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# Preliminary Results of Supra-Hepatic Intraaortic Perfusion with Nitroglycerin for Patients with Significant Hepatic Dysfunction

**Prasanna Simha Mohan Rao**, Parimala Prasanna Simha

Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangalore, Karnataka, India

*Dr. Rao*

## ABSTRACT

**Background:** Preoperative hepatic dysfunction is a risk factor for postoperative fulminant hepatic failure and death. We noted persistent hepatic artery vasospasm in patients dying of postoperative hepatic failure .We hypothesized that an intra-aortic vasodilator such as nitroglycerin could attenuate vasospasm and prevent hepatic failure.

**Methods:** Nineteen consecutive patients with significant preoperative hepatic dysfunction underwent cardiac surgery using cardiopulmonary bypass with continuous infusion of intra-aortic nitroglycerin via a catheter placed above the celiac axis. Serial hepatic artery Doppler studies were done perioperatively with and without the nitroglycerin infusion on. Hepatic artery Doppler, hepatic artery size, alterations in liver function and serum creatinine, and outcomes were noted. Survival was compared to the Euroscore and a hepatic risk score that was based on a historical cohort and reported literature.

Results: One patient could not be weaned off cardiopulmonary bypass. In the remaining 18 patients, reversible hepatic arterial vasospasm was noted, and this persisted at 24 hours in 12 patients and 48 hours in 7 patients. All patients had resolution of vasospasm at 72 hours. Serial paired hepatic artery diameter measurements showed a significant difference ($P < .001$). There was a significant reduction in mortality (5.2 %) compared to historical control and predicted mortality (logistic Euroscore 37.4%, $P = .023$). None of the survivors had a significant alteration in hepato-renal function.

**Conclusion:** Intra-aortic nitroglycerin can attenuate hepatic arterial vasospasm induced by cardiopulmonary bypass and preserve hepatic function. This may reduce the risk associated with cardiopulmonary bypass and surgery in patients with liver dysfunction.

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*Correspondence: Prasanna Simha Mohan Rao, No 33, "Shri" between 2nd/3rd Cross, Sampige Road, Malleswaram, Bangalore 560003, Karnataka, India; 91 9341216294 (e-mail: prasannasimha@gmail.com).*

## INTRODUCTION

Hepatic dysfunction is a well-described cause of mortality after cardiac surgery but is not included as a risk factor in common scoring systems such as the Euroscore. Preoperative hepatic dysfunction was recognized as a risk factor for death in our unit, and we wanted to investigate if a method could be used to eliminate it as a risk factor.

Reviewing deaths that occurred postoperatively in patients who had preoperative hepatic dysfunction, it was noted that deaths in such cases were due to postoperative fulminant/progressive hepatic failure with progressive decline in hepatic function over the ensuing few days despite weaning from inotropes and good cardiac output (except pre-terminally). We suspected that there was fulminant hepatic failure due to hepatic ischemia, and when we did Doppler evaluation of the hepatic and portal circulation, we noted that these patients had hepatic arterial vasospasm with undetectable or monophasic hepatic arterial Doppler signals. We had also noted that administration of intravenous nitroglycerin and high-flow cardiopulmonary bypass did not attenuate this vasospasm. We noted reversal of hepatic arterial vasospasm when nitroglycerin was administered through the central intraaortic balloon pump (IABP) lumen in one such case (for threatened limb ischemia due to femoral artery vasospasm) without any effect on administration via the venous side. We also noted that such patients did not have hepatic arterial flow anomalies preoperatively. We hypothesized that cardiopulmonary bypass (CPB) initiates hepatic arterial vasospasm. If hepatic perfusion could be improved during CPB and postoperatively using an intra-arterial vasodilator, hepatic arterial vasospasm could be attenuated and hepatic function could be preserved. We chose nitroglycerin over sodium nitroprusside due to concerns of cyanide and thiocyanate toxicity during prolonged administration in patients with hepatorenal dysfunction. Nitroglycerin also has the added advantage of lowering portal venous pressure and improving splanchnic perfusion. Its short duration of action also lends itself to easy alteration to allow titration of effect and also to easily demonstrate and monitor the reversibility of vasospasm.

