ORIGINAL ARTICLE

Intraoperative Continuous Venovenous Hemofiltration during Coronary Surgery

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ABSTRACT

Postoperative continuous venovenous hemofiltration decreases acute renal failure in patients with moderate renal dysfunction undergoing coronary artery bypass grafting, but it prolongs intensive care unit stay. We developed a simple method to connect a hemofiltration machine to the cardiopulmonary bypass system. To evaluate the benefit of intraoperative hemofiltration, 124 consecutive patients (mean age, 67 ± 6 years) with moderate renal dysfunction were studied. Surgery was preformed between January 2005 and May 2007. On-pump coronary artery bypass with hemofiltration was carried out in 40 patients (group A), 44 had on-pump coronary artery bypass without hemofiltration (group B), and 40 had off-pump coronary artery bypass (group C). Postoperative acute renal failure was defined as either renal failure requiring dialysis or ≥50% decline from the baseline glomerular filtration rate but not requiring dialysis. The 3 groups had similar demographic data and preoperative renal function. After adjusting for covariates and propensity scores, multivariate analysis showed that intraoperative hemofiltration and off-pump surgery protected postoperative renal function. Independent risk factors for postoperative renal dysfunction were age >70 years, left ventricular ejection fraction <35%, and the preoperative glomerular filtration rate.

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KEYWORDS: Cardiopulmonary Bypass, Coronary Artery Bypass, Hemofiltration, Kidney Failure, Acute

INTRODUCTION

Acute renal failure (ARF) after coronary artery bypass grafting (CABG) is a well-recognized complication that occurs in 1%–10% of patients, requiring dialysis in 1%–5%, and associated with higher mortality, increased length of hospital stay, greater resource use, and a poor quality of life.[1–4] Among the major risk factors, cardiopulmonary bypass (CPB) has been identified as an important determinant of ARF after CABG. CPB-related renal dysfunction can be attributed to renal hypoperfusion, nonpulsatile flow, hypothermia, and stimulation of the inflammatory response. Several measures have been recommended to prevent postoperative ARF, especially in patients with preoperative renal dysfunction.[5] Off-pump coronary artery bypass (OPCAB) was proposed to reduce the incidence of postoperative renal dysfunction in this challenging subgroup of patients, but results are inconclusive because some studies found that the frequency of severe ARF requiring dialysis after OPCAB was similar to that after on-pump CABG.[6–9] Recently, it has been reported that early and aggressive postoperative use of continuous venovenous hemofiltration (CVVH) decreased mortality and morbidity in high-risk patients.[10] However, postoperative CVVH is associated with prolonged intensive care unit (ICU) stay, thus limiting its prophylactic use. We developed a simple method to connect a CVVH machine to the CPB system to provide hemofiltration during

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CABG. This study was conducted to determine the benefit of CVVH during CPB in patients with preoperative renal dysfunction undergoing CABG.

PATIENTS AND METHODS

From January 2005 to May 2007, 124 consecutive patients with moderate renal dysfunction, defined as a glomerular filtration rate (GFR) of 30–60 $mL \cdot min^{-1}$, underwent elective isolated on-pump CABG or OPCAB. Their mean age was 67 ± 6 years (range, 55–80 years) and 45 (36%) were female. Exclusion criteria were end-stage renal failure requiring dialysis and coronary artery anatomy unsuitable for OPCAB. During this period, patients were selected for intraoperative CVVH according to the surgeon's preference. Three groups of patients were compared: 40 underwent CABG with CPB and CVVH (group A), 44 had on-pump CABG without CVVH (group B), and 40 had OPCAB (group C). Data were collected prospectively and recorded in an electronic database. The primary outcome of postoperative ARF was a composite event defined in 2 ways: postoperative renal failure requiring dialysis before discharge or death; or ≥50% decline in GFR relative to the baseline value, but not requiring dialysis. The four-variable Modified Diet and Renal Disease equation was used to estimate GFR.[10] The rationale for using a 50% reduction in GFR was based on its strong association with operative mortality following surgical revascularization.[4] Routine preoperative and daily in-hospital postoperative serum creatinine levels were measured to identify preoperative and peak postoperative values. Operative mortality was defined as all deaths occurring during the hospital stay or within 30 days postoperatively. Moderate renal dysfunction was defined as GFR $<60\ mL \cdot min^{-1}$, in accordance with the National Kidney Foundation guidelines.[11]

