Clinical Investigation

Systemic Effects of Intracoronary Nitroglycerin during Coronary Angiography

in Children after Heart Transplantation

Diego A. Lara, MD
Mary K. Olive, MD
James F. George, PhD
Robert N. Brown, BS
Waldemar F. Carlo, MD
Edward V. Colvin, MD
Brad L. Steenwyck, MD
F. Bennett Pearce, MD

Coronary spasm during coronary angiography for vasculopathy in children can be prevented by the intracoronary administration of nitroglycerin. We reviewed the anesthesia and catheterization reports and charts for pediatric transplant recipients who underwent angiography from 2005 through 2010. Correlation analysis was used to study the relation of post-injection systolic blood pressure (SBP) to nitroglycerin dose. Forty-one angiographic evaluations were performed on 25 patients (13 male and 12 female). Mean age was 9.9 ± 3.2 years (range, 3.3–16.1 yr). The mean total dose of nitroglycerin was 2.93 ± 1.60 µg/kg (range, 1–8 µg/kg).

There was a significant drop between the baseline SBP (mean, 106 ± 21.6 mmHg) and the lowest mean SBP before nitroglycerin administration (78 ± 13.2, P *<0.0001, paired* t *test). There was no significant additional change in SBP (mean after nitroglycerin administration, 80.7 ± 13.1 mmHg;* P=*0.2). There was a significant drop in lowest heart rate between baseline (109 ± 16.5 beats/min) and before nitroglycerin administration (89 ± 14.3 beats/min;* P *<0.0001, paired* t *test). There was no significant additional change in heart rate (mean heart rate after nitroglycerin, 84 ± 17.7 beats/min;* P=*0.09). There were 2 interventions for SBP before nitroglycerin and 2 after nitroglycerin. One child experienced a transient ST-T–segment change during angiography after nitroglycerin. In the highest dose range, the additional decrease in SBP was 7.2 mmHg (*P=*0.03). Routine intracoronary nitroglycerin administration in this dose range produced no significant changes in SBP or heart rate in children.* ***(Tex Heart Inst J 2014;41(1):21-5)***

Key words: *Child; coronary angiography; coronary vasospasm/etiology; dose-response relationship, drug; heart transplantation/adverse effects; hemodynamics/drug effects; nitroglycerin/administration & dosage/therapeutic use; postoperative complications/therapy; retrospective studies; vasodilation/drug effects*

From: *Departments of Pediatrics (Drs. Lara and Olive) and Anesthesiology (Dr. Steenwyck), and Divisions of Cardiothoracic Surgery (Dr. George and Mr. Brown) and Pediatric Cardiology (Drs. Carlo, Colvin, and Pearce), University of Alabama School of Medicine, Birmingham, Alabama 35294*

Address for reprints: *F. Bennett Pearce, MD, 176 F Ste. 9100, 619 – 19th St. S., Birmingham, AL 35294-6852*

E-mail: *pearce@uab.edu*

Allograft coronary disease in children occurs with increasing frequency after transplantation, as a function of time. In a multicenter study,[1] the incidence of coronary artery disease in children 5 years post-transplant was 17% of all recipients. Coronary angiography remains the gold standard in the detection of vasculopathy in heart-transplant recipients.[2] Coronary artery spasm can complicate selective coronary angiography and result in myocardial ischemia. Coronary spasm can simulate the angiographic appearance of graft vasculopathy and cause diagnostic confusion.[3] The spasm can arise from manipulation of the arterial wall by the catheter or from intraluminal injection of contrast material. In cardiac transplant recipients, coronary artery spasm has been reported in as many as 4.9% of coronary angiograms.[3]

In adults, intracoronary nitroglycerin is routinely administered during coronary angiography to prevent coronary artery spasm.[4] In children, however, safety and dosage guidelines for intracoronary nitroglycerin have not yet been firmly established. A dose of 3 µg/kg can be extrapolated by weight from the established adult dose of 200 µg; this dose was used in a study of children after the arterial switch operation and was shown to produce coronary vasodilation—with a small reduction in systolic blood pressure (SBP) and no noteworthy change in heart rate—in a control group of patients.[5,6]

We previously reported a case of coronary artery spasm during routine coronary angiographic monitoring in a 9-year-old boy who had undergone heart transplantation as an infant.[7] After left main coronary artery injection of contrast material, the patient's left anterior descending and left circumflex coronary arteries appeared to be diffusely narrow, and he developed marked ST-segment elevation, hypotension,

and ventricular tachycardia. After cardiopulmonary resuscitation, he recovered uneventfully and displayed normal systolic function. Coronary angiography one month later, with the administration of intracoronary nitroglycerin before the injection of contrast material, revealed normal coronary artery diameter and was accomplished without complication.

