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ORIGINAL ARTICLE

The effect of high-dose nitroglycerin on the cerebral saturation and renal function in cardiac surgery: A propensity score analysis

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Abstract

Background: The aim of the study was to evaluate the effects of high-dose nitroglycerine administered during cardiopulmonary bypass on the intraoperative cerebral saturation and postoperative serum creatinine concentration in cardiac surgery.

Methods: In a retrospective cohort study, a total of 239 patients undergoing cardiac surgery with cardiopulmonary bypass at a tertiary medical center were included. General anesthesia consisted of volatile anesthetic and either intravenous loading of high-dose nitroglycerin (infusion rate 10 to 20 mg·h^{-1} with a total dose of ≥0.5 mg·kg^{-1}) starting from rewarming of cardiopulmonary bypass throughout the end of the surgery (NTG group; N = 96) or without high-dose nitroglycerin (control group; N = 143). Data for intraoperative cerebral saturation and serum creatinine concentrations before and after cardiac surgery were collected. Propensity score method was used to adjust for potential confounders.

Results: Patients receiving high-dose nitroglycerin had significantly lower mean arterial pressure and hematocrit levels during and after cardiopulmonary bypass. The risk of intraoperative cerebral desaturation was left-sided 23.9% versus 38.5% (p = 0.023), right-sided 28.1% versus 35.7% in the NTG and control groups, respectively. The risk of new-onset stroke and postoperative dialysis was 2.1% versus 6.3% and 1.0% versus 3.5% in the NTG and control groups, respectively.

Conclusion: An infusion of high-dose nitroglycerin initiating at rewarming of cardiopulmonary bypass and throughout the postbypass interval may induce hypotension and hemodilution in cardiac surgical patients. Cerebral saturation and renal function were well maintained without increasing the risk of stroke and renal replacement therapy after cardiac surgery with cardiopulmonary bypass.

Keywords: Acute kidney injury; Cardiopulmonary bypass; Cerebral desaturation; Nitroglycerin

1. INTRODUCTION

Cardiopulmonary bypass (CPB) is associated with multiple significant circulatory disturbances, including hypotension, hemodilution, hypothermia, nonpulsatile blood flow, and microemboli. During CPB, endothelial cell dysfunction precipitates a decrease in the production of endogenous nitric oxide (NO), compromising significantly both vascular tone and tissue perfusion.[1] End-organ hypoperfusion and inherent ischemia are common in the setting of extracorporeal circulation; brain and kidneys are among the most vulnerable organs to the devastating complications.[2,3]

In addition, although the risk of overt postoperative stroke has decreased from 1.6% to 1.2% in cardiac surgeries since the 1980s,[2] the impact of overt stroke is profound in terms of worse-adjusted hospital outcomes, longer postoperative hospital stays, and poorer downstream survival.[4] In addition to microemboli, cerebral hypoperfusion is a major risk factor for brain injury or dysfunction after cardiac surgery, particularly in patients with cerebrovascular disease.[5] The inflammatory response to surgery and CPB further contribute to cerebral dysfunction.

The incidence of acute renal failure requiring renal replacement therapy (RRT) after uncomplicated cardiac surgery in patients with earlier normal renal function is infrequent (<2%).[3] However, the incidence of acute kidney injury (AKI) defined by consensus definitions is about 20%–30%.[6,7] AKI requiring RRT after cardiac surgery has a profound impact on mortality, and even mild forms of AKI are consistently associated with later development of chronic kidney disease, multiorgan dysfunction, increased mortality, length of stay, and hospital costs.[8,9]

Administration of intravenous NTG has been proposed to protect against ischemia–reperfusion injuries in a limited number of studies through the mechanism of NO-induced vasodilatation.[10] Intravenous NTG also reproduces the effect of endogenous late preconditioning.[11] Nonetheless, effective tissue perfusion can be compromised if blood pressure falls excessively

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under the vasodilatatory effect of NTG. Considering the effect of high-dose NTG on the risk of cerebral desaturation and renal injury is relatively underexplored, we conducted this retrospective cohort study applying propensity score analysis to investigate the changes in the intraoperative cerebral saturation and postoperative serum creatinine concentration after the treatment of high-dose NTG starting at rewarming phase of CPB in cardiac surgery.

