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Two-hour *Versus* 22-hour Creatinine Clearance in Critically Ill Patients

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Despite aggressive use of hemodialysis, the mortality from isolated postoperative and postraumatic acute renal failure is approximately 60%, and increases dramatically as other organ systems fail. Early diagnosis of renal dysfunction is essential, so that therapy may be altered to prevent further deterioration—for example, the provision of adequate intravenous fluids, or modification of dosages of nephrotoxic antibiotics. In critically ill patients, the creatinine clearance provides the most helpful clinical index of glomerular filtration rate (GFR), and, thereby, the diagnosis and prognosis of acute renal dysfunction.[1–4]

To reduce errors due to residual urine in the bladder, urine for creatinine clearance has traditionally been collected over a 24-h period: the longer the urine collection, the smaller the fraction of the total collection the residual urine represents. However, a long collection introduces greater opportunity for collection errors, disrupts other diagnostic tests, curtails the frequency with which the test is performed, and delays the availability of the information for clinical decisions. In addition, a long urine collection is matched to a single serum sample during a period when serum creatinine may be rapidly changing (0.5–1.5 mg/dl/day in oliguric acute renal failure).

The presence of an indwelling urinary catheter reduces the error due to residual urine and, as long as the urine collection is carefully timed, the duration of collection is immaterial to the principle of clearance studies. We have encountered considerable physician bias in our intensive care units against the concept that a short, timed catheter collection can provide accurate estimates of creatinine clearance. This prospective study was designed to test the hypothesis that creatinine clearance estimations are equivalent, whether obtained from 2-h or 22-h urine collections in catheterized patients in the intensive care unit (ICU).

In critically ill patients, renal function is potentially unstable. The use of *serial* creatinine clearance estimations to detect early changes in renal function is more reliable and more important than a single isolated measurement.[2,5] Therefore, creatinine clearances were measured on a daily, sequential basis to test the hypothesis that short and long urinary collections provide the same information about *changes* in renal function as well. Today, the most common form of acute renal failure in the ICU setting is non-oliguric (characterized by urine flow greater than 15 ml/h), which provides the greatest challenge in the early diagnosis of renal dysfunction. For this reason, and because of the errors caused by variations in residuals and urinary dead space with very slow urine flow rates, it was decided to study subjects with urine flow rates of greater than 15 ml/h.

MATERIALS AND METHODS

Patients admitted to the medical and surgical intensive care units at Stanford University Medical Center were entered into the study. The study was approved by the institutional review board, and written, informed consent was obtained from the patients or their next-of-kin. Patients had both an access site for blood drawing (arterial or central venous catheter) and an indwelling urinary catheter *in situ*. Subjects with established oliguria (urine flow less than 15 ml/h, or who were receiving hemodialysis, were excluded from the study.

Urine was collected continuously, 24 h a day, into an automated urinometer (Model 210, VitalMetrics®, San Diego, CA) checked daily against a conventional weigh-scale. For the 22-h creatinine clearance, urinary collections were made from 1000 h to 0800 h each day, and blood was drawn for serum creatinine at 0800 h. For the 2-h creatinine clearance, urinary collections were made from 0800 h to 1000 h each day, and blood was drawn for serum creatinine at 0900 h. Because the urine collection was continuous, no special methods

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TABLE 1. Range of Renal Function

