Myocardial Blood Flow and Coronary Flow Reserve Late After Anatomical Correction of Transposition of the Great Arteries

FRANK M. BENGEL, MD, MICHAEL HAUSER, MD,* CLAIRE S. DUVERNOY, MD, ANDREAS KUEHN, MD,* SIBYLLE I. ZIEGLER, PhD, JENS C. STOLLFUSS, MD, MAREIKE BECKMANN, MS,* URSULA SAUER, MD,* OTTO MUZIK, PhD†, MARKUS SCHWAIGER, MD, JOHN HESS, MD*

Munich, Germany and Detroit, Michigan

Objectives. Myocardial blood flow (MBF) in children late after arterial switch operation (ASO) was investigated quantitatively by positron emission tomography (PET).

Background. In children with transposition of the great arteries (TGA), ASO is widely accepted as the management of choice. The long-term patency of coronary arteries after surgical transfer to the neo-aorta, however, remains a concern.

Methods. Twenty-two normally developed, symptom-free children were investigated by PET with nitrogen-13 ammonia at rest and during adenosine vasodilation 10 ± 1 years after ASO. A subgroup of 15 children (9 ± 1 years; group A) had simple TGA and underwent ASO within 20 days after birth while 7 (13 ± 3 years; group B) had complex TGA and underwent ASO and correction of associated anomalies later after birth. Ten young, healthy adults (26 ± 6 years) served as the control group.

Results. Resting MBF was not different between groups. After correction for the rate-pressure product as an index of cardiac work, younger children of group A had significantly higher MBF at rest compared to healthy adults (102 ± 29 vs. 77 ± 16 ml/100 g/min; p = 0.012) while flow in group B was not different from the other groups (85 ± 22 ml/100 g/min; p = NS). Hyperemic blood flows were significantly lower in both groups after ASO compared to normals (290 ± 42 ml/100 g/min for group A, 240 ± 28 for group B, 340 ± 57 for normals; p < 0.01); thus, coronary flow reserve was significantly lower in both groups after ASO compared to healthy adults (3.0 ± 0.6 for group A, 2.9 ± 0.6 for group B, 4.6 ± 0.9 for normals; p < 0.01).

Conclusions. Blood flow measurements suggest decreased coronary reserve in the absence of ischemic symptoms in children late after arterial switch repair of TGA. The global impairment of stress flow dynamics may indicate altered vasoreactivity; however, the prognostic significance of these findings needs to be determined.

(J Am Coll Cardiol 1998;32:1955–61)
©1998 by the American College of Cardiology
transposition of the great arteries (TGA) despite normal development and lack of symptoms.

Methods

Patients. Twenty-two children (18 male, 4 female; mean age 10.6 ± 2.4 years; range 8–16 years) with a history of ASO for anatomical correction of TGA were included in the study. Arterial switch operation was performed as previously described (17) with the aid of deep hypothermia and continuous low-flow extracorporeal circulation. For myocardial protection, a cardioplegic solution was used. Mean extracorporeal bypass time was 146 ± 35 min; aortic clamp time was 105 ± 23 min. The surgical procedure consisted of mobilizing and dividing the aortic and pulmonary artery trunk, and subsequently transsecting and switching the trunks. Coronary arteries were transferred by excision of patches of aortic wall surrounding the coronary ostia and reinsertion of these patches into the neo-aorta. For a tension-free transfer, the coronary trunks were sufficiently mobilized.

For analysis of myocardial blood flow and hemodynamic data, the 22 children were divided into two subgroups.

Group A consisted of 15 children (age 9 ± 1 years) who had simple TGA and underwent early one-stage ASO within the first 20 days after birth. The coronary pattern was completely normal in 13 children while the circumflex artery arose from the right coronary artery in 2 children.

Group B comprised the remaining seven children (age 13 ± 3 years) in whom more complex anomalies were present. The ASO was performed later after birth at an age of 134 to 2,847 days. Four had TGA and large ventricular septal defect (VSD), one had associated valvular pulmonary stenosis, one had associated aortic coarctation and one had a complex coronary pattern with three ostia for the right coronary artery. Four of these children underwent two-stage surgery with prior pulmonary artery banding. The median of the 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 in the study for all children was 10.3 ± 1.3 years. Measurement of myocardial blood flow (MBF) by PET was performed as part of a routine clinical follow-up. At the time of inclusion, all children were normally developed, free of symptoms and required no medication. Global and regional left ventricular function, as determined by echocardiography, was normal. None of the children had evidence of aortic stenosis or valvular insufficiency. A mild supravalvular pulmonary stenosis was found in one child in group A, but echocardiographic evidence of pathologic ventricular hypertrophy was not surveyed in any of the children. Additionally, none of the children revealed electrocardiographic signs or symptoms of stress-induced ischemia during maximal physical exercise testing. All parents or legal guardians gave written informed consent prior to PET.