2. METHODS

2.1. Study setting

The study was approved by the medical ethics committee of Taipei Veterans General Hospital, Taipei, Taiwan (TVGHIRB No. 2015-12-018CC). Written informed consent was waived, and all the study materials were anonymized and de-identified before analysis.

At the tertiary medical center, patients undergoing cardiac surgery were frequently given intravenous NTG for the cardioprotective effect. In the past, the regimen of NTG was continuous infusion initiated instantly after anesthetic induction with an infusion rate of 1–3 $mg \cdot h^{-1}$ based on the patients' cardiac function and hemodynamics. If the mean arterial pressure (MAP) dropped to <60 mmHg during the surgery, intravenous bolus or continuous infusion of epinephrine and norepinephrine was given to elevate the systemic blood pressure. A new protocol of NTG treatment was adopted from July 2014 onwards after a review of current literature. There was no significant change in surgical or anesthetic facilities during the study period. The data of the study had been used partly in the authors' earlier work.[12]

2.2. Anesthetic management

For each patient undergoing cardiac surgery, serum creatinine concentration was tested 1 day before the surgery. At the operation room, cerebral oximeters (INVOS, Medtronic, MN, USA) were used to measure and record the bilateral cerebral saturation of surgical patients in real time. Baseline cerebral saturation was obtained before anesthetic induction under room air if patients had no cardiopulmonary distress. Patients were given fentanyl 1–2 $\mu g \cdot kg^{-1}$ and propofol 1–1.5 $mg \cdot kg^{-1}$ for induction, and neuromuscular blocking agents to facilitate tracheal intubation with rocuronium 0.8 $mg \cdot kg^{-1}$ or cisatracurium 0.2 $mg \cdot kg^{-1}$. During anesthetic maintenance, fentanyl 50–100 µg was given before sternotomy and aortic cannulation. Anesthesia was maintained with sevoflurane 2–3 vol% or desfurane 6–8 vol% in oxygen, with a fraction of inspired oxygen of 0.6–1.0 at the anesthesiologist's discretion. Arterial blood gas was tested each 5–10 minutes during CPB and 15–30 minutes during other phases of cardiac surgery.

2.3. Protocol of NTG loading

Intravenous administration of NTG was initiated at the rewarming of CPB with an infusion rate of 10 to 20 $mg \cdot h^{-1}$ and tapered to 5 to 10 $mg \cdot h^{-1}$ after weaning from CPB. The range of targeted MAP was 40 to 60 mm Hg. If MAP was <40 mm Hg or cerebral oxygen saturation decreased to <80% of the baseline value, the NTG would be tapered accordingly. Typically, NTG was given in a total dose of >0.5 $mg \cdot kg^{-1}$ during the surgery. Fluids and blood products were first used to maintain systemic blood pressure instead of vasopressors. If cardiac index (CI) was <2.4 $l \cdot min^{-1} \cdot m^{-2}$, dopamine (3-10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was first given instead of epinephrine or norepinephrine. Milrinone (0.3-1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was used at the anesthesiologists' discretion. After surgery, the infusion rate of NTG was adjusted by the physician of the intensive care unit (ICU) based on patients' hemodynamics. NTG was typically discontinued within 24 hours after surgery.

2.4. Techniques of cardiopulmonary bypass

HL-30 (Maquet, Rastatt, Germany) roller pumps and Affinity NT (Medtronic, Fridley, MN, USA) oxygenators were used for all patients. Infusion of cardioplegic solutions 15°C to 29°C Custodiol HTK (Koehler Chemi, Alsbach-Haenlien,Germany) or blood (blood to crystalloid ratio 4:1) were performed. The pump flow was an adjusted output of 2.2 $l \cdot m^{-2}$ of body surface area. The pump flow was decreased to 0.5 $l \cdot min^{-1}$ in aortic clamping and unclamping. Core temperature was maintained between 32°C and 34°C in valve surgeries and allowed to drift to 34°C in coronary artery bypass grafting (CABG). When the systemic temperature was >36°C, weaning from CPB was attempted.

