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The effect of sodium nitroprusside infusion on renal function during reperfusion period in patients undergoing coronary artery bypass grafting: a prospective randomized clinical trial

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Abstract

Objective: Acute renal failure remains a common and serious complication of cardiac surgery. In this randomized trial, we aimed to assess whether sodium nitroprusside (SNP) infusion during cardiopulmonary bypass (CPB) could prevent renal dysfunction after coronary artery bypass grafting (CABG) surgery. **Methods:** Between October 2004 and May 2006, 240 consecutive patients with stable angina undergoing elective CABG for multi-vessel coronary artery disease were prospectively randomized into control (n = 116, 72 men, mean age 61.3 ± 9.7 years) or SNP groups (n = 124, 81 men, 60.8 ± 10.8 years). SNP group received SNP after initiation of rewarming period during CPB at a dose of 0.1 mg/kg/h and the infusion was concluded by weaning from CPB. The anesthetic and CPB regimes were standardized. Blood urea nitrogen (BUN), serum creatinine (SCr), estimated glomerular filtration rate (eGFR), creatinine clearance (C_{Cr}), urine output, serum cardiac specific troponin I (cTnI), creatine kinase cardiac isoenzyme (CKMB), and CPK were measured preoperatively and daily until day 5 after surgery. **Results:** There were no differences in baseline levels of BUN, SCr, eGFR, C_{Cr}, cTnI, CKMB, CPK levels and EuroSCORES between the groups. Although the durations of cross clamp, CPB times, and postoperative cardiac enzymes were similar in both groups; in the control group, there was a significantly lower urine excretion during CPB (p = 0.002) and the operation (p = 0.041). Peak postoperative SCr levels were significantly (p = 0.001) lower in the SNP group than in the control group (1.29 ± 0.28 vs 1.42 ± 0.34 mg/dl). The incidence of ≥50%ΔSCr was significantly higher in the control group when compared with the SNP group (35.3 vs 13.7%, $p < 0.001$). Development of new C_{Cr} less than 50 ml/min postoperatively was significantly higher in the control group compared with the SNP group (14 vs 38%, $p < 0.001$). **Conclusion:** SNP administration during rewarming period of non-pulsatile CPB in patients undergoing CABG surgery is associated with improved renal function compared with conventional medical treatment providing adequate preload and mean arterial pressures.
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Keywords: Coronary artery bypass grafting (CABG); Cardiopulmonary bypass (CPB); Kidney; Complications; Sodium nitroprusside; Glomerular filtration rate

1. Introduction

Renal dysfunction continues to be one of the major causes of poor outcomes following coronary artery bypass grafting (CABG) surgery. Between 1 and 31% of patients, who undergo cardiac surgery, will experience acute renal failure (ARF) with associated mortality rates between 7 and 38% [1–3]. The incidence of ARF requiring renal replacement therapy following CABG accounted for 3.53% in a recent review of the Society of Thoracic Surgeons adult cardiac surgery database and was strongly associated with perioperative morbidity and mortality [4]. Furthermore, patients with more than a doubled serum creatinine in the postoperative period had a 22-fold increased risk of dying within 90 days after CABG [5].

Available clinical studies have demonstrated that the etiology of renal dysfunction after cardiac surgery is multifactorial. The sources of renal insult are: decreased renal perfusion, reperfusion injury, inflammatory response, vasoconstriction from circulating vasoconstrictors, atheroembolism, loss of pulsatility during cardiopulmonary bypass (CPB) or exposure to nephrotoxic agents [6]. Thus, high-risk patient population for ARF may be targeted for perioperative interventions that may reduce the risk or ameliorate the outcome [6].

Nitric oxide (NO) is an important regulator of vascular tone and tissue perfusion. NO production is increased under

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ischemic conditions, as demonstrated in coronary arteries [7]. NO-donor, sodium nitroprusside (SNP) is a nitrovasodilator that has been widely used to manage perioperative hypertension [8]. At a dose of 0.25–10 μg/kg/min IV, nitroprusside is almost always immediately effective for lowering blood pressure, and the duration of action is between 1 and 2 min [8]. In an experimental model of lung allotransplantation, SNP administration in the flush solution and during reperfusion improved lung allograft function and blood flow, and reduced pulmonary vascular resistance and myeloperoxidase activity in the transplanted lung [9]. Use of SNP during reperfusion period of CABG surgery in patients with severe left ventricular dysfunction was associated with reduced proinflammatory cytokines and less activated leukocytes and platelets in the coronary circulation compared with placebo [10]. Furthermore, pulmonary arterial infusion of SNP during reperfusion can reduce lung injury under CPB [11]. Maximal coronary hyperemia, equivalent to that induced by intracoronary adenosine, can be achieved with intracoronary SNP in doses of 0.3, 0.6, and 0.9 μg/kg, with only a modest decrease in systolic pressure and without significant tachycardia [12]. However, renal effects of SNP after CPB have yet to be determined in humans.

