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Does Mild Renal Failure Affect Coronary Flow Reserve after Coronary Artery Bypass Graft Surgery?

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ABSTRACT

Introduction: There are only a limited number of studies on the link between mild renal failure and coronary artery disease. The purpose of this study is to investigate the effects of mild renal failure on the distal vascular bed by measuring the coronary flow reserve (CFR) in transthoracic echocardiography after coronary artery bypass grafting (CABG).

Methods: The study included 52 consecutive patients (12 women and 40 men) who had undergone uncomplicated CABG. The patients were divided into 2 groups. Group 1 included patients with a preoperative glomerular filtration rate (GFR) of 60-90 (mild renal failure), and group 2 included those with a GFR >90. The CFR measurements were carried out through a second harmonic transthoracic Doppler echocardiography.

Results: The mean age was 60.08 ± 1.56 years in group 1 and 60.33 ± 1.19 in group 2. The mean preoperative CFR was 1.79 ± 0.06 in group 1 and 2.05 ± 0.09 in group 2. The mean postoperative CFR was 2.09 ± 0.08 in group 1 and 2.37 ± 0.06 in group 2. There was a statistically significant difference between the 2 groups as to preoperative creatinine clearance, preoperative estimated GFR, postoperative day 7 creatinine clearance, postoperative month 6 creatinine clearance, postoperative day 7 estimated GFR, postoperative month 6 estimated GFR, preoperative CFR, and postoperative CFR ($P < .05$). After bypass surgery, there was a significant increase in the mean postoperative CFR, when compared with the mean preoperative CFR ($P = .001$).

Conclusion: In our study, we detected a decrease in CFR in patients with mild renal failure. We believe that in patients undergoing CABG for coronary artery disease, mild renal failure can produce adverse effects due to deterioration of the microvascular bed.

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INTRODUCTION

The morbidity and mortality rates of patients with preoperative renal failure, whatever its degree, are higher in the period after cardiopulmonary bypass compared to rates in patients without renal dysfunction [Hayashida 2001; Holzmann 2007; Howell 2008]. For this reason, to prevent possible complications, such patients must be adequately assessed in the preoperative period and prepared well for the operation. Similarly, in patients with coronary artery disease, mild renal failure is considered to be an adverse prognostic indicator [Anevakar 2004]. Coronary atherosclerosis is accelerated in patients with renal failure due to such factors as uremia linked to hypertension, lipid anomalies, anemia, excess fluid, platelet dysfunction, and parathyroid dysfunction accompanied by hypercalcemia [Labrousse 1999]. For this reason, chronic renal failure is frequently accompanied by coronary artery disease. A recent study has shown that the microvascular function deteriorates and the coronary flow reserve (CFR) falls in patients with angiographically normal coronary arteries who undergo hemodialysis on account of chronic renal failure [Tok 2005]. Using transthoracic Doppler echocardiography (TTDE) to measure CFR is an inexpensive, noninvasive, clinically widely accepted method used to evaluate the coronary microvascular bed [Puddu 2012]. This is the first reported study of the use of TTDE to measure the postoperative CFR values of patients with mild renal dysfunction who are not undergoing hemodialysis in order to determine the degree of dysfunction in their microvascular bed after coronary artery bypass grafting (CABG).

MATERIALS AND METHODS

Study Population

The study included 52 consecutive patients (12 women and 40 men) who had undergone uncomplicated CABG. The patients were divided into 2 groups according to their glomerular filtration rate (GFR) measurements. Group 1 included patients with a GFR of 60-90 (mild renal failure) (n = 25; 20 men and 5 women), while group 2 included those with a GFR >90 (n = 27; 20 men and 7 women). Patients with the following conditions were excluded from the study: chronic obstructive lung disease, cerebrovascular disease, atrial fibrillation, emergency treatment, ejection fraction <30%, redo CABG, preoperative dialysis, GFR <60, microalbuminurea, history of prolonged drug use (such as steroids, analgesics, or nonsteroidal antiinflammatory drugs), coronary endarterectomy, administration of inotropic agents (dobutamine, adrenaline) or intraaortic balloon support after surgery, combined heart valve surgery/aneurysmectomy, or acute myocardial infarction after bypass, necessitating a percutaneous coronary intervention. The study received the approval of the ethics board as well as the institutional review board of Baskent University and was supported by the Baskent University Research Fund. The informed consent of all patients was obtained during the preoperative period.