2.5. Selection criteria of patients

In a review of the anesthetic records of cardiac surgical patients, we included the adult patients undergoing either or both CABG and value surgery at Taipei Veterans General Hospital between May 2012 and November 2015. Exclusion criteria were emergent surgeries, off-pump surgery, patients with history of preoperative dialysis or congenital heart diseases, and patients with critical missing data. Patients in the NTG group had the anesthetic management and NTG treatment according to the protocol described earlier. One to two controls were sampled for each NTG subject, matched on age (±5 y), type of surgery, and surgeon. Patients in the control group were treated according to the old NTG protocol (an infusion rate of 1–3 $mg \cdot h^{-1}$) and received a total dosage of NTG <0.5 $mg \cdot kg^{-1}$ during surgery.

2.6. Outcome measurement

Cerebral saturations were recorded before induction (baseline), after induction, before bypass, 0, 30, 60, 90, 120, 150, and 180 minutes after bypass, before the end of bypass, 30 minutes after the end of bypass, and at the end of surgery. Cerebral desaturation was defined as a relative decrease in regional cerebral oxygen saturation to <80% of the preoperative baseline.

Serum creatinine concentrations were collected at the time point of preoperative baseline, postoperative day (POD) 0 to POD 4 on a daily basis. Acute kidney risk and injury were defined by RIFLE classification,[6] namely an increase in serum creatinine 1.5 to 2.0 and 2.0 to 3.0 times baseline, respectively. Creatinine clearance rates before and after the operation were calculated with the Cockcroft-Gault equation.[13]

Intraoperative hemodynamic parameters were collected, including MAP, heart rate, and body temperature before anesthetic induction, 30 minutes after CPB, and 30 minutes after weaning from CPB. Hematocrit levels were collected from arterial blood gas tests at the time of postinduction (baseline), 15 minutes before cessation of CPB, and 30 minutes after cessation of CPB. Pulmonary artery catheterization was routinely performed with continuous cardiac output monitoring after anesthetic induction in cardiac surgical patients. The values of CI, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) were collected at the time of baseline, 30 minutes after the end of bypass, and 4 hours after the arrival of ICU.

Postoperative data included the urine output during the first 24 hours of ICU stay, time to extubation, ICU stay, and postoperative hospital stay. In addition, major complications were also recorded, including acute kidney risk, AKI and RRT, new-onset stroke after surgeries, reoperation within 24 hours, readmission due to cardiogenic causes within 3 months, and in-hospital mortality. Postoperative stroke was based on the brain imaging studies, including computed tomography or magnetic resonance imaging and defined as an event within postoperative 2 weeks. The inotropic score was calculated according the following formula: dopamine in $\mu g \cdot kg^{-1} \cdot min^{-1}$ + dobutamine in $\mu g \cdot kg^{-1} \cdot min^{-1}$ + milrinone in $\mu g \cdot kg^{-1} \cdot min^{-1}$ × 10 + epinephrine in $\mu g \cdot kg^{-1} \cdot min^{-1}$ × 10. Low-dose dopamine was defined as <3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; dobutamine and levosimendan were considered as other inotropic agents. Radiocontrast agents were considered if used within 72 hours before surgery.

2.7. Statistical analysis

Comparisons between the two groups were done with a Pearson's $\chi 2$ test or Fisher's exact test for categorical variables and two sample *t* test or Mann-Whitney *U* test for continuous variables as appropriate. Propensity score method was used to compensate for the potential difference in baseline attributes between groups and diminish the interaction effect of other variables.[14] The propensity score was obtained by using a logistic regression model, with the addition or omission of high-dose NTG as the dependent variable and all baseline characteristics as independent variables (Appendix 1). The propensity score was then used as the only confounding variable, in association with added or omitted high-dose NTG, to estimate the effect of high-dose NTG on the outcomes. A $p < 0.05$ was considered significant. All statistical analyses were conducted with SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Scientific graphing was performed with Prism version 6.00 (GraphPad Software Inc., San Diego, CA, USA).

