Postoperative Changes in Serum Creatinine

When Do They Occur and How Much Is Important?

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The objective of this study was to evaluate the use of the serum creatinine in following postoperative renal function. In this prospective study of 278 patients (mainly hypertensives and diabetics) undergoing noncardiac surgery, the serum creatinines were followed from the first through the sixth postoperative day. Creatinine clearances were evaluated before operation and on the fourth to fifth postoperative day. During the first six days after the operation, 23% (65 of 278 patients) had an increase of serum creatinine ≥ 20%. Such increases were sustained for ≥ 48 hours in 12% of the patients (32 of 278), and half of these patients had not returned to their initial level of renal function by the time of discharge. Patients who sustained such a deterioration were at risk for nonoliguric renal failure if they had a subsequent insult (*i.e.*, hypotension, reoperation, angiography, aminoglycosides.) Such increases occurred early in the postoperative period—on the first or second postoperative day. As judged by the creatinine clearances, postoperative increases of ≥ 20% in the serum creatinine identified most patients whose clearance fell more than 50%, although the serum creatinine did not accurately reflect changes in creatinine clearance among those patients who had undergone an amputation. It is concluded that the serum creatinine is useful in monitoring postoperative renal function. Of those patients who had postoperative increases in serum creatinine sustained for ≥ 48 hours, as many as one third had evidence of impairment in renal function at the time of discharge.

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MOST STUDIES of post-operative renal function have focused on trauma or cardiac surgery patients who have a high risk of postoperative renal failure.[1-4] Although there is substantial data documenting that glomerular filtration rate (GFR) decreases intraoperatively and immediately after noncardiac surgery,[5-11] there is surprising little data available about renal function after the first postoperative day. In the few studies that have followed renal function for more than 48 hours after noncardiac surgery, creatinine clearances were decreased on the first postoperative day, but by the fourth day were > 120% of baseline.[12-14]

Although the creatinine clearance is reasonably sensitive to changes in GFR, when measured routinely on inpatients, it has a 27% within-patient standard deviation, due to measurement error and biologic variability.[15] Usually, only the serum creatinine is routinely monitored. The serum creatinine has a small within-patient standard deviation (*e.g.*, 5%), but may not be sensitive enough to detect important deteriorations.[12,13]

In this prospective study of patients undergoing noncardiac surgery, serum creatinines were followed from the first to the sixth postoperative day in all patients, and creatinine clearances were evaluated before operation on the fourth to fifth postoperative day. The objectives of this study were to determine whether the serum creatinine is sufficiently sensitive to detect important deterioration in postoperative renal function and to identify the postoperative days when the risk of deterioration is highest.

Methods

Assembly of Population

This prospective study included 278 patients who underwent nonemergent general, vascular, or gynecologic surgery at New York Hospital between July 1982 and September 1985. Most of the patients were enrolled in one of several studies of the prognosis of hypertensives or diabetics undergoing noncardiac surgery. Basic demo-

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graphic and clinical data were recorded, including the patients' age, sex, race, and medications. The history of comorbid conditions such as diabetes, hypertension, documented renal insufficiency, ischemic heart disease, congestive heart failure, chronic pulmonary disease, cirrhosis, and cancer were recorded according to specific criteria.[16] A physical examination was performed in a standardized fashion, and the weight and height of the patient were recorded. Basic laboratory data including hemoglobin and hematocrit, blood urea nitrogen, electrolytes, and qualitative urine protein and glucose were recorded. In the analysis, proteinuria is defined as 2+ or greater on the Albustix.

Assessment of Serum Creatinine

Serum creatinines were fasting determinations. Serum creatinines were determined by an autoanalyzer using the Jaffe method.[17] The reproducibility of the serum creatinine is 2–5% when patients are stable.[18] Specimens were obtained on the first through seventh post-operative day or until discharge, reoperation, or death. For example, of the 278 patients, 262 patients were available for study (there had been one death, three reoperations, and twelve discharges) on postoperative Day 1; creatinines were obtained from 84% (221) of those patients who were eligible. Similarly, creatinines were obtained from 82% (221 of 255 patients) on Day 2, from 85% (199 of 236 patients) on Day 3, from 80% (171 of 217 patients) on Day 4, from 83% (161 of 195 patients) on Day 5, and from 73% (120 of 169 patients) on Day 6. Most of the decrement in the denominators was due to discharges; there were only three deaths and eleven reoperations within the first 7 days.

