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# Course of acute renal failure studied by a model of creatinine kinetics

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**Course of acute renal failure studied by a model of creatinine kinetics.** A computerized model of creatinine kinetics was developed to predict the relationship between creatinine clearance [G(t)] and plasma creatinine concentration [C(t)] in patients with postischemic acute renal failure (ARF). A comparison of predicted to measured values in 35 episodes of ARF in 27 patients revealed three patterns of declining G(t) following an ischemic insult. Pattern A, characterized by an abrupt step decrement in G(t) following an isolated renal ischemic episode lasting minutes or hours, was observed in nine patients. It was followed invariably by an immediate ramp increment in G(t), despite which C(t) continued to increase for several days. Urinary indices during the period of increasing azotemia were consistent with the resolving stage of ARF. Patterns B ($N$ = 15) and C ($N$ = 11) were associated with persistent renal ischemia of long (days to weeks) duration and were respectively characterized by prolonged ramp or exponential decrements in G(t). A concurrent increase in C(t) was associated with urinary indices typical of the maintenance or sustained stage of ARF. Recovery of G(t) was observed in only two-thirds of patterns B and C cases and took the form of a ramp or exponential increment. Because G(t) and total body water were changing rapidly in ARF, changes in measured plasma creatinine levels alone failed to identify these patterns of deteriorating or improving renal function. However, when the computerized model was used in conjunction with daily measured values of C(t) and body weight and occasional estimates of G(t), the course and prognosis of ARF in individual patients were illuminated.

**L'évolution d'une insuffisance rénale aiguë étudiée par un modèle de cinétique de la créatinine.** Un modèle sur ordinateur de cinétique de la créatinine a été développé afin de prédire la relation entre la clearance de la créatinine [G(t)] et la créatininémie [C(t)] chez les malades ayant une insuffisance rénale chronique post-ischémique (ARF). Une comparaison des valeurs prédites avec celles measurées dans 35 épisodes d'ARF chez 27 malades a révélé trois types de déclin de G(t) après une atteinte ischémique. Le type A, caractérisé par un décrochement abrupt de G(t) suivant un épisode isolé d'ischémie rénale durant quelques minutes ou heures, a été observé chez neuf malades. Il était suivi invariablement par une augmentation linéaire immédiate de G(t), bien que C(t) continue à s'élever pendant plusiers jours. Les paramètres urinaires pendant la période d'azotémie croissante étaient compatibles avec le stade de guérison de l'ARF. Les types B ($N$ = 15) et C ($N$ = 11) étaient associés à une ischémie rénale persistante de longue durée (plusiers jours ou semaines) et étaient caractérisés respectivement par des décroissances prolongées linéaires ou exponentielles de G(t). Une augmentation concomitante de C(t) était associée avec des index urinaires typiques d'un stade d'entretien ou de prolongation de l'ARF. Une récupération de G(t) était observée chez seulement les deux tiers des cas de types B et C et prenait la forme d'une augmentation linéaire ou exponentielle. Puisque G(t) et l'eau totale de l'organisme changeaient rapidement en ARF, les modifications de la concentration de creatinine plasmatique ne pouvaient pas, à elles seules, tradiure la détérioration ou l'amélioration de la fonction rénale. Cependant, lorsque le modèle par ordinateur était utilisé en association aux valeurs mesurées journalières de C(t) et de poids corporel et à des estimations occasionnelles de G(t), l'évolution et le pronostic de l'ARF chez ces malades, individuellement, étaient éclaircis.

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Transient interruption of renal blood flow is complicated frequently by an abrupt and profound depression of renal excretory function known as postischemic, acute renal failure (ARF). Serial measurements of the urinary clearance of a filtration marker, such as inulin, have revealed two distinct phases of renal injury [1–3]. The first or maintenance phase is often 1 to 2 weeks' duration. Inulin clearance is depressed to 5 to 15% of normal [3–5]. The maintenance phase is followed by a resolving phase, which is characterized by a progressive rise of inulin clearance. Fully 8 weeks may elapse, however, before restoration of inulin clearance to a normal range signifies complete recovery of renal function [1].

It is noteworthy that the urinary clearance of inulin is not a measure of the true glomerular filtration rate (GFR) in the maintenance phase of ARF. This is because a portion of inulin that is filtered leaks back across damaged tubular epithelium and enters the interstitium [2, 6, 7]. Yet another portion is sequestered in obstructed tubular lumina [8, 9]. The resolving phase, by contrast, is characterized by restoration of tubular impermeability to filtration markers and relief of intratubular obstruction [1, 2]. Whereas the changing urinary clearance of a filtration marker may better reflect GFR in the resolving phase, it characterizes a more complex injury to the entire nephron during the maintenance phase.

Among the small endogenous solutes that are retained in the body water, creatinine has the properties that most closely resemble those of a true filtration marker. Accordingly, the duration of the maintenance phase of ARF in humans is monitored most frequently by following the rise in plasma creatinine concentration on a daily basis, while the resolving phase is associated in clinical practice with a spontaneous decline in plasma creatinine concentration from peak levels [3]. There are, however, a number of limitations to the reliability with which the plasma creatinine concentration profile can be used to monitor the course of renal injury in ARF. The level of creatinine in plasma water is determined not only by its urinary clearance but also by its rate of production and its volume of

distribution in the body [10, 11]. In an attempt to relate the prevailing plasma creatinine concentration to its underlying urinary clearance by the injured kidney in ARF, we attempted to isolate net clearance from the other variables that govern the measured concentration of creatinine in plasma. To do this we examined in ARF patients the relationship between plasma creatinine concentration on the one hand and simultaneously changing renal excretory function and body water on the other. The resulting analysis has led to the development of a computerized model which reliably predicts and quantifies changes in the plasma concentration and urinary clearance of creatinine, even when the underlying GFR and tubular contribution to filtration marker clearance are changing very rapidly. The model permits changes in the direction of global nephron function that were unappreciated previously to be identified readily, and in this way allows the course of ARF in individual patients to be delineated with accuracy.

