Normal Coronary Flow Reserve After Arterial Switch Operation for Transposition of the Great Arteries
An Intracoronary Doppler Guidewire Study

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Background—Recent studies performed with positron emission tomography have suggested that coronary flow reserve (CFR) is moderately to severely reduced after the arterial switch operation (ASO). These findings are of great concern but have not been confirmed by other methods.

Methods and Results—Eleven symptom-free children were studied between 4 and 11 (median 6.0) years after the ASO. Flow velocity in the left anterior descending (LAD) and right coronary arteries (RCA) was measured with a 0.014-inch Doppler FloWire (Cardiometrics) before and after intracoronary injection of adenosine (0.5 μg/kg) and nitroglycerin (5 μg/kg). CFR was defined as the ratio of hyperemic to basal average peak velocity (APV). The median (range) CFR in the LAD was 3.7 (3.0 to 4.8) and 3.4 (2.9 to 4.8) in the RCA. The increase in APV after intracoronary injection of nitroglycerin was 300% (240% to 420%) in the LAD and 260% (190% to 460%) in the RCA. APV at rest was 15.0 (14.0 to 21.0) cm/s in the LAD and 16.0 (9.6 to 30.0) cm/s in the RCA. A linear relation was found between right ventricular systolic pressure and resting APV in the RCA (r=0.77, P=0.0056), and between resting APV and CFR (r=−0.61, P<0.05) in the RCA.

Conclusions—The CFR and coronary vasoreactivity to nitroglycerin in children treated for transposition of the great arteries with the ASO was within normal limits. Increased right ventricular pressure and myocardial hypertrophy can cause increased resting coronary flow velocity in the RCA and affect CFR negatively. (Circulation. 2002;106:1696-1702.)

Key Words: transposition of the great vessels ■ surgery ■ adenosine ■ blood flow

The current surgical treatment of choice for neonates with transposition of the great arteries (TGA) is the arterial switch operation (ASO). The operation involves transection of both coronary arteries from the transposed aorta, followed by mobilization and reanastomosis to the neoaorta. Although long-term survival has been excellent, follow-up studies have revealed a significant prevalence (3% to 7.8%) of coronary stenosis and occlusions, even occurring in symptom-free subjects.1,2 Data on the function of the coronary arteries after the ASO are limited, however.

Coronary flow reserve (CFR) measures the extent to which coronary blood flow can be maximally increased above resting flow.3 Recent studies, performed with positron emission tomography (PET), have shown moderately to severely reduced global myocardial CFR in children treated for TGA with the ASO.4-6 Although these results are of great concern, they have not been confirmed by other available methods. The present study used intracoronary Doppler guidewire (IDGW) to measure resting coronary flow velocity and the reactivity of the coronary arteries to both epicardial and microvascular coronary vasodilators in children treated for TGA with the ASO.

Methods

Subjects
Eleven children with TGA were enrolled and examined at a median of 6.0 years (range, 4 to 11 years) after the ASO. Ten of the children (aged between 2 and 14 days at the time of ASO) had TGA with intact ventricular septum, whereas 1 patient (operated at 9 months of age) had TGA with a ventricular septal defect and mild pulmonary stenosis. Eight patients had the usual separate origins of the left and right coronary arteries (Yacoub type A), whereas 2 had a single coronary artery (Yacoub type B), and 1 had the circumflex artery from the right coronary artery (RCA) (Yacoub type D).7 Surgery was performed under hypothermic cardiopulmonary bypass. For myocardial protection, cold crystalloid cardioplegic solution was used. The median (range) extracorporeal bypass time was 158 (134 to 175) minutes; aortic cross-clamp time was 70 (46 to 93) minutes. The median age of the children at the time of the follow-up study was 6 years (range, 5 to 10 years). They had no symptoms, were not on any

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medication, and were submitted for routine follow-up after the ASO. The study protocol received approval from the local ethics committee. The parents, and when appropriate, also the patient, gave written and informed consent before enrollment in the study.

