	156	19	1.3	484
3	140	72.9	3945	35.2	—	22	1.1	786
4	137	70.4	3595	35.0	—	36	1.6	798
5	136	68.9	2935	36.2	141	59	2.0	621
6	136	68.0	2130	35.0	—	64	2.1	741
7	135	66.4	900	33.8	—	60	2.1	521
8	132	70.2	1450	32.3	—	65	2.5	546
9	129	67.6	1930	32.5	206	79	3.0	445
10	133	69.5	2765	30.3	277	102	3.2	528
11	—	67.6	2050	33.6	—	123	3.3	454
12	139	62.5	2180	32.3	—	129	2.5	457
13	140	60.0	2160	29.5	—	129	2.1	247
14	145	65.1	1732	31.3	192	120	2.1	244
15[a]	150	64.9	2760	31.3	—	146	2.2	249
16	153	66.0	2366	30.9	—	154	2.0	—
25	147	70.0	1600	39.9	—	81	1.3	379
26	145	70.5	2280	36.0	—	59	1.1	343

Abbreviations are: CsA, cyclosporine; POD, postoperative day; Hct, hematocrit; BUN, blood urea nitrogen.
[a] A nephrology consultation was obtained on postoperative day 15.

flow, urea clearance approaches 80% of the GFR [3]. In the presence of ADH, urea clearance can fall to 25% of the GFR.

This young man with pre-renal failure presented diagnostic difficulty to the attending physicians because his urine volume was not low. Measurement of the urine osmolarity and concentrations of the main urinary solutes, however, indicated that ADH must have been present and that his renal tubular function was basically intact. Furthermore, it was evident that the BUN had increased because of both an excessive protein catabolic rate and increased tubular urea reabsorption. A rise in plasma ADH levels is mediated both by hypovolemia and by increased extracellular osmolality. Hypovolemia might not have been the only factor driving ADH in this patient. The osmotic and volume stimuli to ADH were exacerbated by the obligate loss of electrolyte-free water required to excrete 30 g/day of urea nitrogen. The loss of "free water" necessitated by urea excretion in turn also increased plasma osmolality and led to further increases in ADH. This obligate water loss created a positive feedback cycle for urea retention in which increased urea production, via effects on systemic volume and sodium concentration, impaired urea excretion. The mechanisms that reduced the GFR in this patient are more complex and will be addressed later, but reduced GFR per se also decreases tubular flow rate and increases urea backdiffusion. This positive-feedback cycle was broken, and the patient improved with the administration of hypotonic saline, which restored volume and reduced serum osmolarity. Pre-renal azotemia was suggested by the fact that treatment not only facilitated urea excretion and decreased the BUN but also reduced the serum creatinine.

Most cases of pre-renal azotemia present little diagnostic challenge, but the condition can go unrecognized when the urine output is high. In a series of patients with polyuric pre-renal failure, renal concentrating defects caused excessive water excretion with relative NaCl retention secondary to volume losses [4]. Hypernatremia due to the loss of electrolyte-free water is an early clue to the presence of a polyuric pre-renal state. The current patient excreted an excessive amount of water because his illness generated an excessive amount of urea. The syndrome of volume depletion and non-oliguric pre-renal failure associated with large solute loads is not uncommon in our experience; it occurs most often in the surgical ICU and in burn and trauma units. Patients with extensive burns are given as much as 2 g/kg of amino acids per day and generate considerable quantities of urea. Glucose and mannitol also commonly produce polyuric pre-renal failure, although hypernatremia is less pronounced in these instances because the osmotic effect of these solutes draws water into the extracellular space [5, 6]. This property is not shared by urea, which easily crosses cell membranes. Mannitol is occasionally prescribed for neurosurgical patients with elevated intracranial pressure after head trauma; in this situation, serum potassium can increase transiently after bolus mannitol administration because of solvent drag and shifts of water from the intracellular compartment. Hypokalemia can follow because of urinary potassium losses [5].

Mechanisms of pre-renal failure

Pre-renal or functional renal failure usually arises as a physiologic response to reduced "effective" extracellular volume, defined by decreased volume receptor stimulation and increased adrenergic activity, and can accompany actual volume loss, congestive heart failure, cirrhosis, nephrosis, or sepsis (Fig. 1). The primary defense against effective volume depletion occurs at the level of tubular reabsorption. These initial compensatory defenses involve increased adrenergic and angiotensin II activity as well as increased aldosterone influence on the tubule; the net effect is increased proximal and distal tubular reabsorption. The subsequent reduction in GFR, required by the definition of renal "failure," arises when this primary defense is inadequate and is mediated, in large part, by further activation of the same neurohumoral systems that modulate tubular reabsorption. This secondary reduction in GFR might be considered the stage of renal decompensation. Badr and Ichikawa have provided an excellent summary of the neurohumoral systems underlying the renal responses in these clinical conditions [7]. These systems include

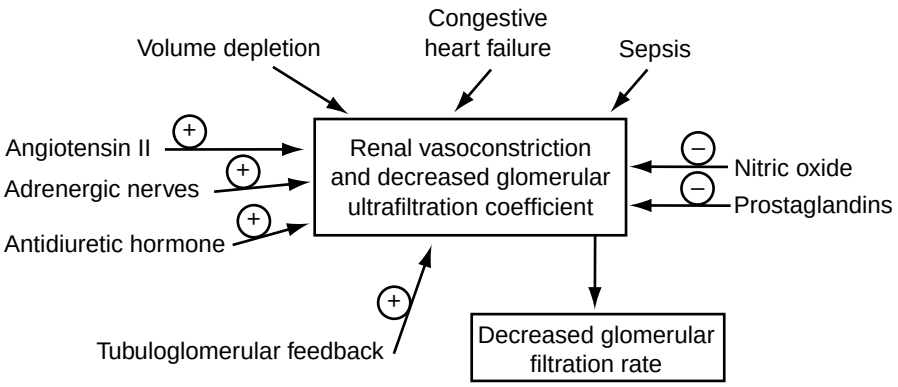

Fig. 1. Functional renal failure. This syndrome commonly derives from three major conditions: volume depletion, congestive heart failure, and sepsis. These conditions, by a variety of mechanisms, constrict the renal vessels and decrease the glomerular ultrafiltration coefficient, thus reducing GFR without damaging the renal parenchyma. Major influences dictating these events in the kidney are vasoconstrictor systems such as angiotensin II (AII), adrenergic nerves, ADH and, under certain circumstances, tubuloglomerular feedback activity. All these potential vasoconstrictor systems are intimately interrelated and are counteracted effectively in the kidney by vasodilatory systems such as local nitric oxide and prostaglandin generation.

the renal sympathetic nerves, renin-angiotensin-aldosterone, and ADH. Also, effective volume depletion can reduce GFR by increasing the sensitivity of tubuloglomerular feedback.