## Methods

### *Rationale*

The change ($\Delta$) in plasma creatinine concentration with respect to time is proportional to the rate of production minus the rate of loss of creatinine, that is

$$\Delta \text{ (creatinine) } \alpha \text{ production—loss}$$

Let Pr be the production rate of creatinine, (mg/day); and the following be functions of time: C(t), concentration of creatinine in plasma (mg/liter); G(t), urinary clearance of creatinine from plasma (liter/day); TW(t), total body water (liter); C′(t), the instantaneous rate of change of the concentration of creatinine in plasma (mg/liter/day).

The rate of change of plasma creatinine concentration with time may be expressed in terms of the rate of production and excretion as modified by the volume of distribution of creatinine. Thus,

$$dC/dt = C'(t) = \frac{Pr - G(t) \cdot C(t)}{TW(t)} \qquad (1)$$

Solving for G(t) yields

$$G(t) = \frac{Pr - C'(t) \cdot TW(t)}{C(t)} \qquad (2)$$

Eq. 2 shows the relationship of the determinants of creatinine: production, volume of distribution times the rate of change of plasma creatinine concentration, and the simultaneous plasma creatinine concentration. The accuracy of a prediction of GFR, minus the tubular backleak and sequestration rate in sustained ARF, or GFR alone in resolving ARF, depends on the knowledge of the determinants of the clearance of creatinine and the success with which creatinine clearance simulates the rate of clearance of a filtration marker in ARF.

For the ensuing analysis it is assumed: *(1)* that the production rate of creatinine is unchanging; *(2)* that the volume of distribution of creatinine approximates the total body water [10]; *(3)* that acute changes in total body water may be estimated from corresponding acute changes in body weight; and *(4)* that filtration marker clearance may be approximated by the clearance of creatinine [G(t)].

If changes in the clearance of creatinine, G(t), are to be estimated reliably by a mathematical model, the model should be sufficiently flexible to account for any perturbation in G(t), real or hypothetical. The imposition of forced perturbations in G(t), using the relationship of Eq. *(1)*, permits derivation of a curve expressed by the time function C(t). Clearly, inserting these derived values of C(t) from Eq. *(1)* into any model that predicts G(t) from changing plasma creatinine concentration should yield the original forced perturbation in G(t). However, when G(t) is changing rapidly this test is often failed by previously published models [10–12]. The mathematical reason for the failure is most often the inaccuracy in estimating the instantaneous rate of change of plasma creatinine concentration C′(t). Previous models have assumed a linear rise or fall in the day-to-day concentration of creatinine [10–12]. Any actual deviation from linearity in the rise or fall of plasma creatinine concentration with time would clearly invalidate a subsequent calculation of G(t). Furthermore, the aforementioned models have assumed also that total body water is a fixed percentage of body weight. When the percentage of body weight that is water is changing along with G(t), such an assumption compounds the error in computing the urinary clearance of creatinine.

Accordingly, we have modified earlier models of creatinine kinetics [10–12] by examining the effects on changes in C(t) that result from a variety of forced perturbations of G(t). **Appendix 1** details solutions for three differing decremental and three corresponding incremental perturbations of G(t). Each of these six changes in G(t) and the corresponding predicted pattern of change in C(t) are shown in Figure 1. The left upper panel (**A**) in Figure 1 represents a step decrement in G(t); the pattern of change in C(t) is a curve which is concave downward. A ramp decrement in G(t) shown in panel **B** by contrast produces a pattern of change in C(t) which is sigmoidal in shape. Only when the decrement in G(t) is proportional to l/time, as in panel **C**, is the pattern of rise in C(t) linear. The effects on C(t) of increasing G(t) where the latter occurs in a step increment (panel **D**), ramp increment (panel **E**) or an increment proportional to l/time (panel **F**), can be seen to produce patterns that are almost mirror images of the corresponding decrements of G(t) (Fig. 1). We have also considered a seventh perturbation which combines a decremental step change in G(t) followed by a mathematically dissimilar ramp increment as depicted in Figure 2. The solution for this more complex perturbation of G(t) is given in **Appendix 2.**

### *Development of a computerized model of creatinine kinetics*

The functional relationship between the urinary clearance and plasma concentration of creatinine is Eq. 2. To permit clinical recognition and quantification of changes in G(t), a computer program was written based on Eq. 2. The program was then tested by assessing its ability to reproduce the seven hypothetical perturbations of G(t) illustrated in Figures 1 and 2, that is, decrements, increments, and a combination of both.

The ability of the model to chart the actual course of ARF was next examined in 27 patients with hemodynamically mediated renal insufficiency. Daily measurements of plasma creatinine concentration and body weight were recorded for 7 to 27 days from the time of ischemic insult in each patient. During this period timed 2 to 4 hr urine collections were made through an indwelling bladder catheter. Blood was sampled at the

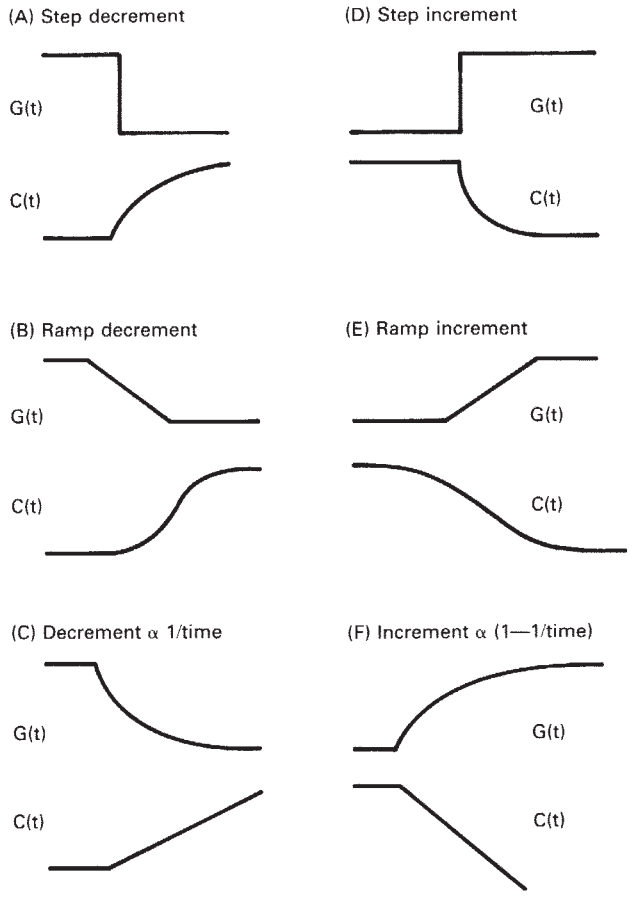


**Fig. 1.** *Hypothetical perturbations of creatinine clearance* [G(t)] *and accompanying alteration of plasma creatinine concentration* [C(t)]. Three differing decrements of G(t) are on the *left*, corresponding increments are on the *right*. Although not shown, both values are plotted as a function of time.