Cardiac Surgery

On-Pump Surgery: Under general anesthesia, median sternotomy was applied to each patient. The ascending aorta was cannulated, provided that this was feasible, and venous return was achieved by a vacuum-assisted 2-stage cannula. For this purpose, a membrane oxygenator and a nonpulsatile roller pump were used. Activated clotting time (ACT) was kept between 480 and 600 seconds after systemic heparinization. Each patient was cooled off to 28-30ºC. A crystalloid cardioplegic solution (St. Thomas II) was applied every 20 minutes to protect the myocardium. The anastomoses were applied to the right coronary artery or to its posterior descending branch, to the circumflex coronary arterial system, and to the left anterior descending artery (LAD) and the diagonal arterial system. In all patients, for the anastomosis to the LAD artery, the left internal mammary artery (LIMA) was preferred (100%). The proximal anastomoses were sewn either onto the aorta by installing a side clamp or onto another graft. Patients were weaned from cardiopulmonary bypass when the rectal temperature reached 37°C.

Off-Pump Surgery: Median sternotomy was performed on each patient. Arterial and venous grafts were prepared. The pericardium and heart were suspended by sutures. The arteriotomy was created using suction-type Octopus tissue stabilizers (Medtronic, Minneapolis, MN, USA), following which an intracoronary shunt (Medtronic) was installed. With the method described earlier, the distal anastomoses were applied using 7/0 propylene. Next the proximal anastomoses were applied.

Patient Follow-up

After surgery, all of the patients were kept in the intensive care unit for 2 days with close follow-up to monitor their hemodynamic parameters and urine output. In the lower-GFR group, a positive fluid balance was maintained and furosemide was administered (0.5 to 1 mg/kg per dose) according to need. All patients were intravenously administered cefazolin (1 g, 3 times daily). After surgery, the patients were taking equivalent amounts of cardiovascular medication, including aspirin (300 mg/day), a lipid-lowering drug (atorvastatin, according to the blood cholesterol level), angiotensin-converting enzyme inhibitors (ramipril, according to the arterial blood pressure), and a β-blocker (metoprololol, according to the arterial blood pressure).

Estimation of GFR

Renal functions of the patients were measured on the basis of estimated GFR, which constitutes the most reliable index of renal function as stated in the guidelines [Eknoyan 2003; Levey 2003] of the National Kidney Foundation. The GFR and serum creatinine values of the patients were estimated in the preoperative period, days 1 and 7 in the postoperative period, and in the sixth month after the operation. GFR was estimated from the Modification of Diet in the Renal Disease equation for men [Levey 1999], GFR (mL/min per 1.73 m^2) = 186 × (serum creatinine mg/dL)1.154 × (age [years])0.203. The results of this equation were multiplied by a correction factor of 0.742 for women. Creatinine clearance was calculated using the Cockroft and Gault formula: (140 – age [years]) × weight (kg)/(serum creatinine × 72 (×0.85 for women), which is adjusted for each 1.73 m^2 of body surface area. The chronic kidney disease classification was used to define the degree of severity of renal failure in each case: class 1 (normal): GFR > 90 mL/min/1.73 m^2; class 2 (mild): GFR 60-89 mL/min/1.73 m^2; class 3 (moderate): GFR 30-59 mL/min/1.73 m^2; class 4 (severe): GFR 15-29 mL/min/1.73 m^2; class 5 (kidney failure): GFR <15 mL/ min/1.73 m^2 [Levey 2003].

Measurement of CFR Values

The patients were called for a check in the sixth month after surgery. Using an Acuson Sequoia C256® Echocardiography System (Acuson, Mountain View, CA, USA), the same cardiologist who had performed the first TTDE performed a second harmonic TTDE on each patient. The distal LAD was visualized by using a modified, foreshortened 2-chamber view, which was obtained by medially sliding the transducer on the upper part, in an apical 2-chamber view, to find the best alignment with respect to the interventricular sulcus. After this, the coronary flow in the distal LAD was studied through color Doppler flow mapping over the epicardial part of the anterior wall, with the color Doppler velocity set in the range of 8.9-24.0 cm/second. The left ventricle was first imaged on the long-axis cross-section, and then the ultrasound beam was laterally inclined. Following this, the coronary blood flow in the LAD (middle to distal) was visualized using color Doppler flow mapping. A Doppler recording of the LAD was made for each patient while a dipyridamole infusion was administered at a rate of 0.84 mg/kg for 6 minutes. When the sample volume was placed on the color signal, the characteristic biphasic flow pattern appeared in the spectral Doppler of the LAD, with larger diastolic and smaller systolic components. The coronary diastolic peak velocities were measured at the baseline and after the dipyridamole (0.84 mg/kg over 6 minutes). The highest 3 Doppler signals were averaged for each measurement. The definition of the CFR was taken as the ratio of the hyperemic to the baseline diastolic peak velocity [Dimitrow 2003; Korcarz 2004]. Echocardiographic images were recorded on VHS videotapes.

