SURGERY FOR ACQUIRED CARDIOVASCULAR DISEASE

CORONARY ARTERY BYPASS GRAFTING IN NON–DIALYSIS-DEPENDENT MILD-TO-MODERATE RENAL DYSFUNCTION

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Objectives: The effect of mild-to-moderate elevation of preoperative serum creatinine levels on morbidity and mortality from coronary artery bypass grafting has not been investigated in a large multivariable model incorporating preoperative and intraoperative variables. Our first objective was to ascertain the effect of a mild-to-moderate elevation in the preoperative serum creatinine level on the need for mechanical renal support; the duration of special care and total postoperative stay; the occurrence of infective, respiratory, and neurologic complications; and hospital mortality. Our second objective was to ascertain which patient variables contributed to an increase in the serum creatinine level in association with coronary artery bypass grafting.

Methods: A total of 1427 patients who had no known pre-existing renal disease and who were undergoing first-time coronary artery bypass grafting with cardiopulmonary bypass were recruited for the study. Patients were divided, on the basis of preoperative serum creatinine level, into 3 groups as follows: creatinine level of less than 130 μmol · L^{-1}; creatinine level of 130 to 149 μmol · L^{-1}; and creatinine level of 150 μmol · L^{-1} or greater. A multivariable stepwise logistic regression analysis was used, and variables significant at the 5% level were included when developing the final multivariable models.

Results: Multivariable analysis showed that elevation of the preoperative serum creatinine level to 130 μmol · L^{-1} or greater increased the likelihood of needing mechanical renal support postoperatively ($P < .001$), as well as the need for postoperative special care ($P < .001$) and total hospital stay ($P < .001$). In-hospital mortality was also significantly elevated as the preoperative creatinine level rose to 130 to 149 μmol · L^{-1} ($P = .045$) and to 150 μmol · L^{-1} or greater ($P < .001$). It was further observed that patients with preoperative serum creatinine levels of 130 to 149 μmol · L^{-1} ($P = .02$), patients with preoperative serum creatinine levels of 150 μmol · L^{-1} or greater ($P = .001$), hypertensive patients ($P = .007$), patients with angina of New York Heart Association class III or greater ($P = .001$), patients having a nonelective operation ($P = .002$), and patients having a prolonged cardiopulmonary bypass time ($P = .008$) had a significantly greater increase in the serum creatinine level as a result of coronary artery bypass grafting. Of particular note was the finding that the method of myocardial protection (cardioplegia or crossclamp fibrillation) did not significantly influence in-hospital mortality, need for mechanical renal support, or special care or total postoperative hospital stay.

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Conclusions: A mild elevation (130-149 µmol · L^{-1}) in the preoperative serum creatinine level significantly increases the need for mechanical renal support, the duration of special care and total postoperative stay, and the in-hospital mortality. As the preoperative serum creatinine level increases further (≥150 µmol · L^{-1}), this effect is more pronounced. No significant difference in outcome was observed between the use of cardioplegia or crossclamp fibrillation for myocardial protection. (J Thorac Cardiovasc Surg 2001;121:1083-9)

Cardiac operations adversely affect renal function, causing varying degrees of postoperative renal impairment.[1,2] In the presence of advanced preoperative chronic renal failure, the deleterious influence of cardiopulmonary bypass is further increased.[3,4] The precise level at which renal dysfunction begins to adversely affect outcome is unknown. Clinical impression suggests that even mild or moderate elevations of serum creatinine levels have an adverse effect on outcome. One of the first studies attempting to address this issue focused on moderate (>150 µmol · L^{-1}) elevations of preoperative serum creatinine levels.[5] In a more recent study of 93 patients, Durmaz and colleagues[6] looked at the effect of milder elevations of the preoperative serum creatinine level and found levels greater than 2.5 mg/dL (>200 µmol · L^{-1}) in non–dialysis-dependent patients to increase the risk of postoperative dialysis, prolonged hospital stay and in-hospital mortality. However, the effect of a more borderline elevation of preoperative serum creatinine levels has not been investigated in a large multivariable model that included other potential preoperative and intraoperative contributors to morbidity and mortality. This study was designed to address these issues.

The first objective of the study was to identify the effect on morbidity and mortality of mild-to-moderate elevation of the preoperative serum creatinine level in non–dialysis-dependent patients undergoing coronary artery bypass grafting. The second objective was to identify the factors that contribute to any observed deterioration of renal function after coronary artery bypass grafting.