We therefore sought to evaluate the renal effects of SNP administered during reperfusion period in patients undergoing CABG surgery, and to determine whether a relationship exists between SNP use and postoperative outcomes.

2. Materials and methods

2.1. Study design and patient characteristics

Between October 2004 and May 2006, 240 consecutive patients with multi-vessel coronary artery disease undergoing elective, primary CABG were prospectively randomized to receive saline (NaCl) or SNP (Nipruss, Adeka, Turkey) infusion from initiation of rewarming period during CPB until weaning from CPB. A computer-generated randomization list was drawn up by our statistician and patients were randomly allocated to either the control or SNP groups. Concealment was assured through the use of sequentially numbered sealed, envelopes. The study medication SNP and NaCl were provided in uniformly appearing 50-ml syringes blinded to attending surgeons, perfusionist and nurses. Furthermore, the details of the series were unknown to any of the investigators. Seven surgeons from two centers participated in the study. The code was revealed to the researchers once recruitment and data collection were complete. The study was approved by the institutional review board and all patients provided informed written consent pre-operatively. Baseline, procedural, and follow-up data were stored in a database located at the Ankara University. Patients were eligible if they had any of the following: (1) left ventricular ejection fraction (LVEF) $\leq$0.50; (2) estimated glomerular filtration rate (eGFR) $>$30 ml/min; and (3) with at least two de novo lesions located in different major epicardial coronary arteries amenable to bypass surgery.

Patients were not enrolled in the study if any one of the following exclusion criteria were met: (1) signs of congestive heart failure class IV, or cardiogenic shock; (2) unstable angina pectoris; (3) myocardial infarction (MI) within the week preceding randomization, (4) dialysis dependent renal failure, (5) microalbuminuria, (6) hepatic dysfunction; (7) sickle cell anemia, (8) serum creatinine (SCr) level $\geq$3 mg/dl pre-operatively; (9) morbid obesity or cachexia; (10) skeletal muscle disorders or paraplegia and (11) concomitant major cardiac procedures.

2.2. Renal function

BUN and SCr levels were performed daily during hospital stay and highest postoperative SCr and BUN within postoperative 5 days were documented. All samples were analyzed immediately after collection. Serum potassium concentration was measured every 4 h during the first 24 postoperative hours, and every 8 h for the next 48 h. Urine output was obtained by way of an indwelling urinary catheter during 48 h postoperatively, and the measurements were made hourly. Patients' urine output during CPB, daily fluid balance and diuretic use were recorded. Preoperative SCr levels were obtained one day before surgery, and the GFR was estimated from the modification of diet in renal disease equation [13]: eGFR (ml/min per 1.73 m^2) = 186 $\times$ (SCr mg/dl)$^{-1.154}$ $\times$ (age [years])$^{-0.203}$. The product of this equation was multiplied by a correction factor of 0.742 for women. Repeated creatinine clearance (C_{Cr}) was estimated from the standard formula of Cockroft–Gault equation [14].

C_{Cr} = (140 - age in years) $\times$ (body weight)/(72 $\times$ SCr in mg/dl). For females, the obtained result was multiplied by 0.85.

Percent change in serum creatinine (%ΔCr) was calculated by: [[(highest postoperative Cr)/(baseline preoperative Cr)] $-$ 1] $\times$ 100%.