Since 2005, intracoronary nitroglycerin has routinely been used in pediatric transplant patients during biennial selective coronary angiographic monitoring at our institution. The purpose of the study is to report our experience with the routine use of intracoronary nitroglycerin for coronary angiography in children: its effects on blood pressure, on heart rate, and on the occurrence of arrhythmia and ST-segment elevation.

Patients and Methods

After approval by the University of Alabama Institutional Review Board, we conducted a review of medical records of pediatric heart-transplant recipients who had undergone routine surveillance via biopsy and coronary angiography (with intracoronary nitroglycerin administration) every other year from 2005 through 2009. Our study cohort consisted of 13 male and 12 female patients (mean age, 9.9 ± 3.2 yr; range, 3.3–16.1 yr) (Table I). Demographic data, including weight and height at the time of angiography, as well as the patient's date of transplant, were recorded. We reviewed hospital and outpatient charts, catheterization reports, and anesthesia logs. Anesthesia records had been archived in a searchable database, the CompuRecord® Peri-Operative System Case Browser (Release F.00.01, 2009-01-01) (Philips Medical Systems; Andover, Mass). Using the archived digital anesthesia record, we retrieved blood pressure measurements and heart rates as they had been recorded immediately after induction of anesthesia and endotracheal intubation or the placement of a laryngeal mask airway. These vital signs were retrospectively defined as baseline measurements. Additional measurements of vital signs were performed throughout the procedures, typically every 5 minutes, and entered into the computerized record. From these records, we noted for the present study each patient's lowest SBP and lowest and highest heart rates—before nitroglycerin injection and after each injection of nitroglycerin. The total dose of nitroglycerin in μg/kg was recorded for each procedure, during which patients underwent from 1 to 3 selective angiograms. The records were searched for any interventions used to augment blood pressure, including the administration of inotropic or vasoactive agents or intravenous fluid. Any notations of arrhythmia, ST-segment change, or other adverse events were recorded.

TABLE I. Characteristics of the Patients

Variable	Value
No. patients/procedures	25/41
Male/female sex	13/12
Age upon first catheterization (yr)	9.9 ± 3.2 (3.3–16.1)
Weight upon first catheterization (kg)	39.7 ± 23.2 (14.4–93.8)
BSA upon first catheterization (m^2)	1.20 ± 0.43 (0.67–2.1)

BSA = body surface area

Data are expressed as mean ± SD (range) or as number.

Anesthesia and Sedation. General anesthesia or propofol-based deep sedation, or both, were used for all procedures. Endotracheal intubation or a laryngeal mask airway was used at the discretion of the anesthesiologist. Treatment of hypotension was also performed, at the discretion of the anesthesiologist. Chemical paralysis was not routinely used. Automated blood pressure and pulse readings were entered into the patient's archived electronic record for each procedure.

Cardiac Catheterization. All procedures except for one included right-sided heart catheterization from the internal jugular or femoral venous approach, with endomyocardial biopsy samples taken from the septal surface of the right ventricle. All procedures included left-sided heart catheterization and selective coronary angiography of the right and left coronary arteries. In most procedures, 2 manual injections of contrast material (a single selective angiogram in each coronary artery) were performed. Before each injection of contrast material, intracoronary nitroglycerin was administered at a dose (between 50 and 100 μg) that was determined by the attending cardiologist.

Statistical Analysis

Paired *t* tests were used to compare the SBP immediately after the induction of anesthesia with the lowest SBP immediately before the injection of nitroglycerin. Paired *t* tests were also used to compare the lowest SBP immediately before the injection of nitroglycerin with the lowest SBP after the injection of nitroglycerin. Similarly, paired *t* tests were used to compare the heart rate immediately after the induction of anesthesia with the heart rate immediately before the injection of nitroglycerin. Paired *t* tests were again used to compare the heart rate immediately before the injection of nitroglycerin with the lowest heart rate after the injection of nitroglycerin. Normality testing of the data was performed by using the Shapiro-Wilk normality test and the Kolmogorov-Smirnov normality test. Linear regression analysis was used to determine the relationship between SBP change and nitroglycerin dose per kilogram of body weight. All statistical calculations were performed with the aid of SAS software version 8.2 (SAS Institute, Inc.; Cary,

NC). *P* values ≤0.05 were considered statistically significant.

Results

A total of 41 catheterizations were performed in 25 post-heart-transplant patients, from 2005 through 2010.

Nitroglycerin Dose. The mean total dose administered was 2.93 ± 1.60 μg/kg (range, 1–8 μg/kg). Approximately 70% of the patients received between 2 and 4 μg/kg. The maximum total dose was 300 μg.