Angiotensin II. Increased intrarenal AII activity is critical among the systems contributing to the renal response to volume depletion and congestive heart failure (Fig. 1). Angiotensin II increases proximal tubular reabsorption, and AII receptor blockade reduces absolute and fractional proximal reabsorption in chronic salt depletion [8–10]. Angiotensin II exerts complex effects on glomerular ultrafiltration by increasing afferent and efferent arteriolar resistances, increasing the glomerular hydrostatic pressure gradient (ΔP), and decreasing the glomerular ultrafiltration coefficient (LpA or Kf) [8]. Increases in afferent and efferent arteriolar resistance also significantly reduce single-nephron plasma flow rate. Thus a balance develops between positive influences (increased ΔP) and negative influences (decreased plasma flow and decreased LpA) that together produce a net effect on GFR. With both modest volume depletion and congestive heart failure, increased AII activity actually can preserve GFR because it causes preferential constriction of the efferent arteriole. Efferent arteriolar vasoconstriction increases ΔP and results in a greater filtration fraction. This increase tends to offset the effect on GFR of reducing nephron plasma flow [9, 11]. With more severe volume depletion or severe CHF, which leads to greater AII activity, the afferent arterioles constrict and reduce both renal plasma flow and filtration fraction [7]. Obviously, therapy directed at restoration of GFR through blockade of angiotensin II activity would not have been appropriate in today's patient, given his volume-depleted state.

The effects of AII in pre-renal states are counteracted by endogenous intrarenal vasodilators, primarily prostaglandins [12, 13] and nitric oxide (NO) [14]. Although vasodilatory prostaglandins and nitric oxide act as primary vasodilators in the systemic circulation, in the kidney these substances primarily mediate their influences by antagonizing the effects of vasoconstrictors such as angiotensin II and renal adrenergic activity. The effects of inhibiting prostaglandin generation in pre-renal states are complex. Acute inhibition of cyclo-oxygenase increases renal vasoconstriction and further reduces GFR [7, 12, 13]. However, chronic inhibition of cyclo-oxygenase reduces intrarenal AII generation [15] and does not decrease GFR. Nitric oxide exerts equally complex effects within the kidney. Although NO can exert tonic influences as an antagonist of angiotensin II, NO also appears to stimulate the renin-angiotensin system such that chronic reductions in NO activity can result in reduced intrarenal angiotensin II generation [16, 17]. In the current patient, prior and concurrent administration of cyclosporine might have suppressed the generation of prostaglandins and NO within the kidney [18], resulting in a state of diminished AII activity within the glomerular microcirculation. This phenomenon has been reported in experimental models of subacute cyclosporine toxicity [16, 17].

Renal adrenergic activity. The renal sympathetic nerves contribute significantly to the pre-renal failure encountered with either volume deficits or congestive heart failure [19–21]. Angiotensin II as well as adrenergic activity contribute to the increased renal vascular resistance during chronic NaCl depletion (Fig. 1) [19]. In this patient, cyclosporine might have further magnified these effects by increasing volume depletion, by decreasing angiotensin II influences within the kidney, and by magnifying renal adrenergic activity [16]. Acute renal denervation restores single-nephron GFR (SNGFR) to normal levels in chronically NaCl-depleted rats via reductions both in afferent and efferent arteriolar resistances; as a result, nephron plasma flow increases [19]. If NaCl-depleted rats are pretreated with AII receptor blockers, acute renal denervation also improves SNGFR and nephron plasma flow, but only via reductions in afferent arteriolar resistance [19]. These studies suggest that in NaCl-depletion, adrenergic activity independently constricts the afferent arteriole and that adrenergic activity influences efferent arteriolar resistance by modulating AII. When renal nerves are stimulated directly, SNGFR decreases by approximately 25% as a result of reductions in both ΔP and nephron plasma flow. However, if AII receptor blockers are administered prior to renal nerve stimulation, the reduction in SNGFR is reduced to less than 10%. This effect could not be attributed to impaired release of norepinephrine during renal nerve stimulation [22].

Renal nerve activity is linked to renin release through β-adrenergic receptors on renin-containing cells. At another level, α_2-adrenergic influences, although purported to decrease renin secretion, increase the activity of AII at effector cells by magnifying the reduction in LpA by angiotensin II [23]. Alpha-1 adrenergic influences within the kidney primarily affect vascular resistances. However, the kidney seems to be less susceptible than is the systemic circulation to α_1-adrenergic influences [24]. In contrast, α_2-adrenergic agonists primarily decrease the glomerular ultrafiltration coefficient, an effect that is mediated via interactions with angiotensin II [23]. These interactions among various subsets of

the adrenergic and angiotensin II systems can be further magnified by treatments applied in the intensive care unit, where agents possessing both α_1- and α_2-adrenergic activity are commonly administered to support blood pressure. A pure α_1-adrenergic agonist such as methoxamine can actually "spare" renal function when compared to more general adrenergic agonists such as norepinephrine [24]. Let me offer one caveat, however: further complex compensatory mechanisms governing intrarenal AII activity can render the response to eliminating renal nerve activity unpredictable [25]. One would predict that acute removal of adrenergic activity would result in vasodilation. In fact, however, this maneuver causes transient acute increases in angiotensin II activity and constancy in GFR and renal blood flow, possibly by altering proximal tubular reabsorption and activating the renin-angiotensin system [25]. However, subacute removal of adrenergic activity exerts further complexities to this relationship because it enhances the kidney's response to angiotensin by increasing the number of AII receptors [26]. In addition, renal vascular sensitivity to AII increases after subacute renal denervation because of major upregulation of AII receptor number [26]. This effect does not appear to be mediated by diminished β-adrenergic activity [27] or by a reduction in the amount of local AII available to cause homologous desensitization of AII receptors [28]. In summary, removal of adrenergic activity, either by pharmacologic means or by renal denervation, produces complex effects on net renin-angiotensin activity within the kidney, both by activating renin-angiotensin activity and by altering angiotensin receptor number. Therefore, removal of adrenergic activity might not result in renal vasodilation.