2.3. Surgical considerations

All the patients were pre-medicated with oral diazepam before anesthesia induction and received 1.5 g Cefuroxime as antibiotic prophylaxis. Anesthesia was induced with 0.04 mg/kg midazolam, 5–10 μg/kg fentanyl and 0.1 mg/kg pancuronium intravenously. Anesthesia maintenance consisted of 0.8 μg/kg/min of midazolam and 0.08 μg/kg/min of fentanyl by continuous infusion. Pancuronium was given as required to maintain neuromuscular blockade. All patients underwent cardiac surgery with non-pulsatile CPB by using roller pumps and disposable membrane oxygenators. The pump was primed with 1200 ml of lactated Ringer solution with 100 mmol of sodium bicarbonate and 5000 IU of heparin were added. CPB was instituted at a flow rate of 2.4 l/min/m^2 body surface area after systemic heparin administration (1 mg/kg). During CPB, the mean arterial pressure target was set at 60 mmHg, and the core temperature of the patients was allowed to drift to 30–32 °C during CPB. Alpha-stat pH management was employed. Intermittent cold-blood cardioplegia (1:4 blood to crystalloid with maximal potassium concentration 22 mEq/l) was delivered antegrade via the aortic root. Cross clamp, total CPB times, and duration of the operation were recorded.

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2.4. SNP protocol

In the SNP group, SNP was commenced together with the onset of the rewarming period at a starting dose of 0.1 μg/kg/h and was ended together with the ending of CPB. The dose was readjusted according to the systemic blood pressure, keeping the mean blood pressure between 50 and 70 mmHg during the rewarming period. During rewarming, a 4–5 °C difference between rectal temperature and CPB perfusate temperature was maintained for all patients. The infusion was stopped after the ending of CPB. The total amount of SNP used for each patient was recorded.

2.5. Measurement of cardiac marker proteins

Serial venous blood samples were drawn just before CPB, and after aortic unclamping at 6, 12, 24, 48, and 72 h. Concentrations of the mass of isoenzyme MB of creatine kinase (CK-MB; Beckman Coulter, USA) and cardiac troponin I (cTnI; Access AccuTnITM, Beckman Coulter, USA) were determined at these time points, and additionally when necessary. Samples were analyzed at the Department of Clinical Biochemistry, Ankara University, with an immunoassay analyzer (Beckman Coulter Access). CK-MB: CK ratio was calculated by dividing CK-MB by the total CK activity at each time point. The upper limit of normal as defined by our laboratory was 0.04 ng/ml for cTnI and 6.3 ng/ml for CK-MB. ECG criteria for perioperative myocardial infarction were new Q wave (0.04 ms) in at least two leads or ECG ST changes in association with significant CK–MB enzyme and/or cTnI release.

2.6. Patient follow-up

The patients were monitored in the intensive care unit (ICU) concerning the hemodynamic parameters like heart rate, mean arterial pressure, central venous pressure and hourly urine output. In both groups, during the postoperative period, urine output was maintained more than 0.5 ml/kg/h while patients were receiving a 2-g sodium diet. Diuretics were used as necessary. Daily measurements of arterial blood gases, serum glucose, electrolytes, hematological parameters, BUN, and SCr were obtained for all patients up to discharge. Routine medications included daily aspirin or clopidogrel, low molecular weight heparin, and resumption of cholesterol-lowering agents, beta-blockers, and ACE inhibitors as appropriate. Nephrotoxic analgesics were avoided for both groups.

2.7. Statistical analysis

Based upon prior observational retrospective data gathered at the Ankara University involving 752 patients with left ventricular dysfunction who underwent CABG, the baseline serum creatinine will be 1.01 ± 0.36 mg/dl. Sample sizes of 110 in each group achieve 90% power at 5% significance level to detect a difference of 10%, considered as clinically important, assuming a 35% incidence of $\geq$50%ΔSCr rate in the control group and a 25% incidence of $\geq$50%ΔSCr rate in the SNP group postoperatively. The primary end points were the effect of SNP on SCr and eGFR compared with placebo from the operation to the 5th postoperative day. Secondary endpoints were changes in cardiac enzymes, urine output per hour, daily fluid balance, changes in creatinine clearance over time, and major adverse events. In-hospital outcomes were analyzed on an intention-to-treat basis. Baseline characteristics and clinical outcomes were summarized by percentages and means (±standard deviation (SD)). Differences in preoperative values between the two groups concerning baseline patient characteristics were analyzed by Student's *t*-test or Fisher's exact probability test. Categorical baseline data were investigated using Pearson Chi-Square or Fisher's exact test. SNP and placebo data were compared by repeated-measures analysis and non-paired Student 2-tailed *t*-test. SPSS version 13.0 for Windows was used for all the statistical calculations. All statistical tests were two-sided with a significance level of $p < 0.05$.