Methods

Patient selection. The computerized prospective cardiac surgical database at the Hammersmith Hospital (London, United Kingdom) maintains data on all cardiac operations performed at the hospital. We recruited 1427 patients operated on between June 1993 and December 1997 for the study. Criteria for selection were that patients were having first-time coronary artery bypass grafting and that no known acute or chronic renal disease pre-existed. The highest preoperative serum creatinine level within 7 days preceding the operation was taken as the preoperative creatinine level. Patients were grouped on the basis of preoperative creatinine level into 1 of 3 groups. The postoperative creatinine level was taken as the highest value in the first 28 days after the operation. Creatinine levels were measured for a minimum of 3 days after peak values were reached on all patients to confirm that levels were decreasing. The preoperative and intraoperative variables used for the study, along with the preoperative creatinine groups into which they were categorized, are shown in Table I. The study cohort consisted of 1197 (83.8%) male and 230 (16.2%) female patients. Of these patients, 1166 (81.7%) were less than 70 years of age, and 261 (18.3%) were 70 years of age or older. The preoperative creatinine level was not normally distributed, with a median of 98 µmol · L^{-1} and an interquartile range of 87 to 110 µmol · L^{-1}. Elevation of the preoperative creatinine level to 150 µmol · L^{-1} or greater in these patients with no known pre-existing renal disease was defined as moderate elevation. Values approximately above the upper limit of the laboratory normal range but below 150 µmol · L^{-1} were defined as mild elevation. Thus, 66 (4.6%) patients had a mildly elevated creatinine level of 130 to 149 µmol · L^{-1}, and 54 (3.8%) had a moderately elevated creatinine level of 150 µmol · L^{-1} or greater. A total of 1307 (91.6%) patients had preoperative serum creatinine levels of less than 130 µmol · L^{-1}.

Surgical technique. The mean number of grafts per patient was 3.3 ± 0.8, and the mean cardiopulmonary bypass time was 77.1 ± 24.3 minutes. The method of myocardial protection used was crossclamp fibrillation in 484 (33.9%) patients and cardioplegia in 943 (66.1%) patients. Cardiopulmonary bypass was performed by means of aortocaval cannulation, a Stockert roller pump (Stockert Instrumente, Munich, Germany) and a Bard (C. R. Bard, Inc, Murray Hill, NJ) or Quadrox hollow-fiber membrane oxygenator (Jostra Medizintechnik AG). The mean blood pressure on cardiopulmonary bypass was maintained at 50 to 60 mm Hg. The lowest core temperature in degrees Celsius was noted as the core temperature of the body during the operation.

Statistical analysis. Analysis of the data was performed with Stata-6 software (Stata Corporation, College Station, Tex). Univariate analysis was initially performed to ascertain associations between explanatory variables and outcome, χ^2 tests were used for categoric variables, and 2-sample *t* tests were used for the continuous variables, core temperature, and cardiopulmonary bypass time. Stepwise logistic multivariable regression analysis was used with both forward and backward variable selection. Variables significant at the 5% level were retained in the final multi-

Table I. *Preoperative and intraoperative variables used in developing all multivariable models presented in the study*