TABLE 1. *Clinical Characteristics of the Patients*

Characteristics	Percentage of Patients	Mean	Standard Deviation
Female	61		
Renal disease	8		
Hypertension	76		
Diabetes	38		
Congestive heart failure	17		
Peripheral vascular	30		
Angina	20		
Myocardial infarction	13		
Chronic bronchitis	16		
Cerebrovascular accident	12		
Cancer	10		
Cirrhosis	3		
Amputation	7		
Beta-blockers	22		
Digitalis	17		
Diuretics	32		
Intra-abdominal	36		
Aortic aneurysm repair	10		
Peripheral vascular	22		
Other procedures	32		
Age		63.1 yrs	±13.3
Pre-operative weight		75.5 kg	±46.4
Lean body weight		49.5 kg	±15.1
Serum creatinine		1.2 mg/dl	±0.6
Urinary creatinine		13.6 mg/kg/24h	±10.1
Clearance		61.3 ml/min/1.73m^2	±27.9

Assessment of Creatinine Clearance

Creatinine clearances were performed before and after the operation. Clearances were based on 24-hour volumes in 93% of the patients and on 12- or 18-hour volumes in 7%. Serum and urine creatinines were determined by an autoanalyzer using the Jaffe method.[17] Postoperative clearances were begun on the morning of the fourth postoperative day. The mean of the serum creatinine from the fourth and fifth postoperative day was used to calculate the postoperative clearance. All reported clearances were corrected for surface area by dividing the calculated surface area by 1.73 m^2; body surface area was calculated using the following formula: 0.02352 height (in cm)$^{0.42246}$ weight (in kg)$^{0.51456}$.[19] Post-operative clearances were adjusted for any change in weight that occurred after the operation.[20] Lean body weight was calculated using the method of Hume.[21]

Preoperative clearances were obtained on 76% (211) of the 278 patients. Postoperative clearances were obtained on 169 of 217 patients (79%) of those eligible (*i.e.*, those who had not been discharged). Pre- and postoperative clearances were available on 135 patients or 62% of those eligible. Work-up bias would have occurred if the characteristics of those patients who had postoperative clearances differed from those who did not. For example, work-up bias would have occurred if patients who had increased creatinines on the first, second, or third postoperative day were found to have significantly more postoperative creatinine clearances performed. To evaluate the possibility of work-up bias,[22] the occurrence of an increase in serum creatinine on postoperative Day 1, 2, or 3 was evaluated as potential predictors of whether postoperative clearances were performed. Logistic regression, using whether or not postoperative clearances were performed as the dependent variable, revealed that increases in the serum creatinine on postoperative Days 1, 2, or 3 did not predict whether a clearance was done. Similarly, comorbid diseases, age, creatinines, and other characteristics listed in Table 1 were examined as predictors of whether a postoperative clearance had been done. Only patients who had abdominal surgery were more likely to have postoperative clearances performed ($p < 0.04$).

Data Analysis

Life table methods were employed to calculate the daily and cumulative risk of increased serum creatinine.[23] In this analysis, patients who were discharged, who died, or

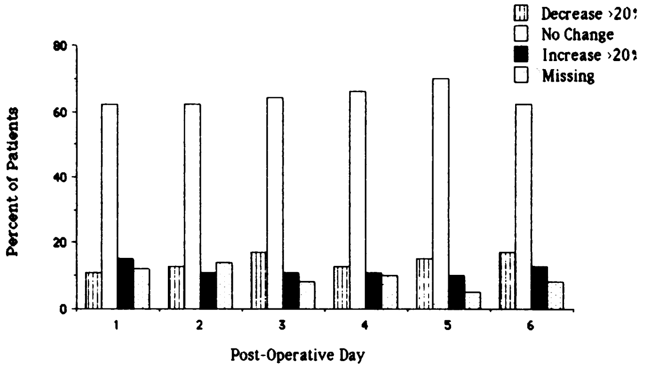


FIG. 1. Changes in serum creatinine according to postoperative day. Proportion of patients with ≥ 20% increase or decrease (or no change) from baseline on any given postoperative day.