3. Results

A total of 250 patients were informed about the trial during the study period; six patients did not want to participate; and 244 patients were randomly allocated to treatment. After randomization, four patients were withdrawn either because of necessity for an additional cardiac procedure or ventricular tachycardia on anesthetic induction. None of the four patients, who were excluded, developed renal dysfunction postoperatively. The final cohort included 116 controls and 124 patients in the SNP group. The flowchart of the patients included in the study is shown in Fig. 1. There was no cross over between the groups and all participants who underwent random allocation were analyzed according to group assignment.

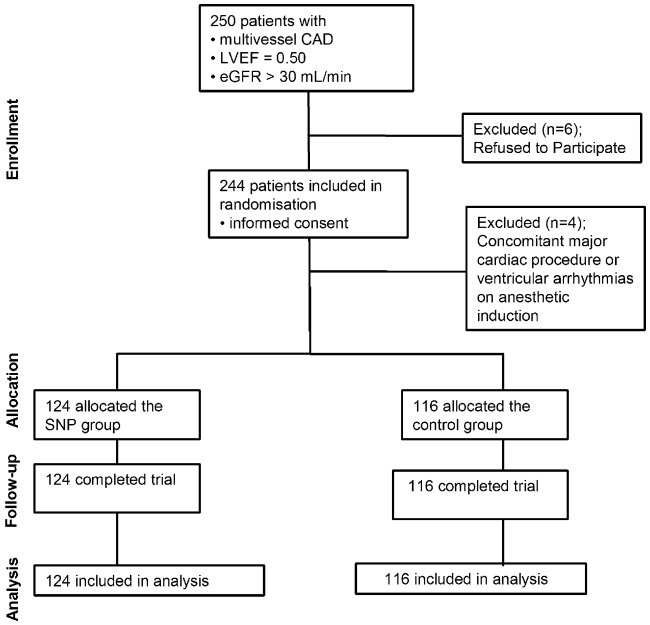


Fig. 1. Trial diagram showing the flow of participants through each stage. CAD: coronary artery disease; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate.

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3.1. Baseline clinical characteristics

Patient baseline characteristics are reported in Table 1. For the entire cohort, the average age of patients was 61 (range 36–84) years, with 24% aged ≥70 years. Mean left ventricular ejection fraction of the study cohort was 38.9 ± 6.8%. Mean arterial pressure at baseline was 82 ± 17 mmHg. There were no black patients in the current cohort. There was no statistically significant difference in preoperative comorbidity between two groups who completed the study. Patients across the two groups had similar left main disease and previous CABG surgery. In addition, both groups had similar EuroSCORES, extents of coronary revascularization, durations of CPB, durations of aortic cross clamping, and operative times. Systemic SNP infusion as per protocol during reperfusion period decreased arterial pressure by 8% ($p < 0.001$ compared with NaCl). Two patients died in the hospital, as a result of sepsis in the SNP group, and mesenteric ischemia in the control group; for an overall mortality rate of 0.83%, with no significant differences between groups (0.80 vs 0.86%; Table 2). Similarly there were no significant differences between the SNP group and the control group in postoperative IABP requirement (1.6 vs 2.6%; $p = 0.675$), perioperative myocardial infarction (2.4 vs 3.5%; $p = 0.715$), permanent stroke (0 vs 0.86%; $p = 0.483$), new atrial fibrillation (12 vs 15%; $p = 0.442$), and deep sternal wound infection (0.8 vs 0.86%; $p = 1.0$) (Table 2). Furthermore, postoperative maximal CK-MB (51.6 ± 27.5 vs 52.6 ± 26.5 ng/ml, $p = 0.762$) and peak cTnI (2.75 ± 1.05 vs 2.83 ± 1.02 ng/ml, $p = 0.557$) levels between the groups were comparable.