Other factors modifying renal vasoconstriction and GFR. The important role of prostaglandins in buffering the effects of renal vasoconstrictors has been reviewed in detail elsewhere [7, 12, 13, 15]. However, prostaglandins are not the only paracrine factors that influence the degree of renal vasoconstriction in pre-renal conditions. Nitric oxide also plays a major role [29–32]. Previous studies from our own [14] and other laboratories have shown that inhibition of nitric oxide synthase (NOS) increases renal vascular resistance and decreases nephron plasma flow and filtration rate, while concurrently increasing systemic blood pressure by increasing systemic vascular resistance. This hemodynamic response implies an important tonic influence of NO on systemic as well as renal vascular resistance [14, 28]. Nonetheless, the systemic and renal effects of NO blockade can be disassociated. For instance, in the normal rat, when AII receptor blockers are administered during NOS inhibition, the effect of NOS inhibition on systemic blood pressure remain, yet renal vascular resistance, nephron plasma flow, and GFR return to normal [14]. These results indicate that although NO exerts normal tonic vasodilatory influences on systemic vascular resistance, in the kidney NO is primarily a major antagonist of vasoconstrictors such as AII. Other studies have suggested that the activity of intrarenal NO is also sustained by renal adrenergic activity, primarily via α_2-adrenergic receptors [28, 29]. The kidney's response to NOS inhibition was blunted by renal denervation or by the α_2-adrenergic antagonist yohimbine, and was restored after denervation by infusion of an α_2-adrenergic agonist [28, 29]. The reports that NOS mRNA in the kidney is more prevalent during salt depletion imply that NO production can increase, thereby mitigating pre-renal failure [30]. But this hypothesis cannot be reconciled with the repeated observation that the renal vasoconstriction resulting from acute NOS inhibition is amplified by volume expansion [31, 32]; this observation implies a lesser role for endogenous NO during volume contraction [31, 32]. The present case was further complicated by the use of cyclosporine, a known endothelial toxin and inhibitor of normal endothelium-dependent vasodilation [16, 17]. Gabbai et al have shown that the renal vasodilatory response to glycine infusion is mediated by NO, blunted by cyclosporine, and restored after cyclosporine administration by the NO substrate L-arginine [18]. Therefore, it is conceivable that cyclosporine administration also limits the normal renal vasodilatory response to the large protein load, an effect that is apparently mediated by nitric oxide.

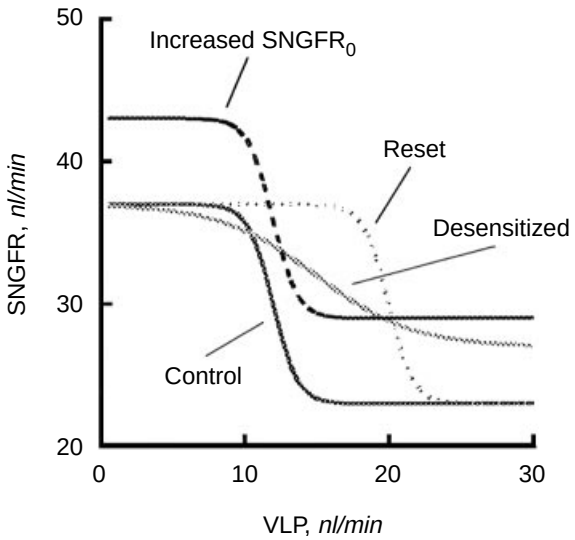

Fig. 2. The relationship between late proximal flow rate (VLP) and the resulting single nephron GFR (SNGFR), which describes the tubuloglomerular feedback system. The system is not static and can adapt by either (*1*) desensitizing, that is, decreasing the efficiency of the system in and around its normal flow rate; (*2*) resetting, that is, altering the relationship between late proximal flow rate and the resulting SNGFR; and (*3*) altering the basal value for nephron filtration rate, at which there is no tubuloglomerular feedback influence (SNGFR).

Tubuloglomerular feedback. The physiologic processes of glomerulotubular balance (GTB) and tubuloglomerular feedback (TGF) comprise a system that coordinates glomerular filtration with tubular reabsorption, and thereby stabilizes both GFR and fluid delivery to the distal nephron [33–39]. Glomerulotubular balance, which determines the dependence of late proximal flow on SNGFR, is mediated by the load dependence of proximal tubular reabsorption [40]. Tubuloglomerular feedback is responsible for an inverse dependence of SNGFR on late proximal flow and is mediated by complex communication between the macula densa and the glomerular microvasculature. The ability of TGF to alter SNGFR in response to changes in late proximal flow is non-linear and saturable. There is a narrow range of flows over which TGF is most reactive. Under normal conditions, GTB and TGF interact to position the normal flow rate somewhere within this narrow range such that TGF is partially activated (Fig. 2). This activation causes SNGFR to be less than it would be if TGF were eliminated. Increases in late proximal flow rate cause renal vasoconstriction and a reduction in SNGFR, as depicted in the normal profile in Figure 2. The basal tone that TGF exerts on

SNGFR can be increased when proximal reabsorption decreases (as during acute tubular dysfunction) or when the TGF mechanism is reset so that it engages at a lower rate of tubular flow.

In a state of uncomplicated pre-renal azotemia, in which the proximal tubule responds normally to neurohumoral influences, fractional proximal reabsorption increases. This rise should reduce the tonic influence of TGF over SNGFR and allow SNGFR to increase. We have utilized a means whereby proximal tubular flow can be measured without being interrupted [37], and we have employed this technique to test for symmetry of the TGF function with respect to ambient tubular flow [38, 39]. A sustained alteration in late proximal flow, whether induced indirectly by an acute change in systemic volume status [38] or directly by supplemented early proximal flow at the level of the single nephron [41], causes TGF to reset such that the ambient flow continues to reside along the steep portion of the new TGF function (Fig. 2). Studies have demonstrated temporal adaptation or resetting of TGF when flow into the loop of Henle increases. Contrasting adaptive phenomena also must occur with reductions in delivery to the macula densa, which should occur in a setting of increased proximal reabsorption. The net effect is that the tonic influence of TGF over SNGFR is reduced in settings of acute volume depletion [38]. Therefore, when the pre-renal state is associated with increased proximal reabsorption, TGF should mitigate the pre-renal reduction in GFR, although this mitigation is partially countervailed by TGF resetting. Studies from this laboratory also have shown that local inhibition of macula densa NOS increases the reactivity of the TGF response and shifts the response leftward relative to the ambient flow, thereby increasing the basal influence of TGF over SNGFR [42]. In other words, endogenous NO within the macula densa likely exerts a tonic desensitizing influence on TGF. Given that the influence of NO on renal function appears to be reduced during volume depletion [31, 32], it is possible that the reduced NO activity in this setting further enhances TGF efficiency, but these specific issues have not been examined experimentally. This degree of leftward resetting would contribute to a further reduction in GFR (Fig. 2). Tubuloglomerular feedback also could contribute to renal vasoconstriction in the presence of modest proximal tubular injury [43, 44], as in patients with major trauma or severe infection who are on the verge of developing acute tubular necrosis. Proximal tubular injury increases the delivery of fluid to the macula densa and leads to TGF-mediated renal vasoconstriction [36, 43]. Pre-renal azotemia or functional renal failure often precedes parenchymal injury and acute tubular necrosis [45]. One can logically assume that there are periods in which a prerenal pattern of vasoconstriction must coexist with early proximal tubular injury and that proximal tubular injury could contribute to the renal vasoconstriction that characterizes the prerenal condition via TGF-mediated mechanisms. One could view this transitional period of early dysfunction of tubular reabsorption as heavily affected by the TGF-mediated defense mechanism, which limits the filtered load per nephron. In this setting, TGF-mediated renal vasoconstriction potentially forestalls tubular injury by reducing the energy demands of the tubule [46, 47].