Variable	*Creatinine level <130 µmol · L^{-1}*	*Creatinine level 130-149 µmol · L^{-1}*	*Creatinine level ≥150 µmol · L^{-1}*
Sex			
Male	1094 (83.7%)	60 (90.9%)	43 (79.6%)
Female	213 (16.3%)	6 (9.1%)	11 (20.4%)
Age (y)			
<70	1088 (83.2%)	42 (63.6%)	36 (66.7%)
≥70	219 (16.8%)	24 (36.4%)	18 (33.3%)
Diabetes mellitus			
No	1008 (77.1%)	44 (66.7%)	35 (64.8%)
Yes	299 (22.9%)	22 (33.3%)	19 (35.2%)
Hypertension			
No	754 (57.7%)	37 (56.1%)	18 (33.3%)
Yes	553 (42.3%)	29 (43.9%)	36 (66.7%)
Hypercholesterolemia			
No	763 (58.4%)	40 (60.6%)	39 (72.2%)
Yes	544 (41.6%)	26 (39.4%)	15 (27.8%)
Angina			
≤NYHA II	789 (60.4%)	37 (56.1%)	26 (48.1%)
≥NYHA III	518 (39.6%)	29 (43.9%)	28 (59.9%)
Past myocardial infarction			
No	570 (43.6%)	28 (42.4%)	21 (38.9%)
Yes	737 (56.4%)	38 (57.6%)	33 (61.1%)
Smoking			
Never	406 (31.1%)	17 (25.8%)	17 (31.5%)
Ever	901 (68.9%)	49 (74.2%)	37 (68.5%)
Ejection fraction			
≥30%	1178 (90.1%)	42 (63.6%)	39 (72.2%)
<30%	129 (9.9%)	24 (36.4%)	15 (27.8%)
Cardiogenic shock			
No	1287 (98.5%)	65 (98.5%)	53 (98.2%)
Yes	20 (1.5%)	1 (1.5%)	1 (1.8%)
Diseased coronaries			
≤2	265 (20.3%)	17 (25.8%)	4 (7.4%)
>2	1042 (79.7%)	49 (74.25%)	50 (92.6%)
Left main stem stenosis >50%			
No	1241 (95%)	57 (86.4%)	49 (90.7%)
Yes	66 (5%)	9 (13.6%)	5 (9.3%)
Preoperative urea			
<7.5 mmol · L^{-1}	1069 (81.8%)	21 (31.8%)	4 (7.4%)
≥7.5 mmol · L^{-1}	238 (18.2%)	45 (68.2%)	50 (92.6%)
Surgical priority			
Elective	983 (75.2%)	39 (59.1%)	29 (53.7%)
Nonelective	324 (24.8%)	27 (40.9%)	25 (46.3%)
Myocardial protection			
Cardioplegia	871 (66.6%)	45 (68.2%)	27 (50%)
Crossclamp fibrillation	436 (33.4%)	21 (31.8%)	27 (50%)
Core temperature (°C)			
Mean ± SD	32.7 ± 2.2	33.1 ± 2.2	32.6 ± 2
Cardiopulmonary bypass time (min)			
Mean ± SD	77 ± 24.3	71.8 ± 24.5	85.5 ± 23

The number and percentage of patients within each preoperative creatinine group for the variable under consideration is shown unless otherwise indicated.

variable models. In-hospital mortality is used for the mortality analysis. Variables considered for inclusion in the multivariable models were as follows: sex, age, diabetes mellitus, hypertension, hypercholesterolemia, New York Heart Association (NYHA) grade of angina, previous myocardial infarction, smoking, ejection fraction, cardiogenic shock, number of diseased coronary arteries, left main stem coronary stenosis of greater than 50%, preoperative urea, surgical priority, type of myocardial protection, core temperature during the operation, and cardiopulmonary

Table II. *Factors contributing significantly toward needing postoperative mechanical renal support*

Covariate	*Odds ratio*	P *value*	*95% CI*
Preoperative creatinine level			
<130 µmol · L^{-1}	1		
≥130 µmol · L^{-1}	24.43	<.001	10.37-57.52
Sex			
Male	1		
Female	2.95	.02	1.19-7.35
Surgical priority			
Elective	1		
Nonelective	3.13	.01	1.35-7.24

Multivariable analysis was done with all variables included in Table I. The 2 higher preoperative serum creatinine groups used in the remainder of the study have been amalgamated to avoid statistical overfitting.

Table III. *Factors contributing significantly toward a prolonged special care (combined intensive care and high-dependency unit) stay of greater than 3 days*

Covariate	*Odds ratio*	P *value*	*95% CI*
Preoperative creatinine level			
<130 µmol · L^{-1}	1		
130-149 µmol · L^{-1}	3.08	<.001	1.65-5.76
≥150 µmol · L^{-1}	3.92	<.001	2.02-7.59
Age (y)			
<70	1		
≥70	1.73	.007	1.16-2.57
Left ventricular function			
Ejection fraction ≥ 30%	1		
Ejection fraction < 30%	2.15	.001	1.37-3.36
Cardiopulmonary bypass time			
For increments of 10 min	1.18	<.001	1.11-1.27

bypass time. Table I shows the distribution of these variables in the preoperative creatinine groups.