3.2. Renal function

At enrollment, the mean creatinine was 1.01 ± 0.22 mg/dl, eGFR was 83.9 ± 16.9 ml/min, and C_{Cr} was 77.1 ± 20.7 ml/min. None of the patients had albuminuria before surgery, as determined using semiquatitative dipstick measurements. In the study population, 93 patients (39%) were classified as having normal renal function (eGFR≥90 ml/min per1.73 m^2), 120 patients (50%) as having mild renal dysfunction (eGFR 60–89 mL/min per 1.73 m^2), and 27 (11%) as having moderate renal dysfunction (30–59 mL/min per 1.73 m^2). Urine excretion during CPB and operation were more pronounced in the SNP group than in control subjects ($p = 0.002$, and $p = 0.04$, respectively) (Table 2). However, fluid intake and urine excretion during the first 24 h after surgery were similar in both the SNP and control groups (3807 ± 1001 vs 3576 ± 911 ml, $p = 0.064$). Daily furosemide doses and serum potassium levels did not differ between the two groups. No patient required renal replacement therapy in neither of the groups in the postoperative period. Postoperative mean SCr and eGFR values are presented in Table 3. Postoperative peak SCr and %ΔSCr were significantly higher in the control group than in the SNP group ($p = 0.001$,

Table 1
Clinical characteristics of the study cohort

Variable	SNP group ($n = 124$)	Control group ($n = 116$)	p-value
Age (years)			
Mean ± SD	60.8 ± 10.8	61.3 ± 9.7	0.697
Range, n	36–84	44–81	
≥70 years, n (%)	29 (23.4)	30 (25.9)	0.764
Male: gender, n (%)	81 (65.3)	72 (62.1)	0.687
Body mass index, (kg/m^2)	26.1 ± 4.1	26.4 ± 4.0	0.541
Mean arterial pressure (mmHg)	82.6 ± 17.3	81.9 ± 17.2	0.744
CCS angina status III–IV, n (%)	112 (90.3)	108 (93.1)	0.490
NYHA functional class III–IV, n (%)	60 (48.4)	61 (52.6)	0.526
History of diabetes mellitus, n (%)	49 (39.5)	44 (37.9)	0.895
History of hypertension	59 (47.5)	58 (50)	0.796
History of pulmonary disease, n (%)	25 (20.1)	19 (16.4)	0.506
History of peripheral vascular disease, n (%)	13 (10.5)	10 (8.6)	0.666
Prior CABG, n (%)	5 (4.0)	3 (2.6)	0.723
History of prior MI within 90 days, n (%)	10 (8.1)	11 (9.5)	0.820
Angiography within 1 week before surgery, n (%)	13 (10.5)	12 (10.3)	0.972
Left main disease (≥50% stenosis), n (%) yes	19 (15.3)	16 (13.8)	0.737
Estimated LVEF	38.1 ± 6.1	39.7 ± 7.3	0.067
Preoperative intra-aortic balloon pump, n (%)	6 (4.8)	5 (4.3)	0.845
Urgent operation, n (%)	21 (16.9)	18 (15.5)	0.861
Preoperative use of ACE inhibitors	38 (30.6)	30 (25.9)	0.411
Estimated GFR level, ml/min per 1.73 m^2, mean ± SD	83.5 ± 17.7	84.3 ± 16.3	0.739
Normal (≥90), n (%)	46 (37.1)	47 (40.5)	0.828
Mild (60–89), n (%)	63 (50.8)	57 (49.1)	
Moderate (30–59), n (%)	15 (12.1)	12 (10.3)	
Estimated creatinine clearance, mean ± SD	76.4 ± 21.6	77.8 ± 19.9	0.602
Estimated creatinine clearance <50 ml/min, n (%)	15 (12.1)	9 (7.76)	0.289
Blood urea nitrogen, mean ± SD	17.1 ± 3.7	17.6 ± 5.0	0.852
Creatinine >1.2 mg/dl, n (%)	23 (18.6)	21 (18.1)	0.929
Creatinine (IQR), mg/dL	1.02 ± 0.23	1.00 ± 0.20	0.534
EuroSCORE	3.6 ± 2.3	3.7 ± 2.1	0.636

CCS: Canadian cardiovascular society; NYHA: New York Heart Association; CABG: coronary artery bypass surgery; MI: myocardial infarction; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme; GFR: glomerular filtration rate. Values are shown as n (%) or mean ± SD.

