PHARMACOLOGIC MANAGEMENT OF ACUTE RENAL FAILURE

Medical Grand Rounds

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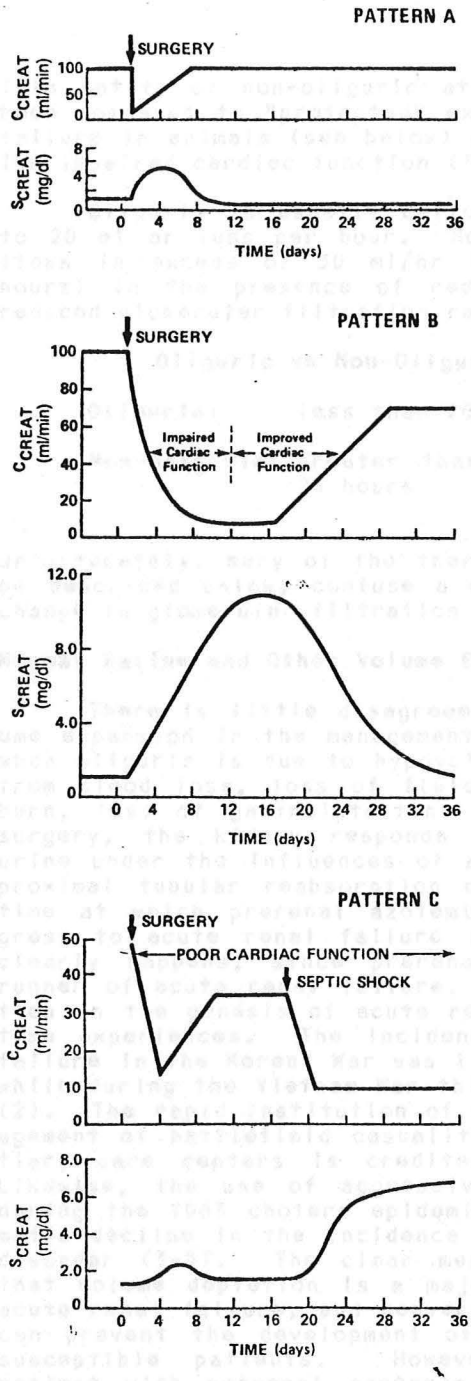
INTRODUCTION

The pharmacologic management of acute renal failure is an area of medicine engulfed by controversy. While the use of normal saline and other volume expanders are of unquestioned benefit in the management of prerenal azotemia and probably prevents many patients from going on to acute renal failure, the role of diuretics, vasodilators, and other drug therapies in the prevention and treatment of acute renal failure is far less clear. In this area of therapy, anecdotal reports rather than carefully designed studies form most of the foundation upon which current practices are based. This grand rounds will examine laboratory and clinical studies that pertain to the use of pharmacologic agents in the treatment and management of acute renal failure . Although important to the survival of patients with acute renal failure, neither the nutritional aspects of acute renal failure, nor specific non-controversial pharmacologic interventions for certain forms of acute renal failure (e.g. intravenous alcohol in patients with ethylene glycol ingestion) will be discussed. Rather the focus will be on drugs that have been used to prevent the development or to alter the natural history of the more common vascular and nephrotoxic varieties of acute renal failure.

PHARMACOLOGIC THERAPIES IN THE MANAGEMENT OF ACUTE RENAL FAILURE

1. Normal saline and other volume expanders
2. Osmotic diuretics
3. Loop diuretics
4. Vasodilators
5. ATP-$MgCl_2$
6. Thyroid hormone
7. Calcium entry blockers

Acute renal failure (synonyms: intrinsic acute renal failure, acute tubular necrosis) will be defined here as an acutely developing azotemic state that cannot be reversed by altering prerenal or postrenal factors. Thus, prerenal azotemia and obstructive uropathy are not aspects of this more restrictive definition of acute renal failure, however, they could be forerunners. Failure to make this diagnostic distinction has caused and continues to cause confusion in evaluating studies and therapies that claim to prevent, reduce, or in some way modify the course of acute renal failure. Lastly, it is important to emphasize that an intermediate form of non-oliguric acute renal failure exists. It has been called "attenuated human acute renal failure", and occurs particularly in patients undergoing cardiovascular surgery (1). In these patients, glomerular filtration rate may be reduced substantially, but not to the profound degrees of classic acute renal failure. Also, the depression of glomerular filtration may be "abbreviated" (a few days), "overt" (2-3 weeks) or "protracted" (irreversible).



Three Typical Courses of Acute Renal Failure after Cardiac Surgery, Illustrated by Creatinine Clearance (°CREAT) and Serum Levels of Creatinine (*CREAT) in Representative Patients Who Did Not Undergo Dialysis.[38]

The upper portion (Pattern A) displays a step decrement that is followed immediately by a ramp increment in creatinine clearance typical of abbreviated acute renal failure. The middle portion (Pattern B) displays an exponential decrement of clearance that is accompanied by a linear increase in the serum level of creatinine (days 1 to 12). Recovery, which follows improved cardiac performance from day 12, is manifested during days 16 through 30 by a ramp increment in clearance that is accompanied by a sigmoidal decline in the serum level of creatinine. In Pattern C (lower portion), successive ramp decrements in clearance (days 1 to 4 and 18 to 21) are accompanied by sigmoid elevation of the serum creatinine level. Recovery of creatinine clearance (ramp increment, days 4 to 7) is seen only after the first episode. A persistent low-cardiac-output state prevents recovery from the second insult.

This entity of non-oliguric attenuated acute renal failure has been compared to "protected" experimental models of acute renal failure in animals (see below) and has as its underlying mechanism impaired cardiac function (1).

Oliguria is usually defined as a reduction in urine flow to 20 ml or less per hour. Non-oliguria usually implies urine flows in excess of 30 ml/hr (or greater than 500 ml per 24 hours) in the presence of reduced excretory capacity, i.e. a reduced glomerular filtration rate.

Oliguric vs Non-Oliguric Acute Renal Failure

Oliguria: less than 20 ml per hour

Non-oliguria: greater than 30 ml per hour, or 500 ml per 24 hours

Unfortunately, many of the therapies for acute renal failure to be described below, confuse a change in urine flow rate with a change in glomerular filtration rate.

Normal Saline and Other Volume Expanders

There is little disagreement about the usefulness of volume expansion in the management of acute oliguria, particularly when oliguria is due to hypovolemia. As blood volume decreases from blood loss, loss of fluid transdermally as with a severe burn, loss of gastrointestinal fluid, or loss of blood during surgery, the kidney responds by decreasing the formation of urine under the influences of antidiuretic hormone and enhanced proximal tubular reabsorption of the glomerular filtrate. The time at which prerenal azotemia becomes severe enough to progress to acute renal failure is variable, but this transition clearly happens, since prerenal azotemia is a frequent forerunner of acute renal failure. The importance of volume depletion in the genesis of acute renal failure is evident from wartime experiences. The incidence of post-traumatic acute renal failure in the Korean War was 1 in 200 battle field casualities, while during the Vietnam War this figure was reduced to 1 in 600 (2). The rapid institution of vigorous resuscitative fluid management of battlefield casualities and early evacuation to tertiary care centers is credited with the improved statistics. Likewise, the use of aggressive saline and alkali replacement during the 1963 cholera epidemic in Calcutta resulted in a dramatic decline in the incidence of acute renal failure from this disorder (3-5). The clear message from these two reports is that volume depletion is a major factor in the pathogenesis of acute renal failure, and conversely, that volume expanders alone can prevent the development of acute renal failure in certain susceptible patients. However, the distinction between a patient with prerenal azotemia and one with early acute renal