Anesthetic management was standardized for all patients. Intravenous prophylactic antibiotic treatment in the 1st 48 h consisted of cefamandole 1 g 3-times daily and gentamicin $5\ mg \cdot kg^{-1}$ daily. In all cases, the surgical approach was through a median sternotomy. In groups A and B, CPB was instituted using ascending aortic cannulation and 2-stage venous cannulation in the right atrium. A standard heparin-coated circuit was used with a Medtronic tubing set (Medtronic, Inc., Minneapolis, MN, USA), a Stockert roller pump (Sorin Biomedica, Midhurst, UK), and a hollow-fiber membrane oxygenator (Affinity; Medtronic). The extracorporeal circuit was primed with 200 mL Ringer's solution (Fresenius Kabi, Verona Italy), 500 mL Voluven (Fresenius Kabi), 250 mL Thamsol (Diaco Biomedicali, Trieste, Italy), and 250 mL mannitol 18%. Heparin (Parke-Davis) was given at a dose of $300\ IU \cdot kg^{-1}$ to achieve a target activated clotting time ≥450 sec before commencement of CPB. The activated clotting time was monitored every 20 min during CPB, and additional heparin was administered if required. Protamine was used to reverse the effect of heparin. Nonpulsatile flow was instituted at a flow rate of $2.4\ L \cdot m^{-2} \cdot min^{-1}$ throughout bypass. Mean arterial pressure was allowed to vary between 60 and 80 mm Hg during CPB. Systemic temperature was kept between 34°C and 36°C. Myocardial protection was achieved with intermittent anterograde hyperkalemic warm blood cardioplegia delivered every 15–20 min. On completing the distal anastomosis, proximal anastomosis was performed with total clamping. In group A, CVVH was carried out during CPB. The ultrafiltrate produced during membrane transit was replaced completely or in part with appropriate replacement solutions to achieve blood purification and volume control.[12] Highly permeable polyacrylonitrile and sodium methyl sulfonate hemofilters (Hospal, Lyon, France) were used with a Prisma tubing set connected to a Prisma monitor (Hospal). Reinfusion flow was $35\ mL\ kg^{-1} \cdot h^{-1}$, blood flow was $150\ mL \cdot min^{-1}$,and no heparin was used for anticoagulation of the circuit. Bicarbonate buffer (Bintensive 32; Hospal) was used as the replacement solution. The ultrafiltration rate was maintained at $500–1{,}000\ mL \cdot h^{-1}$. A connection was made from the CVVH venous line to the CPB venous line, and from the CVVH venous line to the cardiotomy reservoir (Figure 1). In group C, access to the grafting site was gained by heart elevation with a deep pericardial stay suture, and the Octopus III stabilizing device (Medtronic, Minneapolis, MN, USA) was used during anastomoses. Heparin $300\ UI \cdot kg^{-1}$ was administered before the start of the first anastomosis. Visualization was enhanced with a surgical blower-humidifier (model SSVW-002, Surgical Site Visualization Wand; Research Medical, Inc., Midvale, UT, USA) with a 1/4 PVC gas line and fluid administration set connected to a regulated source of medical air. An intracoronary shunt (Chase Medical, Richardson, TX, USA) was used in all cases. After performing the proximal anastomosis with partial clamping, heparinization was partially reversed with protamine. Reductions in arterial pressure caused by handling of the heart, if any, were mostly compensated for by sufficient volume filling and by placing the patient in the Trendelenburg position. In some cases, a bolus of epinephrine was injected or intravenous dobutamine was infused to maintain an adequate perfusion pressure.

Statistical analysis was carried out using SPSS version 12.1 software (SPSS, Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation. Paired and unpaired Student's *t* tests were used to compare continuous variables, and categorical data were analyzed using the chi-squared test or Fisher's exact test, as appropriate. Variables among groups were compared by analysis of variance (ANOVA). Initially, univariate logistic regression analysis was undertaken to identify significant predictors of ARF after surgery.