Results

Morbidity analysis. The effect of the preoperative serum creatinine groups on the need for new mechanical renal support (hemofiltration-hemodialysis), the need for protracted special care (combined intensive care and high-dependency unit) and total postoperative stay, and the occurrence of pulmonary, neurologic, and infective complications in the hospital were analyzed.

Of the 1427 patients in the study, 28 (2.0%) required postoperative mechanical renal support. Because only 28 patients required postoperative mechanical renal support, developing a model with the 3 preoperative creatinine groups was likely to result in statistical overfitting, which is associated with type 1 errors (ie, where a variable is incorrectly identified as significant). This was addressed by combining the 2 higher creatinine categories and reanalyzing as a creatinine level of less than 130 µmol · L^{-1} or 130 µmol · L^{-1} or greater. Multivariable analysis with all variables in Table I showed a preoperative creatinine level of 130 µmol · L^{-1} or greater (P < .001), nonelective operation (P = .01), and female sex (P = .02) to increase the likelihood of needing mechanical renal support (Table II).

Table IV. *Factors contributing significantly toward a prolonged total postoperative hospital stay of greater than 10 days*

Covariate	*Odds ratio*	P *value*	*95% CI*
Preoperative creatinine level			
<130 µmol · L^{-1}	1		
130-149 µmol · L^{-1}	4.68	<.001	2.63-8.34
≥150 µmol · L^{-1}	4.28	<.001	2.31-7.91
Sex			
Male	1		
Female	1.77	.007	1.17-2.68
Age (y)			
<70	1		
≥70	1.64	.013	1.11-2.42
Previous myocardial infarction			
No	1		
Yes	1.67	.005	1.16-2.39
Cardiopulmonary bypass time			
For increments of 10 min	1.12	<.001	1.04-1.20

At this hospital, patients spend the first night after operation in the intensive care unit and the second in the high-dependency unit before transfer to the ward the next morning. The median (interquartile range) for special care stay was 2 (2-3) days and 7 (6-8) days for the total postoperative hospital stay. A stay greater than the 90th percentile was defined as prolonged. This equated to a special care (combined intensive care and high dependency) stay of greater than 3 days in 156 patients and a total postoperative stay of greater than 10 days in 160 patients. On multivariable analysis, patients with a preoperative creatinine level of 130 to 149 µmol · L^{-1} were 3 times as likely (P < .001) and patients with a preoperative creatinine level of 150 µmol · L^{-1} or greater were 3.9 times as likely (P < .001) to have a prolonged special care stay than those with a creatinine level of less than 130 µmol · L^{-1}. Other factors contributing to a prolonged special care stay were being 70 years of age or older (P = .007), having a preoperative left ventricular ejection fraction of less than 30% (P = .001), and having a prolonged cardiopulmonary bypass time (P < .001; Table III). A preoperative creatinine level of 130 µmol · L^{-1} or greater increased the likelihood of a prolonged total postoperative hospital stay by over 4-fold ($P < .001$). Being a woman ($P = .007$), being 70 years of age or older ($P = .013$), and having had a previous myocardial infarction ($P = .005$), or having a prolonged cardiopulmonary bypass time ($P < .001$) also contributed to a prolonged total postoperative stay (Table IV). The preoperative serum creatinine level on multivariable analysis was seen to be not a significant predictor of pulmonary, neurologic, or infective complications. Differences between the use of cardioplegia or crossclamp fibrillation were looked for in the multivariable analysis. No significant difference was seen in the need for mechanical renal support ($P = .10$), special care stay ($P = .67$), or total postoperative hospital stay ($P = .16$).

Mortality analysis. In-hospital intraoperative or postoperative death was defined as mortality for the purposes of the study. There were 45 (3.2%) deaths. The mortality for the 3 preoperative creatinine groups is shown in Fig 1. The odds ratio for mortality on multivariable analysis was 3 times ($P = .045$) higher if the preoperative creatinine level rose from less than 130 $\mu mol \cdot L^{-1}$ to 130 to 149 $\mu mol \cdot L^{-1}$. As the preoperative creatinine level rose further to 150 $\mu mol \cdot L^{-1}$ or greater, the odds ratio for mortality increased to 7 times ($P < .001$) that of patients with a preoperative serum creatinine level of less than 130 $\mu mol \cdot L^{-1}$. Other factors contributing to an increase in mortality on multivariable analysis were being female ($P < .001$), being 70 years of age or older ($P = .004$), having a preoperative left ventricular ejection fraction of less than 30% ($P = .006$), and having a prolonged cardiopulmonary bypass time ($P < .001$; Table V). In contrast, no significant difference was present between the use of cardioplegia or crossclamp fibrillation on mortality ($P = .21$) in the multivariable analysis.