Measurements of Blood Pressure and Heart Rate. The mean baseline SBP was 106 ± 21.6 mmHg. The mean baseline heart rate was 109 ± 16.5 beats/min. All baseline measurements were made just after the induction of anesthesia. Before the administration of nitroglycerin, the lowest blood pressure and heart rate were significantly lower than baseline: 78 ± 13.2 mmHg (*P* ≤0.0001) and 89 ± 14.3 beats/min (*P*=0.0001). There was no significant additional change in SBP and heart rate when we compared values recorded after sedation and anesthesia and after injection of nitroglycerin: mean lowest SBP, 80.7 ± 13.1 mmHg (*P*=0.02) and mean lowest heart rate, 84 ± 17.7 beats/min (*P*=0.09). These relationships are shown in Figure 1.

Nitroglycerin Dose-Response Relationship with Blood Pressure. At doses less than 3 μg/kg, the lowest blood pressure reading obtained after nitroglycerin administration tended to increase slightly in most patients. At doses greater than 3 μg/kg, nearly all patients showed a small decrease in the lowest SBP, but none experienced a drop greater than 15 mmHg. Linear regression analysis indicated only a weak relationship between blood pressure and nitroglycerin dose within the range of dosages used (*P*=0.002) (Fig. 2).

Intervention for Low Blood Pressure, Arrhythmia, and ST-Segment Change. No arrhythmia was recorded. Three patients received interventions for low blood pressure (intravenous ephedrine or phenylephrine) before the administration of nitroglycerin, and 1 patient received phenylephrine in the period after nitroglycerin administration. One patient experienced transient ST-segment elevation before angiography, and 3 patients experienced transient ST-segment elevation after angiography. Transient right bundle branch block was associated with one of these. Lidocaine infusion was begun in the patient who experienced ST-segment elevation before angiography, and there was no arrhythmia. No other adverse events were noted. No allograft vasculopathy was evident in the study population.

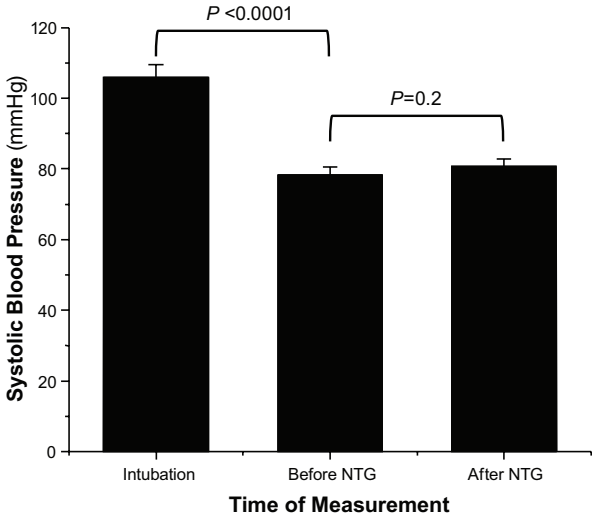

Fig. 1 *Comparison of baseline systolic blood pressure (SBP) with lowest SBP before nitroglycerin (NTG) administration and comparison of lowest SBP before administration of nitroglycerin with lowest SBP after administration of nitroglycerin.*

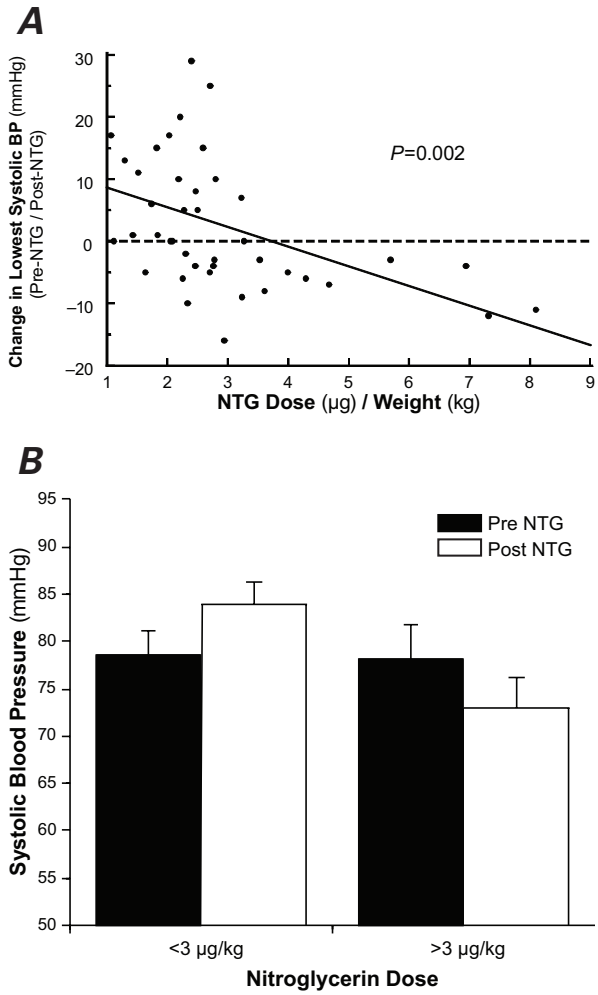

Fig. 2 ***A****) Linear regression analysis of total nitroglycerin (NTG) dose and lowest systolic blood pressure (SBP) after nitroglycerin administration.* ***B****) Bar graph compares lowest SBP after baseline (but before nitroglycerin administration) with lowest SBP after nitroglycerin administration—for cumulative doses less than 3 μg/kg and larger than 3 μg/kg.*

