# NEW THERAPEUTIC STRATEGIES FOR ACUTE RENAL FAILURE IN THE INTENSIVE CARE UNIT

INTERNAL MEDICAL GRAND ROUNDS

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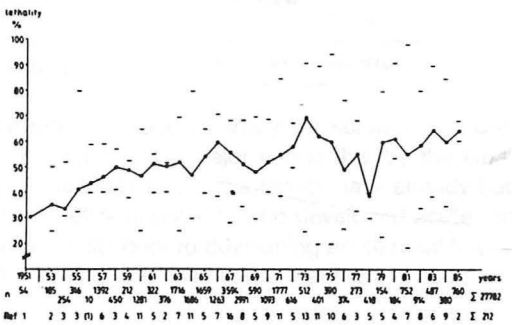
## I. The Problem: HIGH MORBIDITY AND MORTALITY OF ARF IN THE ICU

This presentation on acute renal failure begins where many presentations on acute renal failure end. In most discussions of this subject, emphasis is appropriately placed on the prevention of acute renal failure. The reason for this emphasis on prevention is that the morbidity and mortality of this disease is so high that any progress made in preventing the disease is likely to have the greatest beneficial effect. In particular, the development of acute renal failure in the critically ill patient represents one of the most challenging and frustrating therapeutic aspects in all of medicine. Even though dialysis therapy is effective in controlling volume and electrolyte balance in acute renal failure, the outcome for these patients remains dismal (Figure 1).

**Figure 1. Mortality of acute renal failure from 1951 to 1985.**




**Sieberth et al, Ref. 76**

This point was aptly made in a recent study in which the determinants of survival and recovery in acute renal failure were analyzed in intensive care unit patients (1). These investigators reviewed the clinical course of 43 consecutive critically ill patients who developed acute renal failure and who were first dialyzed in an intensive care unit setting. Twenty of these patients were treated in the surgical intensive care unit, and 18 were treated in the medical intensive care unit; 5 additional patients were treated in the burn unit. The overall mortality rate for these patients was 88% despite aggressive dialysis. Several correlates of recovery of renal function of these patients are provided in Table 1. As can be seen, the existance of comorbid conditions such as ARDS, antibiotic therapy, and mechanical ventilation predicted no recovery of renal function. In this study mechanical ventilation predicted a 100% mortality in this group of patients. This grim outcome mirrors the personal experience of many physicians who deal with acute renal failure in the intensive care unit, particularly in the surgical intensive care unit.

**Table 1. Correlates of recovery of renal function in acute renal failure patients dialzyed in intensive-care units (frequency and percent occurrence of comorbid events by recovery status)**

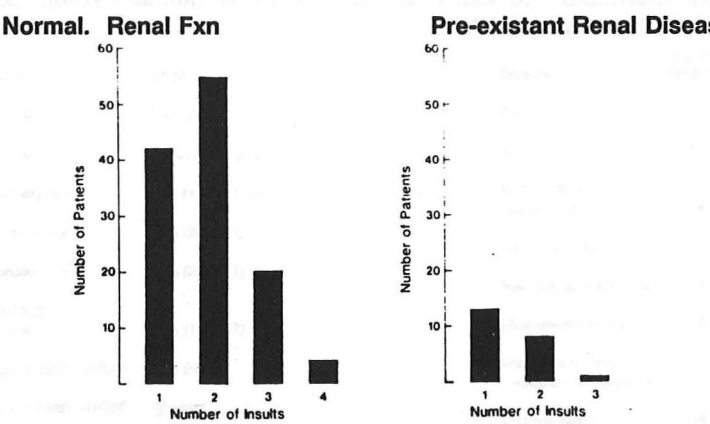
| Comorbid events | Recovery of renal function (n = 10) | No recovery of renal function (n = 33) | $\chi^2$ p value |
|---|---|---|---|
| Coma | 2 (20) | 9 (27) | 0.644 |
| Adult respiratory distress syndrome | 0 | 10 (30) | 0.047 |
| Seizure | 0 | 2 (6) | 0.425 |
| Required antibiotics | 7 (70) | 32 (97) | 0.010 |
| Pneumonia | 4 (40) | 14 (43) | 0.892 |
| Acute myocardial infarction | 0 | 3 (9) | 0.327 |
| Gastrointestinal bleed | 1 (10) | 9 (27) | 0.257 |
| Hepatic failure | 0 | 5 (15) | 0.190 |
| Ventilatory support | 4 (40) | 27 (82) | 0.010 |
| Need for vasopressors | 1 (10) | 8 (24) | 0.330 |
| Need for antiarrhythmics | 2 (20) | 10 (30) | 0.527 |
| Disseminated intravascular coagulation | 2 (20) | 7 (21) | 0.930 |

Figures in parentheses are percentages.

**Spiegel et al, Ref. 1**

What are other reasons for this poor survival record in this subset of patients? Clearly one factor that plays a major role is that by the time renal failure ensues in a critically ill patient, several other major insults have already been incurred. As shown in Figure 2, more than 62% of patients who developed acute renal failure in hospital had more than 2 major insults prior to developing acute renal failure and 48% had more than 1 risk factor (2). Among the risk factors that lead to acute renal failure, hypotension,

**Figure 2. Distribution of the number of acute insults per patient in the 121 patients without pre-existing renal disease (left) and in the 22 patients with pre-existing renal disease (right).**




**Rasmussen, et al Ref. 2**

**Rasmussen et al, Ref. 2**

excessive antibiotic exposure, pigmenturia, and respiratory failure were identified in several patients. Moreover, the older patient, the patient with diabetes, and the patient with pre-existent renal disease were also at risk to developing this disorder. Hence, renal failure often occurs in the context of multiple organ failure when it occurs in hospital and particularly in intensive care unit patients.

## II. MULTIPLE ORGAN FAILURE IN ICU PATIENTS

The complication that both internists and surgeons are encountering with increasing frequency in intensive care units is the disorder known as multiple organ failure syndrome (MOFS). I will not review this syndrome in detail here, but I think it is appropriate to cover several salient features of the disorder to illustrate the challenge facing physicians caring for these individuals. This syndrome is the leading cause of death in critically ill surgical patients and accounts for 75% of all deaths in surgical intensive care units (3). Patients are hospitalized an average of more than 21 days and the medical cost of survivors who require rehabilitation often exceeds $200,000. In one recent study (4), the mortality rate was 10% for all SICU patients; SICU patients who developed the adult respiratory distress syndrome had a mortality rate of 80%, and patients who had multiorgan system failure syndrome had a mortality rate of 96%. About 85% of the patients with the MOFS had more than 3 organ systems involved. These data are summarized in Table 2. The etiology of MOSF syndrome involves a sequential failure of organ systems. The frequency of disorders that precipitated the syndrome is shown in Table 3; the sequence of failure that usually occurs is pulmonary, hepatic, renal, gastrointestinal, cardiac, and central nervous system. The initial insults that occurred to cause the syndrome usually fall into one of several categories:

- Severe tissue injury, loss or ischemia
- Severe hemorrhage
- Severe inflammation, such as pancreatitis
- Infection

**Table 2. Study Results: ARDS and MOFS Syndromes**

| | |
|---|---|
| Total patients | 1,036 |
| Incidence of ARDS | 2.4% (25 of 1,036) |
| Incidence of MOSF | 2.6% (27 of 1,036) |
| Overall mortality rate | 10% (105 of 1,036) |
| ARDS mortality rate | 80% (20 of 25) |
| MOSF mortality rate | 96% (26 of 27) |
| ARDS plus MOSF mortality rate | 94% (16 of 17) |
| Median age of death—ARDS | 38.5 years |
| Median age of death—MOSF | 38 years |

**Smalls, Ref. 4**

**Table 3. Disorders that Precipated in MOFS 25 of the Study Group Patients**

| Disorder | No. of patients | Incidence (%) |
|---|---|---|
| Trauma | 13 | 52 |
| Sepsis | 13 | 52 |
| Multiple blood transfusions | 4 | 16 |
| Gastric aspiration | 3 | 12 |
| Nosocomial pneumonia | 3 | 12 |
| Hypovolemic shock | 2 | 8 |
| Disseminated intra-vascular coagulopathy | 1 | 4 |
| One risk factor | 15 | 60 |
| Two risk factors | 5 | 20 |
| Three risk factors | 5 | 20 |

The clinical course of MOFS is provided in Table 4.