3. RESULTS

In the timeframe of the study, 239 patients were available after meeting the selection criteria. In the NTG group, 96 patients (40.2%) received NTG with a total dosage of ≥0.5 mg·kg^{-1} during cardiac surgery. In the control group, 43 patients (18.0%) were given NTG with a total dosage of <0.5 mg·kg^{-1}, and 100 patients (41.8%) had no infusion of NTG during cardiac surgery.

There was no significant difference in the patients' attributes between the two groups (Table 1). The peak NTG infusion rates during rewarming period were median 20 (range 5-40) mg·h^{-1} in the NTG group and 0 (0-10) mg·h^{-1} in the control group. When dividing the patients into three groups, high-dose NTG group (with a total dosage of NTG ≥ 0.5 mg·kg^{-1}), low-dose NTG group (with a total dosage of NTG > 0 and < 0.5 mg·kg^{-1}) and no NTG group, their baseline characteristics were shown in Appendix 2.

The NTG group had significantly lower MAP during (50 ± 10 versus 57 ± 11 mmHg; $p < 0.001$) and after CPB (59 ± 8 versus 65 ± 11 mmHg; $p < 0.001$) compared with control group (Figure 1). Besides, patients in the NTG group had lower hematocrit levels during (25.5 ± 3.4 versus 26.9 ± 3.0%; $p = 0.001$) and after CPB (27.2 ± 3.7 versus 29.2 ± 3.2%; $p < 0.001$) than in the control group (Figure 2). There was no significant difference in the CI and SVR values between groups at the time of postbypass and ICU stay. However, the PVR after CPB was lower in the NTG group, 110 ± 66 versus and 181 ± 139 dynes·s·cm^{-5} ($p = 0.044$) (Table 2). The effect of high-dose NTG on the hemodynamic change was similar when dividing the patients into three groups (Appendix 3).

The risk of left-sided cerebral desaturation was 23.9% versus 38.5%, $p = 0.023$, and right-sided cerebral desaturation 28.1% versus 35.7% in the NTG and control groups, respectively. NTG subjects had fewer transfusions of fresh frozen plasma (FFP) [0 (0-8) versus 2 (0-12) units FFP; $p < 0.001$] than in the control group. NTG subjects had less perioperative fluid intake (2206 ± 547 versus 2546 ± 841 ml; $p = 0.003$) and less intraoperative inotrope support, including dopamine (32.3% versus 90.9%; $p < 0.001$), epinephrine (6.3% versus 59.4% $p < 0.001$), norepinephrine (6.3% versus 59.4%; $p < 0.001$), and other inotropes (2.1% versus 18.9%; $p < 0.001$) (Table 3, Appendix 4).

The postoperative peak value of serum creatinine was 1.37 ± 0.65 versus 1.47 ± 0.78 mg·dl^{-1}, change of serum creatinine 35.8 ± 38.3 versus 39.5 ± 38.1%, the incidence of acute kidney risk 15.6% versus 19.6% and injury 7.3% versus 8.4%, and RRT 1.0% versus 3.5% in the NTG and control groups, respectively. The postoperative inotropic scores were significantly lower in the NTG group [0 (0-26) versus 4.0 (0-52), respectively; $p < 0.001$]. The risk of major complications was 2.1% versus 6.3% in new-onset stroke, 4.2% versus 4.9% in reoperation, 4.2% versus 10.5% in readmission, and 1.0% versus 7.0% in in-hospital mortality in the NTG and control groups, respectively (Table 4, Appendix 5). Among the cases with stroke, none and five patients had hypoperfusion-type