Ten healthy young adults (seven men, three women; age 26 ± 6 years) with no evidence of cardiovascular disease on the basis of the absence of symptoms and risk factors, normal resting electrocardiogram and normal exercise test were used as a control group. The results of these individuals have been used as a normal control group in a previously published study (12).

Positron emission tomography. Myocardial blood flow was quantified noninvasively at rest and during adenosine-induced maximal vasodilation by dynamic PET with N-13 ammonia. Images were acquired using either an ECAT EXACT or an ECAT 951 scanner (Siemens/CTI, Knoxville, Tennessee). Performance characteristics of these tomographs have been described previously (18,19).

After positioning the patient, a transmission scan of 15 min was acquired for correction of photon attenuation. Subsequently, N-13 ammonia (approximately 0.3 mCi kg\(^{-1}\)) was injected intravenously at rest and a dynamic imaging sequence of 21 frames (12 × 10 s, 6 × 30 s, 3 × 300 s) was acquired over 20 min. After 50 min to allow for decay of N-13, adenosine (0.14 mg kg\(^{-1}\) min\(^{-1}\)) was continuously infused over 5 min. Two minutes after the onset of adenosine infusion, a second dose of N-13 ammonia (0.3 mCi kg\(^{-1}\)) was administered, and a dynamic imaging sequence similar to the rest study was started. Patient motion was minimized by fastening a strap across the chest. Only one child had to be sedated for imaging by intravenous application of 2.5 mg diazepam. Heart rate, blood pressure and a 12-lead electrocardiogram were monitored continuously throughout the procedure.

Data analysis. Attenuation-corrected transaxial images were reconstructed by filtered backprojection. Transaxial slices were then reoriented to 12 short-axis images of the heart.

Myocardial blood flow at rest and during hyperemia were quantified from four midventricular slices. The apex was excluded from quantitative analysis to avoid the influence of partial volume effects due to out-of-plane motion (12). Basal short-axis slices including membranous parts of the interventricular septum or visually detectable defects due to a patched VSD (found in one case) were also excluded from the analysis.

Sectorial myocardial regions of interest were automatically defined and applied to the entire dynamic data set to obtain tissue time activity curves (20). Additionally, a small circular region of interest was placed in the center of the left ventricle to calculate the arterial input function. Time activity curves were then fitted to a previously validated three-compartment tracer kinetic model (21,22).

Because of the relation of myocardial blood flow at rest with the rate-pressure product as an index of cardiac work (23), resting flow was normalized to the corresponding rate-pressure...
was performed for parameters measured at rest and during adenosine stress were compared by the paired Student’s t test according to Bonferroni/Dunn. Changes from baseline to significance by one-way analysis of variance and the post hoc standard deviation. Differences between groups were tested for and proximal anterior, lateral, inferior and septal wall). Persistent defects in nine myocardial segments (apex, distal and proximal anterior, lateral, inferior and septal wall).

Statistical analysis. Values are expressed as mean ± standard deviation. Differences between groups were tested for significance by one-way analysis of variance and the post hoc t test according to Bonferroni/Dunn. Changes from baseline to adenosine stress were compared by the paired Student’s t test. The relation between continuous variables was described by Pearson’s correlation coefficient and tested for significance by Fisher’s r to z transformation. Statistical significance was generally defined by a p-value < 0.05. If analysis of variance was performed for parameters measured at rest and during adenosine, a p-value < 0.025 was defined as significant to adjust for the consecutive measurements. For the post hoc t test by Bonferroni/Dunn, statistical significance was defined by p < 0.0167.

Results

Hemodynamics. The hemodynamic findings of both groups of children and the healthy young adults at rest and during adenosine vasodilation are summarized in Table 1. At rest, systolic, diastolic and mean aortic blood pressure of the children with early ASO and simple TGA (group A) were significantly lower compared to healthy young adults. No differences were found between the group of older children with late ASO and more complex forms of TGA (group B) and the young adults.

In all three groups a significant increase of heart rate and rate-pressure product during adenosine infusion was found. Group A additionally demonstrated a significant rise in systolic blood pressure. During hyperemia, hemodynamic parameters were not different between groups.

Myocardial blood flow. At rest, MBF was not different between both groups of children after ASO and the healthy young adults (Table 2). After normalization to the rate-
pressure product, however, the young children of group A had significantly higher flow values compared to the adult volunteers (102 ± 29 vs. 77 ± 16 ml/100 g/min; p = 0.012; Table 2), while the older children of group B were not significantly different from the young adults (85 ± 22 vs. 77 ± 16 ml/100 g/min; p = 0.5; Table 2).