Table 1. Patient Demographic Characteristics

Characteristics	Group 1 (GFR 60-90)	Group 2 (GFR >90)	*t*	*P*
Mean age, years	60.08 ± 1.56	60.33 ± 1.19	−0.130	.897
Sex*			0.257	.746
Male	20 (80%)	20 (74.1%)		
Female	5 (20%)	7 (25.9%)		
Height, cm	167.04 ± 1.95	164.85 ± 2.11	0.756	.453
Weight, kg	76.28 ± 2.21	79.14 ± 2.18	−0.919	.363
Body mass index, kg/m^2	27.40 ± 0.73	29.24 ± 0.81	−1.670	.101
Systolic blood pressure, mmHg	130 ± 3.04	129.25 ± 1.88	0.211	.834
Diastolic blood pressure, mmHg	78.40 ± 2.30	73.70 ± 1.42	1.733	.091
Heart rate, bpm	76.64 ± 1.80	78.96 ± 1.25	−1.057	.296
Fasting blood glucose, mg/dL†	105.64 ± 7.85	111.40 ± 5.19	237.00	.066
Total cholesterol, mg/dL	182.24 ± 6.58	179.59 ± 8.40	0.245	.807
Triglyceride, mg/dL	177.08 ± 13.18	164.81 ± 20.30	.498	.621
High-density lipoprotein cholesterol, mg/dL	40 ± 1.68	38.74 ± 1.12	0.629	.533
Low-density lipoprotein cholesterol, mg/dL	104.24 ± 5.07	108.48 ± 5.79	−0.547	.587
Preoperative creatinine clearance, mL/min	85.30 ± 3.57	117.09 ± 4.71	−5.314	.000‡
Preoperative estimated GFR, mL/min	79.90 ± 1.40	108.63 ± 2.51	−9.960	.000‡
Preoperative CRP, mg/L	4.01 ± 0.46	3.33 ± 0.51	0.975	.334

*Because sex is a categorical variable, the chi-square test was used to measure the difference between the 2 groups. This value is the value obtained from the chi-Square test and the *P* value.

†Because the fasting blood glucose level did not have a normal distribution, the Mann-Whitney U test was used to measure the difference between the 2 groups. This value is the value obtained from the Mann-Whitney U test and the *P* value.

‡Variables with statistically significant test results ($P < .05$).

Table 2. Postoperative Estimated GFR and Creatinine Clearance Values

Variable	Group 1 (GFR 60-90)	Group 2 (GFR >90)	*t*	*P*
Postoperative day 1 creatinine clearance, mL/min	90.29 ± 5.70	103.53 ± 5.89	−1.610	.114
Postoperative day 7 creatinine clearance, mL/min	94.73 ± 4.56	119.95 ± 6.28	−3.225	.002*
Postoperative month 6 creatinine clearance, mL/min	80.24 ± 4.15	109.08 ± 6.19	−3.512	.001*
Postoperative day 1 estimated GFR, mL/min	85.53 ± 4.72	93.88 ± 4	−1.354	.182
Postoperative day 7 estimated GFR, mL/min	90.29 ± 3.03	111.53 ± 4.10	−4.138	.000*
Postoperative month 6 estimated GFR, mL/min	74.62 ± 3.12	97.98 ± 3.99	−4.276	.000*

*Variables with statistically significant test results ($P < 0.05$).

Table 3. Operation and Echocardiography Parameters

Characteristics	Group 1 (GFR 60-90)	Group 2 (GFR >90)	*t*	*P*
Operation type (off-pump/on-pump)*			1.878	.266
Off-pump	14 (56%)	10 (37%)		
On-pump	11 (44%)	17 (63%)		
Cardiopulmonary bypass time/minute	97.54 ± 6.83	110.75 ± 10.56	−0.944	.354
Number of bypasses*			8.131	.149
1	1 (4%)	5 (18.5%)		
2	11 (44%)	6 (22.2%)		
3	9 (36%)	8 (29.6%)		
4	3 (12%)	6 (22.2%)		
5	0 (0%)	2 (7.4%)		
6	1 (4%)	0 (0%)		
Left ventricular ejection fraction, %	62.77 ± 1.55	59.48 ± 1.85	1.330	.190
Postoperative CFR	2.09 ± 0.08	2.37 ± 0.10	−2.060	.045†
Preoperative CFR	1.79 ± 0.06	2.05 ± 0.09	−2.332	.024†

*Since sex is a categorical variable, the chi-square test was used to measure the difference between the 2 groups. This value is the value obtained from the chi-square test and the *P* value.

