Which method of estimating renal function is the best predictor of mortality after coronary artery bypass grafting?

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Published online: 17 August 2011
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Abstract

Objectives Definitions of renal function in patients undergoing coronary artery bypass graft surgery (CABG) vary in the literature. We sought to investigate which method of estimating renal function is the best predictor of mortality after CABG.

Methods We analysed the preoperative and postoperative renal function data from all patients undergoing isolated CABG from January 1998 through December 2007. Preoperative and postoperative renal function was estimated using serum creatinine (SeCr) levels, creatinine clearance (CrCl) determined by the Cockcroft-Gault formula and the glomerular filtration rate (e-GFR) estimated by the Modification of Diet in Renal Disease (MDRD) formula.

Receiver operator characteristic (ROC) curves and area under the ROC curves were calculated.

Results In 9987 patients, CrCl had the best discriminatory power to predict early as well as late mortality, followed by e-GFR and finally SeCr. The odds ratios for preoperative parameters for early mortality were closer to 1 than those of the postoperative parameters.

Conclusions Renal function determined by the Cockcroft-Gault formula is the best predictor of early and late mortality after CABG. The relationship between renal function and mortality is non-linear. Renal function as a variable in risk scoring systems such as the EuroSCORE needs to be reconsidered.

Keywords Coronary artery bypass grafts, CABG · Kidney, renal function · Statistics, regression analysis

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Introduction

Renal insufficiency is associated with an increased risk of complications and mortality after coronary artery bypass grafting (CABG) [1–3]. Most studies assessed the relationship between renal insufficiency and early mortality [2, 3]; only a few studies described the association between renal insufficiency and late mortality after CABG [1, 4]. The gold standard to determine renal function is the measurement of the glomerular filtration rate, represented by the clearance of an exogenous inert substance such as inulin. This is a cumbersome and time-consuming method to determine GFR and hence some more practical formulas have been developed to estimate the GFR. The Cockcroft-Gault formula is used to estimate the creatinine clearance (CrCl) and more recently, the Modification of Diet in Renal Disease (MDRD) has been introduced to estimate the glomerular filtration rate (e-GFR).

Definitions of impairment of renal function after CABG vary in the literature. Serum creatinine levels (SeCr) [4, 5], CrCl [5–7] and e-GFR [5, 6, 8] have been used, describing renal function as a risk factor for mortality after CABG. We analysed the preoperative and postoperative renal function data of all patients undergoing isolated CABG in our hospital from 1998 until 2007. We used three different definitions of renal function (SeCr, CrCl and e-GFR) in order to investigate the relationship between these parameters and early and late mortality after CABG and to compare their predictive values.

Patients and methods

Patients

This study retrospectively analysed the data of all patients undergoing isolated CABG or off-pump coronary artery bypass (OPCAB) surgery in a single centre (Catharina Hospital in Eindhoven the Netherlands) between January 1998 and December 2007. Clinical data, including demographics and renal function parameters, were prospectively collected in our database. The Institutional Research Review Board approved this study and waived the need for patient consent.

Operative technique

In CABG surgery, all patients received short-acting anaesthetic drugs to facilitate early extubation. Normothermic extracorporeal circulation was performed using non-pulsatile flow. Cold crystalloid cardioplegia (St Thomas' solution) or warm blood cardioplegia was used to induce and maintain cardioplegic cardiac arrest, according to the surgeon's preference. All patients undergoing CABG received low-dose aprotinin (2 million kallikrein inactivating units) during extracorporeal circulation, administered in the prime solution according to the hospital protocol. The anaesthetic management in OPCAB surgery was the same as in CABG surgery, but aprotinin was omitted.

Estimation of renal function

Renal function was determined by SeCr, CrCl (using the Cockcroft-Gault formula) [9], which is different between men $[(140 - \text{age}) \times \text{weight}/(\text{serum Cr} \times 72)]$ and women: $[(140 - \text{age}) \times \text{weight}/(\text{serum Cr} \times 72)] \times 0.85$, and estimated glomerular filtration rate (using the MDRD formula [10]: $e - \text{GFR} = 186 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ for women}] \times [1.212 \text{ for black people}]$). Calculations were based on the most recent preoperative SeCr and the largest value of SeCr within the first week postoperatively or if sooner before discharge.

