Mild preoperative renal dysfunction as a predictor of long-term clinical outcome after coronary bypass surgery

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Background: Renal dysfunction is a prognostic marker in patients with cardiovascular disease. However, no long-term follow-up studies on the influence of mild renal dysfunction on mortality in patients undergoing coronary bypass grafting have been reported. Therefore, we aimed to identify the significance of preoperative (mild) renal dysfunction as a long-term predictor of clinical outcome after coronary bypass surgery.

Methods: In 358 patients who underwent isolated saphenous vein aorta–coronary artery bypass grafting, estimated glomerular filtration rates were calculated with the Cockcroft-Gault equation (GFRc). Patients were categorized into 2 groups (group 1, GFRc >71.1 mL · min⁻¹ · 1.73 m⁻²; group 2, GFRc <71.1 mL · min⁻¹ · 1.73 m⁻²). Multivariate Cox proportional hazard analyses were performed to determine the independent prognostic value of GFRc.

Results: During a median follow-up of 18.2 years, 233 patients (65.1%) died. Patients who died had lower GFRc and were older. Multivariate analysis demonstrated that total mortality in patients with lower GFRc was significantly increased (lower GFRc group vs normal GFRc group: hazard ratio, 1.44; *P* = .019). Lower GFRc was also an independent predictor of cardiac mortality (hazard ratio, 1.51; *P* = .032). No significant differences were observed between groups in the occurrence of myocardial infarction and the need for reintervention.

Conclusions: Our study demonstrates that after long-term follow-up, preoperative mild renal dysfunction is an independent predictor of long-term (cardiac) mortality in patients who undergo coronary artery bypass grafting.

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Several prognostic risk markers for mortality, reintervention, and the occurrence of cardiac events after coronary bypass surgery have been identified over the last 2 decades. We have already demonstrated that age and left ventricular function are continuous incremental risk factors for mortality. Left ventricular function and completeness of revascularization are independent predictors of cardiac death, and age and vessel disease are independent predictors of reintervention. Preoperative risk markers for cardiac events are hypertension, diabetes mellitus, hypertriglyceridemia, obesity, and smoking.¹

Patients with chronic renal failure are known to have an increased risk of cardiovascular disease.^{2,3} In addition, outcome after coronary bypass surgery of

Table 1. Baseline characteristics of both groups at time of surgery

	Group 1 (n = 215, GFR >70.1 mL · min ⁻¹ · 1.73 m ⁻²)	Group 2 (n = 143, GFR <70.1 mL · min ⁻¹ · 1.73 m ⁻²)	Significance (2-tailed)
Mean age (y)	49.7 ± 6.5	57.2 ± 6.0	<.001*
Sex			
Male	96.3%	78.3%	<.001†
Female	3.7%	21.7%	
BMI (kg/m ²)	24.1 ± 1.5	23.1 ± 1.7	<.001*
Serum creatinine (mmol/L)	97.2 ± 11.1	109.0 ± 18.1	<.001*
GFRc (mL · min ⁻¹ · 1.73 m ⁻²)	85.1 ± 11.0	60.8 ± 7.9	<.001*
Diabetes mellitus			
Yes	98.6%	96.5%	.274†
No	1.4%	3.5%	
Smoking			
Yes	41.9%	35.0%	
No	57.7%	65.0%	.186†
Unknown	0.4%	0.0%	
Cholesterol (mmol/L)	7.61 ± 1.42	7.60 ± 1.37	.939*
Triglycerides (mmol/L)	1.70 ± 1.01	1.70 ± 1.30	.968*
BP systolic (mm Hg)	129 ± 12	132 ± 12	.007*
BP diastolic (mm Hg)	85 ± 11	84 ± 8	.602*
Angina pectoris CCS class			<.001†
I	3.3%	0.7%	
II	45.6%	30.8%	
III	37.7%	44.1%	
IV	13.5%	24.5%	
Family history			
Positive	9.3%	7.0%	
Negative	79.1%	76.9%	.561†
Unknown	11.6%	16.1%	
LV function (CASS-WMS score)			
5-7	64.2%	62.9%	
8-10	19.1%	21.0%	.904†
>10	16.7%	16.1%	
One-vessel disease	16.3%	9.1%	
Two-vessel-disease	38.1%	36.4%	.034†
Three-vessel-disease (>50% stenosis)	45.6%	54.5%	
Extracorporeal circulation time (min)	111 ± 49	115 ± 49	.695‡

Data are mean ± SD. *BMI*, Body mass index; *GFRc*, glomerular filtration rate (GFR) according to the Cockcroft-Gault equation; *BP*, blood pressure; *CCS*, Canadian Cardiovascular Society; *CASS*, Coronary Artery Surgery Study; *WMS*, wall motion score; *LV*, left ventricular.

