Myocardial Blood Flow and Flow Reserve After Coronary Reimplantation in Patients After Arterial Switch and Ross Operation

Michael Hauser, MD; Frank M. Bengel, MD; Andreas Kühn, MD; Ursula Sauer, MD; Solvig Zylla, MS; Siegmund L. Braun, MD; Stephan G. Nekolla, PhD; Renate Oberhoffer, MD; Rüdiger Lange, MD; Markus Schwaiger, MD; John Hess, MD

Background—Coronary reimplantation is used in therapy for congenital heart disease, such as in the arterial switch (ASO) and Ross operations. The adequacy of myocardial perfusion may remain a matter of concern. The aim of the present study was to stratify the effect of coronary reimplantation on myocardial perfusion and to highlight the clinical relevance of any attenuation in myocardial perfusion.

Methods and Results—A total of 21 children with transposition of the great arteries at a mean interval of 11.2 ± 2.9 years after ASO and 9 adolescents at a mean interval of 4.2 ± 2.1 years after the Ross procedure were investigated. All patients were asymptomatic and had a normal exercise capacity. On stress echocardiography, 2 of the ASO patients had dyskinetic areas within the left ventricular myocardium, and 5 had adenosine-induced perfusion defects on positron emission tomography. No coronary obstruction was detected on coronary angiography in any patient, but a common finding was right coronary dominance and a small caliber of the distal part of the left anterior descending artery. Coronary flow reserve (CFR) was significantly reduced in all patients after ASO when compared with 10 normal healthy volunteers (age, 25.6 ± 5.3 years). CFR was normal in the 9 patients who had the Ross operation (age, 19.2 ± 7.6 years); exercise-induced perfusion defects were not detected in the Ross patients.

Conclusions—Children after ASO are asymptomatic, without clinical signs of coronary dysfunction. In contrast to patients who had the Ross operation, stress-induced perfusion defects and an attenuated CFR were documented. The prognostic implications of these findings and the clinical consequences are unclear; nevertheless, close clinical follow-up of ASO patients is mandatory. (Circulation. 2001;103:1875-1880.)

Key Words: transposition of great vessels • arteries • exercise • perfusion • imaging

Coronary reimplantation as a part of corrective cardiac surgery is used in some forms of congenital heart disease. The arterial switch operation (ASO) is recognized as the procedure of choice for the treatment of children with transposition of the great arteries (TGA)\(^1\); the Ross procedure is accepted in the treatment of aortic valve disease to avoid oral anticoagulation and to achieve potential valve growth. One major concern about the outcome of these procedures is the adequacy of coronary artery perfusion after coronary reimplantation. The long-term success of these types of operative approaches depends principally on the continued patency and adequate function of the coronary arteries. Because of the high risk for coronary dysfunction, which cannot be assessed by ECG or echocardiography, a reproducible method of determining the integrity of myocardial perfusion in patients after coronary reimplantation is desirable.

Positron emission tomography (PET) is a noninvasive method that was used in a previous study\(^2\) to address the problem of adequacy of myocardial blood supply after ASO. In that study, myocardial blood flow (MBF) was impaired under vasodilatation with adenosine, and coronary flow reserve (CFR) was markedly attenuated. The aim of the present investigation, as part of the clinical follow-up, was to highlight the clinical relevance of the PET findings, to compare the results with patients after the Ross operation, and to stratify the influence of coronary reimplantation on myocardial perfusion.

Methods

Patients
A total of 30 patients were included in the study; 21 were treated with ASO (group 1), and 9 were treated with the Ross procedure (group 2).

Group 1
A total of 21 children without limitations precluding exercise testing (age, 12.3 ± 2.2 years; range, 8 to 16 years) participated in the study.
Fourteen of them (age, 9.3±1.2 years) had d-TGA with an intact ventricular septum and underwent ASO within the first 20 days of life. In the remaining 7 children (age, 13.4±3.1 years), more complex anomalies were present. The ASO was performed at an age of 134 to 2847 days. Four had TGA and a large ventricular septal defect (VSD), one had associated valvular pulmonary stenosis, one had associated aortic coarctation, and one had double outlet right ventricle (DORV) with a single coronary artery, with the left being a branch of the transposed right coronary artery and an accessory anterior descending artery from the left sinus. Four of these 7 children underwent 2-stage surgery with prior pulmonary artery banding. The median time interval between banding and ASO was 12 months. In addition to ASO, all associated anomalies of these children were corrected during the surgical procedures.