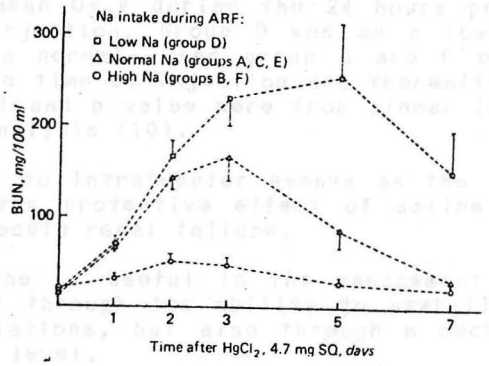
failure may be difficult. Measurement of the fractional excretion of sodium, urinary specific gravity, urine to plasma osmolality ratio, urine to plasma creatinine ratio, and examination of the urinary sediment all may be useful. In difficult cases a challenge with volume expanders may be both diagnostic and therapeutic.

Animal studies have explored various aspects of intracellular volume and its relationship to acute renal failure. The protective effect of long-term saline-loading in experimental acute renal failure has been attributed to its ability to suppress intrarenal renin content (6-8).

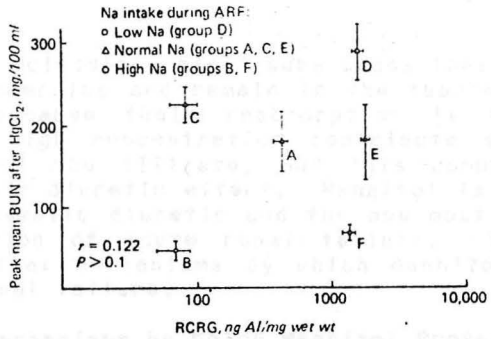
Potential Mechanisms by Which Saline Expansion Protects Against Acute Renal Failure

1. Renin suppression
2. Solute diuresis

However, the induction of a solute diuresis may be equal to or greater in importance than the suppression of renin (9,10). In norepinephrine-induced acute renal failure, saline produced a modest solute diuresis and resulted in a non-oliguric form of acute renal failure (11). Bidani et al (10) dissociated the protective effect of saline on nephrotoxic acute renal failure from suppression of renin. In two nephrotoxic models (mercuric chloride and uranyl nitrate), giving previously sodium-deprived rats 1% sodium chloride to drink for 48 hours prior to the induction of acute renal failure greatly attenuated the severity of renal failure without reducing the high renin levels.

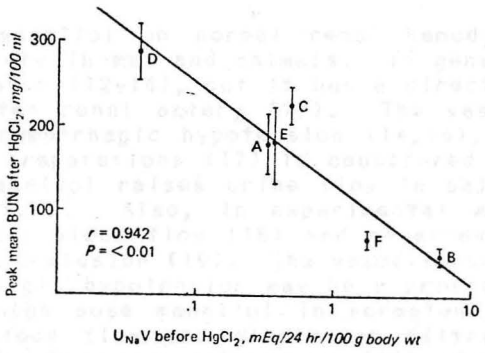


Pattern of ARF, as assessed by BUN following injection with mercuric chloride. Low, normal, and high sodium refer to dietary sodium before and after injection (10).



Dissociation of renal cortical renin content (RCRC) from the severity of ARF induced by mercuric chloride, as assessed by mean peak BUN following induction (10).

Rather, protection correlated with the level of sodium excretion prior to the initiation of acute renal failure.



Inverse correlation between severity of ARF (mean peak BUN) and mean $U_{Na}V$ during the 24 hours prior to mercuric chloride injection. Group D was on a low-, groups A, C, and E on a normal-, and group B and F on a high-sodium diet at the time of injection and thereafter. Correlation coefficient and p value were from linear least-squares regression analysis (10).

These data point to intratubular events as the important factor in determining the protective effect of saline in the nephrotoxic models of acute renal failure.

Thus, saline is useful in the management of acute renal failure not only through its ability to stabilize the systemic and renal circulations, but also through a mechanism operative at the nephronal level.

Osmotic Diuretics

Osmotic diuretics, of which mannitol is the best known and

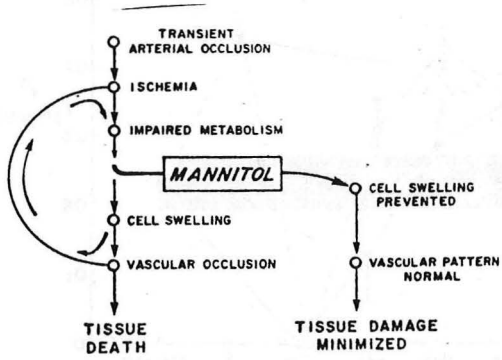
studied, are low molecular weight substances that are freely filtered by the glomerulus and remain in the tubular lumen in high concentrations because their reabsorption is limited. Their small size and high concentration contribute substantially to the osmolality of the filtrate, and this osmotic property is important in their diuretic effect. Mannitol is the most extensively studied osmotic diuretic and the one most frequently used for the prevention of acute renal failure. The table below lists the potential mechanisms by which mannitol might protect against acute renal failure.

Potential Mechanisms by Which Mannitol Protects Against Acute Renal Failure

1. Vasodilatation
2. Osmotic diuresis
3. Increased intratubular pressure
4. Free radical scavenger

The effect of mannitol on normal renal hemodynamics has been studied extensively in man and animals. In general, mannitol is a renal vasodilator (12-14), but it has a direct vasoconstrictor effect on isolated renal artery (15). The vasodilatory action of mannitol in hemorrhagic hypotension (14,16), and in isolated perfused kidney preparations (17) is considered a possible mechanism whereby mannitol raises urine flow in patients with early acute renal failure. Also, in experimental animals, mannitol increases cortical blood flow (18) and reverses cortical ischemia after aortic occlusion (19). The vasodilatory action of mannitol in hemorrhagic hypotension may be a prostaglandin mediated effect (20). High dose mannitol in normotensive subjects decreases renal blood flow and glomerular filtration rate (21). Moreover, studies from our laboratory (11) showed a protective effect from isotonic and hypertonic mannitol in norepinephrine-induced acute renal failure without an accompanying increase in renal blood flow prior to the insult. Mannitol usually produces a modest fall in glomerular filtration rate (11,21-25), but no effect (26-28) or an increase (29) have been reported. Given this variability in the hemodynamic response to mannitol, the protective effect of mannitol in acute renal failure is generally attributed to its predictable diuretic properties. In normal man or animals, water and sodium excretion are increased markedly minutes after the intravenous infusion of mannitol. In the dog 65% of the filtered water and 30% of the filtered sodium is delivered into the urine following high dose mannitol (23). A mannitol-induced diuresis has its origin in a decrease in proximal tubule and loop of Henle sodium reabsorption combined with a washout of the medullary interstitium. This latter effect impairs the capacity of the collecting duct to reabsorb water (30). This effect on solute excretion leads in turn to changes in the intratubular pressure. Micropuncture studies have demonstrated that intratubular pressure increases significantly after the administration of mannitol (24,31), a finding that corresponds to the fall in glomerular filtration rate (24).