who had undergone a reoperation were handled by regarding the patient as 'withdrawn alive' at that time, as is standard with life table techniques.[23] Multiple logistic regression was used to analyze binary outcomes (*i.e.*, to identify the characteristics of patients likely to have a sustained increase in creatinine after the operation). The LOGIST program in SAS was employed.[24] Multiple regression was performed using the General Linear Models program in SAS.[25]

Results

Timing and Extent of Postoperative Changes in Serum Creatinine. The patients ranged in age from 19 to 90 years; their mean age was 63 years. Seventy-six per cent of the patients had hypertension and 38% had diabetes. As shown in Table 1, cardiac comorbidity was common. Eight per cent of the patients had renal disease documented before to admission.

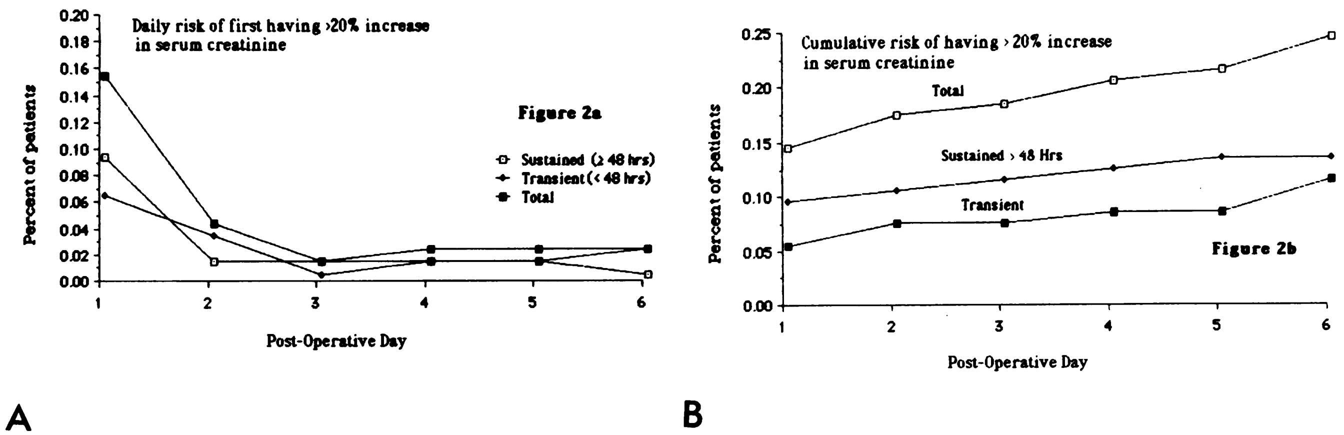
Figure 1 shows the percentage of patients who had either decreases of ≥ 20%, increases of ≥ 20%, or no change in serum creatinine in relation to their baseline level on each postoperative day. On any given postoperative day, the majority of patients had no change in their serum creatinine. On most days, 10–15% of patients had an increase in serum creatinine and 10–15% had a decrease. The remainder of the analysis will focus on patients who had a ≥ 20% increase in serum creatinine after the operation.

During the first six postoperative days, 23% of the patients (65 of 278) had a ≥ 20% increase in serum creatinine. In about half of the patients (32 of 65), the increase was sustained for 48 hours or more. If these patients experienced an additional insult (*e.g.*, angiography, reoperation, sepsis, aminoglycosides, hypotension) within the first 10 days after the operation, all went on to have subsequent further deterioration in renal function. Twenty-eight per cent of the patients (9 of 32) with sustained increase did have further deterioration in renal function. Two patients had renal failure with transient oliguria.[26]

The highest risk of an increased creatinine (15%) occurred on the first postoperative day (Fig. 2A). By the second day, the risk had dropped to 5%. On the third day and thereafter, the overall risk of *first* having an increased creatinine dropped to 3–4% per day. The timing was similar for patients with sustained and transient increases in creatinine (Fig. 2A). The peak risk of both transient and sustained increases occurred on the first postoperative day. Figure 2B shows the cumulative risk of having an increase in serum creatinine. Clearly the majority of patients who had postoperative increases in creatinine experienced their first elevation on the first postoperative day.