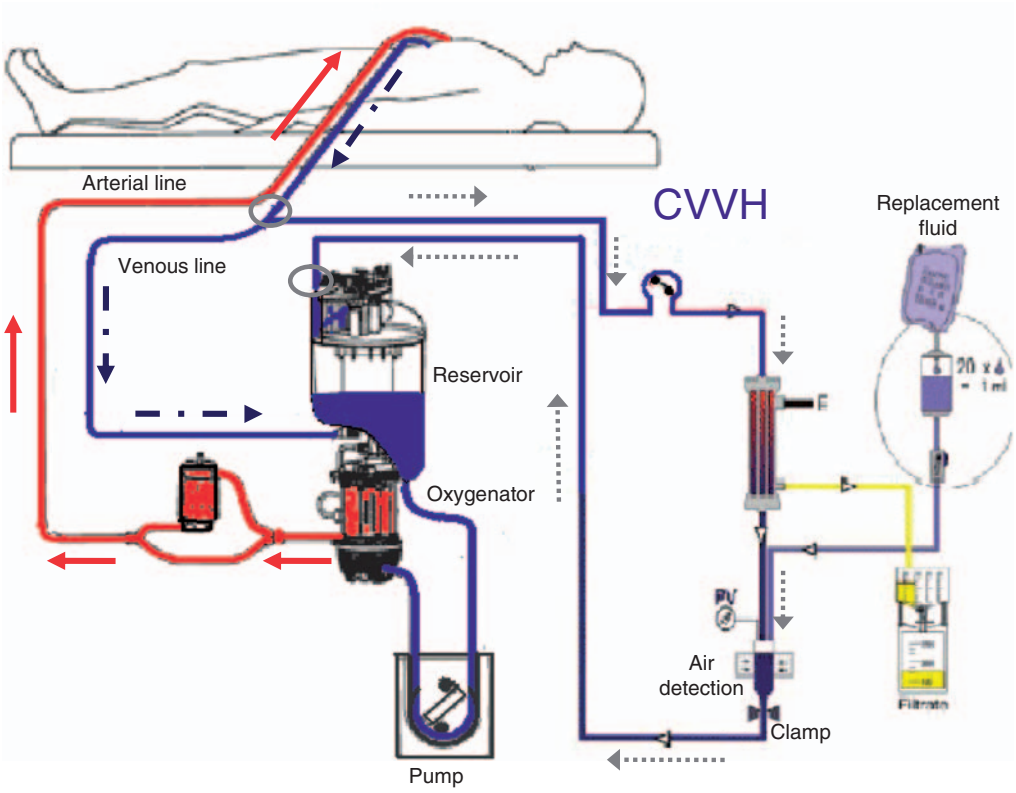

Figure 1. Continuous venovenous hemofiltration (CVVH) while connected to the cardiopulmonary bypass machine.

Variables with a value of $p < 0.05$ in univariate analysis were considered for multivariate analysis, which was performed in a stepwise fashion to identify independent predictors of ARF. Due to the lack of randomization, a propensity score-adjusted analysis was necessary to reduce the effect of preoperative variability among groups.[13] Logistic regression analysis was undertaken with intraoperative CVVH as the dependent variable and preoperative confounding factors as independent variables. The probability of receiving CVVH represented the propensity score for each patient. The propensity score was subsequently regressed as an independent covariate in multivariate logistic regression analysis, using all relevant observations. Models fit analysis was evaluated with the Hosmer-Lemeshow goodness-of-fit statistic. The *C* statistic is reported as a measure of predictive power. The odds ratio (OR) and associated 95% confidence interval (CI) were estimated.