**Study Protocol**

On day 1, the children underwent clinical examination, ECG, and echocardiography. On day 2, cardiac catheterization with selective coronary angiography was performed, followed by measurements of coronary flow velocity with an IDGW. Myocardial scintigraphy at rest was performed on day 3.

**Echocardiographic Studies**

Standard two-dimensional, Doppler, and M-mode echocardiography were performed in all children. Left ventricular shortening fraction and contractility were measured, and wall motion was described qualitatively.

**Myocardial Single-Photon Emission Computed Tomography**

Myocardial perfusion at rest was studied after an intravenous injection of 99mTc tetrofosmin. The dose was 3 MBq per kg body weight, with a minimum dose of 50 MBq. Approximately 60 minutes after injection, single-photon emission computed tomography (SPECT) was performed with a dual head camera. Data were acquired in a 64x64 matrix, >180° from left posterior oblique to right anterior oblique during 20 minutes. The transaxial slices were realigned along the heart axis, and short-axis, vertical, and horizontal long-axis slices were obtained.

**Cardiac Catheterization**

The examination was performed under general anesthesia to maintain stable arterial blood gas values and hemodynamic conditions throughout the study. ECG and blood pressure were monitored continuously. The anesthesia was induced by intravenous thiopental, fentanyl, and rocuronium, and maintained with between 0.2% and 0.5% inhaled isoflurane. Right and left heart catheterization was performed with the use of 4F Judkins right and left coronary catheters. An intravenous bolus of heparin (50 U/kg) was given, and the coronary ostia then identified by small manual injections of contrast medium (Omnipaque, Nycomed) in the aortic root. After entering the coronary orifice, selective coronary angiography was performed by manual injection.

**Measurements of Coronary Flow Velocity and Coronary Function**

After coronary angiography, a 0.014-inch Doppler FloWire (Cardiometrics) was advanced into each target coronary artery. The position of the wire was adjusted to obtain the highest possible quality Doppler flow envelope and pure audio sound throughout the cardiac cycle. Continuous flow velocity profiles and audio signals, along with simultaneous ECG, were displayed on screen and recorded on videotape. Doppler flow velocity spectra were analyzed online by the signal analyzer (FloMap, Cardiometrics) to determine average peak velocity (APV), in which APV is the time-averaged value of the instantaneous peak velocity samples over the last 2 cardiac cycles. Diastolic (PFVd) and systolic peak flow velocity (PFVs) was measured off-line from the videotape and averaged over 3 cardiac cycles. Registrations were performed serially in the left anterior descending (LAD) branch of the left coronary artery and the RCA, respectively. After stable baseline signals were obtained in each vessel after angiography, hyperemic responses to adenosine and nitroglycerin (NTG) were determined. The drugs were given by a rapid bolus injection in the intracoronary catheter. Adenosine was always injected first (0.5 µg/kg). Because the optimal dose of intracoronary adenosine for children is not known, and maximal hyperemia had to be obtained, the measurement was repeated with a double dose (1.0 µg/kg) in the first children enrolled in the study. This did not result in higher CFR values in either LAD or RCA. The coronary flow velocity was allowed to return to baseline before NTG was injected (5 µg/kg). CFR was defined as the ratio of hyperemic APV after intracoronary injection of adenosine to basal APV.

**Statistical Analysis**

Results are presented as median (range). Comparison between coronary flow parameters at rest in the LAD and RCA were performed by Student’s t test for paired observations. Linear regression analysis was used to calculate correlation coefficients (r). A probability value <0.05 was considered significant.