The mean time interval between ASO and inclusion into the study for all children was 11.2±2.9 years. Surgery was performed under hypothermic cardiopulmonary bypass. For myocardial protection, cold cardioplegic solution was used. Mean extracorporeal bypass time was 144±36 minutes; aortic cross-clamp time was 103±23 minutes.

Surgical techniques for the ASO, with or without VSD closure, has been previously reported.3 The postoperative course was unremarkable for all patients, with no clinical signs of ischemia. From the surgical point of view, coronary reimplantation was without complications; no patient had an intramural course of the coronary arteries. All patients were fully active and asymptomatic; no patient was on cardiovascular medication.

Control subjects for spiroergometry were 30 healthy children matched for age (11.6±2.9 years) and body surface area. Ten healthy adults (25.6±5.4 years) were used as a control group for PET.4

**Group 2**

Nine male patients who underwent the Ross operation had PET to assess myocardial perfusion after reimplantation of the coronary arteries into the sinus of the neoaorta; their mean age at the time of the investigation was 19.2±7.6 years, with an average time interval of 4.2±2.1 years after the Ross procedure. Four patients had prior cardiovascular surgical procedures, such as subaortic myectomy, commissurotomy of the aortic valve, and aortic coarctation resection; 2 patients initially had valvuloplasty of the aortic valve. Surgery was performed under hypothermic cardiopulmonary bypass and cardioplegic solutions. Mean extracorporeal bypass time was 164.8±37.7 minutes; aortic cross-clamp time was 117.1±26.1 minutes. Coronary artery ostia buttons were reimplemented into the sinus of the autograft valve, and the right ventricular outflow tract reconstruction was accomplished with an allograft valve. Detailed surgical techniques were previously reported.4 All patients were fully active and clinically asymptomatic, with a normal ECG at rest and exercise; none of the patients was on cardiovascular medication. On cross-sectional echocardiography, 4 patients had moderate left ventricular hypertrophy with normal dimensions of the left ventricle, 7 patients had trivial insufficiency of the neoaortic valve, and no patient had residual aortic stenosis. Right and left ventricular function were within the normal range in all patients (ejection fraction, 0.68±0.04).

**Study Protocol and Testing**

On arrival in the outpatient clinic, an intravenous line was placed to administer the myocardial imaging agent. A blood sample was taken at rest and after exercise for measuring creatine kinase, troponin T, and lactate dehydrogenase isozyme BB (GPBB) as markers for myocardial ischemia. Symptoms, exercise tolerance (by spiroergometry for ASO patients; Ross patients had only a treadmill test without measurement of gas exchange parameters), left ventricular function, wall motion analysis (by echocardiography), rhythm disturbances or ischemic changes on ECG, and myocardial perfusion (by PET) were assessed. A 24-hour ECG monitor was fitted before leaving.

**Spiroergometry (Group 1)**

The patients exercised on a treadmill using the Bruce protocol. To examine their cardiopulmonary exercise capacity, noninvasive determination of gas exchange parameters was used. Oxygen uptake (V\textsubscript{O}\textsubscript{2}) and CO\textsubscript{2} output (V\textsubscript{CO}\textsubscript{2}) were measured by an automated O\textsubscript{2} and CO\textsubscript{2} analyzer system, the minute ventilation and the respiratory rate were measured by a pneumotachometer. The V-slope method according to Beaver et al6 allowed for the determination of the anaerobic threshold and the maximal V\textsubscript{O}\textsubscript{2} during treadmill exercise.

