Changes in glomerular filtration rate after cardiac surgery with cardiopulmonary bypass in patients with mild preoperative renal dysfunction

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Background. Cardiac surgery with cardiopulmonary bypass (CPB) is commonly perceived as a risk factor for decline in renal function, especially in patients with preoperative renal dysfunction. There are few data on the effects of CPB on renal function in patients with mild preoperative renal dysfunction. The purpose of this study was to evaluate renal function in patients with pre-existing mild renal dysfunction undergoing cardiac surgery with CPB.

Methods. In a multicentre study cohort we measured prospectively the glomerular filtration rate (GFR) by radioactive markers both before operation and on the 7th postoperative day in cardiac surgical patients with preoperative serum creatinine $\leq 120 \mu\text{mol} \text{l}^{-1}$ ($n=56$). In a subgroup of patients ($n=14$) in addition to the GFR, the effective renal plasma flow (ERPF) and the filtration fraction (FF) were measured.

Results. While preoperative GFR [77.9 (25.5) ml min$^{-1}$] increased to 84.4 (23.7) ml min$^{-1}$ ($P=0.005$) 1 week after surgery, ERPF did not change [295.8 (75.2) ml min$^{-1}$ and 295.9 (75.9) ml min$^{-1}$, respectively; $P=0.8$]. In accordance, the FF increased from 0.27 (0.05) (before operation) to 0.30 (0.04) (Day 7, $P=0.01$).

Conclusion. Our results oppose the view that cardiac surgery with CPB adversely affects renal function in patients with preoperative mild renal dysfunction and an uncomplicated clinical course.

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Cardiac surgery is a risk factor for postoperative renal function impairment. Although renal failure requiring dialysis is a relatively rare complication, 15–25% of patients show a mild to moderate decline in postoperative renal function.1,2 Importantly, the temporal changes in renal function in these patients, as measured by serum creatinine increase during the first postoperative week, are predictive of long-term mortality.1,3 A small increase in serum creatinine (25% from baseline) resulted in an increase in mortality rate of 22 to 38% at 96 months. In addition to these data, it is generally perceived that preoperative mild to moderate renal dysfunction poses an additional risk in these patients.4

The most accurate method to determine the glomerular filtration rate (GFR) is to measure the clearance of inulin or radiolabelled compounds such as $^{125}$I-iothalamate.5 Perioperative assessment of renal function, using the more definitive measurement of GFR using $^{125}$I-iothalamate clearance, has been reported in cardiac surgical patients but only in individuals with normal renal function.6 These data indicate that GFR and effective renal plasma flow (ERPF) are unaffected by cardiac surgery using

†Declaration of interest. A. J. Rankin is a research employee of Pfizer Global Research and Development, Kent, UK.
cardiopulmonary bypass (CPB). The purpose of this study was to evaluate the effect of cardiac surgery with CPB on GFR in patients with pre-existing mild renal dysfunction. We measured GFR before and 1 week after elective cardiac surgery with CPB in a multicentre study, using radioactive isotopes. In addition, in one of the participating centres, ERPF measurements were included to obtain a more detailed evaluation of renal haemodynamics.

Methods

The patients in the study were enrolled at three participating Dutch centres: University Hospital Nijmegen, Erasmus Medical Center Rotterdam, and University Medical Center Groningen. The protocol was approved by the ethics committee of each institution, and all patients gave written informed consent. Fifty-six patients undergoing cardiac surgery with CPB were prospectively enrolled. Inclusion criteria were serum creatinine >120 μmol l⁻¹, normal urinalysis, and no exposure to nephrotoxic drugs or radiocontrast agents within 1 week of surgery. A serum creatinine cut-off of >120 μmol l⁻¹ is related to a GFR <80 ml min⁻¹.² Patients with unstable angina, recent (<1 month) myocardial infarction, or haemodynamic instability were excluded. Preoperative medication, including angiotensin-converting enzyme (ACE) inhibitors, beta adrenergic receptor blocking agents, calcium-channel blocking agents, and nitrates, was continued until the morning of surgery.