Table 1

Characteristics of the study subjects

	NTG group (N = 96)	Control (N = 143)
Age, y	61 ± 14	63 ± 12
Sex, male	61 (63.5%)	82 (57.3%)
Body mass index, kg·m^{-2}	24.1 ± 3.7	24.4 ± 4.1
Co-morbidities		
Hypertension	52 (54.2%)	79 (55.2%)
Diabetes	31 (32.3%)	43 (30.1%)
PAOD	4 (4.2%)	4 (2.8%)
Stroke	9 (9.4%)	16 (11.2%)
Atrial fibrillation	17 (17.7%)	17 (11.9%)
Carotid artery disease	11 (11.5%)	10 (7.0%)
Perioperative medications		
Diuretics	41 (42.7%)	56 (39.2%)
ACEi or ARB	45 (46.9%)	72 (50.3%)
Digoxin	8 (8.3%)	14 (9.8%)
Contrast dye	22 (22.9%)	33 (23.1%)
Antiaggregants	42 (43.8%)	65 (45.5%)
Coumarins	10 (10.4%)	18 (12.6%)
Heparin and derivative	65 (67.7%)	97 (67.8%)
Other anticoagulants	2 (2.1%)	1 (0.7%)
IABP	5 (5.2%)	5 (3.5%)
LVEF, %	54 ± 11	54 ± 10
Serum creatinine, mg·dl^{-1}	1.01 ± 0.36	1.07 ± 0.55
Crcl, ml·min^{-1}	72.8 ± 30.8	67.7 ± 26.6
Platelet, K·CUMM^{-1}	20.4 ± 6.8	20.7 ± 6.6
PT, s	11 ± 1.3	11 ± 1.3
aPPT, s	28.1 ± 3.6	28.9 ± 5.1
EuroScore II, %	2.9 ± 2.8	2.6 ± 2.3
Type of surgery		
CABG	35 (36.5%)	64 (44.8%)
Valvuloplasty	56 (58.3%)	75 (52.4%)
CABG and valvuloplasty	5 (5.2%)	4 (2.8%)
Anesthetic time, min	413 ± 87	424 ± 95
Bypass time, min	147 ± 53	158 ± 62
Aortic clamp-cross time, min	105 ± 44	107 ± 48

Values were count (percent) or mean ± SD. There was no significant difference in baseline characteristics between groups.

ACEi = angiotensin-converting-enzyme inhibitor; aPPT = activated partial thromboplastin time; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; Crcl = estimated creatinine clearance; IABP = intra-aortic balloon pump; LVEF = left ventricle ejection fraction; PAOD = peripheral arterial occlusive disease; PT = prothrombin time.

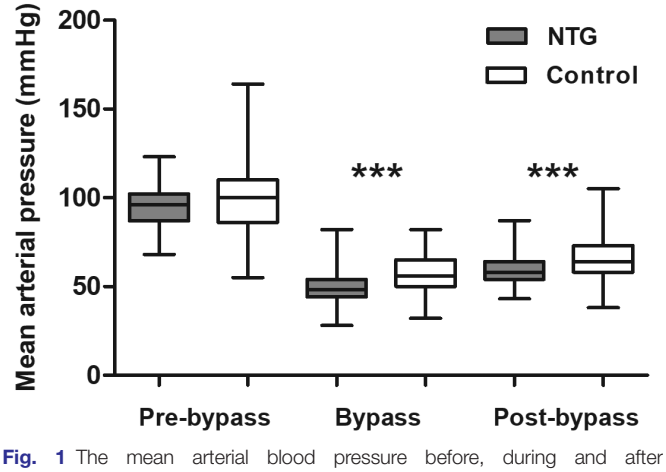

Fig. 1 The mean arterial blood pressure before, during and after cardiopulmonary bypass in the NTG and control groups. Intraoperative mean arterial pressure was significantly lower in the NTG group (N = 96) than the control group (N = 143) during and after cardiopulmonary bypass (***$p < 0.001$).

watershed or lacunar infarction in the NTG and control groups, respectively.

4. DISCUSSION

This study demonstrated that the administration of high-dose NTG during CPB would induce hypotension and hemodilution without elevating the risk of postoperative stroke or renal dysfunction in cardiac surgical patients. The risk of intraoperative cerebral desaturation was lower in the patients treated with high-dose NTG during CPB. Besides, patients treated with high-dose NTG had lower inotropic scores but comparable cardiac performance compared with controls at the arrival of ICU.

