Synergistic Effect of Acute Renal Failure and Respiratory Failure in the Surgical Intensive Care Unit

Stephen J. Sweet, MD, Springfield, Massachusetts
Christopher U. Glenney, MD, Springfield, Massachusetts
John P. Fitzgibbons, MD, Springfield, Massachusetts
Paul Friedmann, MD, Springfield, Massachusetts
Daniel Teres, MD, Springfield, Massachusetts

There has been recent emphasis on the need to identify high risk patients admitted to the intensive care unit. The continued high mortality rates in these patients, despite our sophisticated monitoring systems and improved therapeutic methods, emphasize our incomplete understanding of the underlying pathophysiologic mechanisms involved. Respiratory and renal failure are two factors known to adversely affect prognosis. We undertook this study to investigate further the interrelationships between some of the factors known to be important variables affecting survival in the intensive care unit.

Material and Methods

During a 9 month period from March to December 1976, there were 410 admissions to our surgical intensive care unit. We retrospectively reviewed the discharge summaries, respiratory therapy charts and laboratory reports on all of these patients. We identified those patients who either required mechanical ventilation for 12 hours or greater or had a serum creatinine level of 2 mg/dl or greater. The latter group was reviewed independently by two of the authors, and based on the following definitions, several types of renal failure were identified.

Chronic renal failure was defined as an antecedent chronic elevation in the serum creatinine level to greater than 1.6 mg/dl. *Acute renal failure* was defined as either an acute increase in the serum creatinine level from normal (less than 1.4 mg/dl) to greater than 2.0 mg/dl or an initially elevated serum creatinine level (greater than 2.0 mg/dl) that subsequently returned to normal.

Patients with acute renal failure were separated into four groups based on the following criteria as modified from Miller et al [1]: *Prerenal azotemia:* (1) urinary volume of less than 150 ml/8 hours (in the absence of diuretics); (2) the presence of volume depletion, congestive heart failure or hypotension; (3) a urinary sodium concentration less than 20 mEq/liter; (4) absence of renal tubular cells or cellular casts on urinalysis; or (5) depending on survival, a return of renal function to normal within 72 hours of correction of the volume depletion, heart failure or hypotension. *Oliguric acute tubular necrosis:* (1) urine volume less than 150 ml/8 hours; (2) progressive azotemia despite correction of hemodynamic factor; (3) urine sodium concentration (in the absence of diuretics) greater than 40 mEq/liter; or (4) presence of renal tubular cells and cellular casts on urinalysis. *Nonoliguric acute tubular necrosis:* same criteria as oliguric acute tubular necrosis except a urinary volume greater than 150 ml/8 hours. *Acute obstructive uropathy:* (1) radiologic evidence of obstruction; (2) diuresis immediately after insertion of bladder catheter; or (3) return of renal function to normal within 72 hours after correction of obstruction.

Respiratory failure was defined as mechanical ventilation for 12 to 24 hours during which intermittent mandatory ventilation of greater than 6 breaths/min was used or mechanical ventilation for longer than 24 hours. Lung compliance (tidal volume/peak pressure: "dynamic airway characteristics") and the number of patients on positive end-expiratory pressure were also compared in the various subgroups.

Significance was defined as $p < 0.01$ by the chi-square test.

Results

The overall mortality for the 410 patients was 9.6 percent (Table I). In the absence of renal or respiratory failure, the mortality was 3.6 percent. Respiratory failure developed in 76 patients; the overall mortality in this group was 32 percent. The 41 patients in whom acute renal failure developed had a 44 percent mortality. Of the 76 patients who had respiratory failure, 51 did not have concomitant renal failure; the mortality in this group was 13.5 percent.