Table 1 Preoperative and perioperative demographic and clinical characteristics

Variables	Incidence
Male gender	7698 (77.1)
Age	64.6±9.6
Angina class	2.7±0.9
Hypertension	4161 (41.7)
Diabetes	2098 (21.0)
BMI>35 kg.m ⁻²	233 (2.3)
COPD	1242 (12.4)
PVD	1148 (11.5)
EF<35%	326 (3.3)
Emergency	363 (3.6)
Preop Hb, g/dL	13.9±1.3
No of grafts	3.4±1.1
Use of IMA	8858 (88.7)
Number of RBC transfusions	1.0±2.2
Re-exploration	531 (5.3)
Periop MI	282 (2.8)
Early mortality	198 (2.0)
Late mortality	1111 (11.1)

Results are expressed as numbers (percentage) or mean ± standard deviation

BMI body mass index; *COPD* chronic obstructive pulmonary disease; *EF* estimated left ventricular ejection fraction; *IABP* need for perioperative intra aortic balloon pump support; *IMA* internal mammary artery; *periop MI* perioperative myocardial infarction; *PVD* peripheral vascular disease; *RBC* red blood cell; *Hb* hemoglobin

Follow-up

Follow-up data concerning mortality were obtained from the databases of health insurance companies. The data of 9% of the total patient group could initially not be retrieved from these databases. We therefore contacted the general practitioners to get information about mortality data of these patients or if necessary, the city authorities of the cities where the patients lived at the time of the operation.

Table 2 Renal function parameters

Parameter	Value
Preoperative SeCr	101±27
Postoperative SeCr	99.9±44.6
Preoperative CrCl	74.5±24.4
Postoperative CrCl	79.4±28.3
Preoperative e-GFR	67.4±16.4
Postoperative e-GFR	72.6±21.2

Values are expressed as mean ± standard deviation

CrCl creatinine clearance; *e-GFR* estimated glomerular filtration rate; *SeCr* serum creatinine level

Table 3 Multivariate logistic regression analyses for early mortality and Cox regression analyses for late mortality

	OR early mortality	<i>p</i> -value	HR late mortality	<i>p</i> -value
Age	1.087 (1.062–1.113)	<.0001	1.082 (1.073–1.091)	<.0001
Female	0.85 (0.58–1.26)	.430	0.62 (0.53–0.73)	<.0001
Diabetes	1.66 (1.16–2.37)	.005	1.44 (1.25–1.65)	<.0001
Hypertension			1.11 (0.98–1.26)	.098
COPD	1.88 (1.27–2.78)	.002	1.69 (1.45–1.96)	<.0001
PVD	0.98 (0.62–1.57)	.959	1.68 (1.44–1.97)	<.0001
EF<35%	4.77 (2.88–7.88)	<.0001	2.29 (1.80–2.92)	<.0001
Preop Hb	0.912 (0.811–1.026)	.125	0.829 (0.789–0.871)	<.0001
Emergency	1.76 (0.82–3.73)	.141		
No of grafts			1.00 (0.94–1.06)	.934
Redo surgery	1.34 (0.78–2.29)	.281	1.262 (1.015–1.570)	.036
RBC units transfusion	1.220 (1.160–1.284)	<.0001	1.01 (0.98–1.04)	.369
Re-exploration	1.70 (0.99–2.90)	.051	1.36 (1.03–1.79)	.027
Periop MI	4.62 (2.81–7.61)	<.0001	1.73 (1.26–2.38)	.001

Only significant factors in the univariate analysis were entered into the multivariate analysis

COPD chronic obstructive pulmonary disease; *EF* estimated left ventricular ejection fraction; *HR* hazard Ratio; *Hb* haemoglobin level; *PVD* peripheral vascular disease; *periop MI* perioperative myocardial infarction; *RBC* red blood cell

Early mortality was defined as death within 30 days postoperatively or death at anytime if the patient did not leave the hospital or a transfer tertiary hospital alive, whereas late mortality was defined as any-cause mortality that occurred at anytime after hospital discharge.