**Results**

Echocardiography showed normal left ventricular fractional shortening and wall motion in 10 of 11 studied subjects. Left ventricular fractional shortening was slightly reduced (26%) in one child. Myocardial SPECT showed a left ventricular perfusion defect in 2 subjects, whereas 7 of the remaining 9 subjects studied with myocardial SPECT had normal findings. One of the subjects with a left ventricular perfusion defect had a total occlusion of the LAD branch. All other coronary arteries were without stenosis. The angiographic LAD diameter was 1.3 to 2.2 mm, and the RCA diameter was 1.7 to 4.0 mm. Cardiac catheterization revealed further significant hemodynamic abnormalities in 3 subjects. Moderate pulmonary stenosis was found in one (systolic right ventricular pressure 49 mm Hg), mild bilateral pulmonary branch stenosis in another (systolic right ventricular pressure 36 mm Hg), and a small coronary fistula between the LAD and the pulmonary artery was found in one subject.

Intracoronary Doppler registrations could be obtained in the LAD in 9 of 11 subjects (Figure 1A) and in the RCA in all 11 subjects (Figure 1B).

**Coronary Flow Velocity**

Coronary flow velocities at rest in the LAD and RCA are shown in the Table. The APV and PFVd were similar in the 2 vessels, although PFVs was higher in the RCA (22.0 cm/s) than in the LAD (15.0 cm/s). The difference did not reach statistical significance (paired t test). There was a greater variability in APV in the RCA compared with the LAD (SD 6.8 cm/s versus 2.9 cm/s). There was a significant positive linear relation between right ventricular systolic pressure and RCA flow velocity at rest, both APV (r=0.77, P=0.0056, Figure 2) and PFVd (r=0.67, P=0.023). The patient with the highest resting APV (21.0 cm/s) in the LAD was found to have a small coronary fistula between the LAD and the pulmonary trunk.

**Coronary Flow Reserve**

The CFR values obtained by intracoronary adenosine injection and the coronary flow response to intracoronary NTG are shown in the Table, and examples of CFR registrations are shown in Figure 3A (LAD) and 3B (RCA). The 2 children with the lowest CFR in the RCA (2.9) had right ventricular hypertrophy, moderately increased right ventricular pressure, and the highest resting APV in the RCA. There was a significant negative linear relation between resting APV and CFR in the RCA (r=-0.61, P<0.05, Figure 4) The patient with the lowest CFR in the LAD (3.0) had the highest resting coronary flow velocity, and a small coronary fistula between the LAD and the pulmonary trunk.
Discussion

The present study is the first to evaluate coronary function in children treated for TGA with the ASO by direct measurement of intracoronary Doppler flow velocities at rest and after administration of vasoactive medication. We found the function of both LAD and RCA comparable to what has been reported for healthy children and adults.\(^8\)–\(^10\)

The coronary arteries in children treated with ASO for TGA are surgically relocated to the aortic root, and this may cause coronary flow abnormalities, even late after the operation.\(^1\),\(^2\),\(^11\) Myocardial perfusion defects found in asymptomatic survivors of the ASO have raised further concerns regarding the long-term function and patency of the coronary arteries in this patient group, recently supported by myocardial PET studies revealing reduced global myocardial CFR.\(^4\),\(^6\),\(^12\) Documented cases of true myocardial ischemia or sudden death in this patient group have however been exclusively associated with anatomic coronary stenosis.\(^11\),\(^13\)

Coronary Flow Velocity at Rest

The resting LAD Doppler flow pattern found in this study was similar to previous observations in children and adults with normal coronary arteries.\(^8\),\(^10\),\(^14\),\(^15\) PET studies have indicated that myocardial blood flow at rest may be increased in subjects operated for TGA with the ASO.\(^4\)–\(^6\) The basal flow velocities in both LAD and RCA in this study are lower than what has been reported in previous studies in children of comparable age and in adults, and this speaks strongly against
increased coronary blood flow at rest.\textsuperscript{8,10,14} The peak systolic flow velocity was higher in the RCA than in the LAD (22.0 cm/s versus 15.0 cm/s) in our subjects. This agrees well with earlier animal studies, and may be explained by lower systolic pressure and lower intramyocardial resistance against coronary flow in the right ventricle.\textsuperscript{16}