**Table 4. Clinical Presentation of Multisystem Organ Failure (MOFS)**

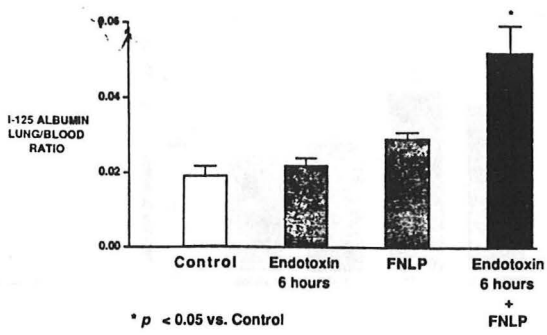
| Stage | Onset After Injury | Clinical Observations |
|---|---|---|
| 1 (Sepsis) | 2-7 d | Fever and leukocytosis<br>Decreased systemic vascular resistance<br>Increased cardiac output and oxygen consumption |
| 2 (Early MSOF) | 7-14 d | Acute respiratory failure<br>Impaired oxygen extraction<br>Hypermetabolism with or without jaundice<br>Ileus and thrombocytopenia<br>Leukocytosis or leukopenia<br>Possible mental status changes |
| 3 (Established MSOF) | 2 wk to months | Progressive adult respiratory distress syndrome (fibrosis)<br>Hemodynamic instability<br>Hypermetabolism and lactic acidosis<br>Jaundice and azotemia with or without oliguria<br>Possible stress gastrointestinal tract bleeding<br>Disseminated intravascular coagulation |
| 4 (Preterminal MSOF) | Weeks to months | Hypodynamic cardiovascular state refractory to inotropic or α-adrenergic support<br>Minimal oxygen extraction<br>Worsening lactic acidosis |

**DeCamp et al, Ref. 9**

Much has been written about the etiology of MOFS syndrome (5-13). The initiating events of the syndrome may be thought of as a 1-hit model, a 2-hit model or a multiple or persistent-hit model (5). The 2-hit model is the more accepted theory, has experimental support, and applies to burns, trauma, and all aspects of surgery. In this setting, an initial event is followed by an adequate resuscitation which sets the stage for the development of the syndrome. A subsequent second hit is received often related to a clinical infection or another complication such as a second operation, and this precipitates the cascade of multiple organ failure. In most of these scenarios, endotoxin is the inciting factor. Endotoxin may stimulate particular endothelial cells such as the Kupffer cell to produce humoral mediators. This in turn stimulates the effector system and lead to the syndrome. Cytokines that have been prominently mentioned as important in the etiology of MOFS are tumor necrosis factor, IL-1, IL-2, IL-6, as well as gamma interferon and platelet activating factor (12). In one experimental study that explored the hypothesis that a 2-hit model could actually lead to MOFS (11), injury was measured by pulmonary protein leak in a group of experimental rats. In this experiment, endotoxin was administered for 6 hrs and albumin accumulation in the lung was accessed. A neutrophil activating (but non injurious) factor (FNLP) was then applied. As shown in Figure 3, lung injury only occurred when FNLP was given after endotoxin administration; in other words, it took **both** stimuli to produce pulmonary capillary disruption (11). The presummed sequence of events that endotoxin caused pulmonary sequestrtion of neutrophils which

then responded to the activating factor.

**Figure 3. FNLP + Endotoxin Cause Lung Damage**



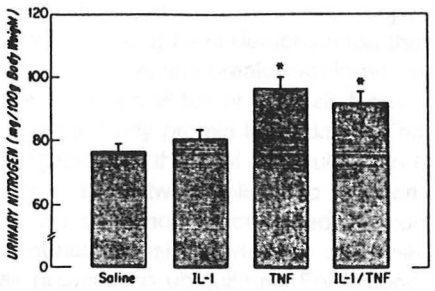

**Anderson et al. Ref. 11**

Patients with this syndrome have a clinical picture similar to septicemia. They often have an increase in cardiac output, fever, an elevated white blood cell count, and a decrease in systemic vascular resistance. However, these patients may not have endotoxemia in all cases. Rather, they seem to have a generalized response to inflammation. The syndrome appears to be a self-destructive phenomenon involving circulating inflammatory cells. Neutrophils and platelet-fibrin thrombi aggregate in involved organs (14), causing capillary occlusion and microvascular hypoperfusion. Activated neutrophils have tremendous inflammatory potential, and their ability to produce reactive oxygen metabolites and release potent granular enzymes makes them prime candidates as mediators of tissue injury. Neutrophils can disrupt endothelial barriers, increase microvascular permeability, and cause the accumulation of tissue edema, which is characteristic of the MOFS. Once endothelial cells are damaged in this syndrome, platelet aggregation, further endothelial cell injury, infiltration of neutrophils, further activation of the compliment - kallikrein-kinin systems occurs, and one incident begins to trigger the next. Fluid begins to leak through the damaged capillary endothelium and this compounds the initial inadequate perfusion problem.

As mentioned above, platelet activating factor released from leukocyte macrophages and platelets may be an important mediator of this syndrome and lead to neutrophil aggregation and stimulation of arachidonic acid metabolism. $PGE_2$ levels are high and this may lead to some amino acid mobilization as well as causing fever and encouraging catabolism. Interleukin-1 is also derived from macrophages and promotes fever, neutrophilia, and acute proteolysis. Reactive oxygen metabolites are released from white blood cells and these may further lead to tissue injury, as may the release of tissue proteases. Tumor necrosis factor is another monocyte-derived cytokine with properties similar to interleukin-1. Tumor necrosis factor causes fever, intravascular coagulation, alters perfusion, and promotes pulmonary permeability, and organ failure in lungs, kidneys, liver, and the gastrointestinal tract. The effects of IL-1 and tumor necrosis factor

on urinary protein excretion (as an index of protein catabolism) are shown in Figure 4.

**Figure 4. Effects of IL-1 and TNF on UNA**




**Flores et al, Ref. 15**

In some ways the patient with the MOFS syndrome is the paradigm for the development of new strategic approaches to the patient with acute renal failure. These patients are catabolic and are hemodynamically unstable. They require meticulous volume control often in the setting of ARDS and low blood pressure. Further, because of their catabolic condition, they require aggressive replenishment of nutrients (16). The next two sections review the nutritional requirements of patients with catabolic acute renal failure and the newer dialytic strategies in treatment.

## III. NUTRITION IN PATIENTS WITH ACUTE RENAL FAILURE

### 1. CAUSES OF CATABOLISM IN ARF.

The prognosis of acute renal failure may be dependent on part in the degree of catabolism present (17). Factors involved in catabolism range from those attributable to well-defined hormonal alterations in ARF to those hypothesized to result from an increase in cytokine secretion.

Plasma levels of catacholamines and glucagon in animals are elevated in acute renal failure (18). The plasma insulin level is elevated, but is low relative to the blood glucose concentration. Insulin resistance occurs primarily at the level to the skeletal muscle and this results in diminished glucose uptake (19). Insulin-mediated amino acid uptake and insulin-stimulated protein synthesis are also reduced in animal models of renal failure (20, 21). Parathyroid hormone levels are also elevated in patients with acute renal failure; this may contribute to protein catabolism in a manner similar to that seen in primary hyperparathyroidism (22). A role for adrenal hormones in protein catabolism is consistent with the observation that urea synthesis is diminished in adrenalectomized rats (22). A role for adrenal hormones in the syndrome is also supported by more recent evidence that the catabolic effect of cytokines and monokines, such as tumor necrosis

factor, is dependent upon glucocorticoids (22-25). Metabolic acidosis is also common in acute renal failure, and this condition accelerates protein breakdown (26).

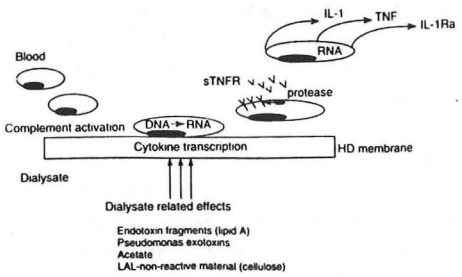
Sepsis and hemorrhage often complicate acute renal failure in the ICU and these are catabolic conditions themselves. Toxins accumulate in the blood, resulting in an enhanced proteolytic activity (27). Alpha-$_2$ macroglobulin inhibits this proteolytic activity, and it has been postulated that reduced levels of protease inhibitors may contribute to the hypercatabolic state (28). Other circulating peptides that have proteolytic activity have also been found in patients with sepsis (29). In addition to these factors, some investigators (30) have demonstrated that partially purified preparations of interleukin-1 can increase protein breakdown in an isolated muscle preparation. It has been shown more recently that tumor necrosis factor is a potent mediator **in vivo** of skeletal muscle and whole body protein breakdown. The effects of tumor necrosis factor appear to be synergistic with those of interleukin-1 in this action (15) (Figure 4). The mechanism of action of these two cytokines to increase catabolism appears to be dissimilar, however (31). Although not demonstrated, it is conceivable that even in patients with uremia who do not have sepsis, interleukins and other cytokines may play a role in proteolysis since their presence is ubiquitous. For instance, the interaction of blood with certain dialysis membranes stimulates the release of interleukin-1 and other monocytes from cytokines. These agents could play a role in the catabolic response in skeletal muscle (32). This interest in cytokines as a mediator of hypotension during dialysis and a cause of proteolysis has received considerable attention as the "interleukin" hypothesis (33). The sequence of events is believed to involve an interaction of complement and the dialysis membrane to produce IL-1 and TNF. Low levels of endotoxin (sometimes present in dialysis) then trigger release of the cytokines (Table 5).