Mannitol has been used in a variety of experimental models of acute renal failure resulting from either vascular occlusion or vasoconstrictor insults (11,32,33). In most instances, mannitol has been protective when it is given before or simultaneous with the injury (11,33). The longer the interval between the insult and the subsequent administration of mannitol, the less likelihood that protection will occur (33). Flores et al (34) proposed in the dog and the rat that mannitol lessened the effect of ischemia on the renal vasculature by preventing the "no reflow" phenomenon following ischemia.

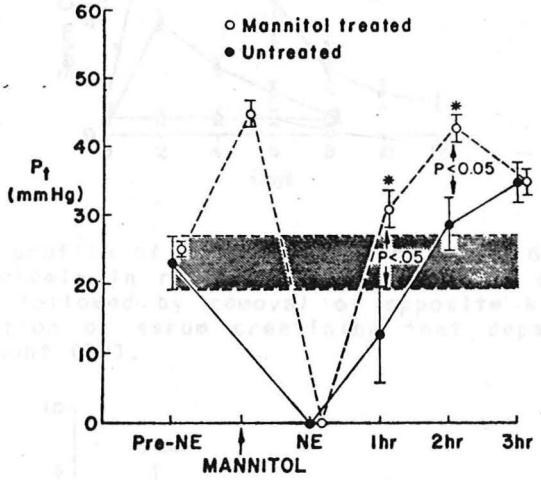


Cell-swelling theory of pathogenesis of acute renal failure and prevention with mannitol. An ischemic event impairs cellular metabolism, which leads to increased cellular solute concentration. Osmotic water movement into the cell then causes cell swelling, which in turn causes vascular occlusion, with resultant tissue damage and more ischemia. Hypertonic mannitol does not penetrate into cells. Thus, the increased ECF osmolality moves water out of cells and prevents cell swelling and vascular occlusion. The efficacy of mannitol is dependent on reversing cell swelling prior to the occurrence of irreversible damage to the metabolic machinery within the cell.

In this hypothesis, swollen vascular endothelial cells that occluded capillaries were "shrunk" by the hypertonic effects of the mannitol molecule that was restricted to the extracellular compartment. However, their later studies suggested that this mechanism was not sufficient to explain mannitol's protection (35).

Cronin et al (11) demonstrated that mannitol, but not saline volume expansion, afforded significant protection against norepinephrine-induced acute renal failure in the dog. Moreover, both isotonic and hypertonic mannitol afforded protection, thus failing to support the theory of Flores et al (34) that mannitol had an effect on the "no reflow" phenomenon. Protection

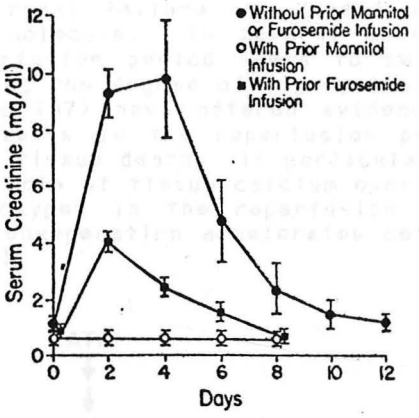
did not correlate with a mannitol effect on inulin clearance, renal blood flow, changes in extracellular fluid volume, or renal histology. Rather, protection correlated with a high solute excretion rate and high intratubular pressures. Subsequent studies demonstrated that the probable mechanism of mannitol protection was prevention of tubular obstruction, since animals pretreated with mannitol had higher intratubular pressures prior to and following the 40 minute period of norepinephrine renal vasoconstriction (36).



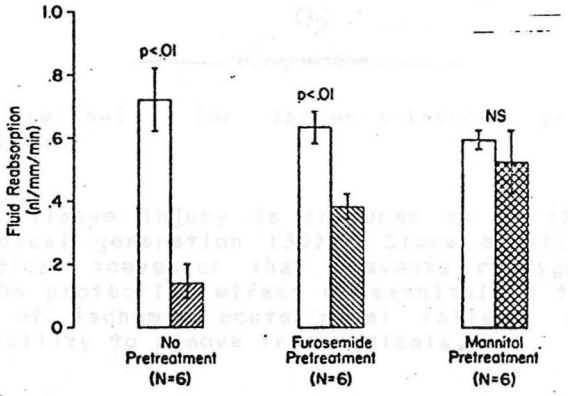
Proximal tubule pressure (P_t) before and at hourly intervals after NE-induced ARF in mannitol-treated (open circles) and untreated (closed circles) animals is demonstrated. Normal range of P_t is indicated by hatched area. P_t is significantly ($p<0.02$) above normal in both gorups at 3 h; however the values are not different from one another (36).

The protection resulting from mannitol does not depend on prevention of tubular injury, since the degree of proximal tubular necrosis was similar in the mannitol and control groups (11).

Hanley and Davidson (32) using the isolated perfused tubule technique, demonstrated that mannitol (5% body weight, 5% mannitol) pretreated rabbits were virtually totally protected from the tubular damage following 60 minutes of total renal ischemia. Furosemide (20 ug/kg/min) afforded significant protection, but less than mannitol.



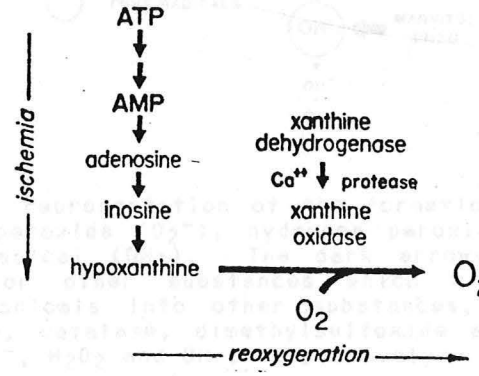
Temporal profile of serum creatinine after 60 min of total renal ischemia in rabbits. Sixty minutes of total renal ischemia followed by removal of opposite kidney produced an elevation of serum creatinine that depends on animal pretreatment (32).



Effect of ischemia on PCT fluid reabsorption. Open bars represent values for control tubules in each treatment group. Hatched or crosshatched bars represent ischemic tubules in each treatment group (32).

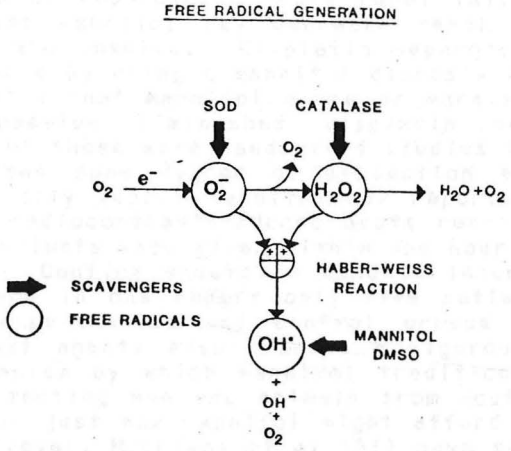
These authors in addition demonstrated that tubular sloughing was less in the mannitol treated groups and suggested that prevention of tubular obstruction was a key element in mannitol protection.

In addition to influencing renal excretion, mannitol protection in acute renal failure may depend upon metabolic consequences of the molecule. In several models of acute renal failure, the reperfusion period seems to be of primary importance in determining the degree of injury that will ensue. Farber and colleagues (37) have offered evidence that it is membrane localized events in the reperfusion period that are the proximate cause of tissue death. In particular, they have emphasized the central role of tissue calcium overload. In addition, the presence of oxygen in the reperfusion fluid seems to be important, since reoxygenation accelerates cell damage in ischemic myocardium (38).