Fluid loading with solutes other than NaCl reduces TGF responsiveness (Fig. 2). The pattern of effects of increased solute load (for example, glucose, mannitol) on TGF is a reduction in homeostatic efficiency or, as depicted in Figure 2, a desensitized TGF system, in which the slope of gain around the normal flow

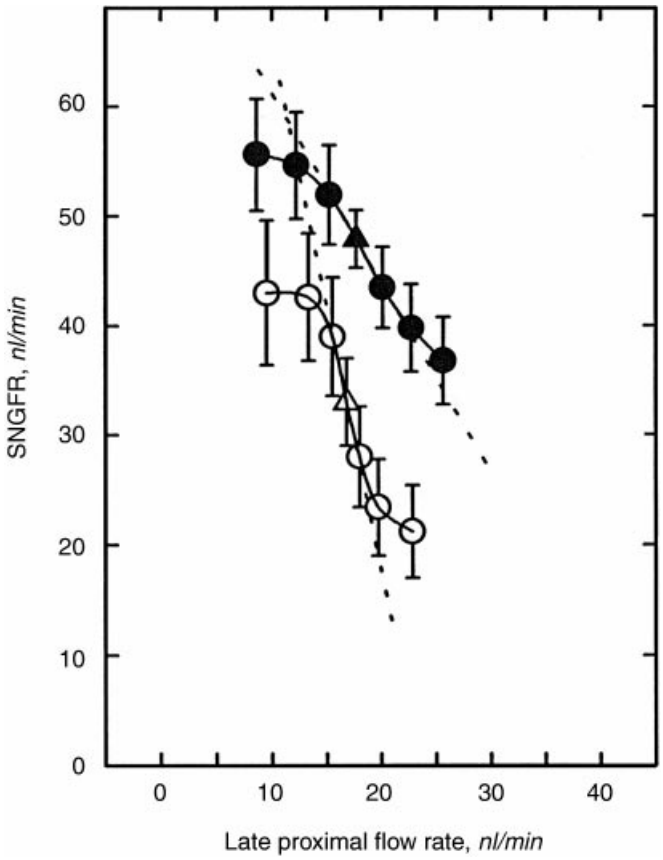

Fig. 3. Dependence of single-nephron glomerular filtration rate (SNGFR) on late proximal flow rate in control animals (○) and in hyperglycemic diabetic animals (●). Two major changes occur as a result of diabetes and hyperglycemia. First, the SNGFR increases. Second, the sensitivity of TGF operation is greatly diminished, whereby the slope around the operating point is decreased. Triangles denote midpoints.

rate is markedly reduced. This reduction has been demonstrated in older studies utilizing traditional methods for the evaluation of TGF during microperfusion of Henle's loop with solutions containing glucose or mannitol [33, 35]. Tubuloglomerular feedback responsiveness is also essentially eliminated in non-diabetic rats made hyperglycemic by systemic infusion of glucose [48]. This blunting of TGF responsiveness during hyperglycemia is not merely the consequence of glucose effects within the tubular lumen. If the loop of Henle of hyperglycemic normal rats is perfused from the late proximal tubule with tubular fluid that is glucose-free, partial inhibition of TGF activity exists. This finding implies that both extraluminal and intraluminal components inhibit TGF during systemic hyperglycemia [48].

We recently assessed the ability of TGF to stabilize flow in free-flowing proximal nephrons in hyperglycemic rats with insulin-treated streptozotocin-induced diabetes [49]. The homeostatic efficiency of TGF was markedly reduced in these animals, and this effect could not be explained by changes in tubular reabsorption (Fig. 3). One might predict that the reduction in TGF efficiency in diabetic rats could be the consequence of intraluminal glucose reducing loop of Henle and macula densa reabsorption. However, specific studies utilizing micropuncture have observed that loop of Henle reabsorption and the macula densa NaCl signal were

essentially normal, while TGF homeostatic efficiency was markedly reduced [49]. Although this response would be expected to reduce the basal influence of TGF on GFR, reduced TGF efficiency also could exacerbate renal NaCl and water losses during an osmotic diuresis. Solute excess in the form of mannitol, glucose, and probably urea suppresses TGF efficiency and can contribute further to urinary NaCl and water losses in addition to the effects of osmotic diuresis [33, 35, 48–50]. Solute-induced suppression of TGF activity interferes with appropriate reductions in GFR. The relative inability of appropriate TGF mechanisms to suppress GFR during solute diuresis results in a higher TGF that could magnify potential NaCl and water losses. In this sense, the normal TGF response should be viewed as a critical mechanism for the conservation of NaCl and water. The greater water loss is recognizable by the patient's tendency to hypernatremia; it is treated by the administration of free water.

A special case: Pre-renal failure in sepsis. The sepsis syndrome, particularly gram-negative sepsis, is characterized by a reduction in systemic vascular resistance and an increase in cardiac output followed by hypotension [51–53]. These cardiovascular events can be recognized early in the ICU during invasive monitoring, because cardiac output increases prior to significant hypotension. Certain aspects of this syndrome have been attributed to cytokine induction of NOS and the subsequent overproduction of nitric oxide, which reduces systemic vascular resistance. However, renal dysfunction in sepsis often resembles pre-renal failure and is not so much the consequence of systemic hypotension as of renal vasoconstriction. This event stands in contrast to the observation that overall systemic vascular resistance is markedly reduced in early sepsis by excess NO production. The questions arise, what is the mechanism of renal vasoconstriction, and why is the response of the renal vasculature opposite to that of the remaining systemic vasculature?

Schultz and Raij have demonstrated that when lipopolysaccharide (LPS) is administered to rats, GFR decreases; if the non-selective NOS inhibitor L-N-arg-methylester (L-NAME) is also administered, the renal dysfunction is aggravated in part because glomerular thrombosis occurs [54]. Recent studies from our laboratory have confirmed that pre-renal failure after LPS administration is markedly worsened by the simultaneous administration of the non-selective NOS inhibitor L-N-monomethylarginine (L-NMMA), by increasing renal vasoconstriction rather than by producing glomerular thrombosis. When the selective blocker of inducible NOS, L-N-imino-lysine (L-NIL), or the inhibitor of iNOS gene transcription, diacetyl-hydropyrimidine (DAHP), is applied to LPS-treated rats, however, GFR is no longer sensitive to LPS. These observations suggest that renal vasoconstriction due to LPS results from feedback autoinhibition of constitutive endothelial NOS when NO is produced by iNOS. We also have demonstrated that agonist-stimulated constitutive NOS is essentially eliminated after the administration of LPS and LPS + L-NMMA, and that L-NIL therapy normalizes endothelial NOS activity [55].

Nitric oxide in the kidney thus is critical to balancing the effects of various renal vasoconstrictors, particularly AII and renal nerves, and the pathogenesis of pre-renal failure and renal vasoconstriction in sepsis is somewhat more complex than that which results from pure volume depletion or congestive heart failure. Selective therapies targeting inducible NOS activity might find practical use in the future.