**Table 5. Dialysis and Activation of Cytokine Release**

- HD membranes (bioincompatible) activate complement
- C5a stimulates IL-1 and TNF gene expression; protein released in the presence of endotoxin
- Dialysis per se seems to slightly increase levels of IL-1 and TNF
- The same cells producing IL-1 and TNF also produce antagnoists
- Ratios of IL-1 and IL-IRa may be critical to disease outcome; the same is true for sTNFR

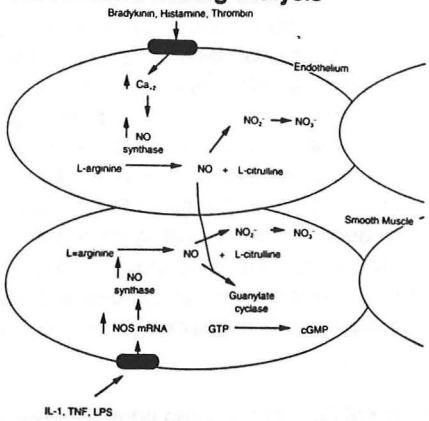
Interestingly, the same cells that produce these cytokines also produce antagonists (Figure 5), so the ratio of agonists to antagonists may determine the final effect. These cytokines are endothelium-dependent vasodilators and probably work through cGMP to cause peripheral smooth muscle relaxation and hypotension (34) (Figure 6).

**Figure 5. Production of IL-1, TNF, IL-1 Ra, and sTNFR**




**Dinarello, Ref. 33**

**Figure 6. Endothelium-Dependent Vasodilators During Dialysis**




**Beasley, Ref. 34**

## 2. NUTRITIONAL NEEDS OF ACUTE RENAL FAILURE PATIENTS IN THE ICU

In some sense, the desire to provide adequate caloric and protein intake to the severely catabolic patient with acute renal failure has resulted in the new dialytic therapy now available in the intensive care unit. From an overall standpoint, however, the value of supplemental nutrition in catabolic patients with acute renal failure has largely been unproven. One study (81) in which a positive energy balance was achieved by parenteral nutrition reported an improved survival in acute renal failure patients (Table 6).

**Table 6. Results of Positive Energy Balance on Survival**

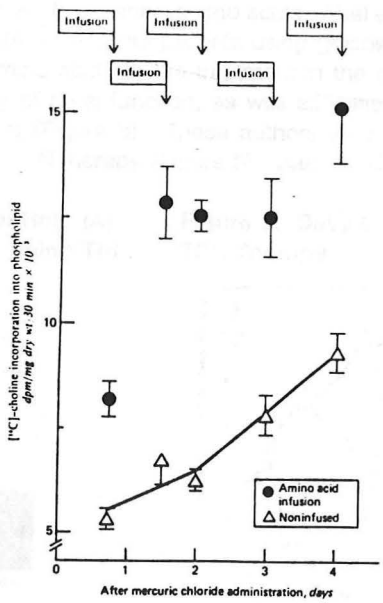
| | High Calorie (24) | | Low Calorie (32) | |
|---|---|---|---|---|
| | Lived | Died | Lived | Died |
| No. | 9 | 15 | 3 | 29 |
| Caloric balance kcal/d | 549 | 398 | -299 | -323 |
| Cum-kcal | 8300 | 3751 | -6459 | -9514 |

**Bartlett, Ref. 82**

The theoretical basis for nutritional therapy in acute stress states is clear: to prevent the adverse effects of starvation in catabolic, immunocompromised patients. Most regimens provide glucose as an energy source to blunt the gluconeogenic stimulus of stress states and amino acids to attenuate gluconeogensis and provide a substrate of protein synthesis. Lipids serve as a two carbon energy source as a high caloric equivalent. Insulin decreases proteolysis and lipid mobilization and increases glucose uptake. Laboratory experiments in rats using glucose + either essential or a combination of essential and non-essential amino acids in acute renal failure have yielded conflicting results. Toback et al (34a) showed a more rapid recovery of renal function in amino acid treated rats compared to animals receiving glucose only. On the other hand, Oken et al (34b) found no differences in recovery rates in glucose + amino acids and glucose only - treated rats (Figure 7 and Table 7).

Human study results have varied as well. Several case reports (35,36) described improved survival and recovery from acute renal failure and hypercatabolic patients who

**Figure 7. Effects of Amino Acid Infusion on New Membrane Formation in Experimental ARF**




**Toback, Ref. 33**

**Table 7. Effect of AA Solution on Recovery From Experimental Acute Renal Failure**

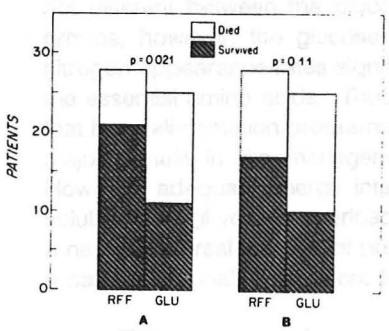
- Same Protocol as Toback

| | AA + Dextrose | Dextrose Only |
|---|---|---|
| BUN, mg/dl | | |
| Baseline | 22±1 | 26±2 |
| 24h | 187±23 | 61±14* |
| 48h | 235±48 | 139±35* |
| Mortality | 10/21 (48%) | 1/11 (9%) |

**Oken, Ref. 34b**

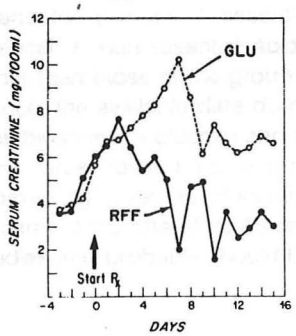
received parenteral glucose in essential amino acids. Abel et al (37) carried out a double blinded study of 53 acute renal failure patients using glucose and vitamins in one group and added essential amino acids to the treatment in the other group. These authors found that the recovery of renal function, as well as patient survival, was significantly better in the latter group (Figure 8). These authors also noted a reduction in serum creatinine as a result of TPN therapy (Figure 9). Baek et al (38) found similar mortality

**Figure 8. ARF Survival Rate (A) and Mortality Rate (B) Using TPN**




**Abel et al, Ref. 37**

**Figure 9. Daily Creatinine During TPN Therapy**




**Abel et al, Ref. 37**

rates using nearly identical treatment formulas of those of Abel et al in 129 acute renal failure patients. Other studies by Leonard and colleagues (39) and Feinstein et al (40) have not supported these earlier favorable results. In Leonard's study, 20 acute renal failure study patients were divided into essential amino acids + glucose and glucose only groups. They found mortality to be identical; however, the daily rate of rise of BUN was significantly less in the amino acid-treated group (Table 8). Feinstein et al (40) examined

**Table 8. No Effect of TPN on Outcome in ARF**

- TPN identical to Abel et al; Groups matched for age, disease, CHO intake
- Less negative N balance in amino acid-supplemented group
- Some decrease in daily BUN increase in amino acid-supplemented group

| ARF Survival | | Long-Term Survival | |
|---|---|---|---|
| EAA | Control | EAA | Control |
| 55% | 56% | 36% | 44% |

**Leonard et al, Ref. 39**

survival and daily nitrogen of appearance rates as an index of catabolism and 30 acute renal failure patients who were treated with 3 protocols. One group received glucose only; a second, glucose and essential amino acids; and a third glucose and essential + non-essential amino acids. There was no difference in recovery from acute renal failure or in survival in these 3 groups even though there was a trend toward a better outcome in the glucose and essential amino acid group. The urea nitrogen appearance rate was not different between the glucose only and the glucose + essential amino acids of groups; however, the glucose and essential + non-essential acid group had urea nitrogen appearance rates significant higher than those of the group that received only the essential amino acids. Thus, on balance, the available data do not clearly indicate that hyperalimentation programs using combinations of glucose and amino acids are of major benefit in the management of the stress-related acute renal failure patient. However, adequate energy intake predominately given as glucose or as glucose + soluble lipids (if volume overload is a concern) at the rate of 20-30 cal/kg day has been a nearly universal element of previous studies and probably should be continued to be a basic nutritional requirement (40,41).

There are several major reasons for considering nutrient administration during hemodialysis or hemofiltration. First, many patients with hypercatabolic acute renal failure

are malnourished at baseline and may benefit from such nutritional supplementation. Second, giving nutrients during dialysis treatment can correct nutrient losses which occur during the procedure and may alleviate this catabolic stress. Finally, the dialysis treatment offers a convenient access to the circulation. There is no firm formula by which to guage the caloric requirements of individuals treated with nutritional supplementation. An average resting adult with a basal metabolic rate of 2,000 kcal/d will need 3,000 kcal in sepsis and will rarely (in severe burn states) require up to 4,000 kcal/d (41). The proportion of carbohydrate, amino acid, and fat is also variable from regimen to regimen. The rate of tissue catabolism is a major factor regarding the nutrition. This rate is determined in large part by the presence of associated illnesses and severity of renal insufficiency. In general, a daily rise in the BUN of more than 30 mg per dl is a reliable sign of marked catabolism. Other indicators of excess metabolism include decreased levels of serum total proteins and albumin, and a low total lymphocyte count.