## MATERIALS AND METHODS

Patients with significant valve disease with hepatic dysfunction that persisted despite adequate decongestive measures

were included in the study. Hepatic dysfunction was diagnosed by jaundice (serum bilirubin > 2 mg/dL), prolonged prothrombin time with an international normalized ratio (INR) > 1.3 despite vitamin K therapy, and rise in biochemical markers (transaminase levels more than 5 times the upper limit of the laboratory reference range). All preoperative biochemical parameters used for analysis were the values obtained within 24 hours of surgery. These patients were recruited from January 2008 to September 2010. They typically had associated risk factors like severe cardiac cachexia. They had a high preoperative Euroscore due to preoperative risk factors that were noted. Hepatic risk was estimated by adding to the logistic Euroscore a predefined empiric "hepatic risk score," which we based on the Child's score of the patient viz an absolute value of 6% for Child's A, 25% for Child's B, and 50% for Child's C. These values were based on a combination of our previous mortality and literature [Suman 2004; Modi 2010]. (For example, if the patient was found to have liver dysfunction categorized as Child's A and had a logistic Euroscore of 18%, then the hepatic risk score was 18% + 6% = 24%). We chose the Child's score over the model for end-stage liver disease (MELD) score due to its simplicity in calculation, easy segregation into defined risk classes, historical data available in both our records and previous literature, and the fact that there is good correlation between the Child's score and MELD score in the nontransplantation setting with no significant advantage of the MELD score over the Child's score [Suman 2004; Durand 2005; Filsoufi 2007; Hoteit 2008; Modi 2010].

Informed consent was taken for all cases, and hospital ethical committee approval was obtained. In view of preoperative hepatic dysfunction and severe cardiac cachexia, all patients underwent preoperative stabilization if the clinical condition permitted consisting of aggressive diuresis, food supplementation with Ensure® (Abbott Laboratories, Abbott Park, IL, USA) and vitamin K on alternate days for at least one week before surgery. If there were no obstructive lesions, dobutamine (3 μg/kg per minute) was started a day before surgery if the patient was not in cardiogenic shock. Patients' hepatic function was monitored using serum bilirubin, aspartate transaminase (AST/SGOT), alanine transaminase (ALT/SGPT), and prothrombin time/INR as markers for liver injury. Serum creatinine was also recorded because patients often had concomitant renal dysfunction. Intravenous glucose potassium insulin (5% dextrose 500 mL + 40 MEq potassium + 10U human plain monocomponent insulin administered at 20 mL/hour) was started the day before surgery, taking care to avoid hyperkalemia. This was continued until 24 hours after surgery. Patients in cardiogenic shock were administered inotropes as required, and glucose potassium insulin was started as soon as notified about the need for emergent surgery.

Induction of anesthesia was done in a conventional manner, avoiding/minimizing hepatotoxic drugs. All patients had continuous cardiac output monitoring using the FlotracTM Sensor with Vigileo MonitorTM System (Edwards Life Sciences, Irvine, CA, USA). After induction a 5 Fr pigtail catheter was placed via the femoral artery to a length measured from the xiphoid to umbilicus to femoral puncture site. This ensured supra-celiac placement of the pigtail catheter. Sonography confirmed the suprahepatic placement. Initially the pigtail was introduced through a 6 Fr pediatric sheath, but later a sheathless insertion was preferred to decrease the possibility of vascular insufficiency, especially in small statured cachectic women and children. Hepatic Doppler profile was noted after placement.

All patients underwent surgery under standard hypothermic CPB. A membrane oxygenator, hemofilter, and an arterial line filter were placed in all patients. Cardiac arrest was with hyperkalemic sanguineous cardioplegia. Cardioplegia was made by mixing St. Thomas I solution and blood as a 1:4 ratio with additional adenosine (6 mg) and esmolol (0.5 mg/kg as an initial bolus and during warm reperfusion) as additives [Kuhn-Regnier 1999; Chauhan 2000; Rinne 2000; Vinten-Johansen 2003]. Hyperkalemic antegrade cardioplegia was administered every 20 minutes. Retrograde continuous cold perfusion (normokalemic) was initiated as soon as technically feasible after critical portions of cardiac surgery (requiring a precise dry field) were over. Hyperkalemic cardioplegia was given if there was any return of cardiac activity. Warm retrograde normokalemic sanguineous reperfusion was initiated with a bolus of adenosine (6 mg) and esmolol (0.5 mg/kg) while cardiotomies were being closed. High flow CPB with an index of 3 to 3.5 L/m2 per minute was used, and patients were cooled to 32 C [Adluri 2010]. Continuous ultrafiltratation was done on CPB during rewarming, and modified ultrafiltration was done for 10 minutes after weaning from CPB. Tranexamic acid (10 mg/kg initial bolus on induction and 10 mg/kg per hour) infusion was maintained through CPB and for 6 hours in the ICU postoperatively.