Adenosine-induced vasodilation resulted in significantly increased MBF for all three groups (290 ± 42 ml/100 g/min vs. 102 ± 29 at rest for group A, p < 0.001; 240 ± 28 vs. 85 ± 22 for group B, p < 0.001; and 340 ± 57 vs. 77 ± 16 for healthy volunteers, p < 0.001; Fig. 1). Hyperemic blood flow, however, was lower in both groups of children after ASO compared to the healthy young adults (Fig. 1). Additionally, a trend toward lower stress flow in group B compared to group A was observed although statistical significance was not obtained (240 ± 28 vs. 290 ± 42 ml/100 g/min; p = 0.021).

As a result of lower MBF during adenosine infusion, coronary flow reserve was markedly attenuated in both groups of children with TGA compared to healthy young volunteers (Table 2).

In the children after ASO, neither blood flow at rest and during adenosine nor coronary flow reserve were significantly correlated to aortic clamp time or total bypass time at surgery.

Coronary vascular resistance. At rest, coronary vascular resistance was not significantly different between groups (Table 2). Minimal coronary resistance during adenosine vasodilation was not different between group A and healthy adults. Group B, on the other hand, showed a significantly higher resistance in comparison to healthy adults as well as group A (Table 2).

Qualitative analysis of myocardial perfusion. The overall concordance between the two observers for visual analysis was high (97% on a segmental basis).

Visual analysis revealed adenosine-induced reversible defects in 5 of 22 children (23%) after ASO (anterior in one child, anterolateral in two children and lateral in two children) (Fig. 2). Persistent defects were found in two additional children (9%; septal in one case and lateral in the second case). On a segmental base, 8 of 198 segments (4%) were judged as reversible and 3 of 198 (1.5%) as irreversible defects. The septal persistent defect in one child (one segment) was attributed to a large VSD, closed by a patch during surgery (Fig. 2). If one neglected this structural defect, the incidence of true perfusion abnormalities in groups A and B was comparable (Table 3).

Discussion

In summary, the present study suggests that adenosine-induced MBF and coronary flow reserve are attenuated in symptom-free, normally developed children 10 ± 1 years after ASO for TGA. These alterations seem to be present not only in children with complex abnormalities and late surgical repair, but also, although somewhat less pronounced, in children with early corrected simple transposition. Regional abnormalities of myocardial perfusion were detectable by visual analysis in a smaller subset of patients; however, quantitative MBF during adenosine and coronary flow reserve were attenuated not only in the children with regional heterogeneity, but also in those without visual abnormalities, suggesting altered global vasoreactivity after ASO.

Impaired stress flow dynamics. The precise etiology of these findings currently remains unclear. Various factors may contribute to attenuated vasoreactivity in the children studied.

Animal studies and angiographic studies in humans demonstrated sufficient growth of aorto-coronary anastomoses if coronaries are transferred together with patches of aortic wall around the ostia (5,6). Using aortic root angiography in a large series of patients, Tanel et al. (7) found a low incidence of previously unsuspected coronary artery occlusions and stenoses (13 out of 366 patients; 3.5%). Previous qualitative evaluation of myocardial perfusion using technetium-99m sestamibi demonstrated small, mainly fixed abnormalities at rest and during exercise (10,11). In these scintigraphic studies, the incidence of stress-induced reversible defects which could have been attributed to coronary stenoses was low; nevertheless, impaired coronary vasoreactivity in children after ASO may still be attributable to coronary manipulation during surgery. Stiffness or tension due to scar tissue in the area of reinserted...
Generally, sympathetic fibers travel along the arterial vascular structures. Disconnection of coronary arteries during ASO may thus result in a complete myocardial sympathetic denervation. If denervation occurs, reinnervation may remain incomplete as has been surveyed after orthotopic heart transplantation (25). No data are currently available on the status of sympathetic innervation and the potential influence on MBF in children after ASO. Alterations of sympathetic innervation may, for example, contribute to an impaired growth of coronary arteries or an impaired development of vasoreactive capacity in these children.

Additionally, development of endothelial function and coronary ostia and proximal coronary arteries may be causative factors even without the presence of significant stenoses.