	Urine Flow Rate (ml/hr)				Serum Creatinine (mg/dl)				Creatinine Clearance (ml/min)			
	22 h		2 h		22 h		2 h		22 h		2 h	
	Max	Min	Max	Min	Min	Max	Min	Max	Min	Max	Min	Max
1	78	51	113	35	2.9	6.0	2.9	6.0	15	4	14	4
2	244	157	362	76	1.0	1.2	1.0	1.2	71	44	66	46
3	157	55	197	35	1.4	1.7	1.4	1.7	17	15	18	13
4	94	59	80	50	1.0	1.5	0.9	1.4	87	86	109	72
5	88	88	64	64	0.7	0.7	0.7	0.7	77	77	94	94
6	114	66	167	66	1.1	1.4	1.2	1.3	36	20	35	28
7	235	69	269	51	1.0	2.4	1.1	2.4	71	17	81	17
8	52	49	26	26	1.3	1.6	1.5	1.5	59	47	62	50
9	197	102	403	53	0.7	0.9	0.7	0.9	102	70	149	116
10	109	109	77	77	1.0	1.0	1.0	1.0	69	69	60	60
11	91	43	91	31	3.3	3.7	3.2	3.7	11	10	11	8
12	187	25	73	27	1.5	5.8	1.4	5.8	37	3	36	3
13	55	55	43	43	0.9	0.9	1.1	1.1	40	40	41	41
14	155	40	458	19	0.5	0.9	0.6	0.9	142	62	163	26
15	224	63	206	74	0.8	1.1	0.7	1.1	99	56	104	64
16	67	33	80	35	2.2	3.0	2.2	3.0	16	12	23	13
17	136	136	124	124	1.3	1.3	1.2	1.2	65	65	72	72
18	53	23	35	5	2.1	3.1	2.1	3.1	20	5	16	2
19	158	48	125	56	2.7	3.3	2.7	3.3	15	8	17	9

The Table indicates the range of renal function encountered in the 19 study patients. 22 h = 22-h urine collection; 2 h = 2-h urine collection; max = maximum value achieved; min = minimum value achieved.

(*e.g.*, injection of air) were used to ensure bladder emptying at the beginning and end of each collection period. Urine samples were stored in an ice bath during the collection procedure. Urine and serum creatinine were measured with an ASTRA-8® Creatinine Chemistry Module (Beckman, Irvine, CA), which employs the Jaffé reaction.

Measurements of urine creatinine (U_{CR}) in mg/dl, urine flow rate (V) in ml/min, and serum creatinine (S_{CR}) in mg/dl were used to calculate creatinine clearance (CC) in ml/min by the standard formula:

$$CC = \frac{U_{CR} \times V}{S_{CR}}$$

Because of technical limitations set by our laboratory, serum creatinine was drawn at the mid-point of each 2-h urine collection, but at the *end* of each 22-h urine collection. Each 2-h creatinine clearance was compared with the 22-h creatinine clearance immediately preceding it. This had the effect of minimizing the time difference between serum creatinine estimations and enhancing any differences due to the duration of urinary collections, in keeping with the goal of the study.

Paired values of 2-h creatinine clearance *versus* 22-h creatinine clearance were analyzed statistically using linear regression and the correlation coefficient (r value). The same analysis was applied to the components of the creatinine clearance estimation between the two collection times: serum creatinine in mg/dl, urine flow rate in ml/min, and urine creatinine in mg/dl. Urinary creatinine excretion in mg/24 h was derived from the urine creatinine concentration extrapolated to the total urine volume for 24 h. The correlation between urinary creatinine excretion during 22-h and 2-h collections was then analyzed.

RESULTS

Ninety-five paired samples of 22-h and 2-h creatinine clearances were obtained from 19 patients over a 2-month period. The patients represented a wide cross-section of serious clinical problems, with differing renal function (table 1). The mean age of the study group was 64.6 yr. Five patients died during the study.

There was a high positive correlation between 22-h and 2-h creatinine clearance (fig. 1), with a correlation coefficient, $r = 0.95$ ($P < 0.0001$). The correlation between the serum creatinine used in the two collections was extremely close ($r = 0.99$, $P < 0.0001$). This was anticipated, since the blood samples were drawn within an hour of each other. Correlation between urine creatinine estimations was only moderate ($r = 0.71$, $P < 0.0001$), and it was worse between urine flow rate measurements ($r = 0.57$, $P < 0.0001$). However, the correlation between the rates of urinary creatinine excretion was much higher ($r = 0.87$, $P < 0.0001$) (fig. 2).

In seven patients, creatinine clearance changed by more than 50% during the period of study. Three patients developed acute renal failure, with a creatinine clearance that decreased to less than 10 ml/min. Five patients had stable but poor renal function (creatinine

clearance less than 25 ml/min). One patient with severe hypertension, aorto-occlusive disease, and renal insufficiency was admitted to the surgical intensive care unit for preoperative stabilization. Preoperative creatinine clearance was approximately 60 ml/min. Renal artery revascularization was followed by a sharp deterioration in renal function, to a creatinine clearance of approximately 30 ml/min. In all these situations, the 2-h creatinine clearance tracked the 22-h creatinine clearance closely. The clinical information and implications provided by the two different collections were no different.

