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Creatinine Clearance for Early Detection of Posttraumatic Renal Dysfunction

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Acute renal failure develops insidiously in the presence of normal urine output and vital signs. A prospective study was carried out to find whether renal impairment can be detected in the immediate postoperative period and to determine the renal function test best predicting the development of renal dysfunction. Forty patients with multiple trauma who required more than 10 units of blood and had a systolic blood pressure less than 80 mmHg on admission were studied.

Creatinine clearance (Ccr), free-water clearance (C_{H_2O}), fractional excretion of Na^+, blood urea nitrogen (BUN), urine flow rate, and vital signs were measured and compared in seven patients who developed renal dysfunction within a week of trauma (Group 1) and 33 patients who maintained normal renal function (Group 2). In all Group 1 patients Ccr remained less than 25 ml/min and C_{H_2O} greater than −15 ml/h for 6 h following surgery. None of the Group 2 patients had Ccr less than 25 ml/min for longer than 4 h following surgery. However, C_{H_2O} values were greater than −15 ml/h in 15 of the 33 Group 2 patients during the first 24 postoperative hours.

Ccr values less than 25 ml/min were present, despite normal urine flow rate and blood pressure, in patients who subsequently developed renal dysfunction. Patients who have Ccr values less than 25 ml/min within 6 h following trauma and surgery may develop renal dysfunction, and some of them may proceed to acute renal failure. C_{H_2O} was not as good a predictor of development of renal dysfunction as Ccr. (Key words: Kidney: clearance, creatinine, free water; failure.)

RECOGNITION AND CORRECTION of the causes of postoperative renal insufficiency are important in minimizing morbidity and mortality following trauma. Due to the numerous therapeutic interventions and changing patterns of acute renal failure (ARF) in critically ill patients, traditional monitoring of renal function with serial determinations of blood urea nitrogen (BUN), serum creatinine, and urine flow rate (UFR) is inadequate for the early detection of renal dysfunction, because oliguria and increase in creatinine may be apparent only several days after deterioration of renal function. Retrospective studies suggest that early detection of postoperative and posttraumatic renal dysfunction is possible. Baek and coworkers reported that free-water clearance (C_{H_2O}) values greater than −15 ml/h preceded ARF by one to two days.[1-3] We have reported that ARF may develop only in patients who have both creatinine clearance (Ccr) values less than 25 ml/min and C_{H_2O} values greater than −15 ml/h.[4] The conflict in these reports may have occurred due to the difference in urine collection time for clearance measurement or because the studies were retrospective. Because it is difficult to detect renal dysfunction in critically ill trauma patients with rapidly changing hemodynamic status unless renal function testing is carried out frequently, a prospective study was conducted to determine how early in the first 24 postoperative hours renal dysfunction can be detected and which clearance test is the most sensitive predictor of ensuing renal dysfunction.

Materials and Methods

Forty consecutive multiple-trauma patients meeting the following criteria were selected: 1) a systolic blood pressure less than 80 mmHg during resuscitation or operation, and 2) transfusion of more than 10 units of blood during resuscitation and operation. Age averaged 32 yrs, ranging from 14 to 65 yr. There were 29 males and 11 females. Thirty-six of the 40 were automobile-accident victims and four were gunshot victims. The number of body systems injured, which included head, chest, abdomen, extremity, pelvis, and spine, averaged 2.7, ranging from one to six. Patients who had gross hematuria postoperatively were excluded from the study because accurate measurement of renal clearance was not possible due to blood in the urine.

During resuscitation and operation, vital signs were continuously monitored with the use of indwelling arterial cannulae, central venous catheters, and electrocardiograms. UFR was monitored hourly with the use of an indwelling urinary catheter. Anesthetics were administered with the use of the nonbreathing system of an Engström ventilator. Nitrous oxide–oxygen with halothane or Innovar-Sublimaze®§ was used for anesthesia in all patients. Pancuronium was used for muscle relaxation as needed. Fluid administration during resuscitation and operation was dictated by vital signs, central venous pressure, and hourly UFR. In patients with a UFR less than 20 ml/h defined as oliguria but with normal blood pressures, plasma protein fraction (PPF) was infused with the use of a fluid challenge technique to optimize preload.[5] None of the patients received diuretics during the first 24 h.

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§ Innovar (droperidol + fentanyl)-Sublimaze® (fentanyl) by McNeil Laboratories, Inc., Fort Washington, PA.

