

From the Southern Association for Vascular Surgery

Glomerular filtration rate is superior to serum creatinine for prediction of mortality after thoracoabdominal aortic surgery

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Background: Clinically evident renal disease (dialysis, history of renal insufficiency, or serum creatinine >2.0 mg/dL) is a known risk factor for mortality after thoracoabdominal aortic aneurysm repair. We extended this concept to the questions of whether subclinical renal disease is also a risk factor and how best to identify subclinical disease. We hypothesized that the glomerular filtration rate (GFR) would be a more sensitive determinant of renal function than serum creatinine alone.

Methods: Between 1991 and 2004, we repaired 1106 thoracoabdominal aortic aneurysms and descending thoracic aortic aneurysms. The median age was 67 years. There were 400 (36%) women and 706 (64%) men. We estimated GFR by using the Cockcroft-Gault equation. We divided baseline serum creatinine and baseline GFR into quartiles and estimated the association of the quartiles with 30-day postoperative mortality by χ^2 testing. We further subdivided the population into patients with and without clinically evident renal disease and repeated the analysis in the patients without clinically apparent disease ($n = 869$).

Results: Clinically apparent renal disease was highly associated with 30-day mortality (odds ratio, 3.2; $P < .0001$). In all patients, serum creatinine quartile and GFR quartile were also both highly significantly associated with 30-day mortality ($P < .0001$). In patients without clinically apparent renal disease, both creatinine and GFR predicted additional mortality, but GFR was a much stronger predictor ($P < .02$ for creatinine vs $<.0001$ for GFR). In these patients, mortality ranged from 5% in the best GFR quartile to 27% in the worst. Taken as continuous variables in logistic regression equations, serum creatinine had no discrimination in patients without clinical disease ($P = .73$), whereas GFR remained strong ($P <.0001$).

Conclusions: Preoperative renal function is an important determinant of early mortality even in patients without clinically evident disease. Estimated GFR is a much more powerful determinant of mortality risk than serum creatinine alone. (*J Vasc Surg* 2005;42:206-12.)

Surgical repair remains the gold standard treatment for thoracoabdominal aortic aneurysms (TAAA; Fig 1). Chronic renal disease is a known risk factor for increased mortality and morbidity after this type of surgery.^{1,2} Renal failure requiring dialysis is the most visible outcome of chronic renal disease. In the United States, more than 320,000 patients have end-stage renal disease treated by dialysis every year.³ The prevalence of earlier stages of chronic renal disease is even higher.⁴ Despite advances in surgical techniques and organ protection, renal failure remains a vexing problem in the surgical treatment of TAAAs.^{1,2,5,6} Published reports on thoracoabdominal aortic surgery have had varying definitions of renal disease.^{5,7-9} Most authors have used serum creatinine as a crude index of

renal function.^{1,5,8,10} We have previously defined preoperative chronic renal disease as a requirement for dialysis, serum creatinine greater than 2.0 mg/dL, or a history of renal insufficiency.^{1,2,5,6}

According to the recent guidelines of the National Kidney Foundation for assessing kidney disease, estimates of glomerular filtration rate (GFR) are the best overall indices of the level of renal function.⁴ Serum creatinine alone is not an accurate index of GFR. The level of GFR should be estimated from prediction equations that, in addition to the serum creatinine concentration, take into account some or all of the following variables: age, sex, race, and body size.⁴ The Cockcroft-Gault equation is the most commonly used equation to estimate GFR.^{4,11} We hypothesized that estimated GFR would be a more sensitive determinant of renal function than serum creatinine alone in predicting patient outcome after TAAA surgery. In this study, we evaluated how best to identify subclinical renal disease and whether subclinical renal disease is also a risk factor for 30-day mortality in patients undergoing TAAA surgery.