Discussion

This study confirms that, in a variety of critically ill, non-oliguric patients, creatinine clearance obtained from a 2-h timed catheter urine collection provides the same information about renal function as it does from a much longer collection time. The correlation between 22-h and 2-h creatinine clearance is high, whether renal function is static or changing, when urine flow rates are greater than 15 ml/h.

Use of the endogenous creatinine clearance as an index of GFR was first suggested in 1937. Over the decades, many authors have reported successful use of the creatinine clearance with urine collections lasting from 20 min to 24 h. However, with spontaneous voiding, a small amount of residual urine remains in the bladder. In order to reduce this collection error, many physicians feel that a long collection time (12–24 h) is necessary for accurate estimation of creatinine clearance. Nephrologists do not agree. In 1962, Tobias *et al.*[6] stated that ". . . duration of collection is not critical, (although) precise timing to the closest minute is essential." Catheterization of the bladder can be avoided if a good urine flow is induced by diuresis. Several studies have been reported using 1-h urine collections in uncatheterized patients.[5,7,8] It was found that the variability of 1-h collections is no greater than that of 24-h collections, as long as care is taken to empty the bladder. Collection errors are less likely if direct supervision is provided and urine flow kept high. In addition, the variability of 1-h collections diminishes as renal function declines.

A diurnal variation in creatinine clearance exists, which tends to provide higher values in the afternoon than the morning.[5] Wesson and Lauler[9] demonstrated that the daytime increase and nocturnal decrease in GFR could vary by up to 25% around mean values. It is not known whether this applies equally to critically ill patients, but it would seem prudent to perform short-collection creatinine clearance estimations at the same time each day to minimize diurnal variability. The fact that, in this study, 2-h creatinine clearances were all performed between 0800 and 1000 h each day may have contributed to the high correlation with 22-h measurements.

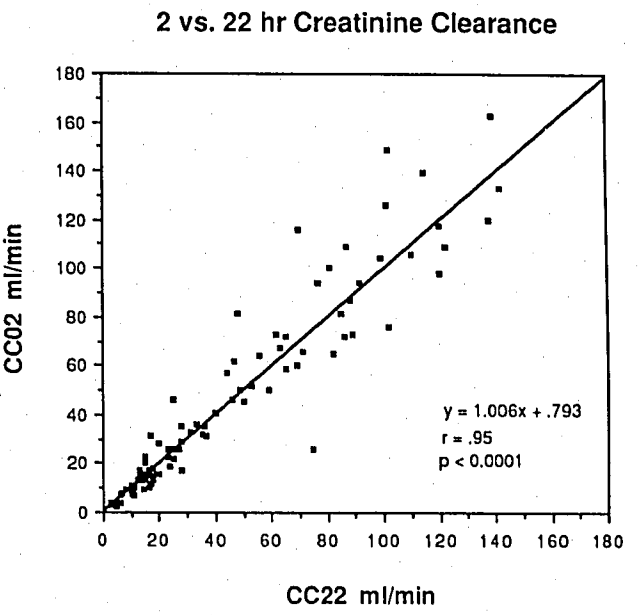

FIG. 1. Correlation between 2-h (CC-2) and 22-h (CC-22) creatinine clearance in ml/min. The line of regression is shown.

Examination of our individual patient data suggests that creatinine clearance derived from a long urine collection tends to "average out" rapid fluctuations in GFR. However, the urine collection is matched with a single blood sample, and if the serum creatinine is changing the creatinine clearance result could vary depending on when the blood sample is drawn. Ideally, it