TABLE 1. Clinical Information

	Group 1 (7)	Group 2 (33)	Significance
Mean age (yr)	35 ± 6.5	30 ± 2.3	NS
Number of body sections injured*	3.5 ± 0.6	2.4 ± 0.2	NS
Fluid volume for resuscitation and operation (l)	22.6 ± 7.2	16.2 ± 1.8	NS
Resuscitation and operation duration (h)	6.8 ± 1.2	5.2 ± 0.8	NS

Values are mean ± SEM.
NS = Not significant; $P > 0.05$.
* Head, chest, abdomen, extremity, pelvis, and spine are each defined as one body section.

Preoperative and intraoperative Ccr and C_{H_2O} were calculated from the values measured from the serum and urine collected during resuscitation and operation. Postoperatively, 1-h Ccr and C_{H_2O} were calculated every second hour for the first 24 h. The serum value for a clearance calculation was averaged from at least two serum measurements during the first 24 h. Urine volumes for clearance calculations were determined following manual compression of the abdomen. Saline or air washout was not used to collect urine for fear of causing infection or septicemia in these patients with multiple trauma. All the patients were followed for at least 5 days with daily measurement of BUN, serum creatinine, excreted fraction of filtered sodium (FE_{Na}), and 24-h Ccr and C_{H_2O}.

Patients were divided into two groups: Group 1 included seven patients who, within 1 week, developed renal dysfunction, and Group 2 included 33 patients who maintained normal renal function throughout their clinical course. Renal dysfunction was defined with all of the following: 1) serum creatinine greater than 2.0 mg/dl; 2) BUN greater than 40 mg/dl; and 3) Ccr less than 50 ml/min during the first 5 postoperative days. Renal failure was defined with all of the following: 1) serum creatinine greater than 3.0 mg/dl; 2) BUN greater than 70 mg/dl; 3) Ccr less than 25 ml/min; and/or 4) death with Ccr value less than 25 ml/min. Oliguria was defined as UFR less than 400 ml/day or less than 20 ml/h.

A comparison was made of Ccr, C_{H_2O}, and other clinical findings in the two groups with the use of *t* test or chi-square test.

Results

There were no statistically significant differences between the two groups with respect to age, severity of injuries, volume of blood and fluid administered, duration of resuscitation, and anesthetic agent (table 1).

CREATININE CLEARANCE

Postoperative Ccr was significantly less ($P < 0.01$) in Group 1 patients, although there were no differences in UFR and blood pressure between the groups (fig. 1). Ccr in all Group 1 patients remained below 25 ml/min for