From the Department of Medicine and the Division of Surgery, Baystate Medical Center, Springfield, Massachusetts.
Requests for reprints should be addressed to Daniel Teres, MD, Division of Surgery, Baystate Medical Center, Springfield, Massachusetts 01107.
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TABLE I Effect of Renal (KF) and Respiratory (PF) Failure on Mortality in Surgical Patients in the Intensive Care Unit

Group	Patients n	Patients %	Mortality (%)
Absent KF and PF	309	75	3.6
PF present	76	19	32*
PF alone	51	12	13.5
KF (acute) present	41	10	44*
KF alone			
Acute	18	4	16.7
Chronic	7	2	14.3
Combined KF and PF			
Acute KF	23	6	65.2†
Chronic KF	2	0.5	100
Total	410		9.6

* $p < 0.01$ compared with absent renal and respiratory failure.
† $p < 0.01$ compared with either acute renal failure alone or respiratory failure alone.

Similarly, 18 patients had acute renal failure without respiratory failure, with a mortality of 16.7 percent. The coexistence of renal and respiratory failure had a synergistic deleterious effect on mortality (65.2 percent).

In the 41 patients in whom acute renal failure developed, mortality was influenced by both respiratory failure and the type of renal failure (Table II). Overall, patients with prerenal azotemia had a higher mortality (57 percent) than those with acute tubular necrosis (41 percent). In the renal failure patients with coexistent pulmonary failure, prerenal azotemia was associated with a significantly worse prognosis (85 percent mortality) than oliguric (50 percent) and nonoliguric (57 percent) acute tubular necrosis ($p < 0.01$). These differences in mortality could not be attributed to differences in age, sex, level of serum creatinine or need for dialysis, which was similar in both groups.

There was no significant difference in mortality in patients with oliguric and nonoliguric tubular necrosis (44 percent versus 38 percent). The major events associated with the development of acute tubular necrosis are summarized in Table III, and as might be expected in a surgical intensive care unit, ischemia, sepsis and aortic aneurysm surgery were most often incriminated. There appeared to be no difference in the pattern of disease in patients with oliguric and nonoliguric renal failure.

TABLE III Events Associated With the Development of Acute Tubular Necrosis

Events	Occurrence (n) in Oliguric Group	Occurrence (n) in Nonoliguric Group
Ischemia	5	7
Sepsis	2	4
Aortic aneurysm surgery	3	2
Drug	2	2
Myoglobinuria	0	1
Contrast dye	1	2

Clinically, patients with prerenal azotemia could be classified into two distinct groups. Eight patients had severe prerenal failure characterized by prolonged hypoperfusion requiring vasoactive therapy to support the blood pressure. Six patients had mild prerenal failure, experiencing a short period of hypoperfusion and maintaining adequate blood pressure without vasoactive drugs. These patients were similar in age, sex distribution and the degree of azotemia as identified by the level of serum creatinine. However, mortality was significantly greater in the patients with severe prerenal azotemia than in the patients with mild prerenal azotemia or those with acute tubular necrosis (Table IV).

Although statistically significant only in the prerenal group, coexistent respiratory failure appeared to increase mortality in each group (Table II). In 20 of 23 patients with combined respiratory and acute renal insufficiency, failure of these two organ systems appeared to develop at approximately the same time (within 24 hours). Positive end-expiratory pressure of 5 cm H_2O or greater was required significantly more often ($p < 0.01$) in patients with combined respiratory and renal failure than in those with respiratory failure alone (Table V). Compliance comparisons showed no statistically significant differences between groups.

TABLE II Effect of Coexistent Respiratory Failure (PF) and Type of Renal Failure on Mortality

Group	Patients (n)	Mortality: Absent PF n	Absent PF %	Coexistent PF n	Coexistent PF %	Overall n	Overall %
Prerenal azotemia	14	2/7	29	6/7	85*	8/14	57
Acute tubular necrosis	22	1/7	14	8/15	53	9/22	41
Oliguric	9	0/1	0	4/8	50	4/9	44
Nonoliguric	13	1/6	17	4/7	57	5/13	38
Other	5	0/4	0	1/1	100	1/5	20

* $p < 0.01$ compared with groups with oliguric or nonoliguric acute tubular necrosis and coexistent pulmonary failure.