Right ventricular systolic pressure seems to affect both resting RCA flow velocity and CFR in the RCA. There was a positive linear relation between resting flow velocities in the RCA (both APV and PFVd) and right ventricular systolic pressure. A significant negative linear relation between APV at rest in the RCA and CFR was also found. The lowest CFR values in the RCA were found in the patients with increased right ventricular pressure, right ventricular hypertrophy, and high resting coronary flow velocity. RCA flow velocity at rest has been shown to have a positive correlation to systolic right ventricular pressure in children with congenital heart defects in one previous study.\textsuperscript{17} Left ventricular hypertrophy and increased left ventricular pressure has similarly been shown to be related to increased diastolic flow velocity at rest and reduced CFR in the LAD in several studies.\textsuperscript{18,19}

Coronary Vasoreactivity

CFR can be measured with PET techniques, cine MR imaging, and Doppler ultrasound.\textsuperscript{4,6,17,20} It is well established that the normal adult heart can increase coronary flow/myocardial perfusion maximally by 2.5 to 4 times the resting value, but normal CFR values are different for each method and vasodilator used.\textsuperscript{4,10,20,21}

Cardiac sympathetic nerves play a part in modulating the function of the coronary arteries.\textsuperscript{22} The ASO causes a loss of coronary adrenergic nerve supply, and it is conceivable that this might affect coronary vasoactivity. The median (range) CFR for the subjects of this study was 3.7 (3.0 to 4.8) in the LAD, and 3.4 (2.9 to 4.8) in the RCA. The only available studies measuring CFR by IDGW in healthy children (aged 10 to 19 years) have shown mean values of 3.4 to 3.7.\textsuperscript{5,9} These CFR values are comparable to our results and indicate that the CFR, or more specifically the vasoreactivity of the myocardial microvasculature, is normal in our patient group.

It has further been speculated that the manipulation of the coronary arteries during the ASO, or development of fibrosis in the area of coronary reinsertion, may negatively affect the function of the proximal coronary vessels.\textsuperscript{4,6} NTG has predominant effects on the epicardial coronary arteries and a lesser effect on coronary resistance vessels <100 μm in diameter.\textsuperscript{23} In the present study, the median (range) increase in flow velocity after intracoronary administration of NTG was 300% (240% to 420%) for the LAD, and 260% (190% to 460%) for the RCA. There are no documented values for increase in coronary flow velocity after NTG administration in healthy children, but our results are comparable to values obtained in healthy adults.\textsuperscript{24,25}

**CFR Measured by Myocardial PET**

CFR has been evaluated in children treated for TGA with the ASO in 3 recent studies with the use of PET for evaluation of global myocardial perfusion.\textsuperscript{4–6} Studies performed by the Munich group have found mean (SD) global myocardial CFR after intravenous administration of adenosine to be between 2.5 and 3.0 (0.6) in children examined 10 to 11 years after the ASO for TGA, compared with between 4.1 and 4.6 (0.9 and 1.0) in healthy adults.\textsuperscript{4,6} An additional PET study in a younger patient group examined 1.8 years after the ASO for TGA found global myocardial CFR to be only 1.19 (0.10) after intravenous administration of dipiridamole (0.56 mg/kg).\textsuperscript{5} The children had normal hemodynamics and the reduced CFR was interpreted as a reduced global vasoreactivity and speculated to be caused by the ASO or the cardiac malformation.

**Comparison of CFR Measurements With IDGW and PET**

Our findings of normal CFR and a normal flow velocity increase after intracoronary administration of NTG in both the LAD and RCA are in contradiction to earlier PET results showing moderately to severely reduced global myocardial CFR in patients treated for TGA with the ASO.\textsuperscript{4–6} Changes in coronary flow velocity measured with IDGW have been shown to be linearly related to absolute flow when the cross section of the vessel remains unchanged.\textsuperscript{26,27} When adenosine is administered intracoronary the epicardial vessels dilate, and the dilatation is linearly related to the increase in flow velocity.\textsuperscript{28} The CFR values obtained by this method are therefore lower than those obtained by measuring increases in global myocardial perfusion, as is done with the PET method.
When this is taken into account, the CFR in our patients (3.4 to 3.7) is equal to the CFR obtained in healthy adults by PET (4.1 to 4.6).4,6