The best measure of the rate of protein breakdown is the urea nitrogen appearance. The UNA has two components, the amount of urea nitrogen excreted and the change in the nitrogen pool. The latter is critical in renal failure patients because excretion of urea is reduced or absent. The urea secretion pool can be calculated using the BUN in grams per liter and total body water in liters since urea is distributed equally throughout body water. Total body water can be estimated as 60% body weight, although the percentage would be greater in patients with anemia. In acute renal failure, changes in the urea nitrogen pool must be considered carefully because impaired kidney function causes accumulation of urea and water retention. The following equations are used to calculate the urea nitrogen appearance (Table 9):

**Table 9.**

1. UNA (g N/day) = change in body urea nitrogen pool
   + urinary urea nitrogen
   + dialysate urea nitrogen
2. Change in body urea nitrogen pool (g N/day) = [change in BUN (g/L)
   × initial total body water] + [change in body weight (kg)
   × final BUN (g/L) × 1 L/kg]

**Moroni et al, Ref. 42a**

The UNA can be used to estimate total nitrogen excretion and, if nitrogen intake is known, nitrogen balance. In patients with chronic renal failure, the combination of other sources of nitrogen loss add to total nitrogen excretion (such as secretion of creatine and uric acid in the urine and gastrointestinal and skin losses) is relatively stable and varies minimally with protein intake (41). The difference between nitrogen intake and the UNA yields an estimate of nitrogen balance that comes close to the nitrogen balance (41,42). An illustration of the effect of dietary protein on nitrogen balance and UNA is shown in Table 10.

**Table 10. Relationship between nitrogen balance, urea nitrogen appearance rate, and steady-state SUN.**

| Dietary protein (g/day) | $I_N$ – NUN (gN/day) | Steady-state SUN (mg/dl) |
|---|---|---|
| 80 | 10.3 | 120 |
| 60 | 7.1 | 83 |
| 40 | 3.9 | 45 |

$$B_N = I_N - U - \text{NUN} \quad [1]$$

if $B_N = 0$, then

$$I_N = U + 0.031 \text{ gN/kg body wt.} \quad [2]$$

$$\text{SUN} = \left(\frac{I_N - 0.031 \text{ gN/kg body wt.}}{C_{urea}}\right) \times 100 \quad [3]$$

**Moroni et al, Ref. 42a**

$B_N$, nitrogen balance (g/day); $I_N$, nitrogen intake (g/day) (16% of protein intake); NUN, the nitrogen in feces and non-urea urinary nitrogen which averages 0.031 gN/kg/day (189); *U*, urea nitrogen appearance rate (g/day); SUN, serum urea nitrogen concentration (mg/dl); $C_{urea}$, urea clearance.

Protein degradation (g/d) may be estimated by using the following formula:

**Net protein breakdown = 6.75 (UNA) + 5.06**

As mentioned above, the ideal nutritional formula for the support of patients with acute renal failure has not been established. Whenever possible, the enternal route of nutrient administration is preferable, since this is the less invasive, least expensive, and is an efficient nutritional support technique. However, gastrointestinal dysfunction from a variety of causes may limit the utility of enteral nutrition. In general, the goals of nutritional support for patients in the ICU and patients with acute renal failure are similar. They can be summarized as follows: (1) To provide nutrition without jeopardizing the patient's fluid, electrolytes, mineral, or acid base status; (2) To attempt to preserve lean body mass by limiting net protein catabolism, but more importantly, to maximize protein synthesis and thereby maintain organ function and enhance renal recovery; (3) To prevent specific deficiencies of vitamins and minerals as well as trace elements.

As described above, most critically ill patients with acute renal failure are characterized by a very high catabolic rate (UNA greater than 10 g/d). A recommended amount of replacement therapy gleaned from several sources (42-44) is provided in Table 11.

**Table 11. Suggested guidelines for providing total parenteral nutrition to patients with acute renal failure.**

| | |
|---|---|
| **Protein:** | 1.2 - 1.5 g/kg/day of 8.5 to 15% solution of mixed essential and nonessential amino acids |
| **Calories:** | 35-40 kcal/day. 10-20% lipid infusion providing up to one third of the caloric intake |
| **Electrolytes:** | Sodium - approximately 70 mEq/L<br>Potassium, phosphorus and magnesium - add to TPN if blood levels fall<br>Acetate or bicarbonate - adjust as needed |

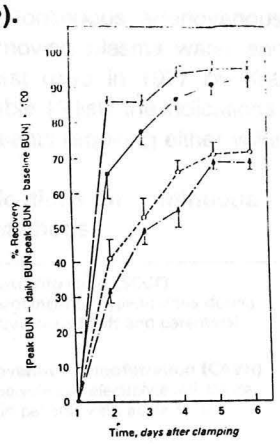
Generally, approximately 70 g/d is given as a mixture of essential and non-essential amino acids. There is some support in the literature for using the branched chained amino acids - leucine, isoleucine, and valine (44). Standard amino acid solutions contain 19-25% branched chained amino acids, whereas branch chained amino acid-enriched solutions contain up to 45%. Branched chained amino acids are transported into the cell by a large nutritional amino acid carrier, which it shares with aromatic amino acids. Once inside the cell they are transaminated to keto acids by the enzyme transaminase. This enzyme is active predominately in heart, kidney, and muscle; it has little activity in the liver. The transamination provides nitrogen for alanine and glutamine production by the muscle. The subsequent metabolism of branched chain keto acids involves oxidative decarboxylation by specific dehydrogenase enzymes. However, the activity of these enzymes will depend on where they are in a dephosphorylated form. The branched chain keto acids are oxidized only in tissues that contain the active form of these enzymes. In humans, the activated enzymes are present in skeletal muscles and, therefore, some branched chain keto acids are decarboxylated to acetylcoenzyme and carbon dioxide, and energy is generated. The rest of the branched chain keto acids are transported to various tissues for further metabolism.

## IV. IMPORTANCE OF ACUTE RENAL FAILURE THERAPY - NEWER THERAPEUTIC STRATEGIES

### 1. BIOCOMPATIBLE DIALYSIS MEMBRANES

One of the more interesting reports in recent literature has been that Schulman et al (45) regarding the independent effects of the choice of dialyzer on the resolution of acute renal failure. These investigators studied the role of compliment activation on the resolution of acute ischemic renal failure in the rat. Acute renal failure was induced by clamping the renal arteries of Sprague Dawley rats for 45 min. On subsequent days groups of rats with acute renal failure were exposed to daily zymosan infusions (an activator of the complement system) or to blood incubated with cuprophane or polyacrylnitrile dialysis membranes. Cuprophane also activates the complement system, whereas polyacrylnitrile does not. They serially measured the changes in BUN daily and also measured glomerular filtration rate 24 hr, and on days 3 and 5 following ischemia. On day 6 the animals were sacrificed and their kidneys examined histologically. Zymosan and cuprophane-exposed rats had a significant delay in the recovery of acute renal failure, reduced glomerular filtration rate, and histologically had more neutrophil infiltration than control or polyacrylnitrile-exposed animals (Figure 10). The investigators next assessed the response of zymosan-exposed rats to infusions of deferoxamine, which is a potent inhibitor of hydroxyl radical formation. The infusion of deferoxamine prior to zymosan significantly improved recovery of renal function. They also measured urinary thromboxane $B_2$ levels in these groups of rats. While the groups of rats exposed to zymosan had the highest levels of thromboxane $B_2$, these levels were not different between the groups exposed to zymosan alone or to zymosan and deferoxamine. Their observations suggested a role for hydroxyl radicals in the prolongation of renal failure in this model of acute renal failure.

**Figure 10. Fractional change in BUN different groups of rats, exposed to zymosan (▲), cuprophane membrane (○), polyacrylonitrile (△), and control (•).**




**Schulman et al, Ref. 45**

This observation has been followed by another preliminary) publication from this group in which the use of biocompatible membranes were tested with regard to the outcome in recovery from acute renal failure in patients (46). In this study, a total of 40 patients were randomized to be either dialyzed with a more biocompatible

membrane (consisting of polymethyl-methacrylate) or a bioincompatible membrane (cuprophane). Each dialysis session throughout the course of the acute renal failure and each patient's illness severity was judged by the Apache scoring system. The results of the study are shown in Table 12. The striking observation is that the acute renal failure recovery rate was 27% in the bioincompatible membrane group versus 67% in the biocompatible membrane group. Moreover, the mortality rate in the bioincompatible group was 73% versus only 39% in the biocompatiblity group. These data strongly support the use of biocompatible membranes in the dialysis of patients with acute renal failure.