Summary

Pre-renal failure is a physiologic response to severe volume depletion, congestive heart failure, or sepsis. In certain instances, pre-renal failure can protect the tubule against injury due to energy depletion. Pre-renal azotemia can occur in the presence of a generous urine flow when the kidney is presented with a large osmolar excretory burden. Large solute loads can magnify urinary volume losses via an osmotic diuresis and by diminishing the efficiency of tubuloglomerular feedback mechanisms. In the patient with sepsis, iNOS inhibitors can reverse both renal vasoconstriction and the characteristic systemic cardiovascular abnormalities. Perhaps these agents will play a clinical role in the future in the treatment or prevention of renal failure due to sepsis.

QUESTIONS AND ANSWERS

Dr. Nicolaos E. Madias (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): Clinical experience indicates that individuals respond differently to renal hypoperfusion in terms of whether they will develop pre-renal azotemia versus acute tubular necrosis. What factors determine this variable response? Would you comment on the transition from pre-renal azotemia to acute tubular necrosis?

Dr. Blantz: This will be a critical area of human and animal research in the next few years. In certain clinical conditions, particularly in the postoperative cardiac patient, a transitional period of functional renal failure often evolves into ATN if the cardiac index does not improve. The question is: can one intervene with a renal vasodilator, reverse the pre-renal process, and somehow prevent or delay the ATN? I am skeptical. I do think that the pre-renal failure component of this response actually may somewhat protect renal function. In fact, clinical efforts at increasing GFR by raising renal blood flow can impose additional reabsorptive obligations on the proximal tubule [46]. In these circumstances, toxic exposure can promote additional renal injury. We cannot assume that the tubule is not injured during the pre-renal phase, because in most instances we deliver potentially toxic substances, or endogenous substances circulate that are potentially toxic to the tubule. So the original question has become more complicated: does reversal of pre-renal azotemia prevent, or does it increase the likelihood of, acute tubular necrosis? If we believe that reversing the pre-renal process prevents ATN, we are assuming that pre-renal failure somehow imposes an ischemic condition on the kidney. The literature suggests that that is probably not the case. The kidney is quite different from the heart. Increasing blood flow to the heart, depending on the work demands at the time, likely reverses or prevents ischemia. If one increases renal plasma flow, GFR usually increases. Thus, vasodilation does not just increase substrate and oxygen delivery; the consequent increase in GFR should impose more demands on the organ by increasing tubular reabsorption consequent to the increase in filtered load. We cannot be certain about whether increasing GFR puts the kidney at risk. Spontaneous reversal of pre-renal failure should always be beneficial, but imposing renal vasodilation might not always be of benefit for the kidneys.

Some nitric-oxide-deficient patients might be at risk for more severe pre-renal events. That particular subset of the population might be one to examine. Atherosclerotic or hypertensive patients

might exist in a relative nitric-oxide-deficient state. I am concerned that interfering with normal renal vasoconstrictor processes will lead to disappointing outcomes, an increase in incidence and severity of acute tubular necrosis.

Dr. Madias: I have a followup question. Patients with congestive heart failure seem to tolerate very low perfusion pressures for a long period. Rather than developing acute tubular necrosis, they remain in what we perceive as functional azotemia while, let's say, patients with the same perfusion pressures (secondary to volume depletion or hemorrhage) march on to ATN. Could you comment on potential mechanisms for this difference?

Dr. Blantz: I agree that acute tubular necrosis is rarely observed in patients with severe congestive heart failure. I don't think it is necessarily the agents that are being used to treat heart failure that provide benefit. Perhaps a temporal adaptation to congestive heart failure allows the kidney to adapt to this adverse circumstance. The only time I have seen profound acute tubular necrosis in the setting of congestive heart failure was in a patient who had had a massive, acute myocardial infarction. On the other hand, acute volume depletion might not allow for such compensation. This is my own opinion, and it is not based on any experimental evidence whatsoever.

Dr. Madias: Do you think ANP might play a role in preventing acute tubular necrosis in patients with congestive heart failure?

Dr. Blantz: I doubt that ANP plays a major ameliorating role in this circumstance. There's not much evidence to support that notion.

Dr. Thomas Ziegler (*Associate Professor of Medicine; University of California, San Diego; La Jolla, California*): Pneumonia, empyema, pleural effusions, tuberculosis, and lung abscess all are classical causes of SIADH. Has "status post lung transplant" joined that list? Could some of the interesting and extreme features of today's case flow from a superimposition of SIADH on vasomotor, functional renal failure? Let me extend that suggestion further. If we had had access to a direct peptide antagonist of ADH for clinical use, would it have made your patient better, or would it have been malicious to treat him with an infusion of ADH antagonist? Given that we don't yet have such a peptide antagonist, when, if ever, would you treat a patient with demeclocycline to block the renal effects of ADH while you are promoting saline or colloid volume expansion?

Dr. Blantz: The real question is whether the patient has an appropriate release of ADH or SIADH; it is often difficult to determine an appropriate ADH level. Let me take the question out of this setting, because I can't give you experimental evidence in support of or against your comment. Let us take the burn unit patient, for example. Even well-hydrated burn patients exhibit seemingly high ADH levels, which might be somehow appropriate for their horrible circumstance. I don't know whether it is inappropriate in this circumstance or not, but they tend to manifest signs of volume depletion while excreting normal and even elevated urine volumes. Patients exhibit low fractional excretion of urea, which is likely ADH dependent. I have difficulty discerning, even in some classical elevated ADH states, how appropriate or inappropriate is the elevated ADH level. Some interesting data do relate to your second point, however. Vasopressin antagonists can be very helpful in congestive heart failure, because aquaporin expression is vasopressin dependent. A water diuresis would be greatly beneficial. Papers coming out in the next year suggest that in animal heart failure models, certain aquaporins are recruited in the kidney by a vasopressin-dependent signaling mechanism that magnifies the prevailing stimulus for water absorption. I would prefer a vasopressin antagonist over demeclocycline, an agent which I have never used with much success.

Dr. Ravindra L. Mehta (*Associate Professor of Medicine, University of California, San Diego*): I am intrigued by your presentation of Dr. Schwartz's new data on the effect of NOS in the setting of sepsis. A similar situation exists in cirrhotic patients who also present with a high cardiac output state. These patients also might have a systemic excess of NO. You have shown us very elegantly that the pre-renal factors are vasoconstrictive and contribute to a further decline in GFR, the effects being that tubular metabolism is preserved and high-energy-demanding processes aren't initiated. Could the corollary be true? That is, could a high NO state (a high vasodilator state) initiate a compensatory, vasoconstrictive response?