*t Test.

† χ^2 -test.

‡Mann-Whitney test.

patients with end-stage renal disease is poor, and in this group a 5-year survival of less than 50% has been observed.⁴ Anderson and colleagues⁵ demonstrated that patients with mild renal dysfunction are predisposed to adverse 30-day outcomes after coronary artery bypass surgery. However, no studies assessed the influence of mild preoperative kidney dysfunction on long-term outcome after coronary bypass surgery. Therefore, we aimed to identify the significance of renal function as a predictor of long-term clinical outcome after coronary bypass surgery.

Methods

Patients

The clinical and angiographic definitions, as well as the surgical technique and patient characteristics, have been previously described in detail.⁶ Between April 1, 1976, and April 1, 1977, a series of 446 consecutive patients underwent isolated saphenous vein aorta-coronary bypass surgery in our hospital. Thirteen patients died within 30 days after surgery, and they were excluded from this analysis. Another 18 patients in whom the revascularization was combined with valve replacement surgery were also excluded. Of the remaining 415 patients, in 57 (13.7%), the esti-

Figure 1. All-cause mortality after coronary artery bypass grafting in patients, based on their calculated creatinine clearance: group 1, cGFR greater than $70.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$; group 2, cGFR less than $70.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$.

mated glomerular filtration rates according to the Cockcroft-Gault equation (GFRc) could not be calculated. This group was excluded as well. Therefore, this study population consisted of 358 patients. Several follow-up methods were used simultaneously to provide the most complete information possible. All patients were followed by using the anniversary method at our outpatient clinic or the outpatient clinic of referring cardiologists.

Measurement of Serum Creatinine

Serum creatinine was measured with standard techniques in the clinical chemistry laboratory of our institution from blood samples drawn the week before surgery. Serum creatinine then was used to calculate GFRc by using the Cockcroft-Gault equation $[(140 - \text{age in years}) \times (\text{weight in kg})] / (72 \times \text{serum creatinine in mg/dL})$, multiplied by 0.85 in women. This equation is closely correlated with measured creatinine clearance (correlation coefficient, 0.83) and gives a more accurate assessment of renal function than serum creatinine alone.⁷

Statistical Analysis

In our analysis we categorized GFRc into quintiles, and the hazard ratios were calculated for the lower GFRc quintiles compared with the (reference) highest GFRc group. Univariate Cox proportional hazard analysis demonstrated that the lowest 2 quintiles and the highest 3 quintiles showed similar hazard ratios. Subsequently, the patients were categorized into 2 groups (group 1: $\text{GFRc} > 71.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, quintiles 3, 4, and 5; group 2: $\text{GFRc} < 71.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, quintiles 1 and 2). Age was dichotomized in a similar manner; this resulted in 2 groups with a cutoff point of 54.7 years.

To identify prognostic covariates that might have been responsible for a difference in survival time between groups, survival curves were estimated by the method described by Kaplan and Meier from the following variables: presence of left main vessel disease, left ventricular function, number of vessels involved, completeness of revascularization, preoperative diabetes mellitus, preoperative cholesterol, number of distal anas-

tomoses, preoperative smoking behavior, and hypertension. The log-rank test was used to calculate the statistical significance of differences in survival curves between groups. All variables with a significance level of $P < .10$ in this univariate test were included in a multivariate model proposed by Cox. The clinical events studied were overall mortality, cardiac mortality, acute myocardial infarction, and reintervention. Cardiac death was defined as death from a documented cardiac cause or death from an unknown cause. End points were scored in an hierarchical manner.⁸ All statistical analyses were performed with SPSS software (version 11.0; SPSS Inc, Chicago, Ill), and all reported P values are 2 sided.

Results

Baseline Characteristics

The mean age of the entire study population was 52.6 years (range, 20-74 years; SD, 7.35 years), and 10.9% were women. The mean (SD) serum creatinine concentration in the 2 GFRc groups was $97.2 \mu\text{mol/L}$ ($11.1 \mu\text{mol/L}$) and $109.0 \mu\text{mol/L}$ ($18.1 \mu\text{mol/L}$), respectively. Only 3 patients had a $\text{GFRc} < 40 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ (minimum, $32.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$). The mean GFRc of both groups was within 2 SD of normal GFR values in the general population.⁹ Other baseline clinical characteristics are shown in Table 1. Thirty-day operative mortality for the study population was 2.9%. Only 1 patient was lost to follow-up. The median duration of follow-up was 18.2 years.