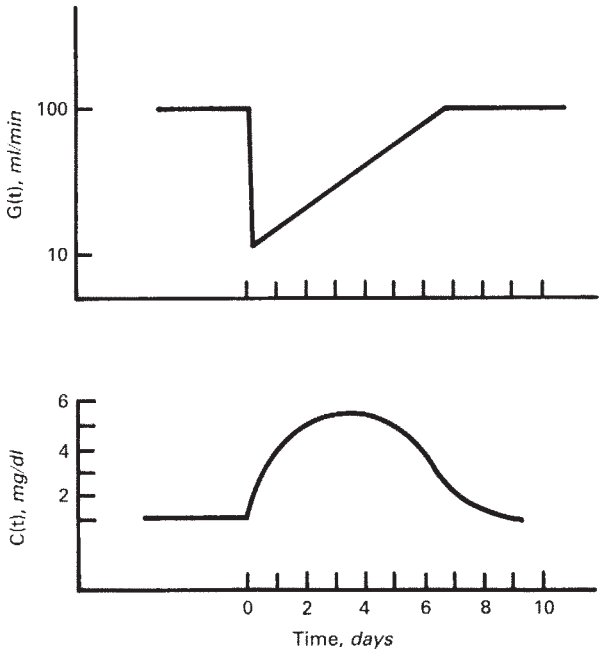


**Fig. 2.** *Effect of hypothetical step decrement followed by ramp increment in creatinine clearance* [G(t)] *on plasma creatinine concentration* [C(t)]. Note each value is plotted as a function of time in days.

midpoint of the urine collection to permit the determination of the creatinine clearance. The number of creatinine clearance determinations obtained in this fashion varied from 3 to 20 per patient. To enhance the clinical application of the program, maximal individualization of input data was attempted. The creatinine production rate was estimated in five instances from measurements of the urinary creatinine excretion rate made prior to the development of ARF. In the remaining subjects creatinine production was calculated from the following formula

$$\text{Pr} = (120 - 1.0 \times \text{age}) \times \text{baseline weight} \div 5 \qquad (3)$$

where age refers to patient age. (This formulation reflects Jeliffe's modification of Siersback-Nielsen's equation. [11, 13]) Conventional estimates of total body water based on body weight (60% males, 55% females) were modified by a clinical appraisal of hyper- or hypovolemia, fixed as plus or minus 10% of body water. Rather than assuming that total body water remains a fixed percentage of body weight, subsequent net changes from baseline in body water were equated with measured daily changes in body weight. For example, a 70-kg man is assumed to have $70 \times 60\% = 42$ liters of body water. If body weight were to increase 3 kg in 24 hr because of fluid intake exceeding output, then total body water would be $42 + 3 = 45$ liters and body water as a percentage of weight would increase to $(42 + 3) \div (70 + 3) = 45/73 = 62\%$. Note, however, that the absolute increment in body water is $3/42 = 7\%$.

A "normalized" plasma concentration of creatinine [C(t)] was determined from the curve of the actual concentration corrected for changes in total body water. The rate of change of creatinine concentration was determined by using a computer technique developed to estimate more accurately this determinant of G(t). The technique incorporates the changes in plasma creatinine concentration from measurements both preceding and following the point of interest so as to adjust the estimated slope of the plasma creatinine concentration curve for nonlinearity. The program samples the input data and ignores minor changes in plasma creatinine concentration (± 0.1 mg/dl) attributable to laboratory error. For creatinine kinetic calculations, the computer was an Apple IIe (64K RAM, Apple Computer, Inc., Cupertino, California, USA). The computer language was BASIC (Applesoft floating point). Curve fitting was performed with a Hewlett-Packard computer (Model 97, Hewlett-Packard, Elkhart, Indiana, USA). An acceptable fit was defined as $r$ greater than or equal to 0.9.

### *Clinical evaluation of acute renal failure*

Of the 27 members of the study population, 21 developed ARF following cardiac surgery, while ARF in the remainder occurred in the wake of surgical repair of a diseased upper (suprarenal) abdominal aorta. The ARF was characterized in each instance by an evaluation of indices that we described previously [5] and that included the urine flow rate, the urinary clearance of inulin, the fractional excretion of sodium, and the urine-to-plasma concentration ratios of inulin, and total solutes. These indices of ARF were determined in each instance during

**Table 1.** Imposed versus predicted changes in G(t)

| Time | Decrements in G(t), *ml/min* | | | | | | Time | Increments in G(t), *ml/min* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A Step | | B Ramp | | C Inverse time | | | D Step | | E Ramp | | F Inverse time | |
| *hr* | Imposed | Predicted | Imposed | Predicted | Imposed | Predicted | *hr* | Imposed | Predicted | Imposed | Predicted | Imposed | Predicted |
| −12 | 120 | 120 | 120 | 120 | 120 | 120 | −12 | 10 | 10 | 12 | 12 | 10 | 10 |
| 0 | 10 | 5 | 120 | 120 | 120 | 120 | 0 | 120 | 130 | 12 | 12 | 10 | 10 |
| 12 | 10 | 5 | 93 | 95 | 26 | 30 | 12 | 120 | 130 | 30 | 27 | 46 | 43 |
| 24 | 10 | 6 | 65 | 67 | 24 | 26 | 24 | 120 | 130 | 48 | 45 | 65 | 63 |
| 36 | 10 | 7 | 38 | 42 | 22 | 23 | 36 | 120 | 126 | 66 | 63 | 76 | 74 |
| 48 | 10 | 8 | 10 | 14 | 20 | 21 | 48 | 120 | 123 | 84 | 82 | 90 | 89 |

**Table 2.** Imposed versus predicted G(t) with step decrement followed by ramp increment

| | G(t), *ml/min* | |
|---|---|---|
| Day | Imposed | Predicted |
| −1 | 120 | 120 |
| 0 | 0 | 5 |
| 1 | 40 | 36 |
| 2 | 80 | 76 |
| 3 | 120 | 126 |
| 4 | 120 | 122 |

a period of increasing azotemia that preceded the attainment of peak concentration of creatinine in plasma. In 5 of the 27 patients the indices were remeasured during the resolving stage of ARF when the plasma concentration of creatinine was declining.