Dr. Blantz: Data in the gastroenterology and the general scientific literature indicate that inducible NOS (iNOS) activity is increased in severe cirrhosis [56]. Whether this increase is due to the leaky gut and thus endotoxin appearing in the circulation, or whether other mechanisms are operative is not clear. Transcriptional activity for iNOS appears to be elevated in cirrhotic models. A second mechanism likely relates to elevated plasma arginine levels. After arginine is normally absorbed in the gut, the liver controls plasma arginine levels through the urea cycle by converting arginine to ornithine. Patients with reasonably normal hepatic function have fairly stable arginine plasma levels regardless of arginine intake [57]. On the other hand, patients with severe hepatic failure or hepatorenal syndrome exhibit progressively increased arginine levels in plasma, possibly because of either portal-systemic shunting of arginine, bypassing the liver, or liver failure. For these two reasons, you are right: arginine substrate levels are elevated in a setting in which transcriptional activity for inducible NOS is increased. The response of the constitutive NOS side of the equation, however, is less well defined in cirrhosis. The data supplied by Dr. Schwartz [55] in some way might be applicable to the cirrhotic state, but I say that in a speculative fashion. It is clear that excess inducible NOS activity can inhibit the constitutive NOS. Also Dr. Gabbai and others have suggested that the role for NO or constitutive NOS in the kidney is different than it is in the systemic vasculature, in that NO does not act as a primary vasodilator in the kidney; rather, it acts as an antagonist of vasoconstrictors such as angiotensin II [14]. This mechanism might explain why the kidney exhibits vasoconstriction while systemic vascular resistance is remarkably low throughout the body. Systemic vasodilation alone contributes to salt retention; however, it doesn't cause the vasoconstriction. I think it is an intriguing mechanism, but I would not suggest running out and giving L-NIL, an iNOS inhibitor, to every cirrhotic patient. Nevertheless, it is something to consider, especially if the sepsis data hold up, which in an acute setting is probably more analogous to what we see in cirrhosis in a chronic setting.

Dr. Mehta: I was questioning a different pathophysiologic aspect. We know that in cirrhotic patients with peripheral pooling of blood, there is the possibility of shunting blood away from the kidney. Is it possible that the inciting event for renal vasoconstriction is not the peripheral shunting but, rather, excessive vasodilation?

Dr. Blantz: This has been a mystery for a while. When the

potent vasodilator minoxidil first became available as an antihypertensive agent, some physicians administered it without a diuretic [58]. A resulting clinical syndrome occurred reproducibly and consistently. The blood pressure didn't decrease appreciably, and the patient relentlessly accumulated salt and water. The peripheral vasculature does talk to the kidney, there is no doubt about that, possibly through adrenergic communications, but I am not sure that this effect produces renal vasoconstriction. I recall no model demonstrating that primary systemic vasodilation per se elicits renal vasoconstriction. The only other condition that I recall is thyrotoxic storm, which I haven't seen more than once or twice in my life. Thyrotoxic storm is characterized by high-output cardiac failure, wide open capillary beds, and extreme increases in BUN and serum creatinine. The mechanism you are postulating might be operative in that condition. The actual mechanism of how vasodilation elicits responses in the kidney is totally unknown to me. I would suspect renal nerves are candidates, and maybe angiotensin II, but on the whole, the mechanisms are ill-defined.

Dr. Madias: You referred to the toxicity of an NO product, peroxynitrite, to various cells, including the renal tubule, and its role in ischemic reperfusion in various organs. Some elegant data from Dr. Goligorsky's group support the view that inhibiting inducible NOS might attenuate ischemic acute renal failure in the rat [59]. Could you please comment on the possible relevance of these observations for sepsis-induced renal dysfunction?

Dr. Blantz: Work from the University of Colorado suggests that after ischemic damage to the proximal tubule, blockade of NOS benefits the kidney [60]. I believe that they thought this reflected the activity of an inducible form, but other NOS isoforms might have been producing NO. I presume this implies that peroxynitrite generation was causing membrane damage. Peroxynitrite formation in large quantities not only requires excess production of NO but also requires an excess of oxygen-free radicals (O_2^-). This means that the oxygen radical generation is sufficient to overload the capacity of superoxide dismutase to consume or metabolize it. Renal ischemia qualifies as one of these circumstances. I don't know of any reports in the literature saying that NOS over-activity alone in the absence of oxygen radical generation produces enough peroxynitrite to generate tubular membrane damage. As you know, if oxygen radical generation is not great, there is generally enough superoxide dismutase to mop up small amounts of oxygen radicals, and the reaction requires both NO and O_2^- to produce peroxynitrite in large quantities. I agree with you that peroxynitrite has a potential for significant membrane damage. The group you mentioned already has suggested that, in ischemic models, NOS blockade has been beneficial.

Dr. Mehta: I have a different question related to clinical practice. We all use fractional sodium excretion and, more recently, fractional urea excretion to define prerenal failure. Do you see an association between these two tests, that is, a high fractional excretion of sodium and a low fractional excretion of urea? Would such an association be a useful tool for identifying the kind of patient you presented? Second, since we cannot change the management of the burn unit patient and the transplant patient in need of high nutritional supplements, can we prevent the clinical consequences?

Dr. Blantz: I hate to be a skeptic, but the original utility of the fractional excretion of sodium (FE_{Na}) or renal failure index was restricted primarily to the oliguric or the nearly oliguric patient. When urine volumes are in the range of 2 to 3 liters/day, it becomes a less valuable index. As an example, if a patient exhibited a FE_{Na} of 1%–2%, would that level be low if the daily urine volume were 2700 cc? In circumstances in which the FE_{Na} is not so helpful, as in a polyuric patient, the demonstration of 20% fractional excretion of urea suggests that the patient doesn't have ATN. I seriously doubt that any patient with full-blown ATN could exhibit such a low fractional excretion of urea.

Dr. Madias: Has the utility of the fractional excretion of urea been studied formally in the evaluation of patients with renal hypoperfusion?

Dr. Blantz: Recent abstracts at the last two ASN meetings suggest the superiority of a low fractional excretion of urea over the sodium indices. I don't know whether these data have been published. As Dr. Mehta suggests, even in clinical circumstances with normal urine volumes, a low fractional excretion of urea suggests reversibility.

Dr. Robert Steiner (*Clinical Professor of Medicine, Department of Nephrology, University of California, San Diego*): I have an observation and a question. In a case like this, we lose the value of urea as a surrogate marker for products of protein catabolism, which are major contributors to the severity of uremia. In fact, this patient was less azotemic as regards to other uremic toxins than was indicated by the high BUN. If a patient's blood urea doubles because the fractional excretion falls in half, in a sense should we "discount" the patient's azotemia by 50%? Second, I think the patient presented might have had a concentrating defect. When one estimates his minute osmolar excretion, it is perhaps too low to justify saying that he had a solute diuresis that was solely responsible for his less-than-maximally-concentrated urine. Are any of the observations you've made relevant to the generation of a concentrating defect in this patient?

Dr. Blantz: Chuck Kleeman and Alexander Leaf created a variety of experimental curves that related urine flow rate induced by osmotic diuretics such as mannitol and the urine concentration in mOsm/kg H_2O. In general, these exponential curves began at either minimal urine tonicity or maximal urine concentration and moved asymptotically toward isotonicity similar to plasma values. Whether our patient "fell off" this normal curve depends on which experimental data you choose. In the Leaf model, our patient fell off the curve. On the other hand, that curve might have been generated with 18-year-old volunteers, and our patient doesn't fall into that category. He was not a well person before his lung transplant. The curves generated by others would have placed our patient at 1.3 mOsm/min osmolar excretion, correlating with a urinary osmolality of around 850 mOsm/kg H_2O. Our patient concentrated to 650–690 mOsm/kg H_2O at this osmolar excretion.