RESULTS

The groups were similar with regard to demographic data and preoperative renal function (Table 1). Groups A and B did not differ in aortic crossclamp time (83 ± 34 vs. 89 ± 26 min; $p = 0.5$) or CPB time (115 ± 33 vs. 112 ± 27 min; $p = 0.2$). Postoperative GFR was lower in group B (group A, 48 ± 7 mL·min^{-1}; group B, 41 ± 10 mL·min^{-1}; group C, 47 ± 8 mL·min^{-1}; ANOVA $p = 0.01$) as shown in Figure 2. In groups A and C, GFR did not change significantly after surgery, but it decreased in group B from 50 ± 8 to 41 ± 10 mL·min^{-1} ($p = 0.02$). The incidence of postoperative ARF was higher in group B (14/44, 32%; ANOVA $p = 0.02$) than in group A (4/40, 10%) or group C (5/40, 12.5%). On univariate analysis, predictors of ARF were age >70 years, male sex, preoperative creatinine clearance, preoperative left ventricular ejection fraction <35%, CPB time, and CPB without CVVH. Multivariate analysis was adjusted for propensity scores to assess independent risk factors for ARF. The propensity score for intraoperative CVVH achieved an acceptable discrimination power (*C* statistic: 0.69; 95%CI: 0.65–0.73; $p = 0.0001$). This analysis showed that intraoperative CVVH and off-pump surgery had protective effects on renal function postoperatively (Table 2). Other independent predictors were age > 70 years, left ventricular ejection fraction < 35%, and preoperative GFR. The multivariate model predicted the occurrence of ARF (model χ^2: 51.4; $p < 0.0001$). The discriminatory ability of the logistic model was acceptable (*C* statistic: 0.78; 95%CI: 0.74–0.82; $p = 0.0001$). The model was well calibrated among deciles of observed and expected risk (Hosmer-Lemeshow χ^2: 9.28; $p = 0.14$). Overall hospital mortality was 5/124 (4.0%) with no significant differences among groups (group A = 4/44, 9%; group B = 0/40, 0%; group C = 1/40, 2.5%; ANOVA $p = 0.08$). There were no differences among groups in the incidence of

Table 1. **Preoperative patient characteristics**

Variable	Group A $n=40$	Group B $n=44$	Group C $n=40$
Age (years)	65 ± 5	66 ± 8	68 ± 4
Males	77%	71%	82%
GFR ($mL \cdot min^{-1}/1.73\ m^2$)	52 ± 6	51 ± 5	50 ± 8
Serum creatine ($mg \cdot dL^{-1}$)	1.35 ± 0.3	1.38 ± 0.65	1.37 ± 0.21
Diabetes	25%	31%	28%
Hypertension	83%	79%	73%
Previous surgery	5%	8%	2%
LVEF < 35%	30%	33%	31%
NYHA class III/IV	30%	40%	31%
Grafts per patient	3 ± 1	3 ± 1	3 ± 1
EuroSCORE (additive)	6 ± 2	7 ± 1	7 ± 2
EuroSCORE (logistic)	8%	11%	9%

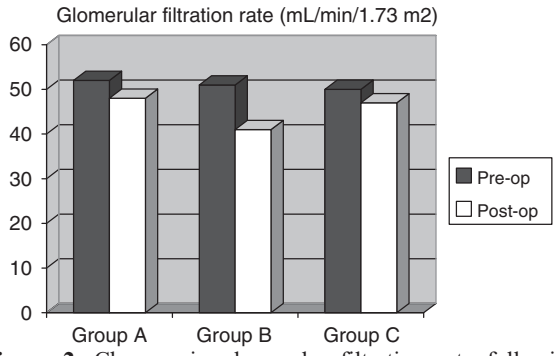

Figure 2. Changes in glomerular filtration rate following surgery.

postoperative inotropic support (4/40 in group A, 4/44 in group B, 1/40 in group C; ANOVA $p = 0.2$).