Postoperative Changes in Clearances Versus *Changes in Serum Creatinine*

Under usual clinical circumstances, the variation in the creatinine clearance on repeated determinations has been shown to be as high as 27%.[15,18,27] Therefore, a change of 50% was chosen to represent a clinically important increase or decrease in clearance. Figure 3 shows the rela-



FIGS. 2A and B. Risk of first having a ≥ 20% increase in serum creatinine: daily and cumulative risk.

tionship of the preoperative clearances to the postoperative clearances. Lines are drawn to delineate patients with the following postoperative changes in creatinine clearance: 50% increase, 30% increase, 20% increase, 20% decrease, 30% decrease, and 50% decrease. Among those patients who had postoperative clearances, 17% of the patients (24 of 135) had a ≥ 50% increase in clearance on postoperative Days 4 and 5, and 11% (15 of 135 patients) had a 50% decrease in clearance. Seventy-one per cent of the patients did not have an increase or decrease of ≥ 50% in clearance.

The changes in clearance among the seven patients who had undergone amputations above or below the knee were not accurately reflected by changes in the serum creatinine. For example, two of these patients had a 50% decrease in their clearance in the face of a decrease in their serum creatinine. Although the numbers are small, caution should be exercised in interpreting postoperative serum creatinines in such patients; an unchanged or improved serum creatinine may mask actual deterioration in renal function after amputation.

Figure 4 shows the receiver-operating characteristic curves for whether or not a decrease of ≥ 50% in the postoperative creatinine clearance (on Days 4 and 5) was reflected by simultaneous changes in the serum creatinine. Patients who underwent amputation are omitted. Figure 4A show the ability of different proportionate increases in the serum creatinine to detect a ≥ 50% decrease in the creatinine clearance. Using the cut-off of a 60% increase in serum creatinine, 50% of patients will have a ≥ 50% decrease in creatinine clearance (true-positive rate), and the false-positive rate would be 2%. At a cut-off of 50%, the true-positive rate will be 50%, and the false positive rate will be 4%. Figure 4B shows the ability of absolute increases in the serum creatinine to detect a ≥ 50% decrease in creatinine clearance. With an increase of 0.4 mg/dl, the true-positive rate is 67%, and the false-positive rate is 3%.