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Table 2
Operative characteristics and outcomes

Variable	SNP group (n = 124)	Control group (n = 116)	p-value
Number of coronary vessels bypassed (mean ± SD)	2.36 ± 1.37	2.56 ± 1.26	0.229
Cross-clamp time (min)	40.3 ± 25.9	38.9 ± 9.6	0.456
CPB time (min)	72.1 ± 28.1	67.5 ± 11.5	0.573
Operation time (min)	165 ± 30	162 ± 31	0.351
Aprotinin usage, n (%)	8 (6.5)	6 (5.2)	0.786
Minimum of rectal temperature during CPB (°C)	31.2 ± 0.6	31.4 ± 0.7	0.094
Time to reach 37 °C of rectal temperature during CPB (min)	17.9 ± 4.4	20.1 ± 3.9	<0.001
Intraoperative/postoperative IABP, n (%)	2 (1.6)	3 (2.6)	0.675
Ventilation time >24 h, n (%)	9 (7.3)	11 (9.5)	0.642
Urine output during CPB (ml)	396 ± 276	304 ± 164	0.002
Total urine output during operation (mL)	848 ± 548	733 ± 261	0.041
Urine output within 24 h (ml)	3807 ± 1001	3576 ± 911	0.064
RBC-transfusion >1000 ml, n (%)	18 (14.5)	19 (16.4)	0.690
Percent creatinine increase, n (%)			
<25	71 (57.3)	45 (38.8)	0.001
25–49	36 (29.0)	30 (25.9)	
50–99	15 (12.1)	33 (28.5)	
≥100	2 (1.6)	8 (6.9)	
New C_{Cr} <50 ml/min, n (%)	16 (14.7)	45 (38.3)	<0.001
Major adverse events			
Major bleeding required revision, n (%)	3 (2.4)	2 (1.7)	0.675
Deep sternal wound infection	1 (0.80)	1 (0.86)	1.000
PMI	3 (2.4)	4 (3.5)	0.715
New postoperative atrial fibrillation, n (%)	15 (12.1)	18 (15.5)	0.442
Stroke, n (%)	0	1 (0.86)	0.483
Renal failure requiring dialysis, n	0	0	1.000
Prolonged length of hospital stay (>14 days), n (%)	7 (5.6)	6 (5.2)	0.872
In-hospital mortality, n (%)	1 (0.80)	1 (0.86)	1.000

Data are presented as mean ± SD or number (%). CPB: cardiopulmonary bypass; IABP: intraaortic balloon-pump; RBC: red blood cell; C_{Cr}: creatinine clearance; PMI: perioperative myocardial infarction.

and $p < 0.001$, respectively) (Figs. 2 and 3). Furthermore, the incidence of ≥50%ΔSCr was significantly higher in the control arm when compared with the SNP arm (35.3 vs 13.7%, $p < 0.001$). Postoperative minimum eGFR were significantly lower in the control group than they were in the SNP group ($p < 0.001$) (Fig. 4). Development of new C_{Cr} less than 50 ml/min postoperatively was significantly higher in the control group compared with the SNP group (14 vs 38%, $p < 0.001$).

3.3. Possible side effects

There were no incidences of unexplained metabolic acidosis, venous hyperoxemia, encephalopathy, seizures, or mental status changes in both groups.

4. Discussion

The results of our study suggest that SNP administration after initiation of rewarming period during CPB in patients undergoing CABG surgery is associated with improved renal function compared with conventional medical treatment in well-hydrated patients. The present study is not limited to a single-surgeon experience and confirms that low dose SNP use during rewarming period of CPB is safe and feasible.

ARF presence is associated with excess mortality independently of baseline characteristics after CABG surgery [5]. Several risk factors have been identified as independent predictors of ARF after cardiac surgery; age [1,3], preoperative renal dysfunction [1–3], left ventricular ejection

Table 3
Time course of serum creatinine concentration and estimated glomerular filtration rate in relation to coronary artery bypass grafting in the control and SNP groups

	Serum creatinine (mg/dl)			eGFR		
	SNP group (n = 124)	Control group (n = 116)	p-value	SNP group (n = 124)	Control group (n = 116)	p-value
Baseline	1.02 ± 0.23	1.00 ± 0.21	0.534	83.5 ± 17.7	84.3 ± 16.3	0.739
PO day 1	1.15 ± 0.26	1.24 ± 0.26	0.007	73.3 ± 17.3	66.7 ± 15.8	0.002
PO day 2	1.28 ± 0.29	1.42 ± 0.34	0.001	64.5 ± 14.8	58.2 ± 15.0	0.001
PO day 3	1.20 ± 0.26	1.29 ± 0.28	0.007	69.5 ± 16.0	63.9 ± 15.1	0.005
PO day 4	1.11 ± 0.22	1.18 ± 0.21	0.012	73.5 ± 14.6	67.9 ± 13.0	0.002
PO day 5	1.09 ± 0.22	1.14 ± 0.21	0.243	76.1 ± 16.2	73.0 ± 14.7	0.127

Values are expressed as mean and SD.
PO: postoperative; eGFR: estimated glomerular filtration rate.