Operative procedures

The patients received total i.v. anaesthesia. Induction started with sufentanil 0.5 μg kg⁻¹, midazolam 0.05–0.1 mg kg⁻¹, and pancuronium 0.1 mg kg⁻¹ to facilitate tracheal intubation. Anaesthesia was maintained with sufentanil 2–5 μg kg⁻¹ and a continuous infusion of midazolam 0.1 mg kg⁻¹ h⁻¹. Patients’ lungs were ventilated with air and oxygen (FiO₂=0.4). Radial artery and central venous pressures were continuously monitored. Non-pulsatile CPB was performed with a non-occlusive roller pump and membrane oxygenator (Cobe Optima; Cobe Laboratories, Lakewood, CO, USA). The extracorporeal circuit was primed with 500 ml of hydroxyethyl starch 6% and 1000 ml of lactated Ringer’s solution. An initial dose of heparin 300 IU kg⁻¹ was given before cannulation of the aorta and right atrium to obtain a kaolin-activated clotting time >400 s. Additional heparin was given during CPB when the kaolin-activated clotting time was <400 s. Flow during CPB was maintained at 2.2 litre min⁻¹ m⁻² during mild hypothermia (32°C) with α-stat pH management. Cold St. Thomas solution was infused into the aortic root for cardioplegia during aortic cross-clamping. During CPB, the mean arterial pressure (MAP) was kept between 60 and 90 mm Hg using phenylephrine or nitroglycerin as needed. Mannitol or aprotinin were not administered during the study period. After weaning of CPB, protamine was given in a dose equal to the initial dose of heparin. Fluids and vasoactive medication were given based on clinical indications but not as part of the protocol. Postoperative haemodynamic management was according to the local treatment protocol of the participating centres and were directed at maintaining the cardiac index >2.1 litre min⁻¹ m⁻² with a MAP of >70 mm Hg and diuresis between 1 and 2 ml kg⁻¹ h⁻¹. Diuretics were not routinely given and used at the discretion of the attending physician.

Renal function measurement

Renal function measurements were obtained in the morning after a light breakfast at two time points: 1 day before and 7 days after surgery. The evening before each study day, the thyroid gland was blocked by giving 10 drops of a saturated Lugol’s solution (iodine in potassium iodide). An i.v. catheter was placed in the vena cubiti for the radioisotope solution. The infusion solution for measurement of the GFR was prepared by adding 3 MBq of ¹²⁵I-iothalamate (Amersham, ‘s Hertogenbosch, The Netherlands) to 100 ml of saline. In addition to the GFR measurement, the ERPF was measured in a subgroup of patients (n=14) by adding 4 MBq ¹³¹I-hippuran to the infusion solution. After drawing a blank blood sample, a priming solution containing 0.4 ml kg⁻¹ body weight of the infusion solution plus an extra 0.6 MBq of ¹²⁵I-iothalamate was given at 8 a.m. Immediately thereafter, the continuous infusion was started by means of an infusion pump. On the basis of earlier observations, the infusion rate was adjusted with respect to estimated renal function to ensure adequate isotope concentrations.⁸ To ensure adequate diuresis, 200 ml of water was given orally every hour. After the stabilization period of 2 h, two clearance periods of 2 h each followed. Urine was collected by spontaneous voiding and blood samples were drawn at the start, middle, and end of each clearance period. Plasma separation was performed immediately after sampling. The activities of ¹²⁵I-iothalamate and ¹³¹I-hippuran in plasma and urine were determined in duplicate by using a LKBG Compugamma scintillation counter [EG & G (Wallac), Breda, The Netherlands].

Calculations of the clearance rates were made by using the standard formulas for plasma clearance:

\[
\text{plasma clearance} = \frac{I \times V}{P}
\]

where I is counts min⁻¹ ml⁻¹ of the infusion solution, V is volume of the infusion, and P is counts min⁻¹ ml⁻¹.

The standard formula for renal clearance (GFR) is

\[
\text{renal clearance} = \frac{U \times V}{P}
\]

where U is counts min⁻¹ ml⁻¹ urine, V is the urine production in ml min⁻¹, and P is counts min⁻¹ ml⁻¹.
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Thus, the GFR was calculated by using the formula:

\[ C_{\text{tot}} = \frac{U_{\text{tot}} \times V}{P_{\text{tot}}} \]

where \( C_{\text{tot}} \) is clearance of \(^{125}\)I-iothalamate, \( U_{\text{tot}} \) is counts of \(^{125}\)I-iothalamate in urine in counts min \(^{-1}\) ml \(^{-1}\), \( V \) is urine production in ml min \(^{-1}\), and \( P_{\text{tot}} \) is \(^{125}\)I-iothalamate in plasma in counts ml \(^{-1}\) min \(^{-1}\).