The other intriguing element of this case is that I have always understood that the only way you replenish urea in the papilla is by having a high ADH and a low urine volume. The collecting duct permeability of urea is not the only factor to consider. The urea concentration gradient also must be considered. The absolute contribution of urea to urine osmolality was only 450–500 mOsm/kg H_2O in this patient. Since the fractional excretion of urea was 25%, major reabsorption of urea had to be driven by a favorable gradient for entry into the papillary interstitium. This requires that papillary urea concentration had to be lower than 450 mOsm/kg H_2O and possibly considerably lower. It is quite reasonable to speculate that this patient's papillary urea had been

relatively low for some time before he was evaluated, thus creating a favorable gradient for urea movement into the papillary interstitium. Whether the lower papillary urea concentration was attributable to the fact that he was sick and protein malnourished prior to entry to the hospital and that somehow he had not been able, in spite of his protein intake, to restore papillary urea, I don't know. Elevated ADH alone is not sufficient if the gradient is not favorable.

Dr. David M. Ward (*Professor of Medicine; Director, Dialysis and Clinical Nephrology; University of California, San Diego; La Jolla*): I'd like to follow up on this question regarding urine osmolality and the fact that this man didn't get his urine osmolality above 650 mOsm/kg H_2O when he supposedly had pre-renal azotemia. The data go back to Glasgow with Robin Luke and Adam Kennedy maybe 25 years ago [61]. The data predicted that if urine osmolality were above 500 mOsm/kg H_2O in a dehydrated patient, volume replacement would restore renal function, whereas an osmolality below this level indicates that you had "crossed the Rubicon" where acute tubular necrosis sets in. Obviously there is a gray zone between pre-renal azotemia and acute tubular necrosis. Most of your discussion today focused on the neurohumoral reasons for the patient's clinical status. But my concern is that he was polyuric when he should have been oliguric, and his urine osmolality might not have been maximal. Does that possibility suggest to you that in addition to neurohumoral problems, a degree of functional proximal tubular damage or dysfunction existed?

Dr. Blantz: I am not concluding that the patient did not have a water-reabsorptive defect. As you recall, the urea reabsorption that occurs in response to ADH is primarily in the terminal collecting duct, whereas the ADH effect on water movement is, for the most part, all along the collecting duct, or at least more proximal. One could speculate that with the large urea load that was filtered in this patient, he had sufficient urea in his upper collecting duct to retard water movement out of the collecting duct. The real question is, why did he continue to have such massive urea reabsorption? That is the issue with which I have the most difficulty. You're implying that he should have exhibited a higher urine osmolality. The reason he didn't have a higher urine osmolality is because he didn't have enough urea in the urine due to its reabsorption, and now we are in a circular argument. The driving force for urea reabsorption has to be a relatively low papillary urea concentration or, as Dr. Steiner has suggested, an astounding medullary blood flow removal, in which urea is washed out of the patient's medulla, perpetuating a favorable concentration gradient at a given ADH level to keep recycling urea into the papilla. I would have preferred the patient's urine concentration at 900 mOsm/kg H_2O, but if you ask me what solute would be required to create this concentration, it has to be urea. So, I don't know exactly how to solve that problem because the problem is the cause, and so on in a circular argument. Part of the problem may be that if you perform a water-deprivation test on someone who has been in the hospital, I seriously doubt that many of them would achieve a urine osmolality of 1200 mOsm/kg H_2O. If you evaluate 18-year-olds who are members of a rugby team, a fair percentage of them would be able to maximally concentrate their urine. Prior protein malnutrition might have contributed to the lower medullary/papillary urea content in this particular patient.

Dr. Madias: Evidently, some patients have been described who developed oliguric acute renal failure following administration of large doses of mannitol resulting in great accumulation of mannitol in plasma [62, 63]. Could you comment on these reports?

Dr. Blantz: I am certain you could "dry out" a patient with mannitol, so I'm not surprised that you could produce oliguria, especially after all the mannitol is excreted. As with massive urea diuresis, mannitol provides the clue pointing to the presence of a polyuric state, a clue of plasma hypernatremia that is not observed as readily with hyperglycemia and glucosuria. Years ago we described some experiences with the use and abuse of mannitol [5]. In addition to producing hypernatremia and profound volume depletion, large-volume mannitol administration can produce wide swings in plasma potassium concentration. If one gives 100 g of mannitol, the serum potassium will increase transiently, but eventually the patient will become hypokalemic if mannitol administration continues. I presume that oliguric renal failure after mannitol administration is a function of massive volume depletion rather than of any intrarenal effect.

Dr. Brian McDonald (*Head, Nephrology Division, Naval Medical Center, San Diego*): Not uncommonly, a consulting nephrologist encounters a patient similar to the one you presented today in whom it appears that a functional component might respond to volume expansion. However, our colleagues are commonly reluctant to rapidly infuse fluids. Often physicians exert pressure on us to perform a dialytic procedure for reduction of BUN. Given the artful pathophysiologic scheme you presented, is it conceivable that provision of an isovolumetric dialysis to reduce the endogenous solute load might help, or could it worsen the pre-renal state due to renal vasospasm?

Dr. Blantz: You have raised a ticklish point in "political nephrology," shall we say. I would like to say that I have never given in to that temptation, but I would be lying. We have, in fact, dialyzed patients who had high blood urea concentrations, although we knew that other treatments would decrease the urea, such as giving more fluids. But you have raised an important point. One could conjecture that if dialysis were utilized to remove urea, we could have cured this patient's problem. However, this seems an expensive way to produce a cure, since D5W must be less expensive than the costs of a nurse and a dialysis session. I see your point, and dialysis *is* another approach for removing urea. This patient ran into real difficulty because many lung transplant surgeons and some burn treatment physicians have a real aversion to making the patient's net volume positive. They believe that a wet lung is the predisposing template upon which transplant rejection occurs. They tend to keep patients very dry, and it is hard to convince these doctors otherwise. So if you think the patient is azotemic as a result of elevated protein catabolism, your hand may be forced, no doubt about it. We have dialyzed for less-academic reasons, so I suppose that would be a potential treatment response if administering fluids and NaCl is not a treatment option.

Dr. Francis B. Gabbai (*Chief, Nephrology Section, Veterans Affairs Medical Center, San Diego; La Jolla*): I'd like to return to the issue of whether pre-renal azotomia is good or bad. One might think that a pre-renal condition with a decreased GFR is good for proximal tubular cells because the filtered load decreases. But in pre-renal conditions, proximal tubular reabsorption, as indexed by fractional reabsorption, is increased. If tubuloglomerular feedback is trying to drive tubular function to its maximum capacity, isn't there a contradiction between these two mechanisms? A reduction in GFR would be beneficial, while an increase in reabsorption would put the cell at increased risk.