Pre-CPB, intra-aortic nitroglycerin at 2 μg/kg per minute was started, and on initiation of CPB it was increased to 5 μg/kg per minute. Five minutes before weaning from CPB, it was reduced to 2 μg/kg per minute. All patients were weaned with 3 μg/kg per minute of dobutamine and dopamine and 0.35 μg/kg per minute of milrinone. Additional inotropic support was initiated as required. An aggressive blood conservation protocol was practiced to limit perioperative nonautologous transfusions. This included withdrawal of 1 to 3 units of autologous blood before heparinization (based on a predicted target circulating packed cell volume [PCV] of 24%) after induction and central line placement, retrograde arterial priming and use of vacuum assist with shortened CPB lines with a "dry" venous line, minimizing tissue dissection, meticulous hemostasis, hemofiltration (both continuous and modified ultrafiltration), and return of the entire pump volume at the end of surgery with saline displacement of the reservoir, reinfusion of autologous blood after sternal closure, and a rapid decision to re-explore if there was any suspicion of surgical postoperative bleeding. The transfusion threshold was 8 g/dL, and no fresh frozen plasma/platelets were given if there was no significant clinical bleeding requiring re-exploration.

Post-CPB, after shifting to the intensive care unit (ICU), hepatic arterial Doppler and diameter with nitroglycerin infusion on were recorded after 10 minutes of stopping the infusion, and a re-record was done after 10 minutes of re-initiation of nitroglycerin using an 8 MHz Doppler probe (Philips Envisor, Andover, MA, USA). Peak systolic "S" velocity and peak diastolic velocity "D" were noted, and normal triphasic

flow and its absence were noted. Recordings were repeated again after 12 hours. The values after reinitiating nitroglycerin were taken for the study. Thereafter, daily recordings were done, and if there was no difference then the infusion was replaced with heparin 100 U/mL infusion at 3 mL/hour for 6 hours and thereafter the catheter was removed. The initial plan was to remove the catheter after 24 hours, but after noting persistent reversible vasospasm even at 24 hours in some patients, it was decided to remove it after it subsided. The presence of delayed vasospasm was noted.

Serial rise in bilirubin, alanine transaminase, aspartate transaminase, and serum creatinine were recorded, with daily values being obtained for the first week and alternate days thereafter if the patient continued to be hospitalized. Peak biochemical parameters were used for the study. Any patient who had an intra-aortic catheter placed but did not survive surgery was noted, and if the patient was unweanable from bypass, it was noted but excluded from the analysis.

All data were recorded in a Microsoft Excel spreadsheet. Power analysis was done using G*Power 3 statistical software [Faul 2009] with estimates being made with data collected in a pre-study and confirmed by a post hoc analysis. Paired data were analyzed with Student's t test. Alteration in postoperative renal and hepatic parameters were analyzed using the Wilcoxon signed rank test. Since most of the biochemical parameters had an abnormal baseline (preoperative) value, the differences between patient differences in baseline values were standardized by computing the percent change from the baseline value for analysis. Categorical data were analyzed with the Fisher's exact test. The software used for analysis was Microsoft ExcelTM, Graph Pad Quick Calcs (GraphPad Software, Inc., La Jolla, CA, USA), and Vassar Stats (http://faculty.vassar.edu/lowry/VassarStats.html, Poughkeepsie, NY, USA). *P* values were reported as actual *P* values if more than $P > .0001$. A *P* value of $< .05$ was considered significant, and $P < .01$ was considered highly significant.

## RESULTS

Nineteen patients who had significant hepatic dysfunction had a pre-CPB placement of an intra-aortic catheter and received nitroglycerin perioperatively. Patient characteristics are detailed in Table 1. The surgical procedures done and the complications are enumerated in Table 2. One patient who had a catheter in place and underwent a high-risk palliative double valve replacement with tricuspid valve repair for mitral, aortic, and tricuspid regurgitation with severe left ventricular dysfunction and hepatic dysfunction in lieu of a cardiac transplant (which we cannot offer) was not weanable from CPB and died. He was excluded from the study. Eighteen patients survived the surgery and postoperative period and were analyzed.