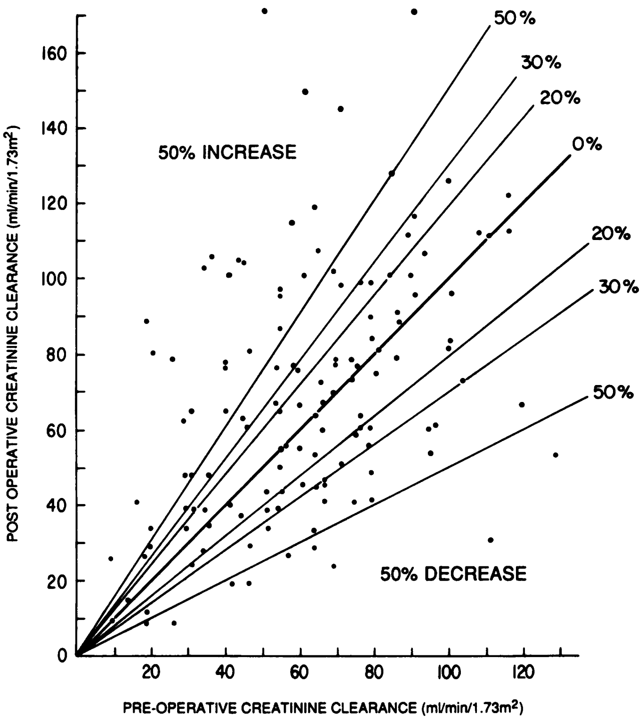
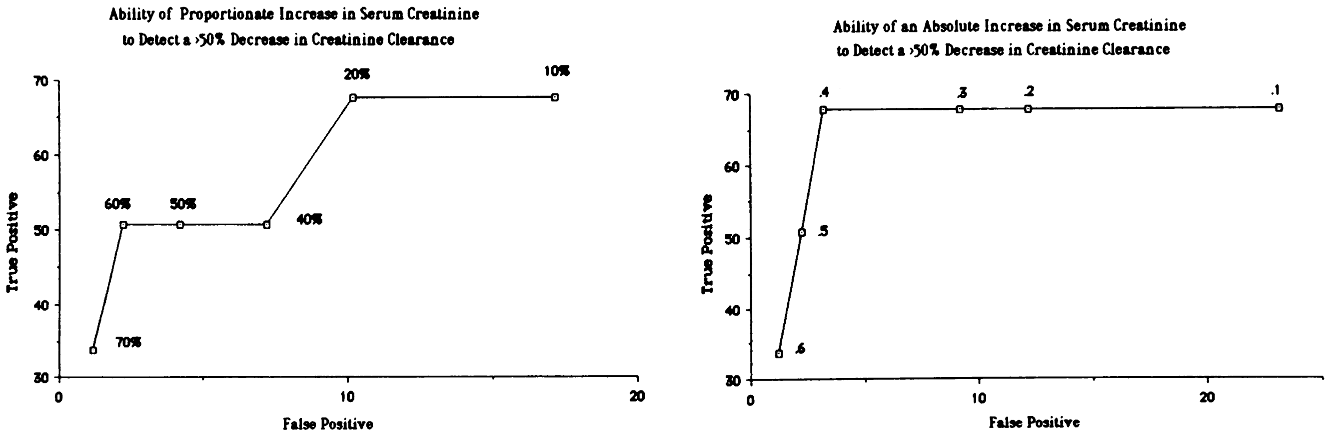


FIG. 3. Preoperative *versus* postoperative creatinine clearances.

Longer-Term Consequences of Immediate Increases in Postoperative Serum Creatinines

In order to create a context in which to analyze the immediate postoperative increases in serum creatinine, the patient's serum creatinine at discharge was compared with their baseline preoperative level. Fourteen patients



FIGS. 4A and B. (A) Ability of proportionate changes and (B) absolute changes in postoperative serum creatinine to identify patients with a clinically important decrease in creatinine clearance. (Receiver-operating characteristic curve for detection of a > 50% decrease in creatinine clearance on postoperative Days 4 and 5). Postoperative clearances obtained on Days 4 and 5 *versus* preoperative clearances are compared to changes from baseline to postoperative serum creatinines (mean of creatinine on Days 4 and 5). Patients with amputations are omitted (see text).

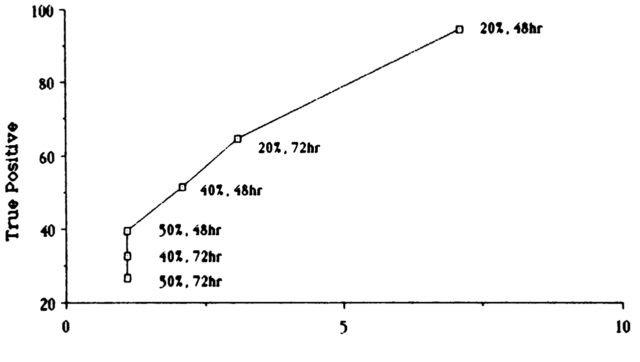


FIG. 5. Ability of different proportionate increases in serum creatinine of different durations to predict patients with a ≥ 50% increase in serum creatinine at discharge.

had serum creatinines that had increased 50% or more over baseline at discharge, and another four had increases of 33–49%. The mean length of stay for these patients was 16.7 ± 8.6 days. For the majority of these patients (15 of 18), the increases in serum creatinine had begun within the first six postoperative days. To determine the optimal magnitude and duration of increased serum creatinine for identifying patients who would have such persistently increased serum creatinine at dischange, a receiver-operating characteristic curve was used. Figure 5 shows the true-positive and false-positive rates for increases in serum creatinine of various magnitudes and durations. Increases of ≥ 20% in creatinine lasting 48 hours or more had a true-positive rate of 93% and a false-positive rate of 7%. The positive predictive value was 46%, and the negative predictive value was 99%.