Proposed mechanism for ischemia-induced production of superoxide.

Oxygen-enhanced tissue injury is presumed to be the result of oxygen-free radical generation (39). Since mannitol is an **in vitro** free radical scavenger that prevents reoxygenation cell injury (39), the protective effect of mannitol in these experimental models of ischemic acute renal failure, may in part depend on its ability to remove free radicals.



Schematic representation of the formation of oxygen radicals: superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxal radical (OH·). The dark arrows refer to either enzymes or other substances which will convert these oxygen radicals into other substances, i.e., superoxide dismutase, catalase, dimethylsulfoxide and mannitol inactivate O_2^-, H_2O_2 and OH·, respectively.

The superior protective effect of mannitol over furosemide in preventing acute renal failure following ischemia in the rabbit, despite the similar effect that both agents had on baseline tubular flow rates, is consistent with such a metabolic effect (32).

A beneficial effect for mannitol in the prevention of acute renal failure in man is far less clear, since there are few studies in which proper controls have been included. Although osmotic diuresis induced by hypertonic mannitol was used to prevent or reduce the severity of acute renal failure in crush injuries as early as 1947, the efficacy of such treatments remains uncertain (40). Early uses of mannitol included hemolytic tranfusion reactions, elective surgery, including aortic resection, extracorporeal circulation, and accidental trauma. Reports utilizing mannitol prior to aortovascular surgery showed that mannitol prevented oliguria, but these reports offered little documentation that renal hemodynamics (i.e. renal blood flow and glomerular filtration rate) were better preserved in the treated groups (41,42). When glomerular filtration rather than urine flow is used as the measure of the presence or absence of acute renal failure, there is little convincing clinical evidence that mannitol in fact prevents or diminishes acute renal failure when the insult is ischemic in nature (43).

In the case of nephrotoxic acute renal failure, there is some evidence that mannitol may decrease renal toxicity when given before certain insults. Cisplatin nephrotoxicity in the dog has been reduced by using a mannitol diuresis (44). Several studies demonstrated that mannitol alone or mannitol in combination with furosemide diminished cisplatin nephrotoxicity, (45,47), and two of these were randomized studies (45,46). Mannitol also provides some degree of protection against amphotericin nephrotoxicity (48). Mannitol was reported to decrease the incidence of radiocontrast-induced acute renal failure in a small groups of patients when given within one hour of the radiocontrast (49,50). Caution should be used in interpreting these later studies since in one report only five patients each were studied in the experimental and control groups (50). Also, since radiocontrast agents also promote a vigorous osmotic diuresis, the mechanism by which mannitol traditionally has been credited with protecting man and animals from acute renal failure, it is unclear just how mannitol might afford protection in this setting. However, Morrison et al (51) have speculated that radiocontrast toxicity might be linked to free radical formation, since **in vitro** mannitol was capable of inhibiting lipid peroxide formation by sodium iothalamate. Other reports fail to demonstrate a protective effect from mannitol (52,53).

When mannitol is given after the renal insult or in cases where acute renal failure is "established", the beneficial effect of mannitol is even less clear. Luke et al (54) demonstrated that oliguric patients with oliguria unresponsive to saline administration could be separated into two categories following the infusion fo 20% mannitol. When responders were compared to nonresponders, responders were characterized by a shorter duration of oliguria (27 vs 44 hours), higher premannitol urinary osmolalities (396 vs 337 mOsm/kg), and higher urine to plasma osmolality ratios (1.29 vs 1.04). These findings suggest that "responders" were patients having less severe acute renal failure to being with and may not have had acute renal failure at all.

In summary, a proper role for mannitol in the prevention and/or management of acute renal failure is yet to be established. The encouraging results from the use of mannitol in studies of experimental acute renal failure have not carried over into clinical acute renal failure. Nonetheless, the use of mannitol is an established routine prior to most cardiovascular surgery and the use of certain nephrotoxic agents. Fortunately, the risks associated with its use are few. However, intravascular volume overload is a potential problem not associated with the use of loop diuretic, the other major pharmacologic agent used for this purpose.

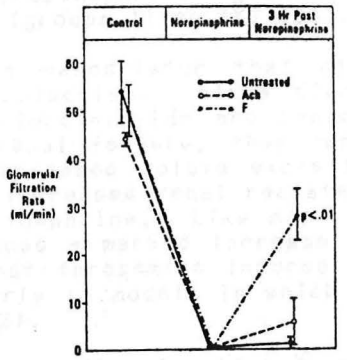
Loop Diuretics.

Furosemide and ethacrynic acid are the two agents in this category, and most experimental and clinical experience has been with furosemide.

Potential Mechanisms of Furosemide Protection Against Acute Renal Failure

1. Solute diuresis.
2. Increased intratubular pressure.
3. Lower preglomerular vascular resistance.
4. Increased transcapillary hydraulic pressure gradient.
5. Stimulation of urinary prostaglandin secretion.

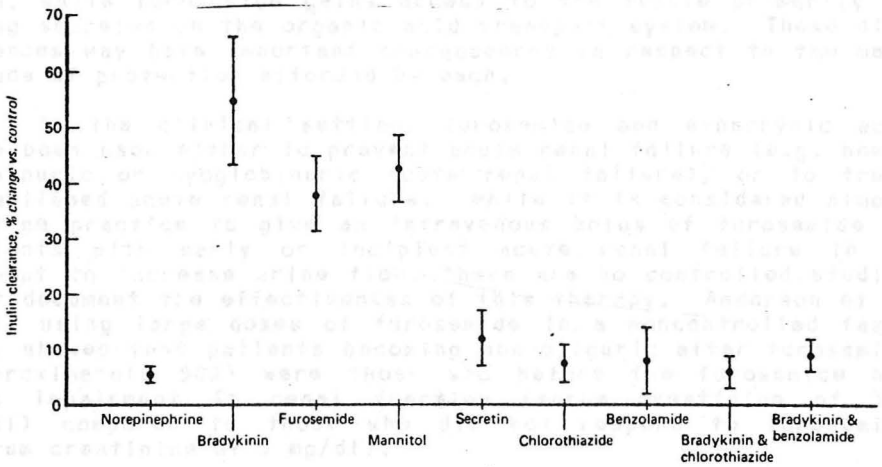
In experimental models of acute renal failure, furosemide administration has prevented acute renal failure (55,56), increased urine volume without changing renal function (57,58), or had no effect (59). While furosemide increases renal blood flow (60), its principal mode of protection against experimental acute renal failure appears to be an increase in solute excretion. DeTorrente et al (55) demonstratred that while both acetylcholine and furosemide produced a marked increase in renal blood flow prior to intrarenal norepinephrine infusion, only furosemide protected against acute renal failure. The protective effect appeared to reside in the significant increase in osmolar clearance that occurred in the furosemide pretreated animals, but not in the acetylcholine pretreated animals



Degree of protection from norepinephrine-induced acute renal failure in dogs pretrated with acetylcholine or furosemide as compared to untreated animals. Three hours after norepinephrine both untreated and acetylcholine-treated dogs had severely depressed glomerular filtration rates whereas furosemide-treated dogs showed a highly significant protection (55).