The concentration of creatinine in urine and plasma was determined by an automated, rate-dependent picrate method, using a creatinine analyzer (analyzer II, Beckman Instruments, Fullerton, California, USA). This method minimizes the influence of slowly reacting, noncreatinine chromogens, and thus provides an estimate of true creatinine concentration in plasma [14]. Inulin concentration was determined by the autoanalyzer method of Fjeldbo and Stamey [15]. Osmolality of urine and plasma was measured directly using an osmometer (Model 332, Advanced), while the corresponding concentrations of sodium were determined by flame photometry.

## Results

### *Response of the model to hypothetical perturbations of G(t)*

Displayed in Table 1 is the model's response to the perturbations depicted in Figure 1. In a hypothetical patient in whom G(t) declines to 10% of normal because of ARF, the current model predicts with accuracy the direction and magnitude of the forced perturbations of G(t). Errors in determining the direction of change in G(t) do not occur. Errors in estimating the magnitude of change are usually small, averaging a few milliliters per minute. The seventh comparison, to the combination of step decrement and ramp increment of Figure 2, is shown in Table 2. With the model's more accurate estimation of the instantaneous rate of change of plasma creatinine concentration, even a very labile G(t) can be monitored with accuracy.

### *Analysis of data in patients with acute renal failure*

There were 35 episodes of acute renal insufficiency in the 27 patients studied. Twenty-one patients had a single episode of

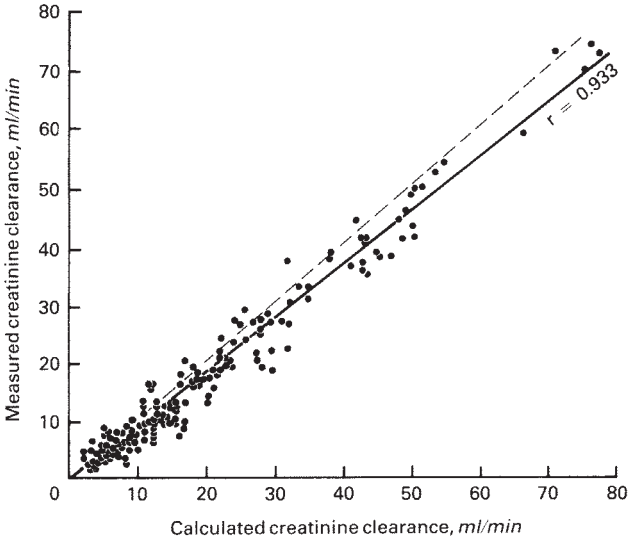


**Fig. 3.** *Correlation of measured values of creatinine clearance with those predicted by the kinetic model.* The data *points* represent 180 estimations made prior to or during the acute renal failure in 27 subjects. The regression and identity *lines* are depicted by *solid* and *broken lines*, respectively.

ARF, while two or three distinct episodes were observed in each of the remaining six patients. A total of 180 measurements of creatinine clearance were made in these 27 patients during the course of their ARF. These measured clearances are compared in Figure 3 to simultaneous clearances of creatinine calculated by the model. Linear regression analysis revealed the calculated and measured clearances to be correlated strongly with a correlation coefficient of 0.933. From examination of the line of identity in Figure 3, it can be seen that calculated clearances slightly overestimated the measured clearances in a majority of instances. The opposite was true for a minority of calculated clearances which tended to underestimate measured clearances. It is important to emphasize, however, that the disparity tended to remain constant for repeated comparisons in a given patient. Thus, irrespective of the source of the small systematic error between measured and calculated clearances, the consistency of the disparity in individual patients permits the direction and magnitude of changes in ARF to be recognized and quantitated with accuracy.

Nine episodes of ARF were associated with the step decrement of G(t) illustrated in panel **A** of Figure 1. A ramp decrement (panel **B**) and inverse time decrement (panel **C**) were

**Table 3.** Type of recovery

| Type of ARF | (Pattern) | (D) | (E) | (F) | None | % Recovered |
|---|---|---|---|---|---|---|
| I | (A) | 0 | 9 | 0 | 0 | 100 |
| II | (B) | 0 | 7 | 3 | 5 | 67 |
| III | (C) | 0 | 3 | 4 | 4 | 64 |

observed in 15 and 11 episodes, respectively. These three patterns of declining G(t) were then used in categorizing ARF as types I, II, and III, respectively.

The ensuing recovery patterns are summarized in Table 3. Nineteen episodes of recovering G(t) were characterized by a ramp increment (Fig. 1, panel **E**) while an additional seven recovery episodes followed an inverse time incremental pattern (Fig. 1, panel **F**). A step increment in G(t) (Fig. 1, panel **D**) was not observed in this group of patients. Without exception all of the patients having type I injury (step decrement) recovered in a pattern reflected by a ramp improvement in G(t). The pattern of recovery was more variable in types II and III injury, including examples of both patterns E and F (Table 3). Of note, five of six patients having more than one episode of ARF failed ultimately to recover renal function. An example of the patterns of loss and recovery of G(t) is illustrated for patients representative of each of the three types of renal injury in Figure 4. As may be clearly seen, there was a remarkable concordance ($r > 0.9$) between the profiles of plasma creatinine concentration and creatinine clearance actually exhibited by our patients and the hypothetical plots displayed in Figures 1 and 2.