MATERIALS AND METHODS

Between 1991 and 2004, we repaired 1106 TAAAs and descending thoracic aortic aneurysms. Seven hundred six

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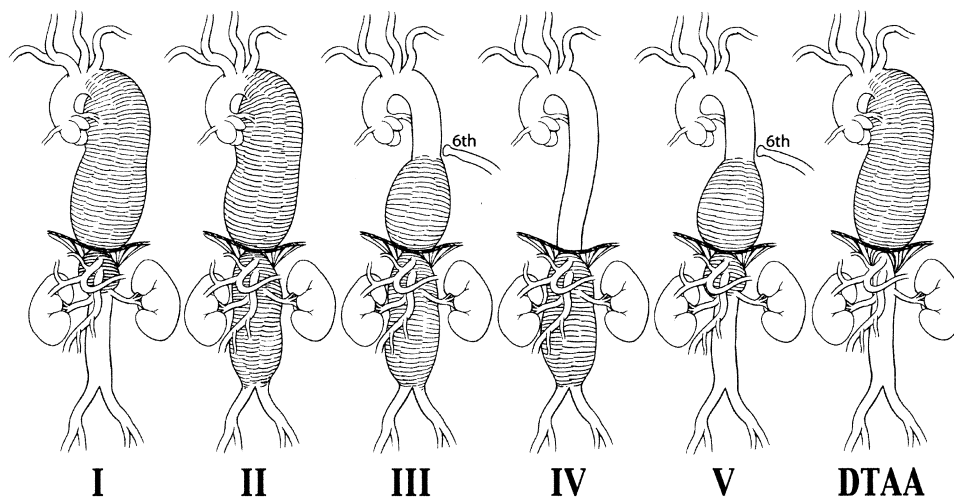


Fig 1. Classification of thoracoabdominal aortic aneurysms. Extent I, distal to the left subclavian artery to above the renal arteries. Extent II, distal to the left subclavian artery to below the renal arteries. Extent III, from the sixth intercostal space to below the renal arteries. Extent IV, the 12th intercostal space to below the renal arteries (total abdominal aortic aneurysm). Extent V, below the sixth intercostal space to just above the renal arteries. *DTAA*, Descending thoracic aortic aneurysm.

(64%) were men, and 400 (36%) were women. The median age was 67 years (range, 8-90 years). We estimated GFR by using the Cockcroft-Gault equation^{4,11}:

$$(140 - \text{age}) \times \text{weight}/72 \times \text{serum creatinine}$$

where age is in years, actual body weight is in kilograms, and serum creatinine is in milligrams per deciliter. For women, the equation is multiplied by 0.85.^{4,11} We divided the baseline preoperative serum creatinine level and estimated GFR into quartiles, and then we evaluated the association of the quartiles with 30-day mortality by χ^2 in all patients. Clinically evident renal disease is now defined as a serum creatinine level greater than 1.5 mg/dL on admission, a history of renal insufficiency, or a requirement for dialysis. A history of renal insufficiency refers to a medical record documentation, the patient's giving a history of renal insufficiency, or a previous requirement for dialysis. Patients are deemed without clinically evident renal disease if they do not have any of these characteristics. We then repeated the analysis in patients without clinically evident renal disease.

Our operative technique for repairing TAAAs and descending thoracic aortic aneurysms has been described previously.^{1,5,6,12} In brief, since 1992 we have used adjunct distal aortic perfusion, cerebrospinal fluid drainage, and moderate hypothermia (33°C-34°C) in all patients except those with complications. These include hemodynamic instability due to rupture of the aneurysm, active infection, and severe coagulopathy. Cerebrospinal fluid pressure is maintained at less than 10 mm Hg throughout the operation and for 3 days after surgery by using a lumbar drain placed percutaneously in the third or fourth lumbar space immediately before surgery. To achieve distal aortic perfu-

sion, we cannulate the left atrium through the left inferior pulmonary vein or atrial appendage. We attach a BioMedicus pump (Minneapolis, Minn) with an in-line heat exchanger to this cannula. We then establish arterial inflow by cannulating the left common femoral artery or, if the femoral artery is not accessible, the distal aorta. To minimize the ischemic time to the spinal cord, viscera, and kidneys, we use a sequential cross-clamping technique. Other adjunctive measures include the use of visceral and renal perfusion with cold blood or a crystalloid solution to decrease the renal temperature to less than 15°C (Fig 2).