Mauk et al (61) demonstrated that prostaglandin E2, a potent renal vasodilator, markedly attenuated the development of norepinephrine induced acute renal failure. Later studies from this laboratory by Patak et al (56) showed that a vasodilator that markedly increased solute excretion, bradykinin, protected against norepinephrine induced renal failure

Modification of Norepinephrine-Induced acute renal failure



Percentage recovery of inulin clearance at 3 hours after infusion of norepinephrine (group I) and test agents + norepinephrine (groups II to IX) (56).

However, secretin, a vasodilator that did not affect solute excretion was not protective. Since diuretics that decreased renal blood flow, chlorothiazide and benzolamide, did not protect against acute renal failure, they concluded that the protective effect of increased solute excretion could be overcome by agents that also increased renal resistance prior to the administration of norepinephrine. Like mannitol, a furosemide induced diuresis produces a marked increase in intratubular pressures, suggesting that furosemide induced protection might have its effect particularly in models in which intratubular obstruction is important (62).

In experimental studies in which furosemide has been given for a long period prior to the insult, the protective effect is less clear and actual enhancement of acute renal failure may have occurred. Also, furosemide is generally not protective in models where the insult is nephrotoxic in origin (58,59,63). In glycerol induced acute renal failure, furosemide pretreatment seems to produce worse renal failure than is seen in animals receiving glycerol alone (59,64). Why furosemide is harmful in some of these models of acute renal failure is unknown, but volume depletion may be involved. Also, potassium depletion, a potential consequence of furosemide, enhances at least one nephrotoxic model of acute renal failure (65). Thus, in experimental animals, mannitol seems more likely to be protective against acute renal failure than furosemide. Mannitol has its major effect as a diuretic on the proximal tubule, the site of

major histologic injury in acute renal failure. In contrast, furosemide has its major diuretic action on the thick ascending limb. Mannitol gains access to the tubule by glomerular filtration, while furosemide gains access to the tubule primarily by being secreted on the organic acid transport system. These differences may have important consequences in respect to the magnitude of protection afforded by each.

In the clinical setting, furosemide and ethacrynic acid have been used either to prevent acute renal failure (e.g. hemoglobinuric or myoglobinuric acute renal failure), or to treat established acute renal failure. While it is considered almost routine practice to give an intravenous bolus of furosemide to patients with early or incipient acute renal failure in an attempt to increase urine flow, there are no controlled studies that document the effectiveness of this therapy. Anderson et al (66), using large doses of furosemide in a noncontrolled fashion, showed that patients becoming non-oliguric after furosemide (approximately 50%) were those who before the furosemide had less impairment in renal function (serum creatinine of 3.8 mg/dl) compared to those who did not respond to furosemide (serum creatinine of 5 mg/dl).

Analysis of 22 Patients Responding and 18 Not Responding to Furosemide (66).

Characteristic	Patients Not Responding	Patients Responding	P Value
Age (yr)	56±4‡	56±7	NS‖
Cause:			
Postoperative	8	8	NS
Toxin-induced	1	1	NS
Nontraumatic rhabdomyolysis	7	2	NS
Post-septicemia	1	2	NS
Prolonged volume depletion or impaired cardiac output	5	5	NS
Blood urea nitrogen (mg/dl)†	71±9	56±7	NS
Serum creatinine (mg/dl)†	5.0±0.4	3.8±0.3§	<0.05
Urine sodium (meq/liter)	67±6	47±6¶	<0.02
Urinary osmolality	340±19	363±19	NS
U/P UN	3±0.6	6±1¶	<0.02
U/P_{Cr}	13±3	16±2	NS
FE_{Na}	6.9±1.4	2.9±0.6¶	<0.02

*Abbreviations as in Table 2.
†At time of furosemide.
‡Mean ±SEM.
§P<0.05.
¶P<0.02.
‖Not significant.

In another retrospective study using furosemide, 79 patients received furosemide after the onset of acute renal failure (67). Of these 79 patients, 51 failed to respond to the diuretic, 11 exhibited a transient diuresis and required repeated doses, and 17 developed a sustained diuresis after a single dose of the diuretic. Patients with a sustained or a partial response to furosemide had significantly less need for dialysis;

however, there was no difference between the responders and non-responders in respect to mortality, prolonged azotemia, or hyperkalemia. Kjellstrand (68) demonstrated a protective effect of ethacrynic acid in 7 of 13 patients with oliguric acute renal failure. As with the study by Anderson et al (66), responders tended to have better renal function initially than non-responders. Also, if the ethacrynic acid was delayed longer than 24 hours after the onset of oliguria, a response was unlikely.

In addition to the bolus method of administering furosemide, which has as its end to convert oliguric to non-oliguric acute renal failure, furosemide has also been used to maintain urine flow at a high rate in patients with established acute renal failure. In one protocol, furosemide was administered in high doses (2000 mg) on a daily basis until there were signs of recovery of renal function (69). The major benefit of this therapy was an increase in urine flow and a decrease in the number of dialyses required; however, there was no significant improvement in the time required to return to a normal serum creatinine, nor was there a difference in mortality between patients who received furosemide and those who did not. A later controlled trial of furosemide used in a similar manner could not confirm a beneficial result (70). Specifically, the mean oliguric period, the number of dialyses, and the mean period of renal insufficiency were no different between the control and the treated groups. Brown and coworkers (71) prospectively studied this question in a randomized study using 56 patients with established acute renal failure following trauma or surgery.

	Control	Furosemide	p value
Urine Output			
Oliguric period (d)	16.8 1.6	5.5 0.1	<.005
Time to reach 1L/d	15.2 1.3	3.2 0.4	<.005
Time to reach 2L/d	19.3 1.5	6.2 1.0	<.005
Plasma Creatinine			
Time to reach 3.4mg/dl	17.2 2.0	16.9 1.5	NS
Time to reach 1.7mg/dl	21.5 2.1	19.9 1.9	NS
Dialysis	7.1 1.1	6.2 0.9	NS
Mortality	57%	64%	NS

The control group received a single injection of 1 gram of furosemide over a four hour period while the experimental group re-

ceived furosemide either intravenously or orally in a dose of 3 grams/24 hours until a urine output of 200 ml/hr was sustained or the plasma creatinine fell below 3.4 mg/dl. Furosemide was successful in reversing or preventing oliguria in 24 of 28 patients compared to only 2 of the 28 control patients. Importantly, however, the number of dialyses and duration of renal failure and mortality between the control and experimental groups was not different. Two patients in the sustained furosemide groups developed deafness, a problem that especially appears to be a risk of using intravenous furosemide (72).

Since renal function, i.e. glomerular filtration rate, seems to be little affected by the use or non-use of loop diuretics and success is usually measured in terms of an increase or lack of increase in urine flow, the question that must be asked is whether a high urine flow during acute renal failure is better than a low urine flow? Stated in more clinical terms, is non-oliguric acute renal failure better than oliguric acute renal failure? Unfortunately, no well controlled study is available to answer this question. Anderson et al (66) concluded that converting oliguric to non-oliguric acute renal failure improved the clinical outcome. However, in this study it is possible and even likely that responders were patients with less severe renal failure to begin with and proved this by their greater response to the diuretic.