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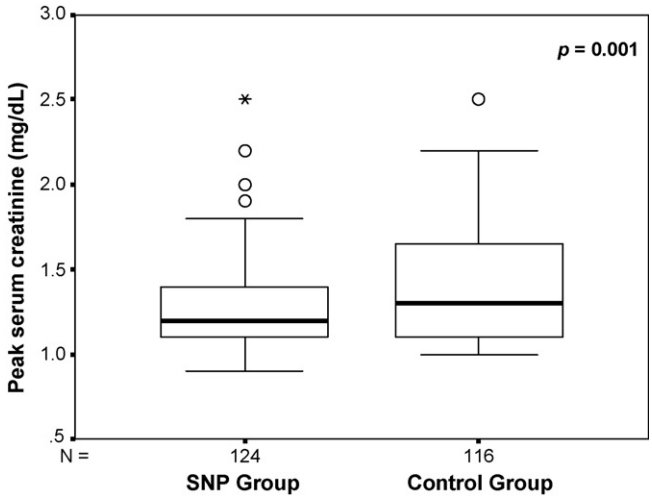


Fig. 2. Peak serum creatinine levels at postoperative period displayed as box and whisker plots (median, interquartile range, and extreme range). SNP group represents sodium nitroprusside administered during rewarming period of CPB; control group, NaCl infusion during rewarming period of CPB.

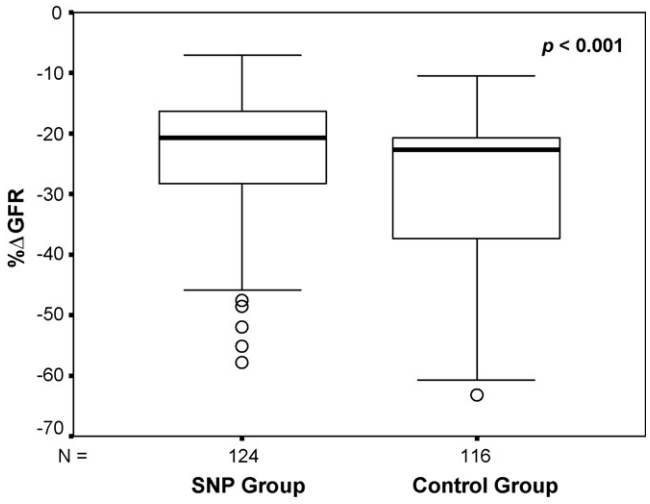


Fig. 4. Percent estimated glomerular filtration rate decrease (%ΔeGFR) from baseline displayed as box and whisker plots (median, interquartile range, and extreme range). SNP group represents sodium nitroprusside administered during rewarming period of CPB; control group, NaCl infusion during rewarming period of CPB.

fraction less than 35% [1], diabetes [1—3], congestive heart failure [3,15], urgent operation, need for intra-aortic balloon pump support [16], prolonged CPB duration [2,3], low cardiac output [1,16], peripheral vascular disease [1], systolic blood pressure less than 120 mmHg or greater than 160 mmHg [1], chronic obstructive lung disease [1], valvular heart disease [1], and previous cardiac surgery [1]. Cardiopulmonary bypass (CPB) has several adverse effects on renal physiology by increasing the vasomotor tonus and non-pulsatile flow properties resulting insufficient renal perfusion [17], and the effect of free hemoglobin released as a result of haemolysis [18]. In fact, afferent arteriolar vasoconstriction has a major impact on the pathophysiology of acute renal insult. Management strategies of CPB and pharmacologic interventions especially in high-risk patient