Data collection for this study was approved by the Committee for the Protection of Human Subjects (Institutional Review Board) of the University of Texas Health Sciences Center at Houston. Data were collected prospectively by a trained master's level research nurse and entered into our specially designed Microsoft Access database (Microsoft Corp, Redmond, Wash). On occasion, missing data were abstracted retrospectively by reviewing patients' medical records. Data were entered into the database and stored on a secure server. Analyses were conducted by using SAS software version 8.2 (SAS Institute, Cary, NC) running under Windows XP Professional (Microsoft). Univariate statistics were computed by using contingency table methods (Tables I and II). Multivariate analysis was performed by using multiple logistic regression (Table III). Continuous data were divided into quartiles for contingency table analysis and were also evaluated in their continuous form by univariate logistic regression. The preoperative serum creatinine level was the level obtained on the day of admission. Preoperative GFR was calculated according to the Cockcroft-Gault equation, by using the serum creatinine and weight on admission. Baseline serum creatinine and GFR

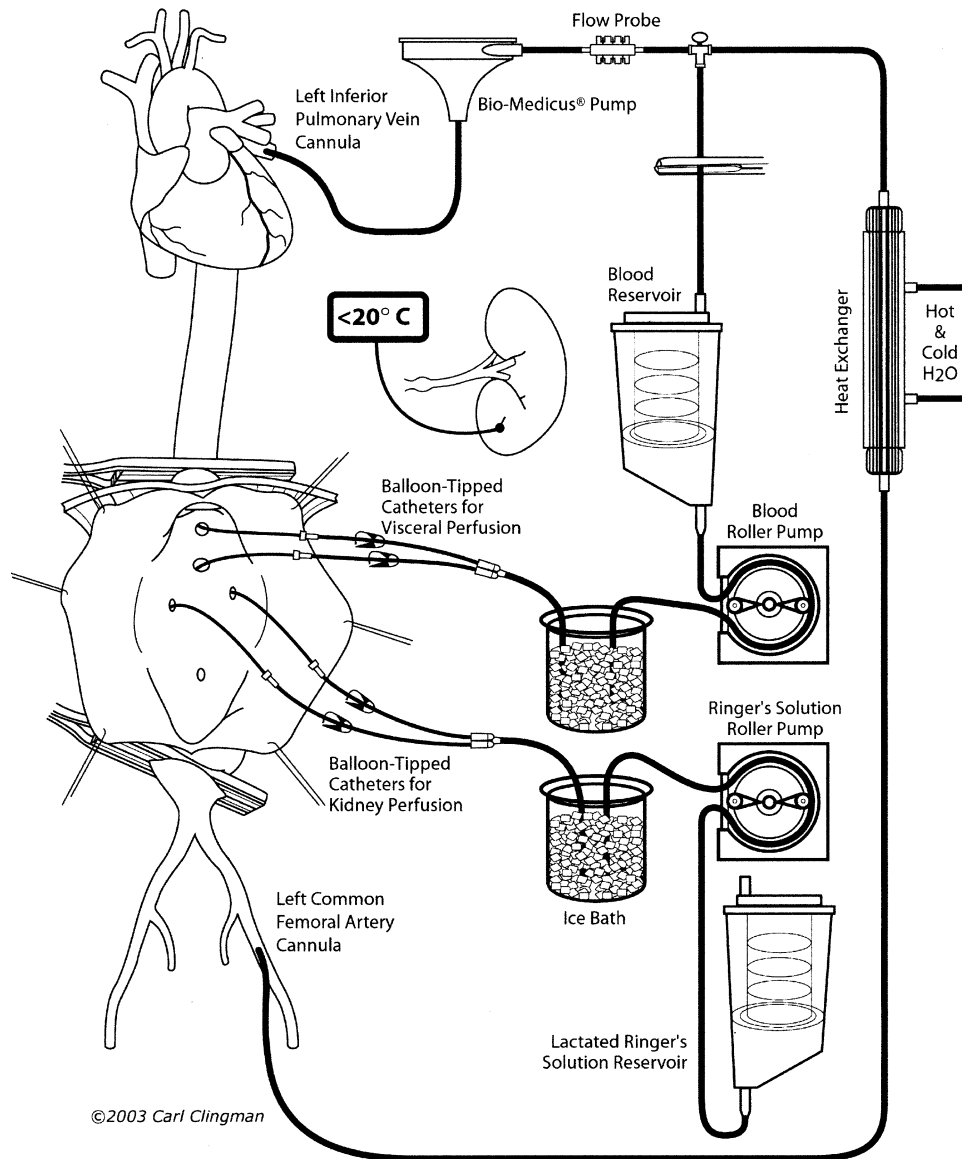


Fig 2. Visceral and renal perfusion. The BioMedicus pump circuit is set up to perfuse the celiac axis, superior mesenteric artery, and renal artery with cold blood (or crystalloid solution) and, at the same time, warm blood to the lower extremities to maintain body temperature at 33°C to 35°C .

were compared across aneurysm extents by using one-way analysis of variance (Tables IV and V). Changes from preoperative to postoperative serum creatinine and GFR were also evaluated by analysis of variance (Tables VI and VII). The highest postoperative creatinine level was used in this subgroup analysis. The null hypothesis for statistical tests was rejected at $P < .05$.

RESULTS

Our 30-day mortality was 14.6% (162/1106). Aneurysm rupture and pre-existing renal disease were strong predictors for mortality (Table I). There was no difference in mortality between women and men. Acute dissection,