**Table 12. Survival in ARF**

| | BICM | BCM | Total |
|---|---|---|---|
| # OF PATIENTS | 22 | 18 | 40 |
| APACHE SCORE | 29 | 28 | 29 |
| # OF DEATHS | 16 | 7 | 23 |
| MORTALITY RATE | 73% | 39% | 58% |
| MEAN # OF HD TREATMENTS | 11 | 11 | 11 |
| MEAN # OF HOSPITAL DAYS | 42 | 45 | 43 |
| ARF RECOVERY RATE | 27% | 67% | 45% |
| MEAN # HD DAYS TO RECOVERY | 27 | 15 | 19 |

**Hakim et al, Ref. 46**

## 2. DIALYTIC THERAPIES IN ACUTE RENAL FAILURE

Because of the hemodynamic instability of many patients who are critically ill with acute renal failure and because of the need for the prodigious amount of volume replacement to provide the parenteral nutrition described above, several continuous therapies of ultrafiltration have been recently incorporated into the dialytic therapy of acute renal failure. Continuous arteriovenous hemofiltration (CAVH) is an extracorporeal method for removing plasma water and solutes by continuous hemofiltration. This method was first used in 1977 by Kramer (47), and has evolved to several other techniques. Table 13 lists the indications for several of the therapies now in place in the ICU care of patients requiring either volume removal or control of uremia.

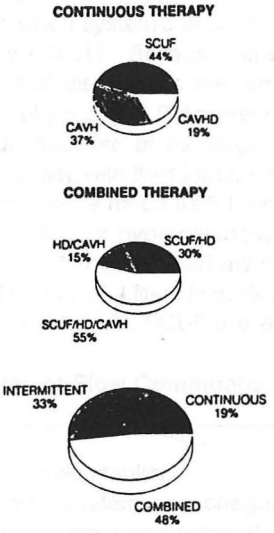
**Table 13. Indications for continuous ultrafiltration methods.**

| |
|---|
| **Slow continuous ultrafiltration (SCUF)**<br>Prevention and management of hypervolemia during administration of intravenous fluids and parenteral nutrition |
| **Continuous arteriovenous hemofiltration (CAVH)**<br>Management of hypervolemia, electrolyte imbalance, and/or mild uremia in patients with acute renal failure |
| **Continuous arteriovenous hemodialysis (CAVHD)**<br>Management of catabolic acute renal failure in hypervolemic, uremic patients who require high solute clearance |

**Slow continuous ultrafiltration** (SCUF) involves removal of plasma water for fluid balance alone. Here no significant azotemic or electrolyte control is obtained. **Continuous arteriovenous hemofiltration** (CAVH) is used for the management of hypervolemia, electrolyte imbalances, and/or mild uremia in patients with acute renal failure. It involves convective plasma water exchange for fluid-electrolyte, acid-base

and azotemic control. A very high porosity membrane is used in this procedure.
**Continuous arteriovenous hemodialysis** (CAVHD) is used for the management for catabolic acute renal failure patients who are also hypervolemic. These patients also require high solute clearances. In this procedure both convective removal of fluid and solute and diffusive removal of solute and fluid is operant. The frequency of use of these therapies is shown in Figure 11.

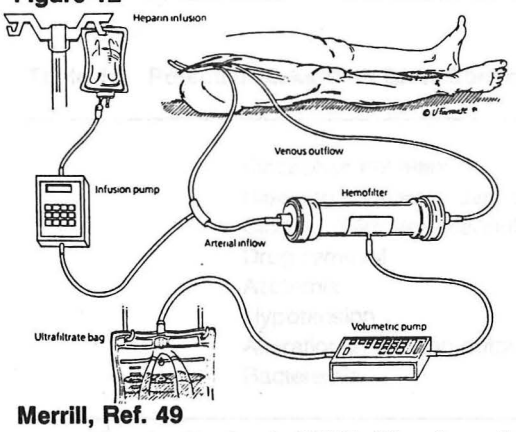
**Figure 11. Acute ICU Renal Therapy 1986 Overall Distribution**




**Paganini, Ref. 48**

The design of the equipment used in SCUF is shown in Figure 6. As can be seen, simplicity is one of the chief advantages of SCUF (49). Arterial blood from the femoral artery is routed through a hemofilter; an ultrafiltrate of serum collects that is rate-determined by the patient's blood pressure. The residual blood is then returned to the patient by the femoral vein. Low-dose heparin is required and is infused into the arterial limb of the extracorporeal circuit to prevent the hemofilter from clotting. This procedure has received considerable favorable attention in the management of patients with acute renal failure and severe volume overload.

**Figure 12**




**Merrill, Ref. 49**

The ultrafiltration in SCUF differs from dialysis in several ways. With dialysis small molecular weight solutes diffuse across the semi-permeable membrane into a dialysate

solution. Diffusion is facilitated by a concentration gradient between the plasma and the dialysate solution. With ultrafiltration, hydrostatic pressure creates an ultrafiltrate of plasma across the semi-permeable membrane. The ultrafiltrate has approximately the same composition of plasma water for molecules of 50,000 or less. The ultrafiltration rate is determined by several factors: 1) transmembrane pressure; 2) blood flow rate; 3) membrane characteristics and surface area; and 4) blood viscosity and hematocrit. In SCUF, transmembrane pressure is determined primarily by the patient's systemic arterial blood pressure. This differs from hemodialysis and intermittent hemofiltration in which a roller pump is used to generate a much higher transmembrane pressure. SCUF may be preferred over hemodialysis when systemic anticoagulation is prohibited and the patient has hemodynamic instability (49-51). Because ultrafiltration is performed continuously over 24 hrs, plasma water and electrolytes are removed more smoothly in a manner similar to normal glomerular physiology. Pulmonary edema and excess total body fluid can be prevented by SCUF because of the large daily volumes of ultrafiltrate. This procedure allows greater flexibility with fluid input, particularly parenteral nutrition, which may require the administration of as much as 5 L per day in order to provide adequate protein and caloric supplements to a hypercatabolic patient. The average ultrafiltration rates in SCUF range between 15 ml/min to 25 ml/min. With an ultrafiltration rate of 10 ml/min, a daily fluid removal rate of 14.4 liters is achieved. The potential benefits of SCUF are listed in Table 14 and the risks with SCUF are shown in Table 15.

**Table 14. Potential Benefits of Slow Continuous Ultrafiltration**

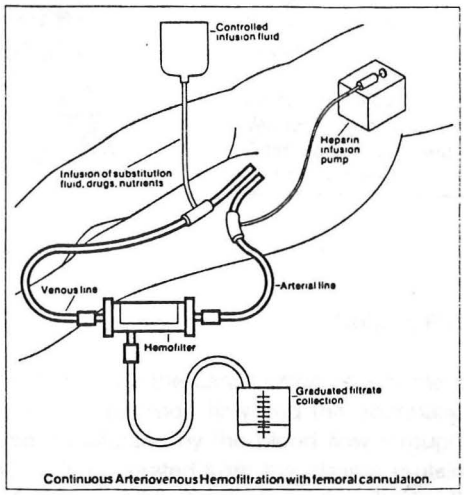
| |
|---|
| Hemodynamic stability |
| No need for systemic anticoagulation |
| Greater fluid input and removal |
| Ease of operation |
| No need for specialized dialysis personnel |

**Table 15. Potential Risks With Slow Continuous Ultrafiltration**

| |
|---|
| Electrolyte imbalances |
| Bleeding (systemic, cartridge) |
| Clotting (cartridge, cannula) |
| Drug removal |
| Azotemia |
| Hypotension |
| Alteration in cardiac output |
| Bacteremia |

The technique of CAVH has been recently widely applied to the entire spectrum of acute renal failure (52-60). The design of CAVH for is shown in Figure 13. The

**Figure 13**



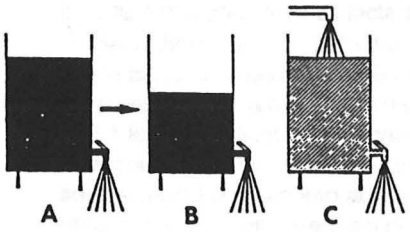

Continuous Arteriovenous Hemofiltration with femoral cannulation.