Power analysis for the sample of size 18 with an α error probability of 0.05 and power (1-β error probability)—with a threshold of 0.80—was 0.824.

The mean logistic Euroscore was 37.4 (standard deviation ([SD] = ±12.98), and the logistic Euroscore with the hepatic risk score was 49.7 (SD = ±18.4). The observed mortality was 5.2%, and there was a statistically significant reduction in mortality against the predicted Euroscore ($P = .02301$) and the hepatic risk score.

Table 1. Patient Characteristics (N = 19)

| | n (%) |
|---|---|
| Child-Pugh class | |
| A | 12 (62.3) |
| B | 7 (36.8) |
| C | 0 (0) |
| Gender | |
| Male | 10 (52.6) |
| Female | 9 (47.4) |
| Age, y | |
| < 20 | 3 (15.7) |
| 21–40 | 12 (63.2) |
| 41–60 | 3 (15.7) |
| > 61 | 1 (5.4) |
| Cardiogenic shock (inotropes or intraaortic balloon pump) | |
| Yes | 5 (26.3) |
| No | 9 (47.4) |
| Acute renal dysfunction (serum creatinine > 2mg/dL) | |
| Yes | 5 (26.3) |
| No | 14 (73.7) |
| Mean logistic EuroSCORE | 37.4 |

Table 2. Surgical Procedures and Complications

| Surgery and Postoperative Variables | n (%) |
|---|---|
| Procedures | |
| Mitral valve replacement + tricuspid repair | 3 (15.8) |
| Mitral valve repair + tricuspid valve repair | 10 (52.7) |
| Aortic valve replacement + mitral + tricuspid valve repair | 4 (21.1) |
| Double valve replacement + tricuspid valve repair | 2 (10.4) |
| Electro-cautery maze | 19 (100) |
| Redo surgery | 1 (5.2) |
| Cardiopulmonary bypass time, min | 68–368 (median = 92) |
| Cross-clamp time, min | 42–126 (median = 91) |
| Major bleeding | 1 (5.2) |
| Blood transfusion | 1 (5.2) |
| Delayed extubation ( > 6 hours) | 8 (44.4) |
| Renal replacement therapy | 0 (0) |
| 30-day mortality | 1 (5.2) |

Twelve patients were in Child's A, and 7 were in Child's B Class. We did not operate on any patient with Child's C Liver disease.

Table 3. Hepatic Artery Doppler Values Showing "S" and "D" Wave Velocities after Induction during Placement of the Intraaortic Pigtail Catheter and Postoperatively with Intraaortic Nitroglycerin (NTG) Switched On and Off*

| | NTG On | | NTG Off | |
|---|---|---|---|---|
| | "S" Wave | "D" Wave | "S" Wave | "D" Wave |
| Pre-CPB | | | 74 ± 23.5 | 28 ± 13.1 |
| On shifting to ICU | 82.44 ± 23.66 | 37.06 ± 11.73 | 44 ± 22.05 | 9.44 ± 11.64 |
| 12 hours after shifting to ICU | 89.80 ± 13.64 | 43.93 ± 10.54 | 55.53 ± 27.00 | 13.60 ± 12.45 |

*All values are in cm/sec and reported with 1 standard deviation. CPB indicated cardiopulmonary bypass; ICU, intensive care unit.

The 18 patients who were successfully weaned from CPB survived to discharge, 1 month follow-up, 3 month follow-up, and are on 6-month follow-up thereafter.

The median ICU stay was 3 days, and one patient with chronic obstructive pulmonary disease (COPD) had an ICU stay of 12 days and required noninvasive ventilation intermittently for type 2 respiratory failure. No patient required renal replacement therapy postoperatively. There was one patient who was re-explored for bleeding. He was the only patient who received transfused nonautologous blood, fresh frozen plasma, and platelets.

Table 4. Median Preoperative Hepatorenal Biochemical Values and the Peak Percentage Change Postoperatively above the Preoperative Values

| Biochemical Parameters | Preoperative Median Value | Peak Percentage Change Postoperatively over Preoperative Value | Standard Deviation | *P* |
|---|---|---|---|---|
| Serum creatinine | 1.8 mg/dL | + 0.28 | ± 14.19% | .488 |
| Serum bilirubin | 3.7 mg/dL | - 2.22 | ± 16.79% | .2549 |
| Aspartate transaminase | 68 IU/L | + 0.67 | ± 8.57% | .782 |
| Alanine transaminase | 158 IU/L | + 0.82 | ± 9.86% | .684 |

Eight patients needed ventilation longer than 6 hours, but all patients who were weaned from CPB were extubated within 48 hours. The median hospital stay was 7 days (range, 5 to 22 days).