### *Correlates of injury patterns*

Using the aforementioned indices of glomerular and tubular functions to characterize ARF revealed that type I injury has striking differences compared with types II and III injury, respectively. For the sake of convenience Table 4 compares the urinary indices in these three categories of ARF to corresponding values for patients making an uncomplicated and nonazotemic recovery from cardiac surgery (control group 1) and to values typical of patients recovering from postcardiac surgical ARF (control group 2). The data from each of these two "control" comparison groups are from an earlier study by us that has been reported in detail elsewhere [5].

Compared to group 1 "normal" controls, glomerular and tubular functions were considerably deranged with all three types of ARF. However, type I [step decrement in G(t)] differed from type II [ramp decrement] and III [inverse time decrement] in that with the former, inulin clearance was threefold higher while the ability to form a concentrated urine was relatively preserved (Table 4). Judged by a lower fractional excretion of sodium and higher urine-to-plasma inulin concentration ratio, the fractions of filtered sodium and water reabsorbed in type I ARF were also substantially higher than corresponding values in types II and III ARF (Table 4). Although plasma creatinine concentration was rising sharply at the time that these urinary indices were determined in type I ARF, a ramp type recovery of G(t) was already underway (Fig. 4 panels **A** and **D**). That the superior glomerular and tubular functions observed in the type I injury appear to reflect the resolving stage of ARF is supported by the data in Table 4. There is a striking resemblance of urinary indices of type I ARF to those of control group 2 with

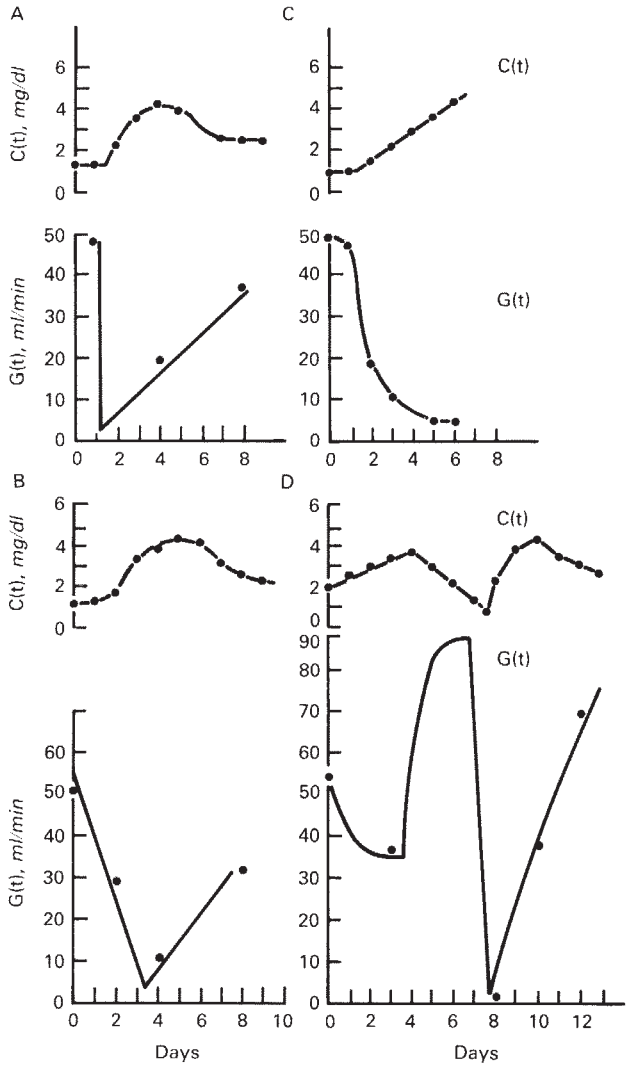


**Fig. 4.** *Computed* (solid lines) *versus measured individual data points in four individual patients who display the patterns of loss and recovery of creatinine clearance depicted in Figure 1.* Values for plasma creatinine concentration, [C(t)] are in the *upper panel;* corresponding values for creatinine clearance [G(t)] are in the *lower panel.* Patient A demonstrates pattern A step decrement followed by pattern E ramp increment of G(t). Patient B demonstrates pattern B ramp decrement followed by pattern E ramp increment. Patient C demonstrates pattern C l/time decrement with no ensuing recovery. Patient D had two episodes of G(t) loss, pattern B and A, respectively, followed by pattern F (l/time) and then pattern E recovery.

recovering ARF, and also to those of the five patients of the present study who were recovering from types II and III ARF.

The ischemic insult underlying the ARF also differed strikingly between type I ARF and types II and III ARF. With the former, the patients appeared to sustain a single insult during surgery and experienced an uneventful postoperative course free of hemodynamic compromise. This was evidenced in type I patients by the fact that the treating surgeons had removed Swan-Ganz catheters and central venous lines by the time the urinary indices of ARF were determined (day 3 ± 2, mean ± SEM). In types II and III patients by contrast, the postoperative course was characterized by prolonged cardiac dysfunction.

**Table 4.** Functional indices in three types (patterns) of acute renal failure[a]

| | | $C_{inulin}$ | V | | | | $U/P_{creat}$ |
|---|---|---|---|---|---|---|---|
| | *N* | *ml/min* | | $U/P_{osm}$ | $U/P_{in}$ | $FE_{NA}$ | $U/P_{in}$ |
| Control group 1 | 44 | 84 ± 8 | 1.8 ± 0.5 | 1.9 ± 0.1 | 68 ± 9 | 1.3 ± 0.4 | 1.3 ± 0.1 |
| ARF Type I | 9 | 30 ± 3 | 1.7 ± 0.3 | 1.4 ± 0.1 | 16 ± 4 | 0.8 ± 0.2 | 1.4 ± 0.1 |
| Type II | 10 | 12 ± 2[c] | 1.1 ± 0.3[c] | 1.0 ± 0.01[c] | 10 ± 3 | 6.8 ± 2.1[c] | 1.5 ± 0.1 |
| Type III | 9 | 9 ± 1[c] | 1.6 ± 0.2 | 1.0 ± 0.01[c] | 7 ± 2[d] | 10.7 ± 2.7[c] | 1.6 ± 0.1 |
| Control group 2 (Recovering) | 10 | 29 ± 3 | 1.5 ± 0.1 | 1.3 ± 0.1 | 22 ± 4 | 1.4 ± 0.6 | 1.3 ± 0.1 |
| Recovering ARF Type II, III | 5 | 28 ± 7 | 1.6 ± 0.2 | 1.3 ± 0.1 | 47 ± 5 | 0.8 ± 0.2 | N/A[b] |

[a] All results are reported as a mean ± 1 SE; one patient with both types II and III ARF had physiological studies performed in each.
[b] $U/P_{creatinine}$ was not measured.
[c] $P < 0.05$ vs. type I.
[d] $0.05 < P < 0.1$ vs. type I.