†Variables with statistically significant test results ($P < 0.05$).

Statistical Analyses

In order to detect the differences between the 2 groups, the K-S normal distribution test was applied first to the variables that could be causing the difference. The test result revealed that the variables postoperative creatine, glucose, and gamma-glutamyl transpeptidase did not have normal distributions. The independent samples t-test was used to find the differences between the 2 groups for the variables with normal distributions, and the Mann-Whitney U test was used for the variables without normal distributions. Chi-square analyses of the categorical variables of sex, operation type, and number of anastomoses were used to determine whether associations existed between the 2. Differences with *P* values <.05 were accepted as significant.

In the second stage, the backward method was used to find the factors affecting the group with a CFR value of <2 and the one with a CFR value of >2. To determine the variables affecting the variable CFR, all of the variables were first subjected to logistic regression analysis. Then, multivariate logistic regression analysis was applied to find among the significant variables those that affected the variable CFR. *P* values < .05 were considered significant.

RESULTS

Clinical Characteristics of the Study Population

The mean age was 60.08 ± 1.56 years in group 1 and 60.33 ± 1.19 years in group 2. The mean preoperative CFR was 1.79 ± 0.06 in group 1 and 2.05 ± 0.09 in group 2. The mean postoperative CFR was 2.09 ± 0.08 in group 1 and 2.37 ± 0.06 in group 2. In group 1, off-pump surgery was applied to 14 (56%) and on-pump surgery was applied to 11 (44%) of patients. In group 2, off-pump surgery was applied to 10 (37%) and on-pump surgery was applied to 17 (63%) patients. There were no significant differences in CFR between the patients who underwent on-pump (mean CFR = 2.25 ± 0.51) and off-pump surgery (mean CFR = 2.23 ± 0.49) ($P = .907$).

There were statistically significant differences between the 2 groups for preoperative creatinine clearance, preoperative estimated GFR, postoperative day 7 creatinine clearance, postoperative month 6 creatinine clearance, postoperative day 7 estimated GFR, postoperative month 6 estimated GFR, preoperative CFR, and postoperative CFR ($P < .05$). On the other hand, there were no statistically significant differences

Table 4. Multivariate Analysis for CFR

Variable	B	Standard Error	Wald	*P*	Odds Ratio	95% CI
Step 1 (first step)						
Postoperative day 7 creatinine, mg/dL	−1.330	4.612	0.083	.773	0.265	0.00-2228.930
Uric acid, mg/dL	−0.038	0.358	0.011	.916	0.963	0.478-1.941
CRP, mg/L	−0.323	0.175	3.420	.064	0.724	0.514-1.020
Preoperative GFR, mL/min	0.011	0.026	0.173	.677	1.011	0.961-1.063
Postoperative day 7 GFR, mL/min	0.030	0.043	0.482	.487	1.030	0.947-1.120
Constant	−7.19	7.023	0.010	.919	0.487	
Step 4 (last step)						
Preoperative CRP, mg/L	−0.346	0.156	4.958	.026*	0.707	0.521-0.959
Postoperative day 7 GFR, mL/min	0.046	0.021	4.865	.027*	1.047	1.005-1.091
Constant	−2.552	2.088	1.493	.222	0.078	

*Variables with statistically significant test results ($P < 0.05$).

in mean age, sex, height, weight, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, preoperative C-reactive protein (CRP), postoperative day 1 creatinine clearance, postoperative day 1 estimated GFR, operation type (off pump/on pump), cardiopulmonary bypass time, left ventricular ejection fraction, and the number of bypasses ($P > .05$) (Tables 1-3). After bypass surgery, there was a significant increase in the mean postoperative CFR (2.24 ± 0.50) compared with the mean preoperative CFR 1.93 ± 0.42) ($P = .001$).

In the multivariant analysis made for CFR, preoperative CRP (0.707; 95% confidence interval [CI], 0.521-0.959; $P < .05$), postoperative day 7 GFR (1.047; 95% CI, 1.005-1.091; $P < .05$) were determined to be independent risk factors (Table 4).