redo surgery, and aneurysm extent were not significant risk factors for death. In all patients, baseline serum creatinine quartile and GFR quartile were both highly significantly associated with 30-day mortality ($P < .0001$). In patients without clinically apparent renal disease, both serum creatinine and GFR predicted additional mortality, but GFR was a much stronger predictor ($P < .02$ for creatinine vs $< .0001$ for GFR). In these patients, mortality ranged from 5% in the best GFR quartile to 27% in the worst. Mortality also correlated strongly with worsening renal disease, in relation to the severity stages defined by the National Kidney Foundation (Table II). Taken as continuous variables in logistic regression equations, serum creatinine had no discrimina-

Table I. Univariate analysis of risk factors for 30-day mortality

Variable	No. patients (%)	No. Deaths (%)	Odds ratio*	95% CI†	P value‡
Overall	1106 (100.0)	162 (14.6)			
Female	400 (36.2)	65 (16.3)	1.21	0.87-1.71	.26
Male	706 (63.8)	97 (13.7)	1		
COPD	363 (32.8)	59 (16.3)	1.21	0.85-1.71	.29
No COPD	743 (67.2)	103 (13.9)	1		
Acute					
Dissection	45 (4.1)	7 (15.6)	1.08	0.47-2.46	.86
Otherwise	1061 (95.9)	155 (14.6)	1		
Extent II	215 (19.5)	38 (17.7)	1.33	0.89-1.98	.17
Other extents	891 (80.5)	124 (13.9)	1		
Rupture	73 (6.6)	24 (32.8)	3.18	1.89-5.34	.0001
Intact	1033 (93.4)	138 (13.4)	1		
Redo	72 (6.5)	14 (19.4)	1.45	0.79-2.66	.24
Primary	1034 (93.5)	148 (14.3)	1		
Adjunct§	823 (74.4)	115 (13.9)	0.82	0.56-1.18	.28
No adjunct	283 (25.6)	47 (16.6)	1		
Renal disease	237 (21.4)	67 (28.3)	3.21	2.25-4.57	.0001
No renal disease	869 (78.6)	95 (10.9)			
GFR (mL/min)¶					
<49	223 (24.3)	62 (27.8)	.98	.97-.99	.0001
49-64	228 (24.9)	40 (17.5)			(.0001)
65-90	232 (25.3)	23 (9.9)			
>90	234 (25.5)	13 (5.6)			
Creatinine (mg/dL)‡					
<0.9	361 (35.6)	36 (9.9)	1.02	.99-1.04	.0001
0.9-1.1	242 (23.8)	33 (13.6)			(.30)
1.2-1.4	201 (19.9)	25 (12.4)			
>1.5	210 (20.7)	59 (28.1)			

CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate.