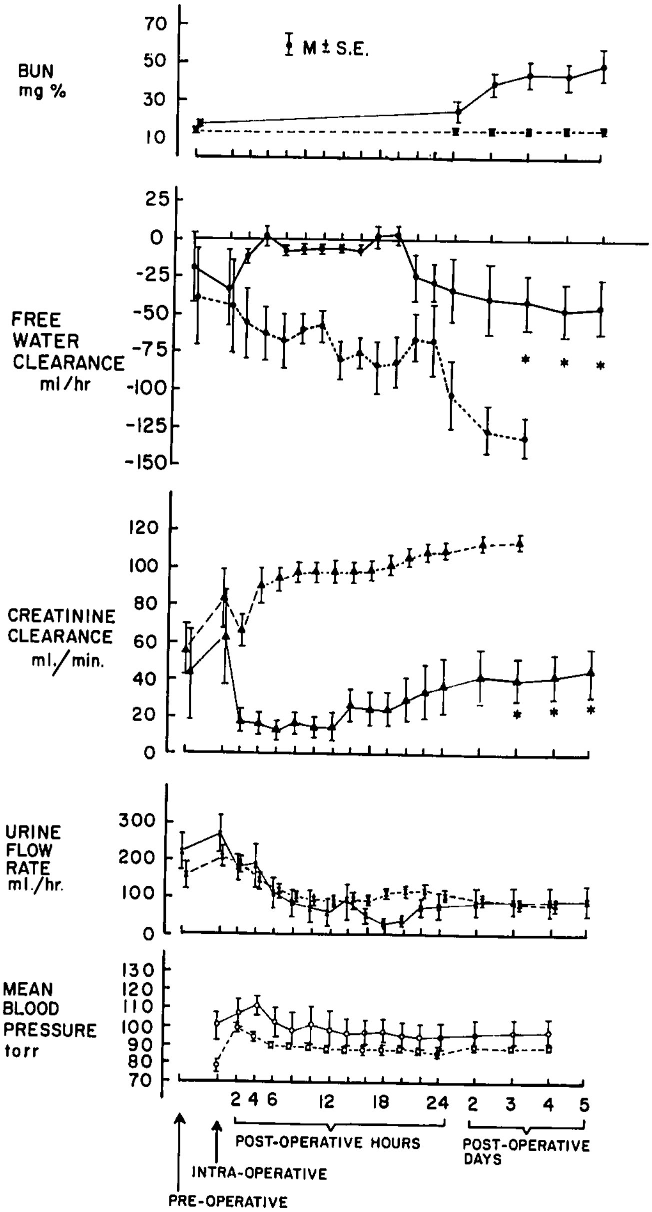

FIG. 1. Sequential changes in renal function and mean blood pressure (mean ± SEM) of the seven patients who developed renal dysfunction (*solid lines*) and the 33 patients who maintained normal renal function (*interrupted lines*). Note the persistently low Ccr in renal dysfunction patients despite well-maintained blood pressures and urine flow rates during the first 24 postoperative hours. * indicates that the values were obtained from five of the seven Group 1 patients. Two patients excluded were one who died and another who was undergoing dialysis.

all measurements made during the first 6 postoperative hours, while none of the Group 2 patients had Ccr values less than 25 ml/min at the sixth postoperative hour. Forty-eight hours after operation, all Group 1 but none of Group 2 patients had renal dysfunction (table 2). Intraoperative Ccr was measured in only five Group 1 patients and 16 Group 2 patients and averaged 66 (SD = 48) ml/min and 88 (SD = 91) ml/min in Group 1 and Group 2 patients, respectively. Values of Ccr during resuscitation (preoperative) were available in five Group 1 patients and 16 Group 2 patients and averaged 45 (SD = 56) ml/min and 58 (SD = 86) ml/min in Group 1 patients and Group 2 patients, respectively. Differences in values during resuscitation and operation between the two groups were not statistically significant ($P > 0.05$).

Free Water Clearance

Postoperative C_{H_2O} was significantly greater ($P < 0.05$) in Group 1 patients than in Group 2 patients except during the second postoperative hour (fig. 1). C_{H_2O} values were greater than −15 ml/h in all Group 1 patients for the first 24 h (table 2). In five of the 33 Group 2 patients, C_{H_2O} values were greater than −15 ml/h at the sixth postoperative hour but returned to values less than −15 ml/h within 24 h. In ten additional Group 2 patients, C_{H_2O}, which was less than −15 ml/h for the first 6 postoperative hours and became greater than −15 ml/h intermittently during the next 18 h.

Urine Flow Rate (UFR)

UFR during the first 6 postoperative hours averaged 170 (SD = 105) ml/h and 160 (SD = 110) ml/h in Group 1 patients and Group 2 patients, respectively (fig. 1). UFR in Group 1 patients decreased briefly to an average of 30 ml/h at the 16th and 18th postoperative hour, but increased with repletion of intravascular volume. There was no relationship between UFR and level of mean blood pressure or between UFR and Ccr value in both groups.

Mean Blood Pressure

Mean blood pressure in Group 1 patients was significantly greater during operation and for the first 4 postoperative hours compared with Group 2 patients ($P < 0.05$, fig. 1). In five of the seven Group 1 patients, mean blood pressure remained greater than 100 mmHg during the first 24 postoperative hours.

Urine Electrolytes

There were no significant differences in urine electrolyte values between the two groups. Fractional excretion of filtered sodium was greater than 1.5% in both groups during the first 24 postoperative hours.

TABLE 2. Number of Patients With Abnormal Clearance and Renal Dysfunction Following Operation

		Hours, Postoperative			
		2	4	6	48
Creatinine clearance (<25 ml/min)	Group 1 (7)*	7	7	7	
	Group 2 (33)	5	1	0	
Free water clearance (> −15 ml/h)	Group 1 (7)	7	7	7	
	Group 2 (33)	9	7	5	
Renal dysfunction	Group 1 (7)				7
	Group 2 (33)				0

* Total number of patients in parentheses.