DISCUSSION

According to the National Adult Cardiac Database of the Society of Thoracic Surgeons, in patients who have undergone coronary artery bypass without dialysis, GFR (mL/min/1.73 m^2) is >90 in 22% of cases, 60-89 in 51%, 30-59 in 24%, and severe in 2% without dialysis, and in 1.5% of cases, dialysis is required [Cooper 2006]. The level of serum creatinine is recognized as a major risk factor in patients who undergo cardiac surgery, and as such it is currently counted among the most accurate operative risk-scoring methods [Parsonnet 1989; Nashef 1999]. It has been recently claimed that estimated GFR is superior to serum creatinine as a measure of renal function [Stevens 2006]. Thus estimated GFR has come to be considered a powerful and independent predictor of mortality after CABG [Hillis 2006].

Various studies reported in the literature have shown that mild renal failure increases the mortality and morbidity rates after CABG [Anderson 1999; Hayashida 2001; Hirose 2001]. Kangasniemi et. al. have shown that an estimated GFR <60 mL/min/1.73 m^2 is a major predictor of long-term cardiovascular mortality and morbidity in the postoperative period [Kangasniemi 2008]. Zakeri et al. have found that the ratios of operative mortality, postoperative stroke, and new need for dialysis are all significantly higher in patients with mild renal failure [Zakeri 2005]. In the prospective study of 7621 patients performed by Howell et al., it was revealed that mild renal dysfunction is an important independent determinant of in-hospital and late mortality in adult patients who have undergone cardiac surgery [Howell 2008].

As is well known, hemodialysis patients commonly suffer from atherosclerosis and in particular from plaque formation in the epicardial coronary arteries [Tyralla 2003]. In patients with end-stage renal failure who also have coronary artery disease, there are diffuse, sometimes even circular, calcifications of the coronary arteries that reach deep into the periphery of the vessels. The reason for this is the increased calcium-phosphate product induced by secondary hyperparathyroidism. Moreover, coronary atherosclerosis is usually accelerated in patients with chronic hemodialysis because of hypertension, hyperlipidemia, and abnormalities in the metabolism of calcium and triglycerides.

CFR measurement is a noninvasive method used to assess the endothelial and microvascular functions of the epicardial coronary arteries. Hyperemia is induced in the coronary bed through intravenous administration of dipiridamol and adenozin, which makes it possible to assess the state of the coronary bed under stress [Rigo 2005]. In the presence of a significant degree of coronary artery disease, a CFR value <2.0 has a sensitivity of 92% and a specificity of 82% [Hozumi 1998]. Thanks to this method, any impairment in CFR can be detected before an angiographically detectable stenosis develops in the epicardial coronary arteries. Thus this method renders it possible to examine early coronary microvasculature pathology [Gould 1974]. In this study, we found by echocardiography that in the postoperative sixth month the CFR values were lower in group 1 than in group 2. In other words, we have observed that mild renal failure reduces microvascular circulation.

Off-pump surgery is a technique of myocardial vascularization recently developed to avoid the harmful effects of on-pump surgery. Most of the studies that investigate the effects of renal failure on CABG have been carried out on patients undergoing conventional on-pump surgery [Labrousse 1999; Nishida 2001]. Various recent studies have shown that the off-pump technique yields superior results in patients with renal failure [Dimitrow 2003; Sajja 2007]. We found no differences in the subgroups, suggesting that type of surgery has no effect on CFR ($P = .907$).

The present study has shown that preoperative estimated GFR can be considered a powerful multivariable predictor of CFR after coronary artery bypass surgery. In the literature we have encountered no previous studies investigating the effects of mild renal failure on the CFR of patients undergoing surgery. We also found no studies that measured CFR to investigate the state of the microvascular bed and determine how it was affected in patients with various degrees of renal dysfunction who underwent coronary artery bypass. In this study, 6 months after surgery, we observed a statistically significant drop in the CFR of patients with a slightly abnormal estimated GFR (<90), compared with that of patients with normal estimated GFR (>90). Moreover, we determined that the choice of the on-pump or off-pump technique had no effect on CFR.

In conclusion, the findings of the study have revealed that the coronary flow is adversely affected even in the presence of only mild renal dysfunction. In our opinion, this is because among the patients undergoing CABG, coronary endothelial function deteriorates more in patients with mild renal failure than in patients without renal dysfunction.

Limitations of the Study

The exact mechanism underlying the link between low CFR and mild renal failure was still unknown when this study was performed. Moreover, the shortness of the follow-up period of the study and the low number of patients included therein has prevented us from showing the effects of mild renal failure on mortality and morbidity. For this reason, we believe that there is a need for longer-term studies including a greater number of patients.

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