Effective renal plasma flow calculation was according to the same formula as for \(^{131}\)I-hippuran. Filtration fraction (FF) was calculated as the ratio of GFR and ERPF. This method has a day-to-day variation coefficient of 2.5% for GFR and 5% for ERPF.

Data analysis

Power calculation revealed that inclusion of 50 patients with a baseline GFR <80 ml min \(^{-1}\) (equal to a serum creatinine >120 \(\mu\)mol litre \(^{-1}\)) would enable the detection of a 15% difference in GFR (power=0.8, \(\alpha\)-risk=0.05) after surgery compared with baseline. Data are expressed as means (sd), unless stated otherwise. Correlation analysis was performed with Pearson’s correlation coefficient. Univariate testing between the two variables was performed with the \(t\)-test for continuous variables. Multivariate analysis was used to test the independent association between change in GFR from baseline (\(\Delta\)GFR) and several known risk factors \(^9\) \(^\text{to}^\text{10}\) for postoperative worsening of renal function. In the analysis, we included preoperative demographic risk factors (sex, age, preoperative GFR, systolic and diastolic blood pressure, diabetes, hypertension, myocardial infarction, and peripheral vascular disease) and procedure-related factors (type of operation, duration of operation, duration of CPB, and duration of aortic cross-clamping). Variables with a \(P\)-value of <0.1 in the univariate analysis were included in the multivariate analysis. Statistical significance was accepted at \(P<0.05\) (two-sided).

Results

Baseline, intra-, and postoperative characteristics of the study group are presented in Table 1. Two patients died from cardiac failure after periooperative myocardial infarction, one patient (preop GFR 125 ml min \(^{-1}\)) on the operative day and the other patient (preop GFR 97 ml min \(^{-1}\)) 1 day after the operation, before the second renal function measurement and were excluded from further analysis. There were no patients with overt renal dysfunction or patients requiring renal replacement therapy. Individual values of GFR are presented in Figure 1. Preoperative measurements showed a reduced GFR [77.9 (25.5) ml min \(^{-1}\)]. On the 7th postoperative day, a small, albeit significant, increase in GFR was observed [84.4 (23.7) ml min \(^{-1}\); \(P=0.005\); Fig. 1]. In contrast, MAP and heart rate were similar at baseline and the 7th postoperative day [MAP: 91.4 (12.3) and 95.5 (12.4) mm Hg, \(P=0.10\); heart rate: 79.1 (13.2) and 74.8 (14.7) beats min \(^{-1}\), \(P=0.12\)].

Despite our inclusion criterion of a serum creatinine >120 \(\mu\)mol litre \(^{-1}\), 12 patients had a normal preoperative GFR (GFR >90 ml min \(^{-1}\), Table 2). To compare postoperative changes in renal function in patients with and without reduced GFR, we classified patients according to the stages of the American Kidney Foundation (K-DOQI guidelines for chronic kidney disease).\(^9\) Interestingly, patients with mildly reduced GFR (GFR 60–90 ml min \(^{-1}\)) demonstrated a significant increase (13%) in postoperative GFR (Table 2). Patients with moderately reduced GFR (GFR 30–60 ml min \(^{-1}\)) showed the same trend towards

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**Table 1** Baseline, intraoperative, and postoperative patient characteristics (\(n=56\)). Data are expressed as mean (sd) or %

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>64.9 (8.4)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>47/9</td>
</tr>
<tr>
<td>BMI, kg m(^{-2})</td>
<td>26.1 (3.9)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>18.5</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>38.9</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>18.5</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>22.2</td>
</tr>
<tr>
<td>Operation CABG, %</td>
<td>59</td>
</tr>
<tr>
<td>Valve, %</td>
<td>27</td>
</tr>
<tr>
<td>Combination, %</td>
<td>14</td>
</tr>
<tr>
<td>Duration of aortic cross-clamping, min</td>
<td>81.5 (39.2)</td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass, min</td>
<td>120.0 (45.8)</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>274.7 (74.3)</td>
</tr>
<tr>
<td>Intensive care unit stay, days</td>
<td>1.6 (1.1)</td>
</tr>
<tr>
<td>Mechanical ventilation, days</td>
<td>0.6 (0.5)</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>9.0 (3.4)</td>
</tr>
</tbody>
</table>

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**Fig 1** Individual changes in glomerular filtration rate (GFR) before and after cardiac surgery with CPB (\(n=56\)). GFR was determined on the preoperative day (pre) and on the 7th day after operation (post) by infusion of radiolabelled compounds. Postoperative GFR increased significantly from baseline [77.9 (25.5) ml min \(^{-1}\) vs 84.4 (23.7) ml min \(^{-1}\); \(P=0.005\)]. The values are mean (sd).
postoperative increase. In contrast, in patients with normal GFR, no change was observed.