TABLE IV Comparative Mortality in Acute Renal Failure

Group	Patients (n)	Mortality n	Mortality %	Mean Peak Serum Creatinine (mg/dl)
Severe prerenal azotemia	8	7/8	87*	3.0
Mild prerenal azotemia	6	1/6	17	2.4
Acute tubular necrosis	22	9/22	41	5.0

* $p < 0.01$ compared with either mild prerenal azotemia or acute tubular necrosis.

TABLE V Respiratory Variables in Patients With Combined Renal and Respiratory Failure and Respiratory Failure Alone

	Compliance (ml/cm H_2O)	On Positive End-Expiratory Pressure ≥5 cm H_2O n	%
Renal failure			
Acute tubular necrosis	18.7	4/7	57
Prerenal azotemia	17.9	5/15	33.3
Total	18.4	9/22	40.9*
Respiratory failure alone	22.2	4/51	3.9

* $p < 0.01$ compared with respiratory failure alone.

Comments

Given the nature of intensive care units, it is difficult to compare patient populations. Nevertheless, the overall mortality of 9.6 percent in the present study is similar to the mortality of 6 to 19 percent reported from other units [2–6]. These mortality rates have remained fairly constant over the past decade [2,4]. As in our present experience, most published series report that the outcome is adversely affected by the development of certain complications or organ system failures. Sixty-four percent of the deaths in our surgical intensive care unit occurred in patients who had respiratory or renal failure, or both.

In our population respiratory failure was associated with a 32 percent mortality, which is consistent with the 30 to 33 percent mortality reported by others [3–5]. Similarly, in our study renal insufficiency was associated with a mortality of 44 percent, which is in agreement with the 21 to 57 percent rates reported by others [3,7–9]. However, further analysis of our data revealed that mortality was less affected by the failure of a single system than by combined systems failure. For patients with either renal or respiratory failure alone, the mortality rates were 16.7 and 13.5 percent, respectively. For patients with combined failure of these two organ systems, the death rate increased significantly to 65.2 percent and accounted for 38 percent of all deaths. These results are similar to the 50.7 to 80 percent mortality rates reported from other units caring for patients with multiple organ failure [5,6,10].

This synergistic effect of combined renal and respiratory failure may be explained by several mechanisms. First, failure of a single system may sequentially lead to other system failures and culminate in the inability to support such a burden. Baue [11] proposed that the failure of one organ contributing to the failure of others is causally related to the persistently high mortality rates seen in the intensive care unit. This hypothesis is supported by the observation that patients in the intensive care unit may have a prolonged course and develop a cascading sequence of systems failure culminating in death. Experimentally, such a link between respiratory failure and subsequent renal failure was suggested by the work of Marquez et al [12]. In their study, increased airway pressure was associated with a significant decrease in the glomerular filtration rate due to a decrease in arterial blood flow and an increase in renal venous pressure. On the other hand, renal failure might lead to a compromise in pulmonary function as metabolites and fluid are retained by the damaged kidney. The significantly greater requirement for positive end-expiratory pressure greater than 5 cm H_2O in the combined renal and respiratory failure group (40.9 percent) compared with those with respiratory failure alone (7.8 percent) suggests a greater impairment of pulmonary function in the group with combined failure. This observation could reflect either an adverse effect of positive end-expiratory pressure on renal function or a worsening of the respiratory status secondary to renal insufficiency.

Second, the severity of the underlying insult or basic disease process, as manifested by the failure of various organ systems, may be the ultimate determinant of survival. Our data seem more consistent with this possibility. We suggest that the initial insult may set into motion certain mechanisms such as impaired myocardial function or loss of capillary integrity which manifest themselves on the organ level as renal and respiratory failure. The simultaneous failure of the pulmonary and renal systems in 20 of the 23 patients who developed combined failure of these two organs suggests the common response to a single initiating insult. The synergistic effect on mortality seen in combined systems failure suggests that factors other than the simple combination of the failure of several organs may play a role. Multisystem failure may be a marker of a severe underlying pathophysiologic process or processes associated with a high death rate.