The patient who had significant COPD died 4 months after discharge due to a lower respiratory tract infection.

All 12 patients who are in Child's A class have not had deterioration of liver function. The remaining surviving patients in Child's B class (5) have not had worsening hepatic function so far, though the follow-up is too short to be meaningful. No survivor has required dialysis for renal dysfunction.

### *Hepatic Artery Doppler*

All patients had a triphasic normal hepatic arterial waveform prior to cardiopulmonary bypass (on induction of anesthesia.) The Doppler values are shown in Table 3.

Serial hepatic Doppler studies were done immediately after shifting to the ICU. The hepatic Doppler profile is detailed in Table 2. The mean hepatic Doppler "S" wave velocity was 82.44 cm/sec (SD = ±23.66 cm/sec), and mean hepatic "D" velocity was 37.06 cm/sec (SD = ±11.73 cm/sec). On stopping the nitroglycerin infusion for 10 minutes, the hepatic "S" wave velocity dropped to 44 cm/sec (SD = ±22.05 cm/sec), and the hepatic "D" wave velocity dropped to 9.44 cm/sec (SD = ±11.64 cm/sec). Four patients developed a monophasic waveform, and after another 5 minutes, 3 of them developed total cessation of hepatic arterial flow on Doppler and color flow interrogation, which returned after reinstituting the nitroglycerin infusion. The difference between the paired S wave and D wave velocities pre- and post-nitroglycerin was highly significant ($P < .001$ for both S wave velocity and D wave velocity).

Hepatic Doppler analysis 12 hours after CPB was repeated. With nitroglycerin on the S and D values were 89.80 cm/sec (SD = ±13.64) and 43.93 cm/sec (SD = ±10.54), respectively. The S and D values with nitroglycerin off were 55.53 cm/sec (SD = ±27.00) and 13.60 cm/sec (SD = ±12.45), respectively. The difference between the paired S and D values pre- and post-NTG at 12 hours were highly significant ($P = .0002$ and $P < .0001$, respectively).

Vasospasm with reduction of nitroglycerin persisted at 24 hours in 12 patients and 48 hours in 7 patients, and all patients had resolution of vasospasm at Doppler interrogation at 72 hours.

### *Hepatic Artery Diameter*

The mean hepatic artery diameter with nitroglycerin on shifting to the ICU was 6.9 mm (SD = ±0.6 mm) and on stopping nitroglycerin was 3.8 mm (SD = ±0.7 mm). The difference in the paired values of the diameters was highly significant ($P < .0001$).

At 12 hours, the mean diameter with nitroglycerin on was 7.1 mm (SD = ±0.4 mm), and on stopping nitroglycerin the mean diameter was 4.1 mm (SD = ±1.2 mm). The difference in the paired values were highly significant, with $P < .0001$. There was no significant change in cardiac output on stopping/reinitiating intra-aortic nitroglycerin when hepatic Doppler and diameter measurements were being obtained.

***Biochemical Parameters***

There was no significant increase in any of the peak postoperative biochemical parameters over the baseline preoperative values (Table 4). Revalidation with absolute differences between preoperative values and postoperative peak values also did not yield any significant difference in any biochemical parameter.

## DISCUSSION

Hepatic dysfunction is a well-recognized risk factor for morbidity and mortality after cardiac surgery, and yet it is not included in major risk scoring systems. The population of cardiac surgical patients with hepatic dysfunction or cirrhosis has been sufficiently small, and this limits the ability to conduct large clinical trials [Orlino 2005]. There is also the possibility of bias regarding referral of these patients for surgery due to known poor outcomes of these patients when subjected to cardiac surgery. Worsening hepatic dysfunction is associated with a higher mortality and was a risk factor in our surgical unit during review of mortality and morbidity statistics. We wanted to neutralize this. While analyzing the modes of death, we noted that most deaths occurred postoperatively, typically between 8 and 14 days after surgery despite weaning from inotropes and with good peripheral perfusion. Patients would go into progressive hepatic failure, develop hepato-renal syndrome, and then develop cardiovascular instability terminally and die after the initial window of hemodynamic stability.