Correlation analysis demonstrated a negative correlation between the GFR at day 0 and the change in GFR (ΔGFR, r = −0.428, P = 0.001). Intra-operative variables (operation time, cross clamp time, and duration of CPB) were not correlated to ΔGFR.

After univariate testing, the variables male sex (P = 0.08), diastolic blood pressure at day 7 (P = 0.05), and preoperative GFR (P = 0.001) were included in a multivariate analysis to test their independent association with ΔGFR. The model showed only an independent association of preoperative GFR with ΔGFR (P = 0.005).

To analyse different aspects of renal haemodynamics, measurements of the ERPF were conducted in one of the participating centres. Changes in GFR, ERPF, FF, and serum creatinine of this subset (n = 14) are shown in Figure 2. Patient characteristics (data not shown) and the GFR in this subset were not different from other patients in this study population (P = 0.28). Also, as observed in the entire cohort, patients included in this subset showed a similarly small, but significant, increase in GFR after cardiac surgery [Fig. 2, preoperative: 77.8 (18.8) ml min⁻¹; day 7: 87.8 (25.0) ml min⁻¹, P = 0.01]. In contrast, the ERPF was unaffected by CPB [Fig. 2, 295.8 (75.2) ml min⁻¹ and 295.9 (75.9) ml min⁻¹, respectively, P = 0.8]. Consequently, an increase in FF from 0.27 (0.05) to 0.30 (0.04) was observed during this period (Fig. 2, P = 0.01). Finally, in keeping with the increase in GFR, serum creatinine concentrations were decreased by Day 7 before operation (Fig. 2).

Discussion

The main finding of the present study is that cardiac surgery with CPB does not adversely affect renal function of patients with preoperative mild renal dysfunction and an uneventful clinical course. Interestingly, we observed an increase in GFR on the 7th postoperative day, which was mainly confined to patients with mild renal function impairment. Furthermore, the ERPF in a subset of patients did not change, and accordingly the FF increased. To our knowledge, this is the first study in cardiac surgical patients with mild renal dysfunction measuring GFR using the gold standard, the clearance of 125I-iothalamate. This study extends previous findings in cardiac surgical patients with normal preoperative renal function.⁶

Few studies of renal function measurements using isotopes are available in cardiac surgical patients, probably because of the complexity of this method. Moreover, these studies were restricted to the intraoperative period. One study of CABG patients with normal preoperative renal function found no change in GFR and ERPF.⁶ Also, in the control group of a double-blind, randomized study on the effects of aprotinin in patients with a normal renal function, GFR did not change during surgery, whereas ERPF increased during CPB.¹² ERPF measurements during CPB, however, may be influenced by incomplete PAH extraction during hypothermia, which may increase ERPF erroneously.¹³ In addition, several factors are known to affect renal function during CPB including hypothermia, haemodilution, changes in haemodynamics, surgical stress, inflammatory response, and ischaemia reperfusion injury. Given this knowledge, we were particularly interested in the perioperative changes in renal function and performed measurements in a clinically more stable situation at Day 7, before discharge from the hospital.

<table>
<thead>
<tr>
<th>GFR stages</th>
<th>Preop GFR (ml min⁻¹)</th>
<th>GFR Day 7 (ml min⁻¹)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately reduced 30–60 ml min⁻¹ (n=9)</td>
<td>46.0 (9.3)</td>
<td>52.0 (9.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mildly reduced 60–90 ml min⁻¹ (n=33)</td>
<td>74.9 (8.9)</td>
<td>84.9 (15.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Normal &gt;90 ml min⁻¹ (n=12)</td>
<td>112.3 (22.4)</td>
<td>110.3 (12.7)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Table 2** Changes in preoperative and postoperative GFR in different preoperative GFR stages. Stages are based on the guidelines of the American Kidney Foundation (K-DOQI) for chronic kidney disease. Data are mean (SD).
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The mechanism underlying the change in GFR after cardiac surgery with CPB is not immediately clear from our data. Small changes in haemodynamic variables (e.g. the observed trend towards a lower heart rate and a higher blood pressure before operation) might contribute to the improvement in GFR. Apparently, this does not result in a concomitant change in ERPF, suggesting that impairment of ERPF in this patient category is because of irreversible structural alterations in the renal vascular bed. However, we have no data to substantiate this assumption. Alternatively, the changes in ERPF may lag behind changes in GFR. Finally, the postoperative increase in FF deserves further consideration as to its possible consequences. In overt renal disease, an elevated FF is considered a sign of elevated glomerular filtration pressure, bearing possible deleterious consequences for long-term renal function. At present it is unclear whether this also applies to the change in renal haemodynamics after cardiac surgery. Renal function measurements were limited to the in-hospital period, and therefore extended measurements in cardiac surgical patients might provide further insight in these issues.