Analysis of increase in serum creatinine level. Having observed the effect of a mild-to-moderate increase in the preoperative serum creatinine level on outcome, we next studied the factors that contribute to its increase after coronary artery bypass grafting. The change between preoperative and postoperative creatinine level was not normal in distribution. The median was an increase of 8.4% above the preoperative value, with an interquartile range of –2.6% to 23.1%. An increase in the serum creatinine level after the operation by 20% or greater of the preoperative value was taken as a significant elevation and occurred in 401 (28.1%) patients. Multivariable analysis with all variables shown in Table I showed that patients with a preoperative creatinine level of 130 to 149 $\mu mol \cdot L^{-1}$ were 1.8 times as likely ($P = .02$) as patients with a preoperative creatinine level of less than 130 $\mu mol \cdot L^{-1}$ to have their serum creatinine level increase by 20% or greater postoperatively, and patients with a preoperative creatinine level of 150 $\mu mol \cdot L^{-1}$ or greater were 2.5 times as likely to have such a result ($P = .001$). Hypertensive patients were 1.4 times as likely to have a significant increase ($P = .007$) in their serum creatinine levels than nonhypertensive patients. Patients with angina in NYHA class III were 1.5 times as likely to have a 20% or greater increase in their serum creatinine level ($P = .001$). Nonelective operations increased the likelihood of a significant increase in the serum creatinine level by 1.5 times ($P = .002$). For each 10-minute increase in the cardiopulmonary bypass time, the likelihood of a 20% or greater increase in the serum creatinine level increased 1.1 times ($P = .008$; Table VI).

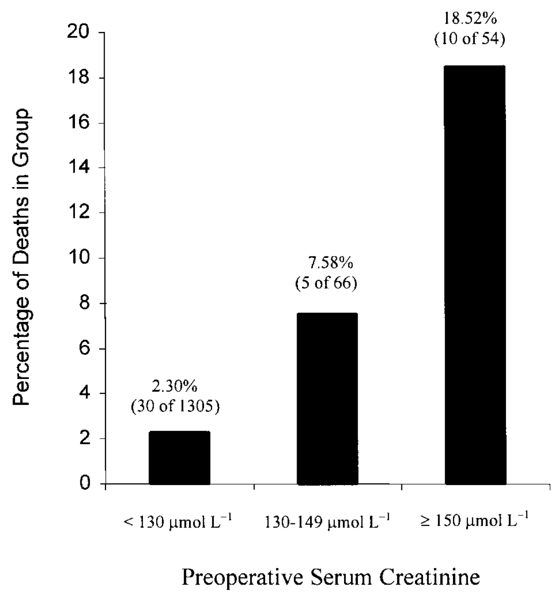

Fig 1. In-hospital mortality by preoperative creatinine group. The mortality within each creatinine group is given as a percentage of the total patients within that group.

Discussion

Serum creatinine level, despite not being as accurate as measuring the glomerular filtration rate, is still the most readily available clinical measurement of renal function. The increase in morbidity and mortality associated with dialysis-dependent renal disease is widely recognized.[3,4] An increased morbidity has also been shown in association with moderately elevated serum creatinine levels in patients with non–dialysis-dependent renal insufficiency.[5]

Table V. *Factors contributing significantly toward increased in-hospital mortality*

Covariate	*Odds ratio*	P *value*	*95% CI*
Preoperative creatinine level			
<130 µmol · L^{-1}	1		
130-149 µmol · L^{-1}	3.00	.045	1.03-8.79
≥150 µmol · L^{-1}	7.01	<.001	3.05-16.14
Sex			
Male	1		
Female	3.58	<.001	1.83-7.00
Age (y)			
<70	1		
≥70	2.62	.004	1.36-5.07
Left ventricular function			
Ejection fraction ≥ 30%	1		
Ejection fraction < 30%	2.74	.006	1.33-5.65
Cardiopulmonary bypass time			
For increments of 10 min	1.29	<.001	1.16-1.42

Table VI. *Factors contributing to a 20% or greater increase in the serum creatinine level in association with coronary artery bypass grafting with cardiopulmonary bypass*