**Golper, Ref. 53**

underlying solute transport mechanism is convection across the filter membrane without osmolar changes in cells or fluid. There is rapid replacement of the removed vascular fluid and solutes by a replacement fluid so that ultrafiltration without hypotension does not occur. This is in distinction to traditional diffusion dialysis which initially removes solute osmoles preferentially from the vascular space in extracellular fluid. Thus, during hemodialysis there is a decrease in extracellular osmolality and cells become hypertonic to extracellular fluid. This results in water movement from extracellular fluid into cells. In CAVH a controlled infusion fluid is added to the venous catheter just prior to reentering the patient's circulation. In CAVH, small and medium sized molecules (molecular weight less than 50,000) are removed from the patient by ultrafiltration for a 24 to 72 hr period. To compensate for the loss of ultrafiltrate, blood volume is reconstituted by the administration of a fluid with an electrolyte composition similar to that of normal plasma. The anticoagulation required for the procedure is heparin in a dose of approximately 10 units per kg per hr. A simplified depiction of the concept underlying hemofiltration is provided in Figure 14. In this Figure, the dark shading signifies the uremic toxins in body fluids. The initial uremic fluid overload is presented by the left panel of the Figure labeled "a". This spigot is opened in the middle of the Figure where fluid is removed but the dark fluid left behind is not diluted and remains dark. The right hand figure represents CAVH in which the spigot is opened, draining the uremic fluid; clear fluid is poured in on the top, diluting the fluid remaining in the container.

Several factors affect the efficiency of the ultrafiltration procedure in CAVH. These are shown in summary form in Table 16. Obviously, the hydrostatic pressure is the single

**Figure 14**




**Golper, Ref. 53**

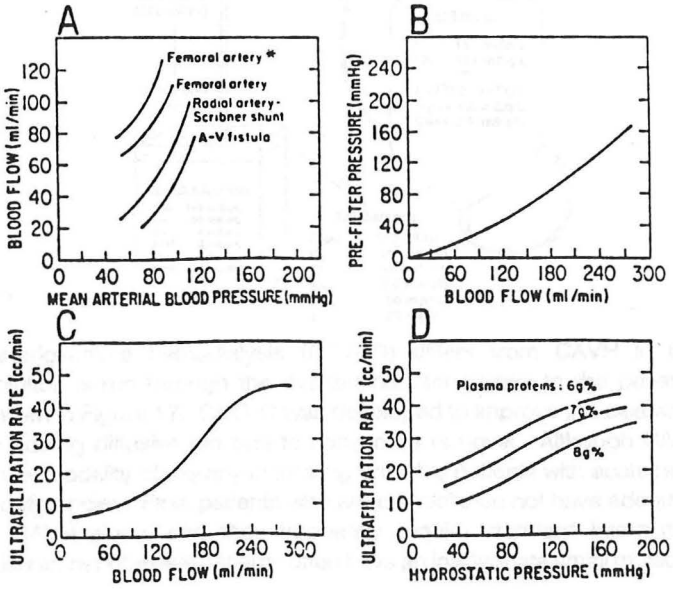
**Table 16. Factors Affecting UFR**

| |
|---|
| Hydrostatic pressure (blood pressure, blood flow, blood access, UF column height, UF suction) |
| Oncotic pressure |
| Viscosity |
| Length and width of blood lines |
| Hemofilter blood pathway patency |
| Venous back pressure |
| Filter surface area and intrinsic membrane characteristics |

**Golper, Ref. 53**

most important factor that governs the ultrafiltration rate in the procedure and this is dependent upon blood pressure, blood flow and the adequacy of the access. The ultrafiltration rate will also be affected by the blood flow through the filter and by the hydrostatic pressure which is generated from the plasma protein concentration in the patient. Each of these features and their effects on the ultrafiltration rate are illustrated in Figure 15. It can be seen that a larger vessel makes a dramatic difference in the blood

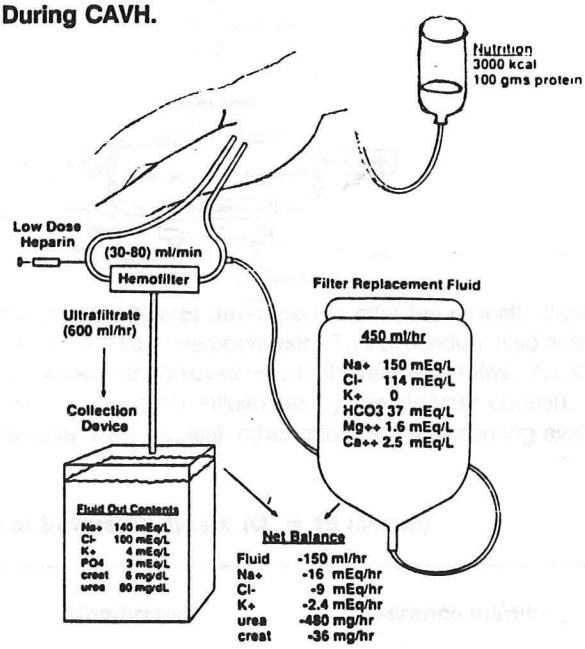
**Figure 15. Hemodynamic Determinants During CAVH.**




**Lauer et al, Ref. 54**

blood flow in CAVH. The replacement solution used in CAVH is similar to that of plasma water. The ideal filter replacement fluid would replace all plasma water constituents except for uremic solutes (eg., BUN, creatinine). Replacement fluids may include standard mixtures such as lactated ringer's solution, saline with addition of other buffers or electrolytes, or a combination of these fluids and total parenteral nutrition solution. There is no commercially available replacement fluid for CAVH in the U.S. at this time; most centers use a combination of commercially available fluids (such as 3 liters of saline and 1 liter of sodium bicarbonate or sodium lactate). The use of lactated ringer solution as replacement fluid is satisfactory, but this fluid contains a small amount of potassium, so this must be taken into account when planning electrolyte management. Of course, other fluids such as parenteral nutrition and vehicles for antibiotics and other drugs must be counted into the entire fluid replacement scheme, and the composition of these fluids must also be taken into account when calculating electrolyte balance. A typical example of the use of CAVH in such an individual is shown in Figure 10.

**Figure 16. Fluid Balance During CAVH.**

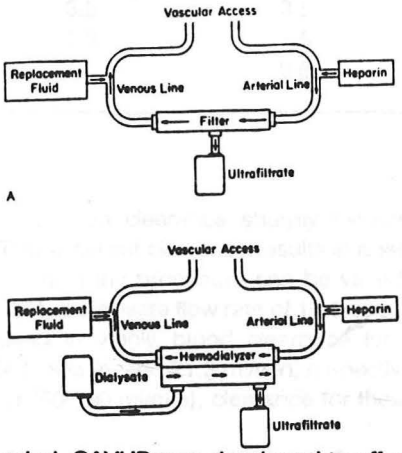



**Bartlett et al, Ref. 55**

Continuous arteriovenous hemodialysis (CAVHD) differs from CAVH in that peritoneal dialysis solution is run through the dialyzer counter-current to the patient's blood flow. This is shown in Figure 17. CAVHD was developed to improve the clearance of uremic solutes by adding diffusive removal to convective removal. Although CAVH offers the clinician a new modality of therapy in treating unstable patients with acute renal failure, it has several deficiencies. First, patients who are catabolic do not have adequate urea removal using CAVH alone, and they frequently require standard intermittent hemodialysis. In particular, hypotensive patients often have an inadequate small molecule

clearance in CAVH. Although supplemental dialysis can be attempted, it is precisely these patients who are unstable on dialysis in the first place and, therefore, placed on CAVH. Furthermore, large volumes of replacement fluids are required in the therapy of patients on CAVH, making nursing management more complicated. Additionally, the replacement solutions are not commercially available in the U.S. in larger than 1 liter containers. It should also be emphasized that CAVH is not an ideal form of therapy in the treatment of acute hyperkalemia.

**Figure 17. Schematic representation of (A) continuous arteriovenous hemofiltration (CAVH) and (B) continuous hemodialysis (CAVHD).**




With these factors in mind, CAVHD was developed to offer the critically ill patient with acute renal failure the best of CAVH and hemodialysis. This procedure also employs highly permeable dialysis membrane and achieves very high clearance rates. As shown in Table 17, the urea clearance is markedly influenced by the dialyzer chosen. The dialysate used in CAVHD is usually 1.5% dianeal; other choices are becoming available (Table 18).