Statistical analyses

Univariate logistic regression analyses were performed to investigate the impact of biomedical variables on early mortality. If significant at $p < 0.05$, the variables were included into the multivariable logistic regression analyses together with the renal function parameters. For each renal function parameter a separate multivariate regression analysis model was made. For late mortality univariate and multivariate Cox regression analyses were performed. Hazard ratios (HR) with 95% confidence interval (CI) with *p*-values are reported. A *p*-value < 0.05 was used for all tests to indicate statistical significance. To compare the discriminatory power of all

renal function parameters, receiver operating characteristic (ROC) curves and the area under the curve (AUC) were calculated. Logistic regression analyses were used to calculate the predicted probabilities (hazard ratio) of SeCr, eGFR and CrCl levels. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, IL).

Results

Between January 1998 and December 2007, 10,626 patients underwent isolated CABG or OPCAB surgery in our institution. Preoperative SeCr was missing in 267 patients and postoperative SeCr was missing in 102 patients due to mortality before renal function could be determined. In 433 patients, we were not able to calculate the CrCl or e-GFR due to missing data. We excluded 122 patients who were lost to follow-up and 24 patients who were on haemodialysis leaving 9987 patients with complete data

Table 4 Multivariate logistic regression analyses for early mortality and Cox regression analyses for late mortality

	HR early mortality	<i>p</i> -value	HR late mortality	<i>p</i> -value
Preop SeCr	1.003 (1.000–1.007)	.026	1.005 (1.004–1.006)	<.0001
Postop SeCr	1.007 (1.006–1.009)	<.0001	1.004 (1.003–1.005)	<.0001
Preop CrCl	0.988 (0.978–0.998)	.018	0.988 (0.983–0.992)	<.0001
Postop CrCl	0.958 (0.950–0.966)	<.0001	0.987 (0.983–0.990)	<.0001
Preop e-GFR	0.989 (0.979–0.999)	.026	0.984 (0.979–0.988)	<.0001
Postop e-GFR	0.960 (0.952–0.968)	<.0001	0.985 (0.982–0.989)	<.0001

SeCr serum creatinine level; *CrCl* creatinine clearance; *e-GFR* estimated glomerular filtration rate

included in this study. Patients' preoperative and perioperative demographic and clinical characteristics are presented in Table 1. Renal function parameters are shown in Table 2.

Risk factors for early mortality, which were identified using univariate analyses and were entered into the multivariate analysis, were: age, diabetes, chronic obstructive pulmonary disease (COPD), left ventricular ejection fraction less than 35% (EF<35%), the number of transfused units of red blood cells (RBCs) and perioperative myocardial infarction (Table 3). These independent risk factors were entered into the multivariate analyses together with the renal function parameters (Table 4). The odds ratios of the preoperative parameters for early mortality were closer to 1 than those of the postoperative parameters.

Age, male gender, diabetes, COPD, peripheral vascular disease (PVD), EF<35%, preoperative haemoglobin level, previous cardiac surgery, re-exploration and perioperative myocardial infarction were significant risk factors for late mortality as identified by Cox regression analysis. These factors were entered into the multivariate analysis. The results are shown in Table 3. Subsequently, the renal function parameters were added to the multivariate analyses together with the independent risk factors. The results of these analyses are shown in Table 4. The hazard ratios for late mortality of the preoperative parameters are close to the hazard ratios of the postoperative parameters (range 0.984–1.005).

The ROC curves for the different renal function parameters as risk factors for early mortality are shown in Fig. 1. The areas under the curve (AUC) are presented in Table 5. The postoperative level of CrCl and e-GFR has the highest discriminatory power. For both preoperative and postoperative levels, CrCl showed the highest discriminatory power, followed by e-GFR and at least SeCr.

Fig. 1 ROC curves of renal function parameters as risk factors for early mortality

Table 5 Area under the ROC curve for renal function parameters

	Area early mortality	SE	Area late mortality	SE
Preop SeCr	.632	.023	.634	.009
Postop SeCr	.778	.020	.651	.009
Preop CrCl	.710	.019	.303	.008
Postop CrCl	.721	.017	.291	.008
Preop e-GFR	.664	.021	.342	.009
Postop e-GFR	.803	.018	.326	.009

SE standard error; SeCr serum creatinine level; CrCl creatinine clearance; e-GFR estimated glomerular filtration rate

Figure 2 shows the ROC curves for the renal function parameters as risk factors for late mortality. The corresponding areas under the curves are shown in Table 5. For the three renal function parameters, the postoperative levels had a significantly better discriminatory power than the preoperative levels. Both preoperative and postoperative CrCl had a higher discriminatory power compared with e-GFR, which in turn was better than SeCr.