We had noted that there was intense hepatic vasospasm in such patients and had tried to attenuate this response by using intravenous vasodilators and high-flow CPB [Adluri 2010] and limiting the amount of hypothermia, but this did not improve results, and hepatic arterial vasospasm persisted. We had noted resolution of hepatic arterial vasospasm in a patient who received intra-aortic vasodilator (nitroglycerin) via the central IABP lumen (for threatened limb ischemia due to femoral arterial vasospasm), which had been placed at the time of weaning from CPB. We hypothesized that CPB causes hepatic arterial vasospasm, which can cause ischemic hepatitis and that attenuation of vasospasm could be beneficial in these patients.

Nutritive flow to the normal liver is mainly via the portal venous system (approximately 75% to 80%), but in patients with compromised liver function and cirrhosis with decreased portal flow, the hepatic arterial flow increases and is known as the "hepatic buffer response." This hepatic buffer response preserves total hepatic flow [Richter 2000; Zipprich 2003; Vollmar 2009]. In patients with severe tricuspid regurgitation, passive venous congestion of the liver, and cardiac cirrhosis, the transhepatic portal venous gradient is increased and hepatic arterial flow and hepatic buffer response becomes important. The hepatic buffer response can increase hepatic blood flow, and this can be as much as 60% of total hepatic blood flow [Vollmar 2009]. With loss of pulsatile hepatic blood flow on CPB, we speculate that there can be a critical loss of hepatic perfusion leading to a vicious cycle of hepatic malperfusion and damage leading to fulminant hepatic necrosis. Decreased hepatic flow has been documented during hypothermic CPB [Fetough 2008] and is partially attenuated by increasing pump flows [Adluri 2010]. We used mild hypothermia and pump flows of 3.0 to 3.5 L/min per m2 previously, and this did not decrease the incidence of liver dysfunction in our unit.

Intravenous nitroglycerin did not attenuate hepatic arterial vasospasm, and it has been previously noted that intravenous nitroglycerin may not alter hepatic blood flow or hepatic resistance in patients with congestive heart failure [Leir 1981]. This may also be related to first pass metabolism of nitroglycerin, so direct intra-arterial nitroglycerin may avoid this. Direct intra-arterial nitroglycerin has been shown to relieve hepatic arterial vasospasm [Andrew 2004].

Institution of intra-arterial nitroglycerin via a pigtail catheter into the aorta in our study was associated with an attenuation of vasospasm and triphasic hepatic arterial Doppler flow. This reversible nature of the vasospasm was demonstrated by stopping the infusion (which caused vasospasm to occur), and reversal was demonstrated on reinstitution of nitroglycerin. Hepatic vasospasm was seen even up to 48 hours post-CPB and was absent only at 72 hours. Hepatic arterial spasm should be monitored or intra-aortic nitroglycerin should be given for at least 72 hours to prevent ischemic liver damage. We had a significant decrease in mortality compared to historical cohort and also in relation to the standard Euroscore. Preservation of hepatorenal function was observed and no patient went into ischemic hepatitis or fulminant hepatic failure. Despite not using selective hepatic cannulation vasospasm was reversed. This is also an advantage because it will allow easy placement and avoids the need for placement under radiological control. There is the possibility that the selective intra-arterial catheter itself may be obstructive and may provoke vasospasm due to manipulations needed to place it.

One of the limitations of this study is that we did not have a randomization or blinding, but the reversibility of hepatic vasospasm was consistently seen in all the cases. There was comparison to historically observed mortality (non-matched), and the Euroscore is currently considered to overestimate mortality. Even if we use some correction methods (eg, observed Euroscore divided by 2 = modified Euroscore, which correlates with our own observed mortality in general, even though in Indian patients the Euroscore has been noted to under predict mortality in patients with valvular heart disease with high-risk comorbidities [Malik 2010]), we still observed a lower mortality with the use of intra-aortic nitroglycerin. Another limitation is that we also did not operate on any patients who were in Child's C category because we do not have an active liver transplantation program in our hospital.

We believe that intra-aortic nitroglycerin can attenuate hepatic arterial vasospasm induced by CPB and preserve hepatic function. This may reduce the risk associated with CPB and surgery in patients with liver dysfunction.

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