Clinical Course

All Group 1 patients developed renal dysfunction in an average of 2.4 days after admission. The highest serum creatinine and BUN values in Group 1 patients averaged 4.5 (SD = 2.0) mg/dl and 73 (SD = 43.6) mg/dl, respectively. Four of the seven Group 1 patients developed acute renal failure: two developed nonoliguric renal failure and two developed oliguric renal failure. Two nonoliguric renal failure patients survived without dialysis. One oliguric renal failure patient died following many dialyses, and another oliguric renal failure patient died suddenly on the third postoperative day. The three remaining Group 1 patients had intermittent oliguria during the first 5 postoperative days but recovered from renal dysfunction. None of the Group 2 patients had renal dysfunction.

Discussion

This study clearly shows that Ccr is an extremely useful clinical measurement for the early detection of renal dysfunction in patients with the potential for development of renal failure. A transient decrease in Ccr is frequently seen following trauma and most anesthetics. It is not known how long Ccr should remain decreased before renal dysfunction results in ARF. In this study it appears that regardless of age and severity of injuries, patients who had Ccr less than 25 ml/min within the first 6 h following surgery may develop renal dysfunction, and some of them may experience ARF. Rosenberg and coworkers reported that a decrease in Ccr in a seemingly normovolemic patient is highly suggestive of renal failure.[6] Others suggest that one-half of the patients who had 24 h Ccr less than 25 ml/min developed ARF.[7] The fact that Ccr is abnormal in the presence of normal UFR and acceptable blood pressure is extremely important. This is especially so because, following the recognition of respiratory distress syndrome, it is a general practice to restrict fluid intake as soon as UFRs and blood pressures are restored to normal ranges. In patients with low Ccr, this practice may lead to further deterioration of renal function and high mortality.

It has been reported that C_{H_2O} is a useful predictor of ARF in postoperative patients.[1,2] Others report that decreases in Ccr and urinary osmolality are seen simultaneously in patients developing ARF.[8] This study demonstrated that C_{H_2O} is not as good a predictor as Ccr in trauma patients. This observation agrees with a reported retrospective study.[4] C_{H_2O} values may be increased to or above zero in patients with head injury, high blood alcohol levels, aggressive fluid infusion, and administration of diuretics. Thus, C_{H_2O} values near zero do not necessarily indicate the complete loss of the renal tubular concentration mechanism. It is also probable that depression of antidiuretic hormone activity may be the cause of abnormal C_{H_2O} in patients with normal Ccr. Even if abnormal tubular dysfunction is present as C_{H_2O} indicates, renal failure may not develop in patients with Ccr values greater than 25 ml/min.

FE_{Na} is useful for differential diagnosis of renal dysfunction only when oliguria is already present.[9] However, oliguria may not be apparent until 1 or 2 days following the loss of renal concentration function.[1,2] In this study, UFR was well maintained for the first 24 h in all patients. Thus, it was not surprising to find that FE_{Na} was not useful in detecting ensuing renal dysfunction.

Patients experiencing renal dysfunction have relatively higher blood pressures during anesthesia and following operation. This hypertension was associated with relatively high urine outputs, low Ccr, and abnormal C_{H_2O}, suggesting that vasoconstriction and decreased renal blood flow may persist despite seemingly successful resuscitation. Such high urine output may be due to lack of concentration power of the renal tubules following a brief period of hemorrhagic shock, as suggested by Selkurt and Elpers.[10]

Early detection of renal dysfunction is only the first step in the prevention of ARF. Recommended management of renal dysfunction includes aggressive repletion of intravascular volume, augmentation of reduced cardiac output, administration of diuretics, and/or administration of dopaminergic drugs. It is generally agreed that administration of diuretics and dopaminergic drugs is not effective unless intravascular volume is adequate. Shin and co-workers reported that a high incidence of nonoliguric renal failure and a low mortality for ARF were observed when fluid repletion in trauma patients was attempted early, guided by monitoring of Ccr and C_{H_2O}.[11] During this study, we attempted to maintain adequate intravascular volume with the use of a fluid challenge technique in patients with low urine output. Except in one patient who had renal injury, UFR was maintained despite persistently low Ccr. Brown reported that UFR could be maintained by administering furosemide in acute renal failure patients.[7] Despite the well-maintained urine output, the mortality of ARF patients and incidence in ARF in Brown's study remained high. Others report that administration of diuretics for ARF shortened the duration of oliguria and renal failure but did not decrease mortality.[12] The present study suggests that UFR can be maintained in the majority of ARF patients without administering diuretics, if fluid repletion can be carried out in the early stage of ARF. It remains to be investigated whether mortality in ARF is lower in patients who maintained urine output with fluid administration alone or in patients who received diuretics.