All-Cause Mortality

Cumulative survival of the 2 groups is shown in Figure 1. In the high-GFRc group, 120 patients (45.2%) died, whereas in the low-GFRc group, 113 patients (79.0%) died. The variables with a significance level of $P < .10$ in the univariate tests were age, left ventricular function, preoperative diabetes mellitus, number of anastomoses,

Table 2. Univariate hazard ratios (95% confidence intervals) for total mortality and cardiac mortality of statistically significant and other predictors for either total mortality or cardiac mortality

Variable	From 30 d after surgery to 18.2 y after surgery			
	Total mortality		Cardiac mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>54.7 y)	2.08 (1.60-2.69)	<.001	1.73 (1.26-2.38)	.001
Completeness of revascularization	1.35 (1.04-1.75)	.026	1.73 (1.26-2.37)	.001
Diabetes mellitus	2.29 (1.08-4.88)	.031	2.00 (0.74-554)	.169
Body mass index	1.00 (0.92-1.08)	.928	0.99 (0.90-1.10)	.895
No. of diseased vessels				
Two-vessel disease	1.23 (0.79-1.91)	.366	2.04 (1.07-3.89)	.031
Three-vessel disease	1.78 (1.16-2.71)	.008	3.03 (1.62-5.68)	.001
LMCA involved	1.63 (1.13-2.35)	.009	1.66 (1.07-2.59)	.024
LV function (CASS-WMS)				
<8 vs. 8-10	2.02 (1.37-3.00)	<.001	1.78 (1.29-2.45)	<.001
<8 vs. >10	3.59 (2.45-5.25)	<.001	2.63 (1.90-3.65)	<.001
Sex (M/F)	1.23 (0.83-1.82)	.311	1.25 (0.77-2.02)	.365
Smoking	1.17 (0.90-1.52)	.235	1.10 (0.79-1.51)	.581
Cholesterol	0.97 (0.88-1.08)	.581	1.00 (0.88-1.13)	.978
Triglycerides	1.05 (0.93-1.18)	.422	1.09 (0.95-1.24)	.245
No. of anastomoses	1.13 (1.03-1.24)	.013	1.20 (1.07-1.34)	.001
GFR ($\leq 70.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$)	1.82 (1.41-2.36)	<.001	1.74 (1.27-2.39)	.001

CI, Confidence intervals; HR, hazard ratio; LV, left ventricular; LMCA, left main coronary artery; CASS, Coronary Artery Surgery Study; WMS, wall motion score; GFR, glomerular filtration rate.

Table 3. Multivariate hazard ratios (95% confidence intervals) for total mortality and cardiac mortality of statistically significant and other predictors for either total mortality or cardiac mortality

Variable	From 30 d after surgery to 18.2 y after surgery			
	Total mortality		Cardiac mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>54.7 y)	1.72 (1.27-2.33)	<.001	1.43 (0.99-2.08)	.058
Completeness of revascularization	1.16 (0.88-1.53)	.298	1.40 (1.00-1.95)	.050
Diabetes mellitus	2.02 (0.93-4.41)	.077	—	
No. of diseased vessels				
Two-vessel disease	0.97 (0.59-1.60)	.895	1.43 (0.71-2.90)	.316
Three-vessel disease	1.03 (0.58-1.84)	.914	1.50 (0.69-3.28)	.308
LMCA involved	1.57 (1.08-2.29)	.020	1.53 (0.97-2.42)	.070
LV function (CASS-WMS)				
<8 vs. 8-10	1.68 (1.22-2.33)	.002	1.43 (0.71-2.90)	.001
<8 vs. >10	2.52 (1.80-3.53)	<.001	3.10 (2.10-4.57)	<.001
No. of anastomoses	1.06 (0.93-1.21)	.366	1.09 (0.94-1.27)	.275
GFR ($\leq 70.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$)	1.44 (1.06-1.96)	.019	1.51 (1.04-2.19)	.032

CI, Confidence intervals; HR, hazard ratio; LMCA, left main coronary artery; LV, left ventricular; CASS, Coronary Artery Surgery Study; WMS, wall motion score; GFR, glomerular filtration rate.

number of vessels involved, left main coronary artery disease, completeness of revascularization, and categorized preoperative GFRc (Table 2). These values were included in a multivariate analysis model. Multivariate analysis identified 3 preoperative risk factors that were related to long-term mortality: age, left ventricular function, and preoperative renal function (Table 3). Patients

in group 2 had a significantly increased risk of mortality during follow-up (group 2 vs group 1: hazard ratio, 1.44; 95% CI 1.06-1.96; $P = .019$).

Cardiac Mortality

Cumulative survival of the 2 groups is shown in Figure 2. In the high-GFRc group, 83 patients (38.6%) died of cardiac

Figure 2. Cardiac mortality after coronary artery bypass grafting in patients, based on their calculated creatinine clearance: group 1, cGFR greater than $70.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$; group 2, cGFR less than $70.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$.

cause, whereas in the other group, 74 patients (51.7%) died of cardiac causes. The variables with a significance level of $P < .10$ in the univariate tests were age, left ventricular function, number of anastomoses, number of diseased vessels, left main coronary artery disease, completeness of revascularization, and preoperative GFRc (Table 2). If only cardiac death was taken into account, categorized preoperative kidney function was still a significant risk factor (group 2 vs group 1: hazard ratio, 1.51; 95% CI 1.04-2.19; $P = .032$). The 2 most powerful predictors of cardiac mortality after multivariate analysis were left ventricular function and preoperative kidney function (Table 3).