**Table 17. Urea Clearance of Several Dialyzers ($Q_p$ = 15 ml/min)**

| Surface area $m^2$ | Membrane | Clearance ml/min |
|---|---|---|
| 0.6 | Regenerated cullulose | 13.3 |
| 0.9 | Cellulose acetate | 14.2 |
| 0.5 | AN69S plate | 16.9 |
| 0.25 | Polysulphone | 9.6 |
| 0.5 | Polysulphone | 11.3 |

**Schneider et al, Ref. 60**

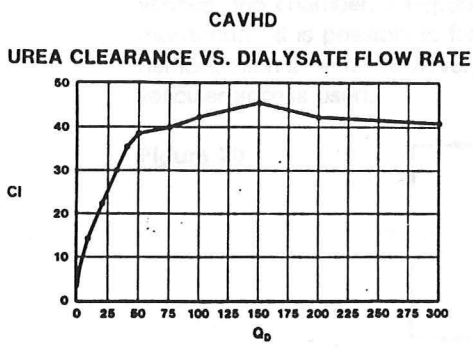
**Table 18. Composition of Dialysates in CAVHD.**

| | 1.5% | Hospal CAVHD |
|---|---|---|
| Na (Meq/L) | 132 | 140 |
| K (Meq/L) | --- | 4 |
| Cl (Meq/L) | 96 | 118 |
| Lactate (Meq/L) | 35 | --- |
| Acetate (Meq/L) | --- | 30 |
| Ca (Meq/L) | 3.5 | 3.5 |
| Mg (Meq/L) | 1.5 | 1.5 |
| Dextrose (G/dl) | 1.5 | 0.8 |

**Geronemus et al, Ref. 61**

As shown in Figure 18, urea clearance sharply increases as dialysate flow increases up to 50 ml/min. This excellent clearance results in adequate solute clearance (Figure 19). Dialysate flow rates in the procedure can be varied markedly from 15-30 ml/min. In one recent study (61), a dialysate flow rate of 16.6 cc per min using a flat plate polyacrylnitrile dialyzer resulted in whole blood clearance for urea, creatinine, and phosphate of 25.3 ml/min, 24.1 ml/min, and 21.3 ml/min, respectively. Over the range of blood flows that were studied (50-190 ml/min), clearance for these solutes were independent of blood flow rate but rather were determined by both dialysate flow rate and ultrafiltration rate. In contrast, the net fluxes of calcium and sodium were correlated only with the ultrafiltration rate.

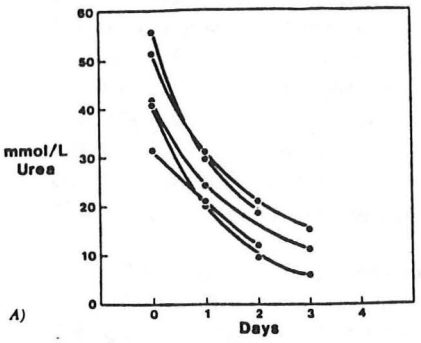
**Figure 18.**




**Geroneumus et al, Ref. 61**

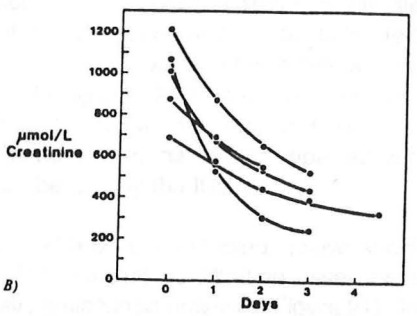
There are two variations of CAVH and/or CAVHD that deserve mention. The first of these is CAVH using a pump to assist the ultrafiltration process. With the use of a blood pump proximal to the dialysis filter, it is possible to achieve higher blood flows than would be achieved by spontaneous blood pressure. This has the advantage of creating a constant transmembrane hydrostatic pressure which yields a greater ultrafiltration rate (62, 63). In addition to this advantage, pump-assisted ultrafiltration in CAVH also allows for improved clearances and longer life of the hemofilters. On the negative side, the use of a blood pump mandates an obligitory ultrafiltration rate in the patient population which is vulnerable to unstable hemodynamics. As a result, the systemic blood pressure needs to carefully monitored in these individuals because they are now at risk for hypotension just as they would be if they were on intermittent hemodialysis.

**Figure 19a. Gradual reduction in blood urea in a sample of 5 patients over a 4-day period.**




**Tam et al, Ref. 56**

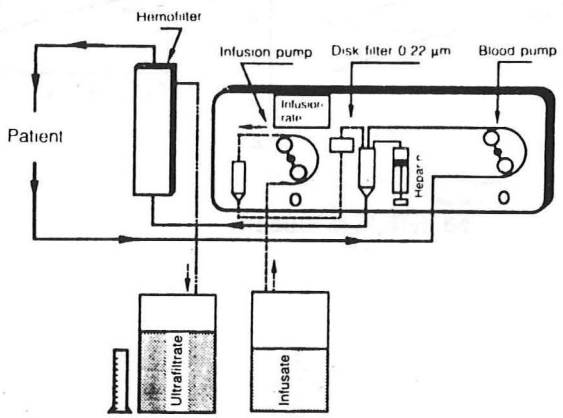
**Figure 19b. Gradual reduction of serum creatinine in the same group of patients.**




**Tam et al, Ref. 56**

The second innovation and alteration of CAVH is termed **continuous venovenous hemofiltration** (CVVH). CVVH has the distinct advantage of simplifying the vascular access problem that CAVH presents. At most institutions, the vascular access is obtained via a single dual-lumen venous catheter. A blood pump is used to provide the needed ultrafiltration pressure. Safety features in the extracorporeal circuit include a venous drip chamber with a bubble detector and an in-line pressure monitor. The diagram for the CVVH circuit is shown in Figure 20. In essence, this set-up is reminiscent of a simple dialysis set-up of years ago, in that there is a blood pump, dialysate infusion pump, a venous drip chamber, a heparin port, and finally the need for a careful hemodynamic monitoring. It is possible to forego the use of the dialysate pump and simply use the hemofiltration scheme; however, a blood pump is necessary when there is a venovenous vascular access used.

**Figure 20**

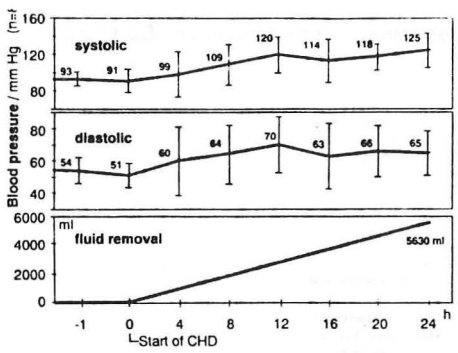



CVVH apparatus set-up consisting of a double-head-pump monitor (BSM 22, Hospal) with safety alarms: one is a blood pump monitoring module, the other is an infusate pump monitoring module (0.1–2.0 liters·h). Ultrafiltrate is collected in a 30-liter plastic container. Bicarbonate infusate produced on-site stored in a 30-liter closed plastic or a rigid container. A disk filter is interposed on the infusion line.

Results with CVVH have been promising, and the use of the technique is growing. In one recent study of critically ill patients subjected to CVVH, a 16% survival rate was obtained. Excellent control of volume was obtained in all of the 25 patients treated, and electrolyte balance was well-maintained by CVVH in all but one hypercatabolic patient (64). Only 4 episodes hypotension occurred during the 193.5 treatment days, a feature noted by others (65-74). Additionally, only 1 patient experienced a hemorrhagic complication during CVVH. About 10% of the hemofilters have to be replaced because of clotting. The procedure was performed in the ICU by the ICU staff.

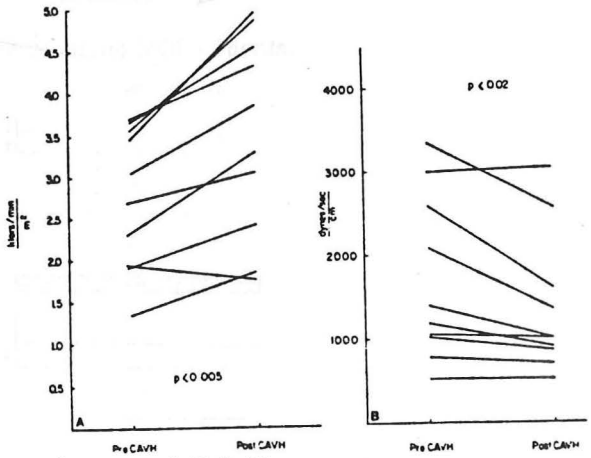
The hemodynamic consequence of CAVH have been studied in several different ways (71-75). The remarkable feature of the CVVH is that ultrafiltration losses averaging 7-9 kg can be obtained without a change in systemic blood pressure (Figure 21). In fact, in most studies, cardiac output actually improves during the ultrafiltration procedure (Figure 22). This is in distinction to conventional hemodialysis in which a decline in cardiac output occurs as ultrafiltration proceeds. Table 19 illustrates the differing effects of dialytic therapy on systemic hemodynamics in acute renal failure.