Vasoactive agents. In examining the experimental and clinical data from studies of acute renal failure, it is an inescapable conclusion that a reduction in renal blood flow is an almost universal consequence. Just a little more than a decade ago there was much enthusiasm that vascular mechanisms were the fundamental abnormality in the pathogenesis of acute renal failure. However, attempts to place vascular factors at the very center of acute renal failure still have not been successful. In several species, temporary occlusion (30-60 minutes) of the renal artery results in a decrease in glomerular filtration rate and renal blood flow (73-78). While it seems clear that absent renal blood flow initiated acute renal failure following this temporary ischemia, it is far from clear that the maintenance of renal failure following restoration of renal blood flow is due to persistently decreased renal blood flow. Riley et al (76) showed that renal blood flow in acute renal failure may return to normal while glomerular filtration rate remains low. In vasoconstrictor models of acute renal failure (e.g. intrarenal norepinephrine) renal blood flow may remain reduced following cessation of the infusion, but immediate restoration of normal renal blood flow with intraarterial acetylcholine does not restore glomerular filtration rate (55).

In heavy metal and nephrotoxic acute renal failure, the initiating injury does not appear to be mediated by events at the vascular level, but a subsequent reduction in renal blood flow is common (79-85). In human acute renal failure, renal blood flow is characteristically reduced to 40-60% of normal during the maintenance phase of both ischemic and nephrotoxic forms

of acute renal failure (86-91). Except for these cases of human acute renal failure which occur following total renal ischemia, the status of renal blood flow during the initiation phase of acute renal failure is generally unknown. However, it seems likely that acute renal failure following shock, hypotension, and sepsis is ushered in by a period of reduced renal blood flow. There is little evidence that the major clinical causes of nephrotoxic acute renal failure (aminoglycoside antibiotics and x-ray contrast material) are mediated initially by an important component of reduced renal blood flow. Rather, reduced renal blood flow is more likely a consequence of nephrotoxicity.

The renin-angiotensin system has received a great deal of attention as a central factor in the pathogenesis of acute renal failure, beginning with the observation that the kidneys from patients dying in acute renal failure had an increase in the size of the juxtaglomerular apparatus, the source of renin (92).

Pharmacologic Interventions Involving Vascular Mechanisms in the Pathogenesis of Acute Renal Failure

1. Stimulation of renin-angiotensin system
2. Prostaglandins modulate vasoconstrictor influences
3. Furosemide is a renal vasodilator and stimulates urinary prostaglandin excretion (PGE_2).
4. Dopamine
   a. Increases GFR in normals
   b. Does not increase GFR in CRF

Also, plasma renin activity is increased in patients with acute renal failure (93). Likewise, in experimental acute renal failure, plasma renin activity is typically increased early in acute renal failure (94-96). However, it has not been possible to establish a causal relationship between stimulition of this potent renal vasoconstrictor system and the pathogenesis of acute renal failure. In fact, several studies have dissociated the development of acute renal failure from changes in the renin angiotensin system (10,97-99). Blockade of the renin angiotensin system with immunization against renin (100), angiotensin (95,101), competitive antagonists of angiotensin (102), and angiotensin converting enzyme inhibitors (103) have not prevented the development of acute renal failure.

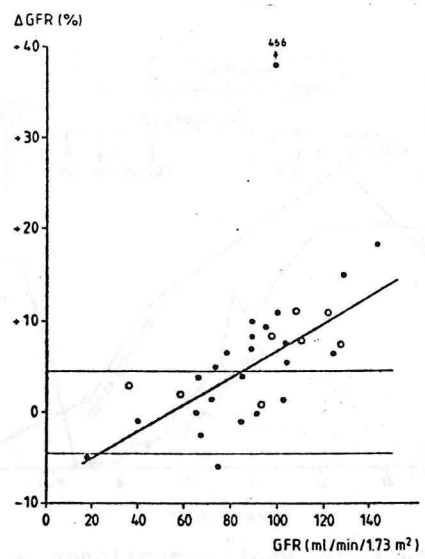
Renal prostaglandins are released following the intrarenal infusions of catecholamines and may function to modulate the vasoconstrictor effects of circulating vasopressor substances (104,105). Thus, blockade of prostaglandins under circumstances where renal vasoconstrictor tone is high might be expected to lead to acute renal failure. Indomethacin enhances the severity of glycerol induced acute renal failure, a model with a strong vasoconstrictor component (106). Studies demonstrating that infused prostaglandins do not modify experimental acute renal failure in the rat do not necessarily exclude a protective role for prostaglandins in man (61,107).

A variety of vasodilating agents has been used to alter the course of experimental acute renal failure. Acetylcholine while restoring renal blood flow to normal following norepinephrine induced acute renal failure, did not restore glomerular filtration (55). Moskowitz et al (108) using a norepinephrine model of acute renal failure were unable to demonstrate protection following the intrarenal infusion of PGE_1, although urine flow and sodium excretion increased markedly. However, Mauk et al (61) demonstrated that PGE_1 infusion into the renal artery of the dog had a protective effect when administered prior to and during norepinephrine-induced acute renal failure.

Furosemide, a diuretic with vasodilating properties, has a protective effect in vasoconstrictor models of acute renal failure (55,56), but is ineffective in nephrotoxic acute renal failure (58). While furosemide produces a brisk sodium diuresis, the factor believed to be central to its protection in vasoconstrictor models of acute renal failure, it also increases the urinary excretion of PGE_2. However, this effect on PGE_2 does not appear to mediate furosemide protection, since blockade of prostaglandin synthesis with indomethacin failed to blunt the protective effect of furosemide in an ischemic model of acute renal failure in the rat (109).

Dopamine at a low doses (1-3 ug/kg/min) vasodilates the renal artery (110,111). In the dog, dopamine increases both outer and inner cortical blood flow, whether the dopamine is given intravenously or directly into the renal artery (111). Andreucci et al (112) demonstrated in the normal rat that dopamine (15-25 g/min) caused a slight fall in systemic blood pressure, but a 22% rise in glomerular capillary pressure. Following hemorrhagic hypotension, similar doses of dopamine raised both systemic blood pressure (57 2 to 86 6 mmHg) and glomerular capillary pressure (23.7 4.5 to 44.3 4 mmHg).

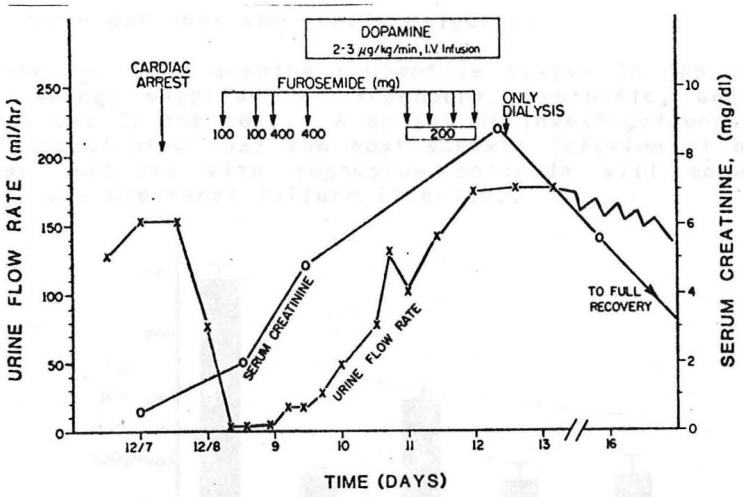
Studies in man indicate that normal individuals respond to dopamine infusions with an increase in renal blood flow, an increase in glomerular filtration rate, and an increase in sodium excretion (112,113). Beukhof et al (114) reported a 12% increase in glomerular filtration rate in 9 normal men infused with 1.5-2.0 g/kg min dopamine. However, when the same dose of dopamine was given to 32 patients with IgA nephropathy and varying degrees of renal insufficiency, only patients with a GFR greater than 73 ml/min responded to dopamine by increasing GFR; none of 8 patients with a GFR below 73 ml/min increased his GFR.