**Echocardiographic Studies**

Standard cross-sectional, Doppler, and M-mode echocardiography were performed in all children. Left ventricular shortening fraction and contractility were measured at rest and after exercise by previously described methods.7 Left ventricular wall motion was analyzed by cross-sectional echocardiography using the 16-segment model advocated by the American Society of Echocardiography.8

**PET**

MBF was quantified noninvasively at rest and during adenosine-induced vasodilatation9 by dynamic PET with N-13 ammonia. A transmission scan was acquired to correct photon attenuation. Subsequently, N-13 ammonia (~0.3 mCi/kg) was injected intravenously at rest, and a dynamic imaging sequence of 21 frames was acquired over 20 minutes. After 50 minutes to allow for decay of N-13 ammonia, adenosine (0.14 mg · kg\textsuperscript{-1} · min\textsuperscript{-1}) was infused over 5 minutes. Two minutes after the onset of adenosine infusion, a second dose of N-13 ammonia was administered, and a dynamic imaging sequence was started. Heart rate, blood pressure, and ECG were monitored throughout the procedure. MBF at rest and during hyperemia were quantified using a volumetric sampling approach and a validated 3-compartment model.10 Because of the relation of MBF at rest with the rate-pressure product as an index of cardiac work,11 resting flow was normalized to the corresponding rate-pressure product.

In addition to quantifying global MBF, regional myocardial perfusion was analyzed visually. Summed images of tracer distribution in the last 3 frames of the dynamic sequence were interpreted by 2 experienced observers for the presence of reversible or persistent defects in 9 myocardial segments.

**Coronary Angiography**

Cardiac catheterization was undertaken in patients with pathological PET perfusion scans. Aortic root and selective coronary artery angiography were performed under local anesthesia in one patient and under general anesthesia in 4 patients using the femoral artery approach.3 Selective coronary artery angiography was performed with coronary catheters between 4F and 5F. Coronary artery angiograms were performed by manual injection of contrast medium.

**Creatine Kinase, Troponin T, and GPBB (Group 1)**

Creatine kinase, troponin T, and GPBB (ELISA, Pace Corp) were measured at rest and 2 hours after maximal exercise as indicators of myocardial ischemia.

**Statistical Analysis**

Mean and SDs were calculated for all continuous variables. Differences between the individual groups were tested for significance by 1-way ANOVA and the post hoc test. Changes from baseline to adenosine stress were compared by the paired Student’s t test. Univariate analysis of the effects of each continuous variable was performed with linear regression. All tests of significance were 2-tailed, and a value of P<0.05 was considered statistically significant.

**Results**

**Spiroergometry**

There was no significant difference in exercise capacity between children after ASO and the group of healthy children matched for age and body surface area. All 21 analyzed children could exercise to exhaustion and achieved the anaerobic threshold. During exercise testing, all patients...
Adenosine-induced vasodilation resulted in a significantly increased MBF for all 3 groups, but it was significantly reduced in those groups after reimplantation of the coronary arteries (ASO: 263.2 ± 44.1 mL · 100 g⁻¹ · min⁻¹ and Ross: 239.0 ± 96.0 mL · 100 g⁻¹ · min⁻¹ versus controls: 310.3 ± 75.4 mL · 100 g⁻¹ · min⁻¹; P < 0.02).

As a result of the increased MBF at rest and the lower MBF during adenosine infusion, CFR was markedly attenuated in the group of patients after ASO than in either those who had the Ross operation or in healthy adolescents. (ASO: 2.54 ± 0.61 mL · 100 g⁻¹ · min⁻¹ versus Ross: 3.99 ± 1.49 mL · 100 g⁻¹ · min⁻¹, P < 0.005; versus controls: 4.09 ± 0.95 mL · 100 g⁻¹ · min⁻¹, P < 0.001; Table).

In ASO patients, no significant correlation could be calculated between MBF or CFR and gas exchange parameters, ejection fraction, fractional shortening, and levels of GPBB, creatine kinase, and troponin T. MBF and CFR in ASO and Ross patients were not correlated to total bypass or aortic cross-clamp times.

### Qualitative PET Analysis

Visual analysis of the PET images revealed adenosine-induced reversible perfusion defects in 5 of 21 children (24%) after ASO (1 anterior, 2 anterolateral, and 2 lateral defects), but no reversible, stress-induced perfusion defects were detected in the group of Ross patients.