The results of the PET studies in children treated for TGA with the ASO are confounding, especially the extremely low CFR values found by Yates et al.5 The children studied were clinically asymptomatic, but would be expected to show signs of myocardial ischemia if they could only increase myocardial perfusion by 1.2 times the resting value. Exercise testing in a group of TGA children with reduced global myocardial CFR (mean value of 2.5) according to PET, did not show any sign of myocardial ischemia.6 Previous studies in which exercise testing has been performed in children operated for TGA with the ASO have shown that ECG changes suggestive of myocardial ischemia are rare.13

Open-heart surgery in the neonatal period may have a temporal adverse effect on the myocardium. Neonates operated for a ventricular septal defect, with entirely normal postoperative hemodynamics, had low CFR (1.5 to 1.6), according to a PET study performed ≈2 weeks after surgery.29 Studies measuring global myocardial CFR with the PET method in patients operated with open-heart surgery in the neonatal period have shown low CFR values, irrespective of the type of heart malformation or type of surgery.4,5,29 CFR in these studies has tended to be higher the older the subjects are at the time of examination. This opinion is further supported by the observation that children operated at an older age with reimplantation of the coronary arteries (Ross operation) have normal CFR, according to PET.6 This sug-
gests that there is a link between decreased CFR and neonatal open-heart surgery, but not to coronary surgery as such. The significance of reduced global myocardial CFR as measured by PET in children treated for TGA with the ASO is unclear, and should not be interpreted as proof of abnormal coronary function or increased risk of myocardial ischemia at long-term follow-up.

**Coronary Angiography After ASO**
Symptom-free patients treated for TGA with the ASO can have coronary stenosis or even occlusions.1,2 Our findings of an unsuspected total coronary occlusion in one of our patients and a coronary fistula in another show that coronary angiography may be of benefit for some patients, even if their clinical status and noninvasive studies do not give a suspicion of coronary abnormalities.30

**Methodology**
Cardiac catheterization was performed under anesthesia, maintained with low-dose inhaled isoflurane, unlikely to affect coronary flow. A higher dose of a similar drug, halothane, has not been shown to affect coronary flow reserve in children.8 Measurements of coronary flow velocity and CFR with the IDGW have been thoroughly validated, both in vitro and in vivo.26,27 The method has been reported to be safe, and there were no coronary complications in our study, neither during selective coronary angiography nor during intracoronary Doppler registration. To minimize systemic hemodynamic effects, we chose to give adenosine intracoronary in the indwelling coronary catheter. Adenosine has been shown to be superior to dipyridamole in inducing true maximal coronary flow, and normal values for CFR after adenosine injection are well established in adults.3,10,21,28 The dose given (0.5 μg adenosine/kg in both LAD and RCA) was estimated to be equivalent to the 12- and 18-μg doses used for respective vessels in adults. We took care to be sure that we were achieving true maximal flow velocity by administrating double adenosine doses in the first patients, and this did not result in a higher CFR than the dose of 0.5 μg/kg.

**Study Limitations**
Intracoronary measurements of coronary flow velocity and CFR in healthy children of the same age could not be included in our study due to ethical constraints, but normal values for healthy children and adults obtained by the same technique are available and can be used as comparison.8–10

Because both adenosine and NTG are endothelium-independent vasodilators, the present study did not evaluate coronary endothelial function. That would require intracoronary injection of acetylcholine, and because this drug may cause coronary spasms and other serious side effects, we found the risk of this procedure unacceptable for our study group.8

**Conclusions**
Intracoronary Doppler measurements of CFR and coronary vasoreactivity to NTG in children treated for TGA with the ASO do not indicate any negative long-term effects of either the operation or the cardiac malformation on coronary function. Residual lesions of hemodynamic significance causing myocardial hypertrophy, however, may have adverse effects on CFR in these patients.

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