**Figure 21. Blood Pressure During CAVH**




Lauer et al, Ref. 54

**Figure 22. Cardiac Index and TVR in CAVH**




Lauer et al, Ref. 54

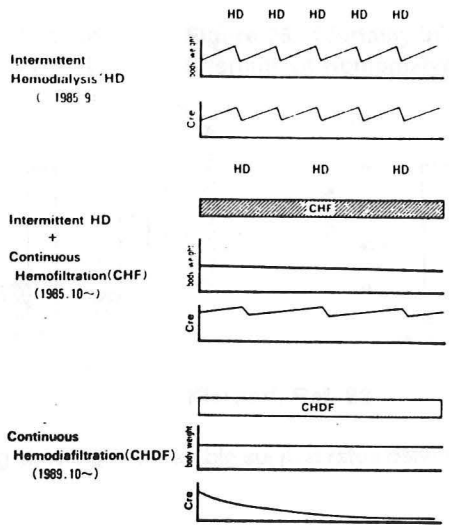
**Table 19. Hemodynamic response to fluid removal with different therapies.**

(D: decrease; I: increase; =: no change)

| | Acetate HD | Bicarbonate HD | Hemo-filtration | CAVH |
|---|---|---|---|---|
| Cardiac output | D | D | D | I |
| Peripheral resistance | DD | I | I | I |
| Blood Pressure | DD | = | = | = |

One of the most useful applications of SCUF and CAVH is in patients with poor myocardial function, particularly those patients who have just undergone cardiac surgery. Several studies have documented the safe removal of ultrafiltration volumes in these patient groups. In one study (54) cardiac index increased as peripheral resistance declined in a group of 10 patients undergoing CAVH with cardiac monitoring. Of interest is the fact that in this patient group, the most striking improvements in cardiac index occurred in patients with the poorest baseline function. The steady nature of volume control with continuous therapy is shown in Figure 23.

**Figure 23. Changes in the management of anuric MOF patients.**

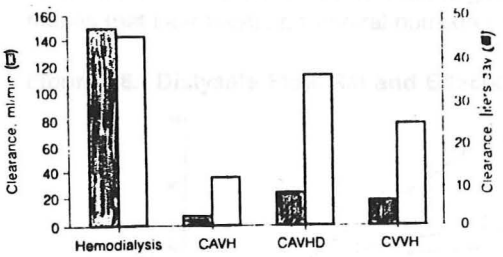



**Sieberth et al, Ref. 76**

Several recent reviews have examined the efficacy of CAVH in the treatment of critically ill patients with acute renal failure (73-83). These studies are characterized by being relatively small and by attempting to use a standardized of patient populations under study by using the Apache scoring. Some of these studies (73,76,81,82) have found comparable survival rates between CAVH and IHD treated patients. Other studies have claimed that CAVH have results in improved survival compared to IHD (73,77,79). Finally, another study (83) claims that the survival rate in CAVH is worse than in patients treated with IHD. It should be noted that in this study (83) more seriously ill patients with poorer hemodynamics were randomized to the CAVH group instead of intermittent hemodialysis. Hence, there may have been a preselection bias in this particular study. All authors agree that the administration of parenteral nutrition is far easier in the CAVH patient than in the intermittent hemodialysis patient.

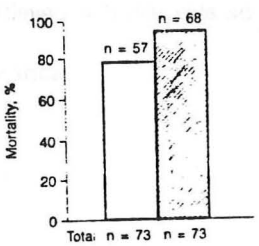
The efficacy of CAVH versus IHD was compared in a very good study by Kierdoff (82). As shown in Figure 24, the clearance rates obtained with hemodialysis, CAVH, CAVHD, and CVVH, were compared in this particular study. As can be seen from the Figure, hemodialysis afforded the greatest clearance per day. When one considers the continuous nature of CAVH, CAVHD, and CVVH, the clearances per week are relatively comparable, assuming that the intermittent hemodialysis procedure is carried out on the rate of 3 to 4 times per wk. As illustrated in Figure 25, the mortality rates in acute renal failure for these studies comparing IHD of CVVH were similar.

**Figure 24. Clearance Rates in HD, CAVH, CAVHD and CVVH.**




**Kierdorf, Ref. 82**

**Figure 25. Mortality in ARF. Comparison of Intermittent Hemodialysis ( ) and CVVH ( ).**




**Kierdorf, Ref. 82**

Another studying showing comparable survival rates between the two procedures is shown in Table 20.

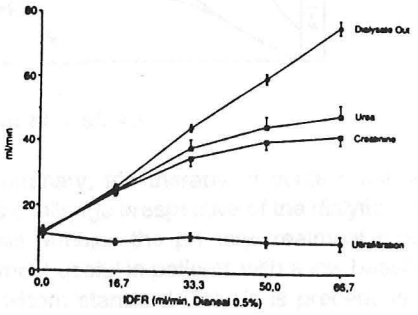
**Table 20. Hospital Survival Rates by Year.**

| | I | C | IC |
|---|---|---|---|
| 1986 | 19% | 19% | 24% |
| 1988 | 54% | 21% | 32% |
| 1989 | 46% | 15% | 15% |

**Sieberth, Ref. 76**

With regard to the clearances obtainable in the continuous procedures, it is interesting to note the recent results of Bonnardeaux et al (84). These investigators performed a study that determined the effects of high inlet dialysate flow rate on the clearances of urea and creatinine and to measure the absorption of glucose through the dialyzer in CAVHD. Acute renal failure patients in the ICU were studied. The dialysate flow rate was increased from 0 to 33.3 ml/min (0-2 L/hr) and produced linear increments in the clearances of urea and creatinine, whereas further increases in the dialysate flow rate from 33.3 to 66.7 ml/min (2-4 l/h) produced less important, but still significant increases in the clearances. This is shown in Figure 26. At 66.7 ml/min, the clearances for urea and creatinine were 48.5 and 42.2 ml/min, respectively. Using a dialysate with a glucose concentration of 25.3 ml/l (0.5 g/dl), the net transfer of glucose through the dialyzer did not change significantly, from 16.7 to 66.7 ml/min of dialysate flow rate. These authors found that a dialysate flow rate of 16.7 ml/min (1 L/hr) yields a urea clearance of 35 L/day, and is equivalent to about 4 hr of conventional hemodialysis. These authors also found that 60% of the glucose is absorbed through the dialyzer; this means that interdialytic parenteral nutrition can be achieved with dialysate solutions

**Figure 26. Dialysate Flow Rat and Effects on Clearance**

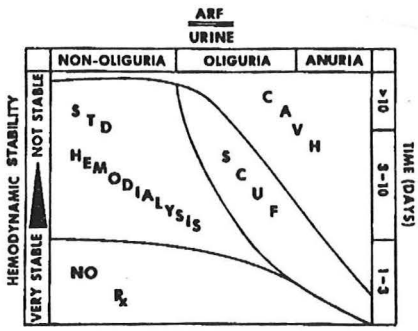



**Clearances of urea (□) and creatinine (■) in relation to IDFR. Ultrafiltration (○) and outlet dialysate flow rate (●) are also shown. Plasma flow rate was 69.4 ± 16.9 mL/min. Values are means ± SEM, n = 5 patients.**

**Bonnardeaux et al. Ref. 84**

containing glucose concentrations of 1.5 and 2.5 g/dl. This yields 2,900 to 5,500 kJ/d (700 to 1,300 kcal/d). A high dialysate flow rate of 66.7 ml/min will provide a daily urea clearance of 70 L, equivalent to about 8 hrs of conventional dialysis. Clearly these clearances obtained with high dialysate flow rates suggest that CAVHD and CVVHD are capable of marked improvements in clearance. One recent review (59) has summarized the applicability of several dialytic techniques to the treatment of acute renal failure in the ICU. In this study a total of 320 patients were reviewed; distribution of therapy into 1 of 3 groups was obtained: continuous therapy (30%), intermittent therapy (42%), and a combination of these therapies (28%). The demographic data were similar in all 3 groups, but the incidence of multiorgan failure was higher in the continuous therapy group than in the other two groups. Required pressor support for underlying hemodynamic instability was more frequent in the continuous and combination therapy groups. The Apache evaluations of these patients at both the time of entry into the ICU and at the time of renal consultation showed that both the continuous and combination groups of patients had higher Apache ratios than the patients on intermittent hemodialysis. The outcome was similar for all groups, implying some advantage for continuous therapy for those patients who were more unstable. A diagram illustrating a relationship of all these therapies and these different demographic construct is shown in Figure 27.

**Figure 27. Indications for SCUF and CAVH.**




**Paganini, et al, Ref. 48**

In summary, the therapy of acute renal failure in the ICU setting represents a therapeutic challenge irrespective of the dialytic mode selected. I believe that intermittent hemodialysis remains the primary treatment modality for these patients. Continuous therapy is most useful in patients with a low baseline blood pressure (and/or low cardiac output) in whom standard dialysis is precarious. Of the continuous therapies, CVVH using a single needle dual lumen access offers the most advantages, but requires its own machine. Nutritional support of these patients should be administered, as outlined above. I have not discussed the role of peritoneal dialysis in these patients, but patients with severe acidemia and low baseline blood pressure are candidates for bicarbonate

peritoneal dialysis. Severely catabolic patients will most often standard intermittent hemodialysis to control uremia. Finally, it seems likely the biggest breakthrough in improving the grim morbidity and mortality of established acute renal failure in the ICU will come with the advent of effective therapies for MOFS. Perhaps trials underway now with IL-1 and TNF antagonists will yield a more effective antidote than any form of dialytic and nutritional therapy.

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