Persistent defects were found in 2 additional ASO patients; one was septal and the other was lateral. The septal persistent defect in one child was attributed to a large VSD, which was closed by patch during corrective surgery. The incidence of perfusion abnormalities was similar in children with ASO in the newborn period and children with complex TGA and 2-stage repair.

### Creatine Kinase, Troponin T, and GPBB (Group 1)

On average, all laboratory parameters measured in the group of switch patients (group 1) were normal at rest and were not

### MBF

MBF at rest, when normalized to the corresponding rate-pressure product, was significantly higher in the group of children after ASO than it was in patients after the Ross procedure and in healthy young adults (ASO: 112.2 ± 27.7 mL · 100 g⁻¹ · min⁻¹ versus Ross: 61.0 ± 17.2 mL · 100 g⁻¹ · min⁻¹, P < 0.001; versus controls: 77.4 ± 16.49 mL · 100 g⁻¹ · min⁻¹, P < 0.005). The MBF of Ross patients and normal adolescents did not differ significantly.

### Echocardiographic Studies

Echocardiographic measurements of fractional shortening and ejection fraction were normal in all patients at rest and after maximal exercise. Satisfactory images for regional wall motion analysis were available in 28 patients. Wall motion abnormalities were absent under resting conditions, despite a dyskinetic area in the septal region of one patient, which was attributed to a large, patch-closed VSD. Dyskinetic areas could be detected after exercise in 2 patients in the ASO group; they were located in the anterolateral segments of the myocardium. One patient had isolated d-TGA with both coronary arteries transposed and was operated on as a newborn, and the other had DORV with a single coronary artery and the left coronary artery being a branch of the transposed right coronary artery and had 2-stage surgery, with initial pulmonary artery banding.

None of the children had evidence of neoaortic stenosis or significant aortic regurgitation; 1 child had mild supravalvular pulmonary stenosis with a maximal Doppler gradient of 40 mm Hg. None of the Ross patients had obstruction of the left or right ventricular outflow tract.

### Quantitative and Qualitative PET Results With N-13 Ammonia

<table>
<thead>
<tr>
<th></th>
<th>ASO</th>
<th>Ross</th>
<th>Normals</th>
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<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age, y</td>
<td>12.3 ± 2.2</td>
<td>19.2 ± 7.6</td>
<td>25.6 ± 5.4</td>
</tr>
<tr>
<td>Time since operation, y</td>
<td>11.2 ± 2.9</td>
<td>4.2 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>66 ± 11</td>
<td>72 ± 12</td>
<td>66 ± 12</td>
</tr>
<tr>
<td>With adenosine</td>
<td>105 ± 16*</td>
<td>98 ± 18*</td>
<td>107 ± 15*</td>
</tr>
<tr>
<td>RPP, mm Hg · min⁻¹</td>
<td></td>
<td></td>
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<tr>
<td>At rest</td>
<td>7.113 ± 1.458</td>
<td>7.543 ± 1.243</td>
<td>7.821 ± 1.147</td>
</tr>
<tr>
<td>With adenosine</td>
<td>12.119 ± 3.065*</td>
<td>12.784 ± 2.983*</td>
<td>12.961 ± 2.442*</td>
</tr>
<tr>
<td>MBF, mL · 100 g⁻¹ · min⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest normalized</td>
<td>112.2 ± 27.7</td>
<td>61.0 ± 17.2</td>
<td>77.4 ± 16.4</td>
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<tr>
<td>With adenosine</td>
<td>263.2 ± 44.1</td>
<td>239.0 ± 96.0</td>
<td>310.3 ± 75.4</td>
</tr>
<tr>
<td>CFR</td>
<td>2.54 ± 0.61</td>
<td>3.99 ± 1.49</td>
<td>4.09 ± 0.95</td>
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<tr>
<td>Perfusion defects</td>
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</table>

Values are mean ± SD. RPP indicates rate-pressure product.

*P < 0.05 vs at rest.