There was no significant difference in the overall mortality in each of the forms of acute renal failure (Table II). However, when the group with severe prerenal azotemia was looked at separately (Table IV), a significantly greater mortality was identified compared with the other forms of acute renal failure.

Yet the high mortality in this group of patients cannot be attributed to the loss of renal function since there was insufficient time for the accumulation of many urinary excretory products, as evidenced by the mean time to death of 32 hours and a mean peak serum creatinine level of only 3.0 mg/dl. Likewise, close inspection of the data of Baek et al [13] shows an unexpectedly high mortality in their patients with acute renal failure who had a low urinary sodium concentration, presumably indicating prerenal azotemia.

Anderson et al [14] reported a significantly higher mortality in a general hospital population with oliguric as compared with nonoliguric acute renal failure. They attributed this difference to the greater degree and duration of azotemia in the oliguric group. In contradistinction, our study and that of Baek et al [13] showed no significant difference in mortality among patients with oliguric versus nonoliguric acute renal failure, thus bringing into question the significance of renal failure itself. These observations suggest the lesser importance of the loss of excretory function as the cause of increased mortality in patients in the surgical intensive care unit who develop acute renal failure.

Despite the initial dramatic decrease in mortality for patients with acute renal failure between World War II (90 percent) and the Korean War (50 percent), there has been little subsequent improvement during the last 2 decades [9]. The initial improvement had been attributed to better management of the problems associated with the loss of renal excretory function. The continued high death rate seems to be due to the nature of the underlying illness and not renal insufficiency itself. Studies that fail to show a significant decrease in the mortality associated with acute renal failure despite the early and frequent use of dialysis [7] support this concept. Similarly, Cullen et al [15] observed a progressively increasing mortality as the intensity of care increased, and McMurray et al [8] noted an inverse correlation between the number of complications and survival in patients in the intensive care unit.

Whatever the event inducing the original injury, we suggest that if severe enough, mechanisms possibly related to abnormalities of myocardial function or fluid leaking across capillary membranes may be set into motion that will lead to multisystem failure and increase the likelihood of death. Further efforts to identify and reverse such processes are clearly needed if we are to be successful in decreasing the mortality in these patients.

Summary

A retrospective evaluation of the effect of renal and respiratory failure on mortality in our surgical intensive care unit was undertaken. The coexistence of combined renal and respiratory failure had a synergistic adverse effect on survival. Combined pulmonary and kidney failure appeared to develop simultaneously. A subset of patients with severe prerenal azotemia but without uremia had the highest mortality. These results are not consistent with the simple combination of single systems failure but rather suggest that renal and respiratory failure are markers of a generalized underlying defect.

References

1. Miller TR, Anderson RJ, Stuart LL, et al. Urinary diagnostic indices in acute renal failure. A prospective study. Ann Intern Med 1978;1:47–50.
2. Young RKB, Campbell D, Reed JM, Relfer ABM. Respiratory intensive care: a 10 year survey. Br Med J 1974;1:307–10.
3. Thibault GE, Mulley AG, Barnett GO, et al. Medical intensive care: indications, interventions, and outcomes. N Engl J Med 1980;302:938–42.
4. Nunn JF, Milledge JS, Singaraya J. Survival of patients ventilated in an intensive therapy unit. Br Med J 1979;1:1525–7.
5. Bell JA, Bradley RD, Jenkins BS, Spencer GT. Six years of multidisciplinary intensive care. Br Med J 1974;2:483–8.
6. Kraman S, Kahn F, Patel S, Seriff N. Renal failure in the respiratory intensive care unit. Crit Care Med 1979;7:263–6.
7. Kennedy AC, Burton JA, Luke RG, et al. Factors affecting the prognosis in acute renal failure. Q J Med 1973;42:73–86.
8. McMurray SD, Luft FC, Maxwell DR, et al. Prevailing patterns and predictor variables in patients with acute tubular necrosis. Arch Intern Med 1978;138:950–5.
9. Stott RB, Ogg CS, Cameron JS, Bewick M. Why the persistently high mortality in acute renal failure? Lancet 1972;8:75–8.
10. Eisenman B, Beart R, Norton L. Multiple organ failure. Surg Gynecol Obstet 1977;144:323–6.
11. Baue AE. Multiple progressive or sequential systems failure. Arch Surg 1975;110:779–81.
12. Marquez JM, Douglas ME, Downs JB, et al. Renal function and cardiovascular responses during positive airway pressure. Anesthesiology 1979;50:393–5.
13. Baek SM, Makabali WC, Shoemaker WC. Clinical determinants of survival from postoperative renal failure. Surg Gynecol Obstet 1975;140:685–9.
14. Anderson RJ, Linas SL, Berns AS, et al. Non-oliguric acute renal failure. N Engl J Med 1977;296:1134–7.
15. Cullen DJ, Ferrara LC, Briggs BA, Walker PF, Gilbert J. Survival, hospitalization charges and follow-up results in critically ill patients. N Engl J Med 1976;294:982–7.