Previous studies showed a relative decrease in regional cerebral oxygen saturation of cerebral oximetry to <80% of the preoperative baseline or to absolute levels <50% increase in the risk of adverse postoperative outcomes, including stroke, major organ dysfunction, length of hospital stay, and mortality.[15–17] In this study, the patients treated with high-dose NTG during CPB had lower risk of intraoperative cerebral desaturation despite their lower MAP and hematocrit levels during and after CPB. The finding is consistent with the prior reports.[18,19]

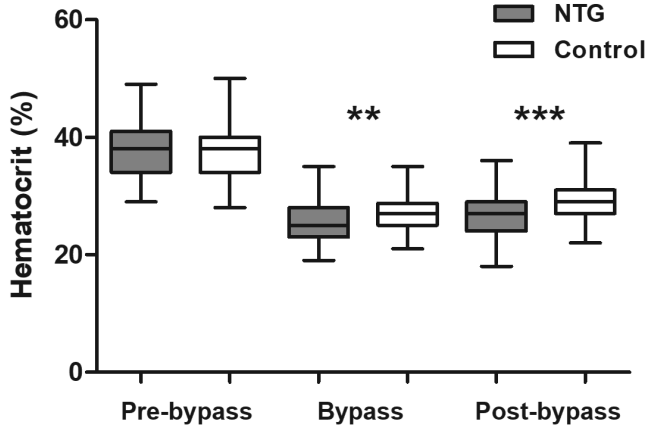

Fig. 2 The hematocrit concentration before, during and after cardiopulmonary bypass in the NTG and control groups. Intraoperative hematocrit concentrations were significantly lower in the NTG group (N = 96) than the control group (N = 143) during and after cardiopulmonary bypass (**$p < 0.01$; ***$p < 0.001$).

Additionally, the NTG subjects had lower risk of postoperative stroke in the study. The finding is against those reported by Gold and colleagues, who demonstrated that patients with controlled minimal MAP of 50 mmHg were associated with higher risk of neurologic complications in contrast to those with targeted MAP of 80 to 100 mmHg.[20] The sample size of the present study cannot provide enough statistical power to detect a difference in postoperative complications. However, our results suggested that the intravenous infusion of NTG as anesthetic strategy to correct episodes of cerebral oxygen desaturation in high-risk patients seems quite promising and warrants further investigations.

Extracorporeal circulation has detrimental effects on kidneys, including greater reduction in renal perfusion than systemic perfusion, impaired auto-regulation of renal blood flow, hemolysis with release of free hemoglobin, an established nephrotoxin, and stress hormone and inflammatory responses.[21,22] During CPB, hypotension with nonpulsatile flow promotes renal vasoconstriction and decreases renal blood flow, predisposing kidneys to further perioperative ischemic and nephrotoxic insults. Treatment modality in promoting renal vasodilatation has been tested to prevent development of postoperative renal dysfunction, including dopaminergic agents, prostaglandins, and atrial natriuretic peptide.[23] However, none of the above agents has been proved effective in preventing early AKI.[24]

Peguero and colleagues demonstrated that an intravenous infusion of NTG before percutaneous coronary intervention was associated with a decreased risk of contrast-induced nephropathy,[25] which shared similar pathophysiologic mechanisms with CPB-induced renal injury. In the current study, patients receiving an infusion of high-dose NTG during CPB had a trend of lower risk of acute kidney risk and injury, RRT and comparable urine output in spite of lower systemic blood pressure and hematocrit levels during and after CPB, although not reaching statistical significance.