(groups 1 and 2) remained asymptomatic and did not complain of chest pain. None of the 30 patients had ECG evidence of ischemia or ectopic activity, and there was a normal increase in heart rate.
elevated 2 hours after exercise. Patients with stress-induced perfusion defects on PET scanning, when compared with those without defects, had high resting levels of GPBB and a significant rise in these levels after exercise (from 23.4±7.6 to 28.9±9.3 μg/L in those with defects and from 14.0±5.3 to 13.5±4.8 μg/L in those without defects; P<0.002).

Coronary Angiography
Aortic root and selective coronary artery angiography were performed in 5 patients with reversible perfusion defects after vasodilatation with adenosine in PET. Three children had isolated d-TGA, one had an associated perimembranous VSD that was closed during the ASO, and one patient had DORV with subpulmonary VSD. Four children had previous balloon atrioseptostomy. The ASO was performed in 4 children within the first 2 weeks of life, and the one with DORV was operated on at the age of 234 days. No coronary obstruction was detected in any of the 5 patients with postoperative cardiac catheterization and coronary angiography; the coronary ostia tended to appear elliptical 7 to 10 mm cranial of the aortic sinus (Figure 1). The region of the sinotubular junction was generally not detectable anymore. All patients had right dominance of the coronary circulation, with a large right coronary artery that gave rise not only to the posterior descending artery, but also to the posterolateral branches, thereby perfusing the right ventricular free wall and the inferoseptal and posterolateral wall of the left ventricle. A remarkably small caliber of the left anterior descending artery in the distal part was a common finding in all patients. There was no circumscription stenosis, disruption, or obstruction of the left anterior descending or other coronary artery branches (Figure 2).

Discussion
In our study, all surveyed children were clinically asymptomatic and able to perform normal physical activity. Spiroergometry revealed a normal exercise capacity, which did not differ from that of healthy volunteers. The lack of symptoms, the normal exercise capacity, and the normal resting, exercise, and Holter ECG monitoring suggested normal myocardial perfusion, without clinical signs of ischemia.
Global left ventricular function was normal in all patients (groups 1 and 2), with a physiological increase of the ejection fraction and fractional shortening after exercise. However, on 2D echocardiography, 2 patients in the ASO group had stress-induced dyskinetic areas within the anterolateral region of the myocardium; this observation could be confirmed by PET imaging, which showed reversible stress-induced perfusion defects in the same area of the left ventricle.

Three patients in group 1 had reversible, stress-induced perfusion defects on PET scanning but had normal echograms at rest and after exercise. Most of the defects involved only a small area of a segment; these perfusion scan abnormalities reflect arteriolar or capillary processes, and the high sensitivity of PET myocardial perfusion imaging may result in the detection of defects that are too small to cause detectable alterations in ventricular function or regional wall motion on echograms. In contrast to the findings of Weindling et al.,12 who could not detect any perfusion abnormalities assessed by technetium-99 sestamibi in the subgroup of primary ASO, the incidence of perfusion abnormalities in our study was comparable between patients with primary and 2-stage ASO. Perfusion defects may be related to inadequate coronary perfusion due to fibrosis of the suture line around the implanted coronary artery ostia, kinking, stenosis, or abnormal vasomotion of the coronaries in response to increased myocardial oxygen demand. In addition, one can hypothesize that the translocation of the coronary arteries initiates an intimal proliferation that progresses gradually postoperatively and may lead to impaired myocardial perfusion.13

In general, reimplantation of the coronary arteries may have some adverse effect on myocardial perfusion because in Ross and ASO patients, the MBF after vasodilatation was significantly reduced, with significantly impaired CFR in ASO patients but normal CFR in Ross patients. In all of our switch patients, the orifice of the reimplanted coronary arteries was located high in the ascending aorta, at least 7 mm above the aortic sinuses. Bellhouse and Bellhouse14 observed that the sinus ridge is an invariable and well-marked anatomical feature and that the coronary ostia always lie within the sinuses; if the ostia lay outside the sinuses on the aortic wall, the normal function of the sinus would be lost, and a serious reduction in coronary flow will occur.14 This might explain the difference in coronary flow in the Ross group, where the reimplantation usually happened at the level of the sinuses. The consequence for the surgical procedure would be a reimplantation of the coronaries within the neoaortic sinus. Nevertheless, the angiographic findings in the ASO group did not reveal any concrete stenosis of the coronary arteries. A common finding was hypoplasia of the left anterior descending artery in the distal part; however, this finding does not explain the global decrease in CFR, because the right coronary artery was dominant in all of those patients.