Myocardial Infarction and Reintervention

No significant differences were found between groups in the occurrence of (re)myocardial infarction (group 2 vs group 1: hazard ratio, 1.29; $P = .219$) or in the reintervention rate (group 2 vs group 1: hazard ratio, 1.38; $P = .198$). These data are not shown.

Discussion

In this long-term follow-up study, we demonstrated that mild preoperative renal dysfunction is an independent predictor of long-term mortality. Ischemic heart disease is the most common cause of death in patients with chronic kidney disease,^{10,11} and renal dysfunction has now been generally recognized as a risk marker in a wide variety of patients with cardiovascular disease.¹² It has been well established that patients with severe chronic renal failure have a high risk for adverse outcome after coronary bypass surgery.^{5,13,14} Several studies showed that patients with mild renal dysfunction have an increased risk of dying within 30 days after coronary surgery.^{5,13,15} Patients with

decreased renal function (serum creatinine $\geq 2.0 \text{ mg/dL}$) carry significant operative risks, require prolonged hospital stays, and have a higher risk of dying within 3 years after coronary surgery.¹⁵ Nakayama and colleagues¹³ demonstrated that in a group of patients with a preoperative serum creatinine level of 1.5 mg/dL or greater ($\geq 133 \mu\text{mol/L}$), the 10-year actuarial survival was significantly lower than in a group of patients with normal serum creatinine levels ($<1.0 \text{ mg/dL}$; $<88 \mu\text{mol/L}$). Most patients in our population had a milder preoperative renal dysfunction than described in these studies, yet this parameter was still an independent predictor for mortality. It is interesting to note that Kaplan-Meier analysis clearly demonstrated that differences between GFR groups occurred only after approximately 10 years of follow-up. Possibly, this mirrors an accelerated rate of atherosclerosis, although in our population no difference in myocardial infarction was observed between groups.

Several explanations have been proposed for the association between renal dysfunction, cardiovascular disease, and mortality.^{3,16,17} First, renal dysfunction is often associated with the presence of other cardiovascular risk factors, such as hypertension and diabetes. In these cases, renal dysfunction and cardiovascular morbidity would both be the results of end-organ damage. However, the effect of renal function on mortality in this study was independent of other known cardiovascular risk factors. Second, renal dysfunction might be the direct effect of cardiac dysfunction. In patients with a reduction of cardiac output, there is a decline in renal perfusion and an activation of compensatory mechanisms, which leads to renal function impairment.^{18,19} In these cases, renal dysfunction is a reflection of the cardiac function and may therefore be used as a risk marker for

cardiovascular morbidity and mortality.²⁰ In our patients, this mechanism probably does not play a role, because only a few patients had a significantly reduced left ventricular systolic function. Finally, renal dysfunction also has a negative effect on lipids, oxidative stress, homocysteine, and fibrinogen; this could lead to endothelial dysfunction.²¹ However, the question of whether endothelial dysfunction is the connecting bond between cardiovascular risk factors and renal dysfunction remains to be answered.

Patients receiving venous coronary bypass grafts often need reintervention and also have a worse prognosis compared with patients receiving arterial bypass grafts.²² Angiographic and necropsy studies have found evidence of accelerated atherosclerosis in saphenous vein conduits, possibly as a result of chronic endothelial activation.²³ Nowadays arterial grafts are preferred to venous grafts, yet venous conduits continue to be used in a large proportion of coronary artery bypass grafting patients. Consequently, it is important to identify all patients at risk.

Limitations

This was a post hoc analysis of prospective data. Therefore, the results and conclusions are subject to the limitations inherent to such analysis. However, the principal variables of interest—serum creatinine and death—are objective measures. The Cockcroft-Gault equation is an estimate of the GFR and might lead to an overestimation of these parameters. Because this estimation was used for all patients and because GFR was an independent predictor of poor outcome, this should not affect our conclusions. Furthermore, GFR is only a surrogate marker for kidney function. In patients with an impaired GFR, no conclusions can be drawn concerning the etiology of the problem. Our study is also limited by a lack of data on the progression of renal impairment during follow-up. Finally, the study is limited by the number of (mainly white) patients participating and the fact that they were all in the same hospital.

Conclusion

This study demonstrates that preoperative mild renal dysfunction is an important independent risk marker of long-term survival in patients after coronary bypass surgery.

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