Our analysis showed that the patients treated with high-dose NTG had less frequent use of exogenous catecholamines, lower MAP during and after CPB but comparable cardiac output when compared with control group. Some studies have revealed that it is not low pressure during CPB but post-CPB cardiac output that actually best correlates with postoperative renal dysfunction.[26,27] Furthermore, renal dysfunction is associated with increased renal sympathetic activity.[28] Petersson and colleagues have showed that high-dose infusion of NTG has renal sympathoinhibitory effects in spite of a reduction in both arterial pressure and cardiac

Table 2

Propensity score-adjusted hemodynamic variables

	NTG (N = 96)			Control (N = 143)		
	Pre-bypass	**CPB**	**Post-bypass**	**Pre-bypass**	**CPB**	**Post-bypass**
MAP, mmHg	95 ± 11	50 ± 10***	59 ± 8***	99 ± 17	57 ± 11	65 ± 11
HR, bpm	79 ± 15	N/A	76 ± 14*	80 ± 17	N/A	84 ± 14
Temperature, °C	36 (34.3–37.2)	35.6 (32.6–36.9)	36 (34.6–37.0)	36 (34.1–37.4)	35.4 (33.4–37.2)	35.9 (34.4–37.2)
Left ScO_2	64 ± 13	58 ± 12	63 ± 10	62 ± 12	59 ± 11	61 ± 11
Right ScO_2	63 ± 14	57 ± 12	62 ± 10	60 ± 12	58 ± 10	59 ± 11
Hematocrit, %	37.8 ± 4.7	25.5 ± 3.4**	27.2 ± 3.7***	37.1 ± 4.3	26.9 ± 3.0	29.2 ± 3.2
	Pre-bypass	**Post-bypass**	**ICU stay**	**Pre-bypass**	**Post-bypass**	**ICU stay**
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.4 ± 0.7	2.8 ± 0.8	2.7 ± 0.7	2.6 ± 0.9	2.8 ± 0.9	2.8 ± 0.6
SVR, $dyne \cdot s \cdot cm^{-5}$	1175 ± 444	914 ± 481	1223 ± 360	1309 ± 490	1057 ± 409	1196 ± 386
PVR, $dyne \cdot s \cdot cm^{-5}$	179 ± 126	110 ± 66*	196 ± 107	180 ± 120	181 ± 139	191 ± 96
	Baseline	**Pre-bypass**	**Post-bypass**	**Baseline**	**Pre-bypass**	**Post-bypass**
ACT, s	150 ± 19	543 ± 108	132 ± 21	165 ± 31	543 ± 103	132 ± 23

Values were mean ± SD or median (range).

ACT = activated clotting time; CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; PVR = pulmonary vascular resistance; ScO_2 = cerebral saturation; SVR = systemic vascular resistance.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 3

Propensity score-adjusted intraoperative parameters

	NTG (N = 96)	Control (N = 143)
Cerebral saturations		
Lowest Lt ScO_2	50 ± 11	49 ± 9
Lt cerebral desaturation	23 (23.9%)*	55 (38.5%)
△ Lt cerebral saturation, %	−13.2 ± 14	−15.1 ± 14
Lowest Rt ScO_2	50 ± 11	49 ± 9
Rt cerebral desaturation	27 (28.1%)	51 (35.7%)
△ Rt cerebral saturation, %	−15.0 ± 13	−15.6 ± 13
Vital signs		
Pulse pressure, mmHg	64 ± 23	67 ± 25
Lowest MAP on CPB, mmHg	38 ± 7**	42 ± 8
Lowest HCT on CPB, %	23 ± 4	23 ± 3
Lowest temperature on CPB, °C	32.6 ± 2.1	32.5 ± 2.8
Fluid management		
Allogeneic pRBC, unit	3.2 ± 2.6	3.9 ± 2.8
FFP, unit	0 (0–8)***	2 (0–12)
Platelet pheresis, unit	0 (0–2)	0 (0–3)
Intake fluid, ml	2206 ± 547**	2546 ± 841
Blood loss, ml	515 ± 272	639 ± 500
Urine output, ml·kg^{-1}·h^{-1}	2.6 ± 1.4	2.7 ± 1.7
Inotropes		
Low-dose dopamine	31 (32.3%)***	130 (90.9%)
Epinephrine or norepinephrine	6 (6.3%)***	85 (59.4%)
Other	2 (2.1%)***	27 (18.9%)
Heparin, U·kg^{-1}	331 ± 58	327 ± 55
Protamine, mg·kg^{-1}	3.2 ± 0.6	3.3 ± 0.7

Values were count (percent), mean ± SD or median (range).