The significantly elevated levels of GPBB in patients with stress-induced perfusion defects are interesting; these levels corroborate the presence of myocardial ischemia. The isoenzyme BB of glycogen phosphorylase is the predominant isotype in human myocardium; because it is the key enzyme of glycogenolysis, the release of GPBB from injured myocardi um may reflect the burst of glycogenolysis initiated during acute myocardial ischemia.15

The specific mechanism of GPBB release adds some new aspects to the laboratory diagnosis of acute myocardial ischemia that are different from other blood serum markers of myocardial damage, such as creatine kinase and its isoenzymes MB and MM and cardiac troponin T; levels of these markers were normal in our patients.

The reason for the increased MBF at rest in the group of ASO children remains unclear and contributes to the attenuated CFR. The effects of hemodynamic alterations in the expression of genes coding for the contractile proteins are well established16; whether this leads to derangements in myocardial energy metabolism, elevated oxygen demand, and elevated MBF under resting conditions remains hypothetical and needs further investigation.

Cardiac efferent sympathetic signals modulate MBF.17 Increased sympathetic activity dilates the coronary resistance vessels and thus increases MBF, which is modulated by endothelial function; however, resting coronary flow is not substantially affected by either humoral or neural adrenergic influences. The increase in coronary flow response to sympathetic stimulation correlates with the magnitude of regional stores of norepinephrine in cardiac sympathetic nerve terminals, which correlates with contractility, oxygen demand, and reactive metabolic vasodilatation or direct activation of β-adrenergic receptors on smooth muscle and endothelial cells in the vessel wall. Coronary vasodilatation may also result from the direct stimulation of α-adrenergic receptors in intact endothelial cells and the release of nitric oxide, presumably through the activation of local kinin synthesis.18

Translocation of the coronary arteries may result in partial myocardial sympathetic denervation, with a potential influence on MBF, and impaired development of vasoreactive capacity or growth potential of the coronaries in Ross and (more so) ASO patients.

In addition, abnormalities of the coronary walls may occur as a primary abnormality or as part of a multisystem disorder, and they may mimic atherosclerotic disease, with impairment of MBF and CFR.19 Endothelial function and coronary vasoreactivity may be altered substantially in children with TGA, independent of surgical manipulations and coincident with congenital abnormalities of cardiac anatomy.

The limitations of the study are mainly derived from the ethical constraints concerning radiation exposure in children; no published blood flow data in normal children at any age are available. Young adult volunteers older than 18 years of age were used as a normal control group, and adolescents with a previous Ross operation were used as controls for coronary reimplantation; in both groups, age-related influences on the results cannot be ruled out completely. By splitting patients with TGA and Ross operations into different age groups, no trend in myocardial flow parameters, which may be influenced by age, was identified.

Conclusions

The patients surveyed in our study were asymptomatic, had normal echocardiographic left ventricular function and normal exercise capacity, and did not require cardiac medica-
tions. The observed perfusion defects in the ASO group (the impaired MBF and CFR) did not result in any functional compromise and could not be evaluated sufficiently by ECG and echocardiography. The comparison with patients after Ross operation indicates that the procedure of reimplantation alone could not explain the findings in the ASO group and that more complex factors must be present. Whether these defects will continue after longer periods of time is unknown. Although the cause of these myocardial perfusion abnormalities cannot be clarified in this study, congenital and developmental anomalies of the coronary arteries, the insult from open heart surgery, and coronary manipulation during the ASO must be studied more extensively. Nevertheless, the function of the coronary arteries remains a matter of concern in patients after ASO, and the prognostic implications must be discussed. Close follow-up is mandatory, even in clinically asymptomatic patients.

References
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