Discussion

With inhalation or spinal anesthetics, a decrease of 30–50% in glomerular filtration rate occurs probably because of systemic hemodynamic changes—specifically, a fall in mean arterial pressure with a resultant decrease in renal blood flow.[5-11,28,29] If the patient is volume depleted, the decreases in glomerular filtration rate are significantly greater.[30,31] Most of the studies of postoperative renal status have focused on those patients who developed acute oliguric renal failure after cardiopulmonary bypass or aortic cross-clamping.[1-4] Methods of preventing or attenuating the insult to the kidneys have been studied in these specific circumstances.[4,32,33] Recent work has suggested that with current cardiopulmonary bypass techniques, nonoliguric acute renal failure has become more common than oliguric renal failure[3] and that those cardiac surgical patients who experience an early postoperative renal deterioration and who experience a subsequent insult (*e.g.*, reoperation, hypotension, and aminoglycosides) may be at high risk for later nonoliguric failure.[3]

In the setting of noncardiac surgery, there are only a few studies that document in small numbers of patients the magnitude or sequence of changes that occur after operation.[12-14,34] In one study of 17 patients who had undergone cardiac or abdominal surgery, the clearance dropped by about 30% on the first postoperative day and rose to levels that were 110–150% of baseline values by the fourth postoperative day.[13] In another study of 17 volunteers who underwent anesthesia either with enflurane or halothane but who did not undergo surgery, creatinine clearance decreased intraoperatively but subsequently increased to values higher than those that existed before anesthesia.[14] The largest study of patients who underwent surgery for cancer (68 patients, mean age of 55 years) demonstrated that about 60% of patients had a decrease in clearance of ≥ 20% on the first postoperative day, but that only 16% continued to have such a decrease on postoperative Day 4.[12] By the fourth postoperative day, one quarter of the patients had increases to 120% or more of baseline clearances Thus, our findings of increased clearances on postoperative Day 4 confirm earlier findings.[12-14]

In clinical practice, because inulin clearance (the true gold standard for renal function) is almost never measured and creatinine clearances are rarely performed, the issue is whether changes in serum creatinine can be used to identify patients who have had an important deterioration in renal function. We selected apriori a 20% increase in serum creatinine as indicative of a potentially important change. This magnitude is clearly beyond the usual intrapatient variability in serum creatinine.[30,35,36] Patients were serially followed to ascertain who developed clinically important dysfunction or failure.

Most of the important deterioration began within 48 hours after the operation. In considering the sequence of changes after operation, it should be noted that deterioration in function may take longer to be noted than improvement.[20] As creatinine clearance decreases, the half-life of serum creatinine increases, so that a 50% decrease in clearance leads to a doubling of the serum half-life.[20] Because it takes over three half-lives to establish a new equilibrium, it takes longer to reach an equilibrium with decreasing rather than increasing renal function; thus, with a 50% decrease in renal function it may take 36 hours to reach a new equilibrium, but with an increase of 50%, it less than 12 hours are required.[20,37]

Attempts to evaluate the utility of the serum creatinine for monitoring postoperative renal function are important for several reasons. Postoperative acute renal failure has been reported in as many as 10% of the patients undergoing major elective surgery.[38-40] This complication is associated with prolonged hospitalization and increased mortality.[3,33] For the small percentage of patients who develop frank failure, there is a larger proportion of patients who have less dramatic damage.[3] Twelve per cent of the patients had sustained increases in creatinine after noncardiac surgery. As reported previously, patients who experienced an early deterioration in renal function and who were subsequently exposed to a second insult (*e.g.*, reoperation, angiography, hypotension, and sepsis) tended to have substantial and sustained subsequent deterioration.[3] The study of the entire spectrum of changes in postoperative renal function may help to elucidate etiologically important factors. Some patients had a significant decrease in renal function without an increase in the serum creatinine; this was especially true among patients who had undergone amputation. Among such patients, stable or decreasing serum creatinines can occur, despite important decreases in creatinine clearances, and therefore actual clearances should be measured.

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