*For dichotomous variables, the odds ratio represents a test against a reference category whose referent odds ratio is 1. For continuous data, the odds ratio refers to the increase in odds associated with a one-unit increase in the variable value. Although continuous data are presented in quartiles, the odds ratios are against the continuous variable.

†This reflects the units against which its companion odds ratio is computed. Confidence intervals are test based.

‡P indicates the probability of type I statistical error (common P value). Values without parentheses are Pearson Chi-square probabilities. Probability values in parentheses are univariate logistic regression likelihood ratio p values.

§Adjunct includes combined distal aortic perfusion, cerebrospinal fluid drainage, and moderate hypothermia.

¶GFR was estimated by using the Cockcroft-Gault equation; GFR could not be computed for 189 cases.

‡Creatinine data were not available for 92 cases.

Table II. Thirty-day mortality according to stages of kidney disease

Stage*	GFR (mL/min per 1.73 m ²)†	No. Patients (%)	No. Deaths (%)	P value‡
1	>90	239 (25.8)	13 (5.4)	.0001
2	60-89	290 (31.3)	37 (12.8)	
3	30-59	324 (35.0)	70 (21.6)	
4	15-29	41 (4.4)	12 (29.3)	
5	<15 or dialysis	32 (3.5)	12 (37.5)	

GFR, Glomerular filtration rate.

*Stages are defined according to the National Kidney Foundation.

†GFR could not be computed for 189 cases.

‡P indicates the probability of type I statistical error (common P value) by Pearson χ^2 .

tion in patients without clinical disease ($P = .73$), whereas GFR remained a strong predictor ($P = .0001$). In multiple logistic regression analysis, only rupture and GFR were significant predictors of early mortality (Table III). Creatinine was not significant in this model. Plotting preoperative serum creatinine vs GFR (Fig 3) showed that GFR misses an abnormal creatinine in only 2 occurrences (two

boxes), but creatinine misses an abnormal GFR 572 (71%) of 804 times. That is, when creatinine is normal, GFR is abnormal 71% of the time in this population.

When mortality was evaluated according to these thresholds, it was 94 (11.7%) of 804 among patients with normal creatinine, compared with 13 (5.6%) of 234 among those with normal GFR. Further analysis of renal function

Table III. Multiple logistic regression model effect of variables on mortality

Variable	Parameter estimate	Odds ratio	95% CI	P value
Intercept	-0.2717			
GFR	-0.0233	0.98	0.97-0.99	.0001
Creatinine*	-0.0326	0.97	0.89-1.05	.4255
Rupture	0.9665	2.63	1.42-4.86	.003

CI, Confidence interval; GFR, glomerular filtration rate.

*The term for creatinine would ordinarily be positive (increasing mortality with increasing creatinine), but it is not significant, and the confidence interval overlaps the null value of 1.0.

Table IV. Glomerular filtration rate by aneurysm extent

Extent	Mean GFR (mL/min per 1.73 m ²)	Lower CI	Upper CI
I	67.6	62.7	72.5
II	71.6	66.5	76.6
III	68.2	60.4	76.0
IV	66.0	60.0	72.0
V	65.0	55.4	74.6
Descending*	80.5	76.3	84.7

GFR, Glomerular filtration rate; CI, confidence interval.

*Significantly greater GFR ($P < .008$) than all other extents.

Table V. Serum creatinine by aneurysm extent

Extent	Mean creatinine (mg/dL)	Lower CI	Upper CI
I	1.24	0.64	1.84
II	1.39	0.78	2.00
III	1.38	0.42	2.33
IV*	2.24	1.51	2.96
V	1.18	-0.04	2.40
Descending	1.57	1.06	2.08

CI, Confidence interval.