Covariate	*Odds ratio*	P *value*	*95% CI*
Preoperative creatinine level			
<130 mmol · L^{-1}	1		
130-149 mmol · L^{-1}	1.83	.022	1.09-3.09
≥150 mmol · L^{-1}	2.57	.01	1.44-4.56
Hypertension			
No	1		
Yes	1.39	.007	1.09-1.77
Angina			
≤NYHA II	1		
≥NYHA III	1.51	.001	1.18-1.93
Surgical priority			
Elective	1		
Nonelective	1.95	.012	1.16-3.30
Cardiopulmonary bypass time			
For increments of 10 min	1.20	<.001	1.08-1.32

Despite suspicions that even creatinine levels only mildly elevated above the laboratory normal range are associated with increased morbidity and possibly mortality, confirmation from a large multivariable model including preoperative and intraoperative factors has until now been unavailable. In the design of this study we included, in the multivariable analysis, other preoperative factors that are known to be associated with renal dysfunction and poor outcome. Despite including these risk factors in the multivariable analysis, even a mild increase in the preoperative serum creatinine level over the normal range significantly increased the risk of needing mechanical renal support postoperatively, as well as prolonging the special care and total postoperative hospital stay.

One of the most important observations from the study was the pronounced effect a mild-to-moderate elevation in the preoperative serum creatinine level had on the mortality from coronary artery bypass grafting. A recent study on the basis of the Veterans Affairs database demonstrated that patients with a preoperative serum creatinine level of 1.5 mg/dL to 3 mg/dL (120-240 µmol · L^{-1}) had an increased 30-day mortality after coronary artery bypass grafting.[7] The current study further highlights the importance of the preoperative creatinine level on mortality by demonstrating that the effect is significant even at milder (130-149 µmol · L^{-1}) elevation of the preoperative serum creatinine level. This is the first study in which this pronounced effect has been seen in a multivariable model incorporating both preoperative and intraoperative risk factors. The large number of patients studied is likely to have helped reveal this significant association. These results are important because they identify the effect the preoperative serum creatinine level has on morbidity and mortality independent of the presence of other risk factors, such as sex, age, left ventricular function, and cardiopulmonary bypass time.

Analysis of the factors contributing to an increase in creatinine level in association with coronary artery bypass grafting showed that patients with higher preoperative serum creatinine levels were more likely to show an increase in their creatinine levels of 20% or greater above the preoperative levels. Patients with higher preoperative serum creatinine levels are likely to have a higher proportion of functionally borderline glomeruli, which potentially are more susceptible to deterioration of their function when exposed to the insults of an operation. It was also seen that hypertensive patients were more likely to have an increase in serum creatinine levels as a result of an operation. Hypertension contributes to progressive renal failure by inducing myointimal hyperplasia of arcuate and afferent arterioles, causing glomerular ischemia[8] (hypertensive glomerularsclerosis), which is likely to increase the susceptibility of the kidneys to cardiopulmonary bypass. The greater increase in serum creatinine levels in patients with angina of NYHA class III or greater is likely to be due to a greater likelihood of concomitant renal vascular disease. The increase in creatinine level was also seen to be greater with increasing cardiopulmonary bypass times. Hemolysis and release of free hemoglobin[9] may increase with prolonged cardiopulmonary bypass times, increasing the risk of hemoglobinuria and acute renal dysfunction. The study was not designed to analyze postoperative events, and thus a potential weakness is that it does not investigate their possible contribution to the increase in serum creatinine levels.

On performing multivariable analysis to include all the risk factors outlined in Table I, it was seen that the type of myocardial protection used did not influence mortality significantly. Similarly, there was no difference on multivariable analysis between crossclamp fibrillation or cardioplegia on the need for mechanical renal support or on the special care or total postoperative stay. The lowest core body temperature achieved during the operation also had no independent effect on morbidity or mortality.

This study confirms clinical observations that the morbidity and mortality from coronary artery bypass grafting increase with even mild-to-moderate elevation of the preoperative serum creatinine level. The factors that contribute significantly to renal dysfunction as a result of coronary operation are also outlined. We hope the insights gained from this study will help in a more rigorous design and assessment of strategies aimed at reducing the increased morbidity and mortality from coronary artery bypass grafting seen in patients with non–dialysis-dependent renal dysfunction.

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