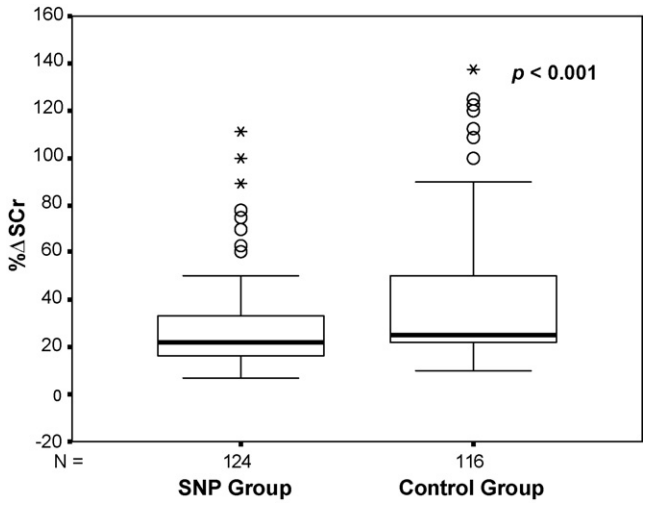


Fig. 3. Percent creatinine increase from baseline (%ΔSCr) displayed as box and whisker plots (median, interquartile range, and extreme range. SNP group represents sodium nitroprusside administered during rewarming period of CPB; control group, NaCl infusion during rewarming period of CPB.

population may provide renoprotection after CABG surgery. However, potential benefits of increased renal blood flow, and decreased renal vascular resistance with dopamine; inhibition of sodium reabsorption increasing tubular solute flow with diuretics have not been consistently shown to be renoprotective in the cardiac surgical patients [19]. Recently, fenoldopam mesylate, the first selective dopamine-1 receptor agonist failed to reduce the risk of ARF after cardiac surgery in high-risk patients compared with dopamine in a prospective, double-blind, randomized trial [20].

SNP, an exogenous NO donor, is frequently used to control hypertension and/or to improve cardiac output following cardiac operations. It is able to antagonize vasoconstricting signals and increases end-organ perfusion [21], facilitates rewarming [22], decreases complement activation [23], decreases reperfusion injury, and increases renal blood flow by 20% [24]. The renal effects of SNP are considered to reduce renal vascular resistance and increase renal blood flow and furthermore, selective dilatation of the afferent arterioles increases the GFR. In the postoperative cardiac surgical patients, SNP administration can be expected to improve renal blood flow, providing avoidance of left atrial hypotension. Bates et al. postulated that the main mechanism of action of SNP is mediated through the genesis of nitric oxide that subsequently produces direct smooth muscle vasodilation [25]. The drawbacks of SNP are photosensitivity and potential cyanide and/or thiocyanate toxicity with high doses or prolonged infusions. Thus, current practice in many institutions reserves the use of SNP for persistent hypertension after cardiac surgical procedures.

In this study, our postoperative strategy for management of CABG patients was strictly to maintain adequate right and left heart filling pressures and mean arterial pressure between 60 and 80 mmHg. In the case of hypotension during perioperative period, catecholamines

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were aggressively introduced. Our data showed that SNP infusion improved urine output during CPB and early after the operation. The overall incidence of renal dysfunction and %ΔSCr observed in our study was similar to that in other series [1,5] however no patient required renal replacement therapy in our study cohort possibly as result of small sample size. Potential explanation of our findings, however, may be drug-mediated increased renal blood flow, afterload reduction resulting in better cardiac performance, and decreased renal ischemia-reperfusion injury.

4.1. Study limitations

There are several limitations to this study. SCr as a marker of eGFR should be cautiously interpreted because of intrinsic variability of SCr in patients undergoing cardiac surgery. Given that, this limitation was present in both of the groups; it is unlikely that it affects the results of our study as a confounding variable. However, severe malnutrition, morbid obesity and skeletal muscle disorders were accepted as exclusion criteria in order to achieve more reliable results. Furthermore, use of exogenous markers such as radionuclide-labeled markers or radio-contrast markers to measure GFR in cardiac surgical patients had ethical concerns in our institution. Use of the Cockcroft—Gault equation to estimate C_{Cr} also relies on patients being in steady state. Secondly, the study cohort was restricted to white race, thus, the results could not be applied to other races. Furthermore, because of the inclusion criteria regarding LV function the results of this study could not be extrapolated to all patients seen in cardiac surgical practice. Finally, laboratory assays for blood cyanide or thiocyanate concentrations were not performed in the study, however, we are aware of the fact that these assays are often nondiagnostic.

5. Conclusions

This prospective study confirmed the safety and the renal beneficial effects of low dose SNP administered during the rewarming phase of CPB of CABG surgery in well-hydrated patients; and in clinical practice, prophylactic use of SNP may be considered in high-risk patients for ARF. Further prospective, randomized studies with SNP or combination therapies assessing renal plasma flow and tubular function are warranted.

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