*Significantly ($P < .04$) greater than extent I.

Table VI. Change in preoperative to postoperative GFR by aneurysm extent

Extent	GFR change from before surgery (mL/min per 1.73 m ²)	Lower CI	Upper CI
I	-8.8	-14.2	-3.4
II*†	-20.1	-25.9	-14.3
III*†	-24.1	-33.1	-15.2
IV*†	-21.3	-28.0	-14.6
V	-11.0	-21.6	-0.5
Descending	-5.5	-10.2	-0.8

GFR, Glomerular filtration rate; CI, confidence interval.

*Significantly ($P < .006$) worse than extent I.

†Significantly ($P < .0004$) worse than descending.

according to the extent of the aneurysms showed that the patients with descending thoracic aortic aneurysms had the highest preoperative GFR compared with all other TAAA extents (Table IV). After surgery, these patients also had

Table VII. Change in preoperative to postoperative serum creatinine by aneurysm extent

Extent	Creatinine change from before surgery	Lower CI	Upper CI
I	0.45	-0.23	1.12
II*	0.97	0.26	1.69
III	1.08	-0.04	2.20
IV	-0.02	-0.86	0.81
V	0.73	-0.63	2.08
Descending	-0.02	-0.61	0.56

CI, Confidence interval.

*Significantly ($P < .05$) worse than descending.

the best preserved GFR, as compared with significant decreases in GFR for TAAA extents II, III, and IV (Table VI). Conversely, the highest preoperative serum creatinine level was found in patients with extent IV (Table V), and the postoperative changes in serum creatinine did not correlate with the TAAA extent (Table VII).

DISCUSSION

Major advances have been made in the surgical treatment of TAAAs. The high incidence of paraplegia and paraparesis after TAAA surgery during the cross-clamp-and-sew era has been markedly reduced by using adjunct cerebrospinal fluid drainage, distal aortic perfusion, and passive moderate hypothermia, particularly in patients with extent II.¹ Chronic renal disease remains an important risk factor for mortality and morbidity.^{1,2,8} We have identified that patients with known pre-existing renal disease are at higher risk for 30-day and late mortality and also have an increased incidence of immediate and delayed neurologic deficits.^{1,2,5,13-15} Accordingly, we have shifted our attention to the evaluation of preoperative renal disease and its effect on patient outcome.

In this study, we confirmed that preoperative renal disease is an important predictor of 30-day mortality for TAAA surgery. In addition, we uncovered that subclinical renal disease is prevalent in our patient population, with mean GFR ranging from 65 to 80 mL/min per 1.73 m² (stage 2: mild to moderate renal disease) across all TAAA extents and descending thoracic aortic aneurysms.⁴ Using serum creatinine levels of greater than 1.5 mg/dL as a marker for renal disease would fail to detect almost three quarters of patients with decreased GFR (<90 mL/min).