DISCUSSION

Despite major advances in surgical techniques, anesthesia, and CPB, serious complications can still develop after CABG; ARF is one of the most serious. The influence of preoperative and intraoperative factors on the development of ARF is well known from previous studies.[14–17] Patients with mild to moderate ARF are usually responsive to medical therapy and eventually recover spontaneously, but a small number continue to deteriorate into severe ARF. Many of these patients have multiorgan failure and require mechanical ventilation and continuous administration of inotropic/vasopressor drugs. In this subgroup, mortality has remained high (>60%) despite the aggressive use of intermittent hemodialysis.[13] However, several studies have shown that patients with mild renal dysfunction have an increased risk of death within 30 days after coronary surgery.[2,11,12] Nakayama and colleagues[18] demonstrated significantly lower 10-year actuarial survival in patients with preoperative serum creatinine $\geq 1.5\ mL \cdot min^{-1}$ than in those with normal serum creatinine levels. van de Wal and colleagues[19] found that preoperative mild renal dysfunction was an independent predictor of late mortality in long-term follow-up after CABG. Early identification and appropriate nephrologic management of patients is important to delay the progression of renal disease and modify risk factors for comorbidities.

Postoperative CVVH has been used in the treatment of critically ill patients with ARF after cardiac surgery. It is better-tolerated hemodynamically than intermittent hemodialysis, and usually applied in patients with multiple organ failure and hemodynamic instability.[12–17] In addition, postoperative CVVH has been proposed as prophylactic treatment for patients with preoperative renal dysfunction undergoing cardiac surgery, to prevent the development of ARF. In fact, in this challenging group of patients, postoperative steady fluid removal and toxin clearance may protect the kidney against volume overload and uremic toxicity. Journois and colleagues[20] showed that CVVH removed inflammatory mediators including cytokines, modifying the adverse immunologic and proinflammatory effects of CPB, which have been implicated in the development of postoperative renal damage.

We used CVVH during CPB and found that these patients had better postoperative renal function than those undergoing CABG on CPB without hemofiltration. As reported by others, OPCAB was not related to a deterioration of renal function, but our results showed an advantage of intraoperative CVVH over OPCAB, in terms of renal function. Furthermore OPCAB, is not suitable for all patients because its use is limited in those with extensive native coronary disease or instability during heart manipulation. These results support the intraoperative use of CVVH in patients with preoperative renal dysfunction because it was safe and effective in preventing renal dysfunction. We suggest that the potential advantages of intraoperative CVVH over postoperative prophylactic CVVH in this group of

Table 2. **Multivariate logistic regression analysis[1,2] for risk factors associated with acute renal failure adjusted for propensity score[3] to receive intraoperative CVVH**

Covariate	Odds Ratio (95%CI)	*p* Value
Age > 70 years	2 (1.1–3.0)	0.001
Left ventricular ejection fraction < 35%	1.25 (1.01–2.2)	0.01
Preoperative glomerular filtration rate*	1.1 (1.01–1.71)	<0.001
Intraoperative CVVH	0.8 (0.71–0.99)	0.02
Off-pump surgery	0.9 (0.87–0.99)	0.04

*Per 1 mL·min^{-1}/1.72 m^2 decrease. [1]Model χ^2: 51.4; $p < 0.0001$; *C* statistic: 0.78. [2]Hosmer-Lemeshow χ^2: 9.28; $p = 0.14$. [3]*C* statistic for propensity score: 0.69; $p = 0.0001$. CI = confidence interval, CVVH = continuous venovenous hemofiltration.

patients may be more rapid control of volume overload and uremic toxicity, and better control of the potassium level due to cardioplegia and removal of CPB-related proinflammatory cytokines. As postoperative CVVH is frequently delayed by early postoperative hemodynamically instability. Moreover, postoperative application of CVVH is associated with hypothermia, so patients require more assistance from ICU staff and qualified dialysis nurses, as well as prolonged ICU stay. These considerations may limit its routine application as a postoperative prophylactic treatment. We found that intraoperative CVVH did not prolong ICU stay and there were no intraoperative or postoperative complications.

This study was retrospective in design and lacked randomization, thus it may be influenced by treatment bias. However, we performed statistical adjustments that included the use of propensity scores in an attempt to account for the nonrandomized nature of CVVH use. We concluded that intraoperative CVVH might be useful in patients with preoperative renal dysfunction and in those at high risk of postoperative ARF, according to the most commonly used risk estimation methods. Further studies with a larger sample size are needed to confirm these findings and to determine the degree of benefit of intraoperative CVVH in patients undergoing cardiac surgery with preoperative renal dysfunction.

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