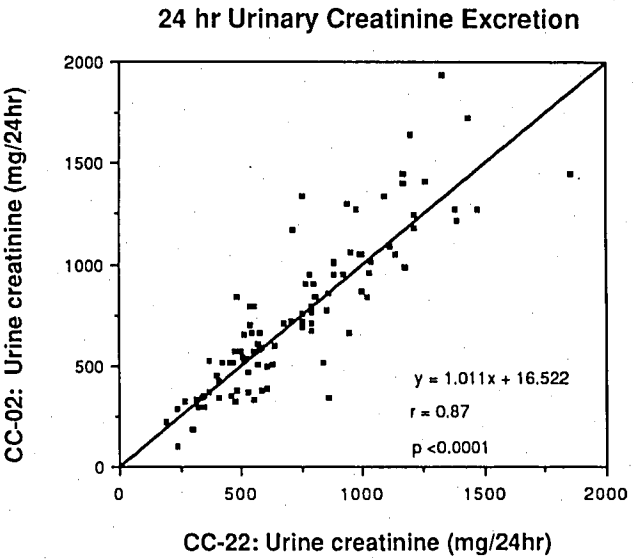

FIG. 2. Correlation of urinary creatinine excretion in mg/24 h between 22-h and 2-h creatinine clearance. The line of regression is shown.

should be drawn at the mid-point of the urine collection. In this study, a terminal blood sample was drawn for the 22-h creatinine clearance to diminish the discrepancies between serum creatinines and focus on the differences between the duration of urine collections. Although not addressed in this study, it is possible that a 2-h creatinine clearance might provide an earlier indication of changes in renal function than the longer, "averaged" collection.

Wilson *et al.*[10] collected 12 consecutive 2-h urine specimens for creatinine clearance in 30 surgical patients. Although they found a high correlation between 2-h and 24-h creatinine clearance ($r = 0.85$, $P < 0.001$), the collections were made in a single day and did not track the correlation over time, and through changing renal function. The differences that did exist appeared to be due to variability in urine output. When samples with similar urine flow were compared, the correlation was even higher ($r = 0.94$). They concluded that, since collection inaccuracies are more likely with longer collections, the volume of urine collected is not as important as the constancy of urine output.

Recently, Shin *et al.*[3] published a study based on 1-h urine collections in multiple trauma patients. They demonstrated that patients developing postoperative renal dysfunction or failure had a creatinine clearance of less than 25 ml/min 6 h after surgery, despite normal urine flow and blood pressure. Ironically, the authors commented that "one hour creatinine clearance is less accurate than twenty-four hour creatinine clearance because of the difficulty in accurately measuring urine flow rate." The present study would appear to make this apologia unnecessary.

As indicated in figure 1, 2-h and 22-h creatinine clearance correlated best when creatinine clearance was less than 50 ml/min—when, in fact, the information would be the most critical. The increased variability in creatinine clearance at higher levels may, in part, be due to the wide range of values in patients with normal renal function. Indeed, a fixed creatinine clearance within the lower limits of normal actually suggests renal dysfunction. Wilson[10] found that correlation between 2-h and 24-h creatinine clearance was highest when creatinine clearance was less than 80 ml/min: the largest differences were seen when the creatinine clearance was greater than 120 ml/min. Tobias *et al.*[6] reported a range of 88–148 ml/min (with serum creatinine varying from 0.9–1.5 mg/dl) in a single healthy individual over a 5-y period. Doolan[5] pointed out that the range of normal values of creatinine clearance is as wide as the range of normal values of body sizes. Creatinine clearance is usually related to body surface area, but this depends on weight, which fluctuates widely in critically ill patients. This impairs the sensitivity of single creatinine clearance estimations in lesser degrees of renal dysfunction. Serial determinations of creatinine clearance are preferred, since the rate of change, rather than a single value, is the best guide to prognosis.

In conclusion, this study suggests that creatinine clearance derived from a 2-h urine collection in nonoliguric patients provides the same clinical information as that derived from a much longer urine collection. The correlation in oliguric patients was not tested. It may be that a longer collection time is necessary at low urine flow rates. The patients represented a wide variety of clinical problems. Correlation was obtained in situations of both static and changing renal function. In seven patients, renal function changed by more than 50%, and three patients developed acute renal failure. Despite this, the correlation coefficient between 2-h and 22-h creatinine clearance was 0.95 ($P < 0.0001$). Of the components of the clearance calculation, urine flow rate and urine creatinine correlated poorly between groups, but correlation of urinary creatinine excretion was high. Two-hour creatinine clearance enables useful assessment of renal function to be performed in a rapid and convenient manner. Acceptance of the accuracy of short, carefully timed urine collections for creatinine clearance by anesthesiologists could improve assessment of renal function in the operating room and intensive care unit.

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