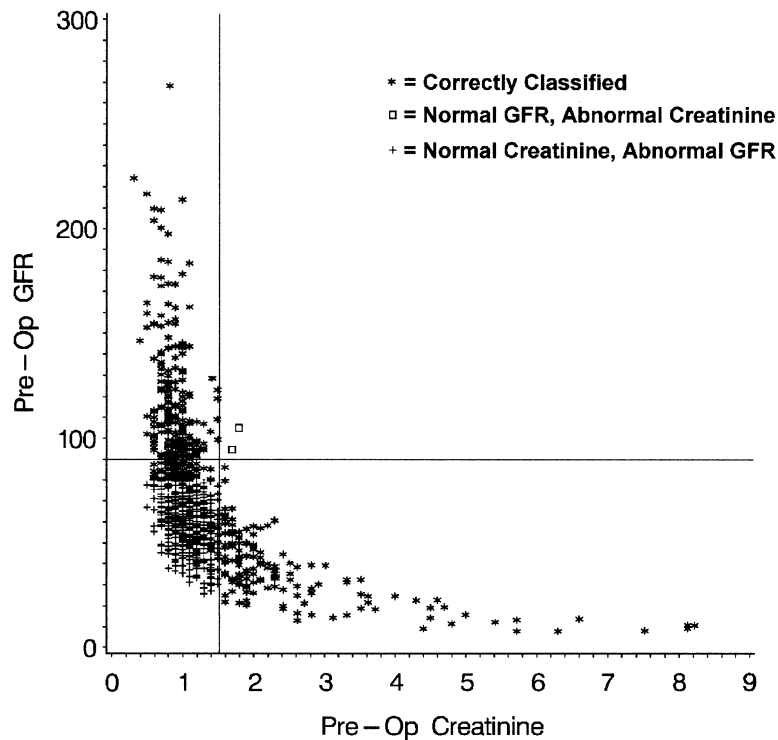


Fig 3. Glomerular filtration rate (GFR) vs serum creatinine. Reference lines are at normal values: creatinine 1.5 mg/dL and GFR 90 mL/min. *Correctly classified by both tests; + normal creatinine and abnormal GFR; □ = normal GFR and abnormal creatinine. Creatinine misses abnormal GFR in 71% of cases. *Pre-op*, Preoperative.

Furthermore, even the presence of mild to moderate preoperative renal disease was associated with increased 30-day mortality. For TAAA patients with subclinical renal disease, the estimated GFR is a much more powerful determinant of mortality than the serum creatinine level alone. Serum creatinine is influenced by muscle mass and hydration, and its level alone may fail to detect mild to moderate stages of kidney disease.⁴ Presumably, this is the reason for the mortality rates of 9% to 13% in patients who have a normal preoperative serum creatinine level (less than 1.5 mg/dL) but who may have subclinical renal disease. Using GFR as a measure of renal function, the 30-day mortality was only 5% for patients with a normal GFR (>90 mL/min per 1.73 m²); it was doubled for patients with mild renal disease (stage 2; GFR of 60-89 mL/min per 1.73 m²), and it approached 22% in patients with moderate renal disease (stage 3; GFR of 30-59 mL/min per 1.73 m²).

The other important finding in our study was the reduced preoperative renal function in all patients with TAAA compared with those with descending thoracic aortic aneurysms, according to their estimated GFR. This difference would not have been detected if preoperative renal function were based on the serum creatinine level alone. We postulate that there is an increased incidence of antecedent renal disease when the aneurysmal process involves the abdominal aorta related to atherosclerosis of the renal arteries, dissection, or atheroemboli. In addition, although we did not focus on postoperative

renal function in this study, GFR was a more sensitive index of changes in renal function than serum creatinine alone. However, future studies are required to further delineate the differential renal function with regard to preoperative aneurysm extent and surgical repair.

The Cockcroft-Gault equation is a simple method for estimating the GFR.¹¹ Although the equation was originally designed to calculate creatinine clearance, it has been validated as a good estimate of GFR and is commonly used in clinical practice to evaluate renal function.^{4,16-18} A newer, more complex equation, known as modification of diet in renal disease, produces a direct normalized index of GFR.⁴ The modification of diet in renal disease equation is available on the Internet (http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm) and is increasingly being used by clinicians and researchers.^{16,19} The serum creatinine level alone is a crude index of renal function and has no discrimination in patients with subclinical disease. Because evidence supporting the importance of chronic renal disease in cardiovascular diseases is emerging, we propose that estimates of GFR should be used to evaluate renal function, particularly for population such as ours with a high prevalence of subclinical renal disease.¹⁶⁻²⁰

In summary, preoperative renal function is an important determinant of early mortality, even in patients without clinically evident disease. Elective TAAA surgery should be considered with great caution for patients who

have pre-existing moderate to severe renal disease. In our experience, estimated GFR is a much more powerful predictor of mortality risk than serum creatinine alone. Future studies are required to further elucidate the relationship between pre-existing renal disease and postoperative mortality after TAAA surgery.

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