Thus, at the time of measurement of urinary indices (postoperative day 7 ± 1, range 4 to 12), all 18 patients were receiving inotropic agents and undergoing intravascular hemodynamic monitoring. Cardiac performance in five of these 18 patients required additional augmentation with an intra-aortic balloon pump. In all but one of six patients in whom cardiac output was determined at the time of measurement of urinary indices, the former value was depressed below 4 liters/min. The superimposition of other insults upon the poor cardiac performance, including administration of nephrotoxic drugs and contrast agents, and brief episodes of hypotension related to cardiac arrhythmias or hypovolemia, were observed commonly in types II and III but never in type I ARF. It appears then that type I injury occurs in the wake of a brief and isolated ischemic renal insult and is followed rapidly and invariably by recovery. Types II and III injury by contrast, appear to ensue after prolonged, and sometimes repeated, episodes of renal ischemia and to manifest a failure of recovery in a substantial subset of patients (Table 3).

## Discussion

Serial determinations of the clearance of inulin have proven useful in charting the course and outcome of postischemic ARF [1, 3]. Unlike inulin, creatinine is cleared from plasma into urine not only by glomerular filtration but also by tubular secretion [16]. Judged by the observed, average creatinine-to-inulin clearance ratios of 1.3 to 1.6 (Table 4), the normal predominance of glomerular creatinine filtration over creatinine tubular secretion appears to be true also of the kidney injured by ARF. As discussed previously, the lowered inulin clearance of ARF may be ascribed, in part, to transtubular backleak of inulin [2, 6, 7]. Because inulin backleak is passive (that is, occurs solely by ultrafiltration and/or diffusion through the damaged tubule wall), filtered creatinine, with its smaller size and molecular weight (113 vs. 5200 daltons for inulin) should leak back with at least equal facility. The opposing contributions to the urinary clearance from passive backleak and active secretion of creatinine must remain conjectural. Nevertheless, we note with interest that the creatinine-to-inulin clearance ratio in all three categories of ARF encountered in the present study (I to III), as well as during recovery in an earlier study, is relatively constant (Table 4). Given this parallel relationship with inulin clearance, we propose that the utility of the creatinine clearance to detect rapid alterations in global renal function should be perfectly adequate for clinical purposes. As this study clearly demonstrates, changes in creatinine clearance during ARF are indeed common and measurable. Moreover, the accuracy of the assessment of both the magnitude and direction of such changes may be improved by the simultaneous use of standard creatinine clearance techniques and the proposed, computerized analysis of creatinine kinetics.

Our reformulation of creatinine kinetics in ARF and the aforementioned analysis of forced perturbations of creatinine clearance reveal a number of findings that are at once somewhat surprising and of considerable clinical import. The common perception is that a rising level of plasma creatinine is synonymous with a falling glomerular filtration rate, and that the converse is true of a declining plasma creatinine concentration. However, a re-examination of Figure 1 reveals that the anticipated, inverse relationship between these two quantities may be dissociated. As shown in panels **A** through **E**, plasma creatinine concentration may rise *or* fall when G(t) is unchanging. The most surprising finding, shown in Figure 2 and demonstrated by nine of our patients, is that the concentration of creatinine may be increasing rapidly while G(t) is actually rising. Clearly, a knowledge of nephron function in ARF demands an approach which examines more than the simple day-to-day variation in the plasma concentration of creatinine.

Our computerized analysis provides other insights which are pertinent to patient care. Following an acute insult which results in increasing azotemia, the number of days during which creatinine continues to rise is of prognostic value. A re-examination of Figure 1 illustrates this point. According to our computations, progressive increases in plasma creatinine concentration of greater than 5 days' duration are characteristic of ARF in which recovery has not begun or is quantitatively insignificant; examples are shown in panels **A, B,** and **C.** However, as depicted in Figure 2, a profound step decrement in renal excretory function followed immediately by gradual recovery over 7 days is computed to result in a plasma creatinine

Table 5. Effects of increasing total body water on serum creatinine concentration in ARF

| | Day | Creatinine clearance *ml/min* | Weight *kg* | Total body water *liters* | Laboratory[a] creatinine *mg/dl* | Corrected[b] creatinine *mg/dl* | Total body water *weight, %* |
|---|---|---|---|---|---|---|---|
| Patient (A) | −1 | 44 | 68 | 40.8 | 1.4 | 1.4 | 60 |
| | 0 | 44 | 68 | 40.8 | 1.4 | 1.4 | 60 |
| | 1 | 37 | 80.4 | 53.2 | 1.2 | 1.6 | 66 |
| | 2 | 35 | 82 | 54.8 | 1.1 | 1.5 | 67 |
| | 3 | 29 | 82.5 | 55.3 | 1.4 | 1.9 | 67 |
| Patient (B) | −1 | 38 | 50.4 | 27.7 | 0.9 | 0.9 | 55 |
| | 0 | 38 | 52 | 29.3 | 0.9 | 1.0 | 56 |
| | 1 | 11 | 58 | 35.3 | 1.2 | 1.5 | 61 |
| | 3 | 12 | 65 | 42.3 | 1.6 | 2.3 | 65 |
| | 6 | 5 | 67.5 | 44.8 | 2.0 | 3.1 | 66 |
| | 10 | 5 | 69.4 | 46.7 | 3.9 | 6.2 | 67 |

[a] The values are measured values.
[b] The computed value was normalized for the increasing body water.

concentration that peaks on day 4. Even if recovery were to be more gradual, requiring 14 days instead of 7, we calculate that plasma creatinine concentration would nonetheless peak on approximately day 4 post injury, albeit at a higher level. Thus, if plasma creatinine concentration is still increasing 4 or more days after rising azotemia is noted, the clinician may be reasonably certain that recovery of renal function has not yet begun. Under these circumstances, anticipation of a prolonged period of sustained ARF and clinical planning for dialytic support would be prudent.