Our patient population was characterized by a reduction in baseline GFR amounting to 25% compared with the group of healthy elderly. Interestingly, ERPF seems even more impaired in our study group, with a 40% reduction. Notably, a similar discrepancy between preoperative impairment of GFR and ERPF was also observed in previous studies of CPB in patients with normal renal function. Also, this discrepancy between impairment of GFR and ERPF has been observed in patients with co-morbid cardiovascular conditions, such as hypertension and heart failure, showing a reduction in GFR and ERPF of 11 and 22%, respectively. Consequently, these data add to the notion that impairment of ERPF is an important feature of this specific patient population.

Preoperative renal dysfunction has been associated with a prolonged procedure as demonstrated by duration of CPB, duration of operation, prolonged mechanical ventilation, and increased cost of hospital stay. In general, our study confirmed these findings, as longer aortic cross-clamp time, CPB time, and duration of operation were found compared with cardiac surgical patients with normal renal function.

Cardiopulmonary bypass in our study was performed at mild hypothermia in all patients. Early experimental studies in an isolated, perfused rat kidney showed a protective effect of hypothermia. Therefore, hypothermia during CPB to reduce metabolism and ischaemic stress seemed a logical renal protective strategy. More recent clinical studies, however, using estimated GFR measurements, did not demonstrate a clear benefit for neither a hypothermic nor a normothermic renal protective strategy. In line with these observations, our results obtained with radioactive isotopes, showed no adverse effects of mild hypothermia on GFR.

Usually, cardiac surgical patients use chronic medication. In the current study, all cardiovascular medication was continued until operation. Of the drugs used, the influence of ACE inhibitors and angiotensin II receptor antagonists (ARAs) on postoperative renal function is questioned most often and several studies evaluated their effects on renal function in cardiac surgery with CPB. Generally, in the setting of CPB, contradictory results have been reported with ACE inhibitors showing postoperative improvement of GFR and ERPF when administered for 2 days, absence of effects of chronic use on renal haemodynamics and function, and indications of a decline in postoperative renal function in patients on chronic ACE inhibitor therapy. In addition, Oh and colleagues demonstrated that chronic ARA treatment resulted in more hypotension during CPB than ACE inhibitor therapy. Thus, the results as to the effects of ARA and ACE inhibitors with respect to renal function after CPB are still undetermined.

This study has several limitations. Despite the abovementioned longer operative procedure, the clinical course seemed uneventful based on the short ICU stay. Probably, this is because of the low rate of complications observed in this cohort and a different effect on renal function measurements may be anticipated in patients with serious complications. Few patients had moderate renal dysfunction (GFR<60 ml min⁻¹), and future studies are needed to address the influence of cardiac surgery on the postoperative renal function and its postoperative course. The second GFR measurement was 7 days after operation and therefore a transient postoperative change in renal function could have occurred earlier. Furthermore, our data confirm that serum creatinine is not a very good estimate of GFR. The selection of patients for future studies should be based on different methods, such as the modification of diet in renal disease equation. This equation provides a better estimate of true GFR than serum creatinine as demonstrated in a recent study. Finally, in multivariate analysis, it was found that only preoperative GFR was independently associated with ΔGFR, probably reflecting an inadequate sample size to detect additional associations.

In conclusion, the data of this study suggest that renal function was not adversely affected in patients with preoperative mild renal dysfunction undergoing uncomplicated cardiac surgery with CPB. Interestingly, the basal ERPF in a subset of patients was severely compromised before operation, and did not change after operation. Finally, the present study suggests that current clinical procedures, as applied in patients with normal renal function, are adequate to preserve renal function in patients with mild preoperative renal dysfunction.

Funding

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References