Figure 3 shows the non-linear relationship between the preoperative and postoperative CrCl and e-GFR and predicted probability of mortality (hazard ratio).

Discussion

In this study of 9987 patients undergoing CABG in a single institution, renal dysfunction measured by CrCl showed the highest discriminatory power to predict early and late mortality. The predictive power of CrCl was greater than

Fig. 2 ROC curves for renal function parameters as risk factors for late mortality

that of e-GFR and SeCr. The postoperative values of all the three parameters had a higher discriminatory power than the preoperative values. All the three parameters were revealed as independent risk factors for early as well as late mortality confirming the findings of others [4, 6, 7, 11].

This study confirms the superiority of the Cockcroft-Gault formula (as expressed by CrCl) over the MDRD

equation (as expressed by e-GFR) in terms of predictive power for in-hospital mortality, confirming the finding of Lin et al. [6]. This may be explained by the fact the Cockcroft-Gault formula includes weight as a variable which indirectly reflects the body mass index (BMI). BMI is known to be an independent risk factor for early mortality after CABG [12]. Other studies [13, 14] revealed that the MDRD equation tends to underestimate the actual GFR in patients with chronic kidney disease but normal serum creatinine. This may explain why renal function estimated by the MDRD equation is a less accurate predictor for early mortality when compared with renal function estimated by the Cockcroft-Gault formula. In an earlier study [15] we showed the value of preoperative creatinine clearance in predicting early and late mortality after CABG.

We found a small non-significant decrease in the mean value of postoperative serum creatinine level compared with the preoperative value. This is in disagreement with some earlier reports [16]. This small change in serum creatinine in our patient group could be explained by the perioperative intravenous crystalloid administration protocol in our patients, which is different from that in other centres.

For SeCr, CrCl and e-GFR, the postoperative renal function has a higher discriminatory power for predicting early mortality compared with the preoperative renal function. This seems logical because the postoperative renal function is the result of the preoperative renal function and the subsequent trauma of the operation [10, 17]. This operative trauma may lead to further deterioration of the renal function with subsequent higher early and late mortality. Furthermore, the hazard ratios for the postoperative levels were further away from the value '1' compared with the hazard ratios of the preoperative levels. This means that when the preoperative and postoperative renal function

Fig. 3 Mean predicted probability of mortality for the pre- and postoperative e-GFR and CrCl

measurements are equally deteriorated, it is the postoperative value which strongly predicts the poor outcome. In other words, the preoperative renal function is mostly a stable situation whereas the postoperative renal function is, as stated above, the result of the surgical trauma on top of the preoperative renal function. On the other hand, postoperative renal function measurement is strongly dependent on the preoperative value. This association is also stronger with the estimated CrCl than with serum creatinine levels [18].

In patients who survive the operation, the postoperative renal function reflects a stable situation. The hazard ratios for late mortality do not differ between preoperative and postoperative renal function parameters. In addition, the areas under the ROC curves of preoperative and postoperative parameters are almost the same. We also found that the Cockcroft-Gault formula is a better predictor for late mortality after CABG followed by the MDRD equation and then the SeCr.

We found a non-linear relationship between CrCl and e-GFR and the predicted probability of early mortality (=odds ratio), calculated by logistic regression analysis. Any arbitrary cut-off point in a risk scoring system will be inevitably inaccurate. Considering the non-linear predicted probability curves, commonly described cut-off points for CrCl and e-GFR of 30–59 mL/min as moderate renal failure and <30 mL/min as severe renal failure do not seem to be accurate when used as a dichotomous variable in risk scoring systems. The cut-off point of serum creatinine of >200 µmol/L used in the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [19, 20] will inevitably be inaccurate and needs to be reconsidered.

Conclusions

In patients undergoing isolated coronary artery bypass grafting, renal function estimated by the Cockcroft-Gault formula has the highest discriminatory power to predict early and late mortality followed by the Modification of Diet in Renal Disease (MDRD) formula and finally the serum creatinine level. The postoperative parameters were better predictors for early and late mortality compared with the preoperative parameters. The relationship between renal function and mortality is non-linear. Any cut-off point used in a risk scoring system will be inaccurate. Renal function as a variable in the EuroSCORE risk scoring system needs to be reconsidered.

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