The analysis of creatinine kinetics described here is novel in that it makes allowances for the unsteady state that characterizes acute renal failure. An important departure from previous analyses is that the effect of rapidly increasing body water on the concentration of plasma creatinine is considered. Two examples of the effects of augmentation of body water caused by fluid administration in excess of losses in two of our patients with ARF are depicted in Table 5. In patient A a rise in plasma creatinine concentration was completely offset by the simultaneous increase in total body water. To the contrary, an apparent fall in plasma creatinine concentration in patient A gave the misleading impression that renal function was improving. In patient B of Table 5, although the rise in plasma creatinine was not made occult, it was considerably blunted by progressive hypervolemia, suggesting that the renal injury was less serious than in reality. As shown in Table 5, the percentage of body weight which was water was increasing progressively with time in both instances. These two examples serve to emphasize that it is incorrect to apply fixed percentages of body weight in calculating body water when daily weight is changing due to fluid overloading.

The present analysis also differs from previous approaches in that the instantaneous rate of change of plasma creatinine concentration is calculated as a function of simultaneous changes in G(t) and in several of its determinants [Eq. *(2)*]. One previous analysis [11] has related changing G(t) to changing plasma creatinine concentration in ARF by assuming *(1)* that the rate of change of creatinine concentration in plasma is approximated adequately by the difference in measured creatinine concentrations separated by intervals of 24 hr or more, and *(2)* that these long intervals between successive measurements of creatinine concentration in plasma would introduce no significant error into the calculation of G(t) [11]. That these earlier assumptions may be the source of considerable error in the estimation of changing nephron function in ARF is illustrated by an examination of panel **D** in Figure 4. On days 5, 8, and 13 postinjury, the measurements of concentration of creatinine in plasma normalized for changing body water are identical, 2.0 mg/dl. In the absence of intervening measurements, the above-mentioned analysis would suggest that G(t) had remained constant, when such was clearly not the case in this patient who manifested a profound fall followed by a progressive rise in renal function during the interim.

The single determinant of G(t) that was not modified from earlier formulations in the present study was the production rate of creatinine. Although the production rate of creatinine may decline with chronic renal insufficiency [17], there have been no studies of the stability of creatinine production during postischemic ARF. Our assumption of an unchanging rather than an increase or decrease of creatinine production rate may account for the systematic error observed between calculated and measured creatinine clearance (Fig. 3). As noted previously, however, the excellent correlation between these measured and calculated values suggests that any over- or underestimation of creatinine's production does not impair the ability of the present kinetic model to detect and quantify the direction and magnitude of changes in G(t).

In addition to its clinical utility, the present model of creatinine kinetics has also provided intriguing insights into the pathophysiology and pathogenesis of postischemic ARF. This is particularly true of type I injury, which is revealed to be most consistent with a postischemic step decrement followed almost immediately by a ramp increment of filtration marker clearance. The brevity of the maintenance phase of ARF implicit in type I renal injury is typical of analogues of postischemic ARF in experimental animals when prophylactic mannitol has been administered prior to the ischemic insult [18–21], as it was to each subject of the present study. Recovery of filtration marker clearance within 24 hr of a transient episode of complete renal ischemia has also been demonstrated by us previously in mannitol-protected humans [22]. Determination of urinary indices during the stage of early resolution of ARF reveals an ability

of the recovering tubules to concentrate the urine and to conserve water and sodium (Table 4). Traditionally, these findings have been used to distinguish patients with so-called "prerenal azotemia" from those with established intrinsic ARF, in which the ability to concentrate the urine and conserve sodium is lost [23, 24]. In the present study, plasma creatinine concentration continued to rise for several days after the resolving stage had begun (Figs. 2 and 4). It is easy to see, therefore, how prerenal azotemia might be confused with recovering type I ARF in a clinical setting of recent renal ischemia. The use of creatinine kinetics permits these two very different entities to be distinguished readily.

Our analysis also suggests that the postischemic ramp or inverse time decrement of types II and III injury, respectively, are typified by long sustained renal ischemia (days) and a protracted course of ARF. When the prolonged ischemia that appears to underlie types II and III injury is complicated by additional renal insults, a particularly unfavorable outcome, nonresolution of ARF, is likely to ensue (Table 3). The use of our computerized model to identify types II or III injury and to detect recurring renal insults might prove useful under these circumstances. Vigorous measures to stabilize renal perfusion, and the scrupulous avoidance of nephrotoxic substances in this setting, may prove efficacious in preventing an ultimate and irreversible loss of renal function.

## Appendix 1

The rate of change with time in the concentration [C'(t)] of a marker of glomerular filtration, for example, e.g. creatinine, is represented by the following equation:

$$C'(t) = [Pr \div TW(t)] - [G(t) \cdot C(t) \div TW(t)] \quad (1)$$

Where Pr, TW(t), G(t), and C(t) are as defined in **Methods**. Rearranging Eq. 1 yields,

$$C'(t) + [G(t) \div TW(t)] \cdot C(t) = Pr \div TW(t) \quad (2)$$

Eq. 2 is an ordinary differential equation of the form

$$y' + A \cdot y = B \quad (3)$$

where A and B are functions of time. Eq. 3 may often be solved formally by employing a "multiplier function" of the form exp ($\int A\,dt$). Multiplying both sides of Eq. 3 by this function yields,

$$y' \cdot \exp(\int A\,dt) + y \cdot A \cdot \exp(\int A\,dt) = B \cdot \exp(\int A\,dt) \quad (4)$$

The left side of Eq. 4 may be expressed as

$$d\,[y \cdot \exp(\int A\,dt)] = y' \cdot \exp(\int A\,dt) + y \cdot A \cdot \exp(\int A\,dt)$$

Thus,

$$d\,[y \cdot \exp(\int A\,dt)] = B \cdot \exp(\int A\,dt) \quad (5)$$

Integrating both sides of Eq. 5 yields,

$$y \cdot \exp(\int A\,dt) = \int B \cdot \exp(\int A\,dt) \cdot dt + K \quad (6)$$

where K is a constant of integration. Rearranging Eq. 6 yields,

$$y = \frac{\int B \cdot \exp(\int A\,dt) \cdot dt}{\exp(\int A\,dt)} + \frac{K}{\exp(\int A\,dt)} \quad (7)$$

Thus the solution to Eq. 1 assumes the form of Eq. 7

$$C(t) = \frac{\int [Pr \div TW(t)] \cdot \exp\{\int [G(t) \div TW(t)]\} \cdot dt}{\exp\{\int [G(t) \div TW(t)]\} \cdot dt} + \frac{K}{\exp\{\int [G(t) \div TW(t)]\} \cdot dt} \quad (8)$$

Whether Eq. 8 can be expressed in simple form depends on the integratability of the enclosed terms. As will be demonstrated, the function G(t) is the primary determinant of the final form of C(t).