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

FFP = fresh frozen plasma; HCT = hematocrit; MAP = mean arterial pressure; pRBC = packed red blood cells; ScO_2 = cerebral saturation.

Table 4

Propensity score-adjusted postoperative outcomes

	NTG group (N = 96)	Control (N = 143)
Renal function		
Peak serum creatinine, mg·dl^{-1}	1.37 ± 0.65	1.47 ± 0.78
Lowest creatinine clearance, ml·min^{-1}	56.4 ± 24.9	51.3 ± 22.7
△ Serum creatinine, %	35.8 ± 38.3	39.5 ± 38.1
△ Creatinine clearance, %	−21.9 ± 17.7	−23.8 ± 17.6
Acute kidney risk	15 (15.6%)	28 (19.6%)
Acute kidney injury	7 (7.3%)	12 (8.4%)
RRT-ARF	1 (1.0%)	5 (3.5%)
24 h urine output, ml·kg^{-1}·h^{-1}	2.2 ± 1.0	2.1 ± 1.2
Major complications		
Reoperation	4 (4.2%)	7 (4.9%)
New-onset stroke	2 (2.1%)	9 (6.3%)
Readmission	4 (4.2%)	15 (10.5%)
In-hospital mortality	1 (1.0%)	10 (7.0%)
Fluid balance at 24 h, ml	−638 ± 842	−467 ± 1033
P/F ratio, mmHg	309 ± 130	336 ± 132
Time to extubation, h	29.6 ± 21.0	36.6 ± 73.2
Inotropic score	0 (0–26)***	4.0 (0–52)
ICU stay, d	3.5 ± 3.3	3.6 ± 3.2
Postoperative hospital stay, d	15 ± 8	16 ± 12

Values were count (percent), mean ± SD or median (range).

*** $p < 0.001$.

P/F = partial pressure of arterial blood oxygenation/fraction of inspiratory oxygen concentration; RRT-ARF = renal replacement therapy-acute renal failure.

filling pressures in patients with chronic heart failure.[29] In addition, renal vasoconstriction and inherent decreased renal blood flow during CPB might be exacerbated by the use of exogenous catecholamines that further increase the peripheral and visceral arterial resistances.

NTG is superior to sodium nitroprusside as a NO donor for less concern of possible coronary steal phenomenon and cyanide poisoning. Besides, sodium nitroprusside has been showed to exert detrimental effects on microcirculation.[30] If so, what is the effective infusion rate of NTG to maintain adequate end-organ perfusion in the setting of CPB? The therapeutic dosing of NTG for acute myocardial infarction is 1.5 to 12 mg·h^{-1}. Our results showed an intravenous loading of NTG up to 20 mg·h^{-1} during CPB might be effective in stabilizing cerebral saturation without increasing the risk of postoperative major complications in cardiac surgical patients. In consideration of the short half-life of NTG and the dilution effect of extracorporeal circulation, an infusion rate up to two times greater might be required to ensure adequate concentrations of NTG at the vascular beds of end-organs.

This study has several potential limitations: (1) The retrospective design and small patient sample limit drawing strong conclusions. (2) There was no direct measurement of renal and cerebral blood flow, such as Doppler ultrasonography. (3) The blood concentrations of NO and NTG during and after CPB were unknown. (4) Although there was no significant difference in the patients' attributes between groups, it is unclear whether there exist unrecorded confounders for the observed differences in study endpoints. In addition, the intravenous loading of NTG should be given cautiously with adequate hydration to maintain normovolemia and prevent profound hypotension. Despite these potential limitations, the study showed the safety of high-dose NTG administered during CPB and its potential, beneficial effects on cerebral and renal perfusion in cardiac surgical patients.

In conclusion, the infusion of high-dose nitroglycerin initiating at rewarming of CPB and throughout the post-bypass interval may induce hypotension and hemodilution. Cerebral saturation and renal function were well maintained without increasing the risk of new-onset stroke or RRT after cardiac surgery with CPB.

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A12.

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