Discussion

Richard E. Wilson (Boston, MA): I would like to try to place this in more simplistic terms. I think the real problem in these patients is prerenal azotemia, that is, the presentation of a tremendous load to the kidneys that causes two system failures: renal and lung.

But isn't the common denominator the extensive multisystem failure in these very sick patients? Aren't we looking at a multiplicity of systems? As you add one more system, the two systems you are looking at fall apart. In your patients, isn't the denominator for the patient who dies really irreversible disease of a system other than the two systems you are examining, each of which could be treated if it alone was the problem?

Menelaos A. Aliapoulios (Worcester, MA): I congratulate the authors for their care and diligence in presenting these complex and interesting cases in such a careful manner. My remarks corroborate Dr. Wilson's. When several systems begin to malfunction, a domino or cascading effect often is the result. In our Surgical Intensive Care Unit at St. Vincent Hospital in Worcester, we have

recognized 11 systems that can malfunction: cardiac, pulmonary, arteriovenous shunt, capillary bed, brain and central nervous system, kidney and genitourinary tract, hepato-biliary-pancreatic, gastrointestinal tract, electrolyte balance, infection, and musculoskeletal. We have found that when any 5 of the 11 systems fail to operate normally, no patient survives.

Daniel Teres (closing): One of the main points of this paper is multiorgan failure, a common end point for patients who are failing despite massive nursing, physician and technological intervention. Our conclusion is that these patients have a common underlying abnormality. I would like to expand on other possibilities.

One is a cascade effect. A patient may start out with renal failure and because of treatment or factors related directly to renal failure, will develop lung complications. The initial therapy for a reduced urinary output is usually administration of a volume challenge. If there is a minor abnormality in the lung, fluid will lead out of capillaries and cause coexistent respiratory failure.

The same thing can happen with the lung as the primary failing organ. With acute respiratory failure, increased mean airway pressure with mechanical ventilation and positive end-expiratory pressure causes complex hemodynamic effects on both the right and left ventricles, causing a decrease in cardiac output as well as a possible increase in renovascular resistance. Thus, a mode of treatment for respiratory failure will have deleterious effects on renal function.

It is also possible that patients in the intensive care unit may have separate coexisting injuries. For example, a patient with blunt trauma to the chest may also have an aminoglycoside-induced injury to the kidney, both occurring at the same time. Another possibility relates to the patient who may have a substrate of chronic systemic disorders, especially cardiac and respiratory. With one acute insult, the precarious balance is tilted, and the patient is unable to handle stress because of inadequate reserve. In a similar manner, a patient may have random accumulation of multiple injuries, insults or iatrogenic complications that reach a critical number. Each problem in itself may be resolvable, but the sum puts the patient in a seemingly hopeless category.

In our study, we favor a common underlying abnormality such as prolonged shock or sepsis, where the hemodynamic and immunologic injuries affect both organs simultaneously.