Each of the six single changes in G(t), three decrements and three corresponding increments, will be used to solve for the respective C(t) functions.

**Step decrement** (Refer to Fig. 1A)

$$\begin{aligned} G(t) &= G(O) && t \le 0 \\ &= G(O)/N && t > 0,\ N > 1 \\ C(t) &= C(O) && t \le 0 \\ &= N \cdot C(O) - (N-1) \cdot C(O) \cdot \exp[-G(O)/(N \cdot TW)] \cdot t && t > 0 \end{aligned}$$

**Ramp decrement** (Refer to Fig. 1B)

$$\begin{aligned} G(t) &= G(O) && t \le 0 \\ &= \{[G(O)/N - G(O)] \div \zeta\} \cdot t + G(O) && 0 < t < \zeta \\ &= G(O)/N && t \ge \zeta \end{aligned}$$

Where $\zeta$ = the number of days required for G(t) to decline from G(O) to G(O)/N.

$$C(t) = C(O) \qquad t \le 0$$

$$C(t) = \frac{k1 \cdot \int \exp Z\,dt}{\exp Z} + \frac{k4}{\exp Z} \qquad 0 < t < \zeta$$

Where $k1 = \dfrac{G(O) \cdot C(O)}{TW}$

$$k2 = \frac{G(O)/N - G(O)}{\zeta \cdot TW}$$

$$k3 = \frac{G(O)}{TW}$$

$$k4 = C(O)$$

and $Z = \dfrac{k2}{2} \cdot t^2 + k3 \cdot t$

Finally,

$$C(t) = N \cdot C(O) - (N-1) \cdot C(O) \cdot \exp[-G(O)/(N \cdot TW)] \cdot t \quad t \ge \zeta$$

**Decrement** $\propto 1/t$ (Refer to Fig. 1C)

$$\begin{aligned} G(t) &= G(O) && t \le 0 \\ &= \frac{G(O)}{1+t} && t > 0 \\ C(t) &= C(O) && t \le 0 \\ &= Z \cdot (1+t) + \frac{[C(O) - Z]}{(1+t)G(O)/TW} && t > 0 \end{aligned}$$

Where $Z = \dfrac{G(O) \cdot C(O)}{G(O) + TW}$

**Step increment** (Refer to Fig. 1D)

$$G(T) = G(O)) \qquad t \le 0$$
$$= N \cdot G(O) \qquad t > 0, N > 1$$
$$C(t) = C(O) \qquad t \le 0$$
$$= \frac{C(O)}{N} + \left(\frac{N-1}{N}\right) \cdot C(O) \cdot \exp\{-[(N - G(O)] \cdot t/TW\} \qquad t > 0$$

**Ramp increment** (Refer to Fig. 1E)

$$G(t) = G(O) \qquad t \le 0$$
$$= G(O) + [N \cdot G(O) - G(O)] \cdot t/\zeta \qquad 0 < t < \zeta$$
$$= N \cdot G(O) \qquad t > \zeta, N > 1$$

and where $\zeta$ is defined as before.

$$C(t) = C(O) \qquad t \le 0$$
$$C(t) = \frac{k1 \cdot \int \exp Z\, dt}{\exp Z} + \frac{k4}{\exp Z} \qquad 0 < t < \zeta$$

Where $k1 = \dfrac{G(O) \cdot C(O)}{TW}$

$$k2 = \frac{N \cdot G(O) - G(O)}{\zeta \cdot TW}$$

$$k3 = \frac{N \cdot G(O)}{TW}$$

$$k4 = C(O)$$

and $Z = \dfrac{k2}{2} \cdot t^2 + k3 \cdot t$

Finally,

$$C(t) = \frac{C(O)}{N} + \left(\frac{N-1}{N}\right) \cdot C(O) \cdot \exp[-(N \cdot G(O) \cdot t/TW)] \quad t > \zeta$$

**Increment $\propto$ t/(t + 1)** (Refer to Fig. 1F)

$$G(t) = G(O) \qquad t \le 0$$
$$= N \cdot G(O) \cdot t/(t+1) \qquad t > 0, N > 1$$
$$C(t) = C(O) \qquad t \le 0$$
$$C(t) = \frac{k1 \int Z\, dt}{\exp Z} + \frac{k3}{\exp Z} \qquad t > 0$$

Where $k1 = \dfrac{G(O) \cdot C(O)}{TW}$

$$k2 = \frac{N \cdot G(O)}{TW}$$

$$k3 = C(O) \cdot \exp k2$$

and $Z = k2 \cdot (1 + t)/(1 + t)^{k2}$

## Appendix 2

**Step decrement and linear recovery** (Ref to Fig. 2)

$$G(t) = G(O) \qquad t < 0$$
$$= G(O)/N \qquad t = 0, N > 1$$
$$= \frac{G(O)}{N} + [G(O) - G(O)/N] \cdot t/\zeta \qquad 0 < t < \zeta$$
$$= G(O) \qquad t \ge \zeta$$
$$C(t) = C(O) \qquad t \le 0$$
$$= \frac{k1 \cdot \int \exp Z\, dt}{\exp Z} + \frac{k4}{\exp Z} \qquad 0 < t \le \zeta$$

where k1, k1, k3, k4, and Z are defined as for ramp recovery, **Appendix 1.**

Finally,

$$C(t) = C(O) + (N - 1) \cdot C(O) \cdot \exp(-G(O) \cdot t/TW) \qquad t > \zeta$$


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