Discussion

Despite emerging techniques such as intracoronary ultrasound, angiography remains important in evaluating the health of the coronary arteries after cardiac transplantation in children. Most centers perform routine coronary angiographic monitoring by protocol.[1,2]

Coronary artery spasm can complicate coronary angiography and has been reported to occur in adult allografts at a rate of 4.9%.[3] A recent multicenter study reports the occurrence rate of this sequela at less than 2% in children.[8] More severe spasm can produce hemodynamic deterioration and arrhythmia, whereas milder spasm can lead to diagnostic confusion without hemodynamic or electrocardiographic change. Diagnostic confusion occurs because coronary artery spasm can resemble allograft coronary vasculopathy in its diffuse angiographic narrowing and rapid tapering of the epicardial coronary artery, and in its attendant loss of distal-branch opacification.[4,9] Moreover, coronary intravascular ultrasound produces coronary artery spasm in an estimated 2.9% of procedures.[10]

Nitroglycerin has been widely used in the management of coronary artery disease in adults; its vascular effects are endothelium independent and are mediated at the cellular level by nitric oxide.[11,12] The routine use of intracoronary nitroglycerin to prevent coronary artery spasm in allograft coronary angiography is commonplace in adult practice, as it has been shown to produce vasodilation in such allografts.[4,11] The dose of intracoronary nitroglycerin in adults arises from an earlier in vivo angiographic study.[5] In this earlier study, the degree of coronary artery dilation as revealed by angiography increased with increasing doses of intracoronary nitroglycerin. A reduction in mean blood pressure correlated with an increased nitroglycerin dose, but substantial additional coronary vasodilation was not seen at doses greater than 150 µg. Another reference text recommends a dose of 200 µg in adults.[13]

The optimal dose of intracoronary nitroglycerin in children after transplantation has not been published. A previous study of coronary flow reserve reported the use of 3 µg/kg for each coronary artery injection in control patients and in patients after an arterial switch operation.[6] This dose was intended by the investigators to produce maximal coronary artery dilation. The children (mean age, 5.4 ± 3.2 yr) experienced a decrease in SBP of approximately 10 to 25 mmHg and no notable change in heart rate.

Most of our patients underwent 2 coronary angiograms per procedure with a total dose of 2.93 µg/kg, receiving half of this dose without coronary spasm by angiography or a significant change in blood pressure. The only significant changes in heart rate and SBP occurred between the baseline SBP and heart rate (immediately after intubation or placement of a laryngeal airway) and the lowest SBP and heart rate before the administration of nitroglycerin. This probably reflected the cumulative effects of sedation and anesthesia.

Our objective was to prevent coronary artery spasm rather than produce maximal vasodilation, and this study concerns itself only with the safety of the dose range in our patient sample. The threshold dose of nitroglycerin for the prevention of allograft coronary artery spasm in children cannot be determined from the present study; however, our patients experienced no coronary artery spasm, nor did they experience substantial hemodynamic alteration in the dose range that we studied. A patient who experienced coronary artery spasm that was subsequently treated with 1.25 µg/kg of intracoronary nitroglycerin during repeat coronary angiography experienced no recurrence of coronary artery spasm.[7]

In 188 coronary angiographic procedures in children, the incidence of adverse events was reported at 1.2%.[8] The criteria used to define coronary artery spasm were not stated, so the actual incidence might be higher; but spasm appears not to be as common in children as in adults. Whether intracoronary nitroglycerin should be used routinely cannot be answered by our study.

Finally, because no patient in our study manifested allograft vasculopathy, we do not know the effectiveness of the reported dose range in preventing spasm in children who have significant vasculopathy. It is worthwhile to note that adult patients with atherosclerotic disease have experienced vasodilation in earlier dose-response studies.[5]

Conclusions

Our study reports our institutional practice of routine intracoronary nitroglycerin use. To the best of our knowledge, it is the largest study to date of the use of intracoronary nitroglycerin in pediatric heart-transplant recipients. We conclude that intracoronary nitroglycerin use in coronary arteriography in pediatric heart-transplant recipients produces minimal hemodynamic alterations at cumulative total doses of 1 to 8 µg/kg.

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