Relation between percent increase ( ) in GFR during dopamine infusion and baseline GFR. The shadowed area depicts the 95% confidence limits of the GFR determination. o = Women; o = Men (114).

The conclusion from this study was that patients with a reduced GFR failed to increase the GFR following dopamine because they were already using their renal reserve to compensate for a reduced renal mass. While this study has not been extended to acute renal failure, it is likely that the remaining few functionally intact nephrons in this condition are also operating at reserve capacity and unable to further increase their filtration rate in response to a renal vasodilator.

In the dog model of uranyl nitrate induced acute renal failure (10 mg/kg/intravenously), Lindner et al (63) demonstrated early protection of the glomerular filtration rate when dopamine (3 ug/kg/min) and furosemide (1 mg/kg bolus followed by 1 mg/kg/hr intravenously) were given 15 minutes after the uranyl nitrate and for the next 6 hours. A later, uncontrolled report in 6 patients with oliguric acute renal failure and 2 patients with prerenal azotemia by Lindner (115) documented that low dose dopamine (1-3 ug/kg/min intravenously) and furosemide (100-200 mg every 6-8 hours) produced a brisk diuresis and a stable or reduced serum creatinine in two-thirds of the patients.



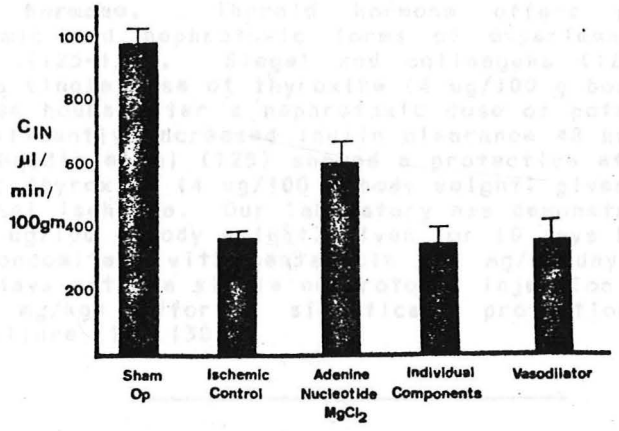
Conversion to a nonoliguric form of acute renal failure after dopamine and furosemide in case 4. Despite adequate diuresis, serum creatinine continued to rise and hemodialysis was required once before recovery occurred (115).

Although this was felt to be an encouraging response, 4 of the 8 patients died. Regarding the possible mechanism of action of the dopamine and furosemide combination, Lindner (63) suggested that the patients who benefitted did so not because of the vasodilation, but rather that dopamine enhanced delivery of furosemide to its tubular secretory site and induced a solute diuresis. While it is implicit in these reports that improving urine flow is somehow synonymous with improvement in excretory function of the kidney, there has been little evidence presented that this is the case (i.e. that glomerular filtration rate increased or serum creatinine decreased)(116,117).

Does the use of dopamine or furosemide pose any hazard to the patient with acute renal failure? The risks are probably small. However, furosemide use in acute renal failure may cause temporary deafness (72). Dopamine because it may alter systemic blood pressure, often is used only in conjunction with an arterial catheter for blood pressure monitoring and a Swan-Ganz balloon tiped catheter for determination of atrial filling pressure and cardiac output. Both of these devices have associated risks, require an intensive care setting for their use, and greatly increase the material and personnel costs. Thus, in the absence of proven benefit, there is little to recommend longterm diuretic or vasodilator therapy in either established acute renal failure or mild to moderate degrees of renal insufficiency (e.g. as occurs with aminoglycoside nephrotoxicity) developing in the hospital setting. There is little evidence that conversion of an oliguric state to a non-oliguric state with chronic diuretic or vasodilator therapy gives such patients a better out-

look than those patients who remain oliguric.

ATP-$MgCl_2$. The adenine nucleotide system in the cell is the major energy supplier for transport, synthetic, and metabolic functions of the cell. A series of investigations in the rat have demonstrated that the postischemic infusion of adenine nucleotides combined with magnesium chloride will accelerate recovery from acute renal failure (118-120).

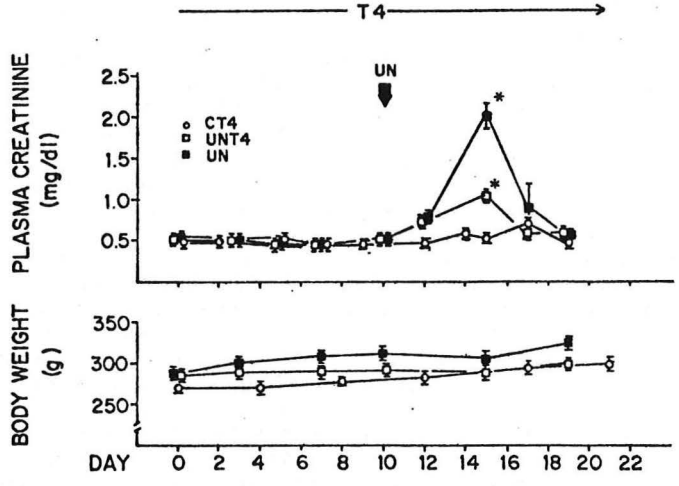


Inulin clearance 24 hours after bilateral renal artery occlusion. Enhanced recovery of C_{In} was seen only in animals that received a postischemic infusion of one of the adenine nucleotides (AMP, ADP, or ATP) combined with magnesium chloride. Values of C_{In} for animals that received individual components of the mixture (ATP, magnesium chloride alone, or adenosine) or a potent vasodilator (phenoxybenzamine or dopamine) were similar to those of ischemic control animals. Bars represent the means + SEM (122).

Since ATP levels fall dramatically in the renal cortex shortly after the onset of ischemia (121), the occurrence of disordered mitochondrial function, disruption of cellular and organelle membranes, and ultimately cell swelling and death are not unexpected consequences. Seigel (122) has extensively reviewed the use of ATP and other adenine nucleotides in the treatment of acute renal failure. At present the mechanism of ATP-$MgCl_2$ protection is in doubt, but several possibilities have been proposed. ATP may directly replenish diminished ATP stores in the cell. Although ATP has traditionally been viewed as a molecule that was unable to cross cell membranes, Seigel (122) has reviewed why this might not hold in the case of injured membranes. $MgCl_2$ when adminstered intravenously has a marked vasodilating effect, but since $MgCl_2$ in combination with ATP is beneficial when adminstered after the insult and other vasodilators are unsuccessful in reversing the defect, a solely vascular

effect seems unlikely. Since the drug combination is effective when given after the insult, Gaudio et al (123) have concluded that the preservation of sublethally injured cells and/or enhanced regeneration of new cells may be the basis of the beneficial effect. At present there are no clinical uses of this combination in the United States. However, addition of ATP-MgCl2 to the perfusion medium used to preserve kidneys has improved the survival of transplanted dog kidneys (124).