In severely traumatized patients, the lung and the kidney are the first organs to fail, leading to high mortality. Appropriate treatment of only one of these organ systems is counterproductive. Routine restriction of fluid intake may lead to renal failure, while overly zealous fluid administration precipitates respiratory failure. Accurate assessment of renal function and careful repletion of intravascular volume avoids aggravation of respiratory failure without impairing renal function. In patients with a low Ccr, left ventricular filling pressure and cardiac output should be monitored to evaluate intravascular volume and myocardial contractility.

Despite the reported usefulness of Ccr in renal function monitoring,[13,14] it has not been used frequently in clinical practice. One of the main reasons for this underutilization is the report that Ccr overestimates glomerular filtration rate (GFR) measured with the use of inulin.[15] Ccr in renal dysfunction is approximately 100% greater than GFR but only 20% greater in patients with normal renal function; however, the difference between absolute values of Ccr and GFR is clinically insignificant as a measure of renal dysfunction. For example, when Ccr is 10 ml/min, GFR would be approximately 5 ml/min, while a Ccr 120 ml/min is equivalent to a GFR of 100 ml/min. Despite the differences in Ccr and GFR, changes in Ccr parallel the rise and fall of GFR.[15] Ccr values less than 25 ml/min should not be regarded as GFR less than 25 ml/min but regarded as an indication of poor renal function.

One-hour Ccr, which we used in this study, is less accurate in assessment of renal function compared with 24-h Ccr because of difficulty in accurately measuring UFR. Inaccuracy stemming from short urine collection time and the crude collection technique can be minimized by sequential measurement of Ccr. Another source of error in Ccr measurement in this study was that we used average serum creatinine values for the calculation of Ccr.

Serum creatinine in Ccr calculation may overestimate or underestimate Ccr when serum creatinine change is significant, such as in renal dysfunction. Serum creatinine increases at a rate of 0.4–1.0 $mg \cdot dl^{-1} \cdot day^{-1}$ in oliguric renal failure. With the dilutional effect of aggressive fluid replacement, serum creatinine values do not change significantly during the first 24 postoperative hours, even in renal dysfunction. Of the 40 patients we studied, there were only two patients with renal dysfunction and serum creatinine values greater than 2.0 mg/dl at the 24th postoperative hour. In these two patients, Ccr calculated with the use of average serum creatinine value might have been only 3–5 ml/min different from the expected true Ccr values of 6–10 ml/min. For the first 6 postoperative hours, averaging serum creatinine causes overestimation of Ccr. Despite these potential measurement errors, Ccr appears to be superior to serum creatinine, BUN, C_{H_2O}, FE_{Na}, or UFR in assessment of renal dysfunction and can predict ensuing renal dysfunction.

We did not attempt to adjust Ccr according to body surface area because it was not possible to weigh patients with multiple trauma on the day of admission. Even if we weighed patients occasionally, it was not clear that calculated body surface was accurate in patients who had interstitial edema from trauma and resuscitation, metal protheses for orthopedic surgery, and plaster casts. In patients with Ccr values less than 25 ml/min, adjustment of Ccr according to body surface does not change the Ccr values significantly. Overall, Ccr is an easy, inexpensive and noninvasive measurement and can be repeated as often as needed.

Most anesthetic agents decrease GFR, which is reversed on termination of anesthetic administration.[16] The persistent decrease in postoperative Ccr in this study may be due to unrecognized continuing hemorrhage and/or persistent vasoconstriction of renal vessels.

In conclusion, despite normalization of vital signs and UFR following hemorrhagic shock, renal dysfunction may persist and may result in ARF. Persistent renal dysfunction can be recognized early by sequential measurement of Ccr for the first 6 h following anesthesia. C_{H_2O} as a predictor of ensuing azotemia and renal failure was not as useful as reported. Further studies should be done to determine whether the incidence of ARF can be minimized and the clinical course of ARF can be attenuated by monitoring Ccr and optimizing cardiac function and oxygen supply to the tissues.

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