Dr. Blantz: You raise an interesting point, and I am going to offer a view that is borderline radical. Many of our textbooks state that with volume depletion, proximal reabsorption increases. In fact, I challenge anyone to find a single publication demonstrating that absolute proximal reabsorption increases as a result of volume depletion. Ed Weinman and Mike Weiner several years ago [64], and Bob Steiner and I [9], examined volume depletion with micropuncture techniques. We could not find a time at which absolute proximal tubular reabsorption increased. The reduction in GFR was always a contributing factor to the increase in fractional reabsorption. One could argue that in the more severe, second phase of volume depletion, GFR reduction via angiotensin II or renal nerves preserves salt and water and proximal tubular integrity. I wonder, however, whether reductions in blood flow and GFR in response to volume depletion really are risks for tubular injury. This second phase of volume depletion and pre-renal azotemia might subserve a beneficial purpose by actually reducing the risk of renal damage. In older studies in isolated perfused kidneys, oxygen consumption was primarily determined by filtration rate [65]. This shouldn't be a surprise to anyone, because oxygen consumption is primarily linked to sodium/potassium ATPase activity and tubular reabsorption of sodium as a function of GFR. Unless a diuretic is supplied, the best predictor of renal oxygen consumption is the GFR. Reductions in GFR are not always deleterious, and these decreases actually can exert a protective effect. I argue this conclusion in part from a philosophic perspective, because evolution has not discarded this renal mechanism over the millennia. One could argue that we should not reverse the process of GFR reduction in pre-renal conditions. I refer you primarily to the Thurau and Boylan article in the *American Journal of Medicine*, "Acute renal success," in which they argue that the tubuloglomerular feedback system prevents volume losses when tubules are injured [66]. In addition to preventing volume losses, tubuloglomerular feedback-mediated reductions in GFR might prevent the injured tubule from being overworked.

Dr. Madias: Your almost iconoclastic comment brought to mind a number of observations that have demonstrated a dose-dependent, bimodal effect of angiotensin II on proximal tubule sodium and fluid reabsorption, low concentrations increasing and high concentrations decreasing proximal functions [67–70]. In fact, several laboratories, including our own, have shown this differential effect of angiotensin II on the activity of the proximal-tubule sodium/hydrogen exchanger and sodium/bicarbonate symporter [69, 71]. Can you put these observations in a clinical context, and do you think that these data are relevant to the idea that you just expressed?

Dr. Blantz: I can only quote data that I have already cited that have been largely misinterpreted. Those are the studies in which Di Nicola and Gabbai examined NOS blockade and the effect on the tubule and glomerulus [14]. When they gave losartan, an angiotensin II receptor blocker, it eliminated the stimulatory effects of angiotensin II on reabsorption. Losartan alone modestly reduced the absolute proximal tubular reabsorption. Interestingly, losartan also totally prevented the effect of NOS blockade, which was to reduce proximal reabsorption. It would appear that NO exerts a modulating influence on the inhibitory component of angiotensin II. Studies have shown that when one perfuses the peritubular and luminal aspects of the proximal tubule, respectively, with different angiotensin II concentrations, there is an inhibitory reabsorptive influence of angiotensin II that occurs in the sub-micromolar range, which is close to the observed angiotensin II concentration in the lumen of the early proximal tubule. Additionally, the luminal angiotensin II concentration effects appear to dominate over the peritubular effects. At high levels of AII, it is possible that one could move into the inhibitory range, especially under conditions of NO deficiency. The data in the literature suggest that there are bi-directional influences of angiotensin II on reabsorption, which are about 2–3 log concentration orders apart.

Dr. Madias: Could you please comment on the renal consequences of the various adrenergic substances, including low-dose dopamine, used in ICUs.

Dr. Blantz: The justification for low-dose dopamine therapy has gradually assumed the position of an article of faith rather than science. Multiple articles suggest some benefit of such treatment. Low-dose dopamine does exert some beneficial diuretic effect. It should decrease proximal reabsorption. Low-dose dopamine probably has no effects relevant to our discussion today in terms of benefits to GFR and renal vascular resistance. Higher doses of dopamine can spill over into alpha adrenergic receptors with rather unpredictable renal contributions. What concerns me more in the ICU setting is that many of our surgical colleagues have developed what I would call a "bad habit" of infusing nitrovasodilators on a routine basis. A favorite treatment in the post-cardiac patient is to provide sodium nitroprusside or some equivalent agent in rather significant quantities. I'm not sure this therapy is based on any scientific principles, and what concerns me, based upon comments of Dr. Mehta, Dr. Schwartz's study [55], and other reports in the literature, is that certain nitrovasodilators inhibit intrinsic constitutive NOS activity, which we've already postulated as an important buffer of renal vasoconstrictor activity. Studies should be conducted, possibly in readily available, circulating cells, to determine whether constitutive NOS activity is downregulated by these exogenous nitrodonors. The paracrine effects of exogenous nitrodonors must be significantly different than the activity of intrinsic NOS-generated nitric oxide. There is a generally reciprocal relationship between exogenously supplied nitrates and the resulting reduction in endogenous nitric oxide synthase activity. In the postoperative cardiac surgical patient, nitrodonors can autoinhibit intrinsic NOS enzymes, thereby contributing to unopposed activity of renal vasoconstrictors, thereby increasing the likelihood of pre-renal failure.

Dr. Ziegler: Between approximately 1930 and 1960 a huge amount of data accumulated about urinary enzyme assay as a diagnostic approach to acute tubular necrosis. As far as I know, this approach was summarized in Laurence Wesson's *Physiology of the Human Kidney* [72], and no one's used it since. The subject of crossing the line from functional renal failure to acute tubular necrosis is an exceedingly important issue clinically, and I'm sure physiologically. Do you think we'll have some modern methods for looking at either enzyme regurgitation into blood or urine as a way of getting a handle on early acute tubular necrosis? It seems to me that one interesting aspect of today's case might be that this patient actually developed some early acute tubular necrosis but that it remained below our current diagnostic threshold.

Dr. Blantz: As I mentioned previously, I wish there were a distinct border, the Rubicon as Dr. Ward calls it, between pre-renal failure and ATN, at which physicians could raise a red flag in the ICU and state unequivocally, "This patient has ATN."

There's a tremendous overlap between ATN and pre-renal failure. If there are excessive N-acetyl-glucosaminidases, beta-microglobulins, and other enzymes coming out in the urine [73], the patient should have ATN but, concurrently, the patient could be concentrating the urine to 650 mOsm/kg H_2O. Some patients exhibit diagnostic characteristics suggesting an overlap of pre-renal failure and ATN. In addition, all renal failure that we define as ATN is not a model of proximal tubular injury. Rhabdomyolysis is a cause of acute renal failure associated with very little direct proximal tubular damage. Therefore, enzyme excretion might not be increased. Undoubtedly tubular damage occurs while the patient is still manifesting signs of pre-renal failure. In fact, proximal tubular damage can contribute to renal vasoconstriction via activation of tubuloglomerular feedback systems.

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