Thyroid hormone. Thyroid hormone offers protection against ischemic and nephrotoxic forms of experimental acute renal failure (125-130). Siegel and colleagues (128) demonstrated that a single dose of thyroxine (4 ug/100 g body weight) administered 24 hours after a nephrotoxic dose of potassium dichromate significantly increased inulin clearance 48 hours after the insult. Gaudio et al (125) showed a protective effect of a single dose of thyroxine (4 ug/100 g body weight) given after 45 minutes of renal ischemia. Our laboratory has demonstrated that thyroxine (10 ug/100 g body weight) given for 10 days before and for 8 days concomitant with gentamicin (60 mg/kg/day) or continued for 4 days after a single nephrotoxic injection of uranyl nitrate (0.5 mg/kg) afforded significant protection against acute renal failure (129,130).



Protective effect of T4 on uranyl nitrate-induced acute renal failure. T4 begun 10 days prior to uranyl nitrate (UN, 0.5 mg/kg body weight).

There are several potential ways in which thyroxine might provide protection against ischemic and nephrotoxic acute renal failure.

Potential Mechanisms of T4 Protection In Acute Renal Failure

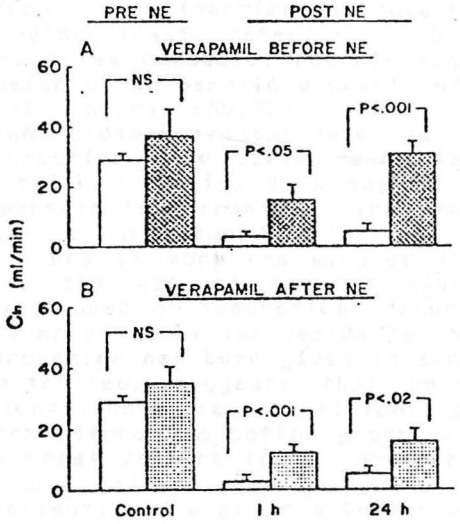
1. Increases in GFR
2. Stimulates Na-K ATPase
3. Stimulates Ca-ATPase in red cell
4. Accelerates cell growth and regeneration
5. Enhances Na-phosphorus cotransport

The influence of thyroid hormone on normal renal function is well documented; hypothyroidism depresses glomerular filtration rate below normal, whereas hyperthyroidism increases glomerular filtration rate above normal (131). However, in both studies from our laboratory, clearance and excretion data indicated that this protection did not result from an increase in glomerular filtration rate or filtered load of solutes (130,131). Thyroid hormone has an important stimulatory action on the plasma membrane pump that maintains cellular constancy of sodium and potassium (132). Prevention of a fall in Na-K ATPase activity by thyroxine after gentamicin administration might make the cell more resistant to injury. In both of our studies, T4 had a marked stimulatory effect on renal cortical homogenate Na-K ATPase activity in protected animals (130,131). In addition, thyroxine directly stimulates Ca-ATPase in the red cell membrane (133). If a similar action occurs in cells of the renal cortex, it would serve to buffer a rise in cytosolic calcium concentration. Our most recent study demonstated histologically that T4 administration accelerated cellular regeneration, a conclusion also reached by other investigators studying the effect of T4 in postischemic acute renal failure (130). In our study, thyroxine also was associated with a reduction in the activity of the brush border enzyme alkaline phosphatase in the cortical homogenate, a phenomenon previously described and accompanied by enhanced sodium-phosphate cotransport in brush border membranes (130,134). Such an increase in renal tubular phosphate transport could in turn make available more phosphate for the formation of high energy phosphate compounds, particularly ATP, the substrate for Na-K ATPase and CA-ATPase.

Thus, the protective effect of T4 in both ischemic and nephrotoxic models of acute renal failure indicates that protection is likely to be non-specific. Moreover, the effect may depend on different effects in the different models, since T4 has been protective when given after as well as before the insult. For the present, the use of thyroxine in acute renal failure must remain an experimental tool from which useful information may come regarding the pathogenesis of this disease.

Calcium entry blockers. The calcium entry blocking agents are potent vasodilators in many vascular beds. However, in addition to these known vascular effects, there is some evidence that calcium entry blockers have another independent effect that affords some protection against acute renal failure. Verapamil,

an agent that blocks the slow calcium channel, and at high doses competes for calcium membrane binding sites, affords protection against norepinephrine-induced acute renal failure in the dog and reduces the late elevations in tissue and mitochondrial calcium that characterizes this model at 24 hours post insult (135). Verapamil protection was demonstrable when the drug was administered for 30 minutes before and for 2 hours after the norepinephrine-induced ischemic period.



V administered for 30 min before NE (cross-hatched bars, top) significantly attenuated the fall in inulin clearance (C_{in}) induced by NE alone (open bars) both 1 and 24 h after NE. (B) V administered for 2 h after NE (stippled bars, bottom) also significantly attenuated the fall in C_{in} both 1 and 24 h after NE (135).

However, other groups have failed to demonstrate protection in this model when the verapamil was given after the insult (136,137). When verapamil was given pre-insult, mitochondrial function was protected as assessed by cellular respiration and calcium kinetics in vitro (135). Animals not receiving the calcium channel blocker had an increase in mitochondrial calcium content, a decrease in active calcium uptake rate by mitochondria, and an increase in mitochondrial calcium release 24 hours post insult.

Despite evidence that calcium overload may be an important pathway in nephrotoxic acute renal failure, there are few studies that conclusively show that calcium entry blockers produce a more favorable outcome. Verapamil was recently shown not to afford protection in man against a cisplatin-induced fall in the GFR (138).

Conclusions. Acute renal failure, as strictly defined at the beginning of this grand rounds, is still a relatively uncommon disorder in hospitalized patients. For these reasons a study to test whether the pharmacologic interventions described above can prevent acute renal failure would be difficult in a prospective, pre-insult fashion, as has frequently been done in the laboratory models of acute renal failure. One exception to this might be the elderly patient or the patient with diabetic nephropathy and reduced renal function who requires a radiologic procedure using radiocontrast material. While controlled studies are lacking, a few anecdotal reports suggest that prior use of volume expansion or an osmotic diuretic may be beneficial in decreasing renal injury (50,52). Since this clinical situation bears the closest resemblance to the laboratory reports showing protection from acute renal failure by prior establishment of a brisk diuresis, this may be the one setting in which such an approach is warranted. The remaining cases of acute renal failure occur sporadically and often are not diagnosed until 24 hours or more has elapsed from the time of the insult. Thus, the use of osmotic diuretics in this situation can be questioned on theoretical grounds. However, a trial with a 200-400 mg bolus of furosemide can be given without much risk. When furosemide has been given in such a manner, the data although uncontrolled, suggests that non-oliguric acute renal failure patients have fewer clinical and biochemical complications and are afforded a better prognosis than patients with oliguric acute renal failure (66). However, patients with non-oliguric acute renal failure have less of a reduction in the GFR than oliguric patients and a prior a better outcome would be anticipated. Presently there is no data proving that patients initially having oliguric acute renal insufficiency have an improvment in glomerular filtration rate or clinical outcome when changed from an oliguric to a non-oliguric state with a continuous diuretic and/or vasodilator infusion. The argument that patients pharmacologically converted to non-oliguric acute renal failure are more easily managed from the standpoint of fluids and nutrition is difficult to substantiate and must be weighed against the complexity introduced into the management by the pharmacologic intervention itself.

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