Recently, the relevance of sympathetic innervation for regulation of MBF has been demonstrated in adults (24). Generally, sympathetic fibers travel along the arterial vascular structures. Disconnection of coronary arteries during ASO may thus result in a complete myocardial sympathetic denervation. If denervation occurs, reinnervation may remain incomplete as has been surveyed after orthotopic heart transplantation (25). No data are currently available on the status of sympathetic innervation and the potential influence on MBF in children after ASO. Alterations of sympathetic innervation may, for example, contribute to an impaired growth of coronary arteries or an impaired development of vasoreactive capacity in these children.

Additionally, development of endothelial function and coronary vasoreactivity may be altered congenitally in children with TGA independent of surgical manipulations, coincident with congenital abnormalities of cardiac anatomy. Although speculative, the trend toward lower MBF during adenosine together with significantly higher minimal coronary resistance in older children with more complex congenital abnormalities may be attributed to a concomitant more severe congenital abnormality in vasoreactivity.

Using technetium-99m sestamibi for qualitative assessment of myocardial perfusion after ASO, Hayes et al. (11) hypothesized that open heart surgery itself may lead to myocardial damage. In this study, the authors found fixed perfusion abnormalities at rest and during exercise in a group of children after ASO, but also in a group of children who underwent open heart surgery for other noncoronary cardiac lesions. The authors thus speculated that microinfarction due to embolism during surgery may be a potential explanation for their findings. In the present quantitative study, however, resting MBF was not lower compared to normals as could be expected in the case of extensive microinfarction. Additionally, MBF or coronary flow reserve were not correlated with cardiopulmonary bypass time or aortic clamp time as parameters for the length of open heart surgery and thus for the likelihood of surgery-related myocardial damage. It therefore seems unlikely that myocardial damage during open heart surgery alone accounts for the impairment of vasoreactivity and coronary flow reserve in our study population.

In adults, it has been previously suggested that pathologic ventricular hypertrophy may result in abnormalities of coronary flow (26). In children after ASO, existing valvular dysfunction or previous pulmonary artery banding may result in pathologic hypertrophy and thus have an impact on MFB. In this study, however, none of the children showed echocardiographic evidence of ventricular hypertrophy or major valvular disorders, rendering an influence of hypertrophy on the observed results unlikely.

Baseline conditions. Myocardial blood flow at rest was not different between children after ASO and young normal adults; however, at rest it has been previously demonstrated that cardiac work is a strong determinant of MBF (23). If resting flow was normalized to the rate-pressure product as an index of cardiac work, the young children with early ASO showed significantly higher resting flow values compared to normal adults. Blood pressures at rest were significantly lower compared to healthy adults in this group. Normalized resting flow values and blood pressures of the older children who underwent ASO later after birth were between those for the young children and those for the healthy adults.

It is a well-known, age-related phenomenon that blood pressure increases during adolescence. Although higher resting flow in the young children (group A) cannot be readily explained in the present setting, it may be speculated that this finding is an age-related phenomenon as well. In children, PET has been applied for quantification of MBF in only one previous study after Kawasaki disease (12). The age of these children (12 ± 3 years) as well as normalized resting MBF
(82 ± 14 ml/min/100 g) were comparable to group B; however, due to the substantially different pathophysiology, a comparison of MBF in children after ASO and after Kawasaki disease does not seem to be valid. Further studies focusing on the dependence of resting MBF on age in childhood would be desirable.

Adenosine-induced hyperemic blood flow, however, was attenuated compared to healthy adults in both groups of children after ASO, suggesting that resting flow is not the main determinant of attenuated coronary flow reserve after ASO. Furthermore, there was a nonsignificant trend toward lower hyperemic flow in the group of older children compared to both younger children and healthy adults. Reduced hyperemic flow therefore seems unlikely to be an age-related observation in children after ASO.

**Prognostic implications.** Impairments of MBF and coronary flow reserve were found despite a normal development and lack of cardiac symptoms in the present study. Additionally, one of the studied children had impaired left ventricular function; thus, the prognostic significance of flow alterations after ASO remains uncertain. Follow-up over a longer period of time will be necessary to determine the importance of the reported findings for long-term outcome.

**Study limitations.** Limitations of this study are mainly derived from ethical constraints concerning radiation exposure to children.

Although radiation exposure through the use of PET with N-13 ammonia is markedly lower compared to myocardial perfusion single-photon emission computed tomography with technetium-99m sestamibi (total body absorbed dose in adults is approximately 0.2 mSv mCi⁻¹ for technetium-99m sestamibi vs. approximately 0.6 mSv mCi⁻¹ for N-13 ammonia), recruitment of age-matched control groups for any radionuclide study is difficult in childhood. Young adult volunteers at >18 years of age were used in the present study as a normal control group. No published blood flow data in normal children at any age are available. Age-related influences on the results therefore cannot be ruled out completely. We sought to overcome this problem by splitting children after ASO into two subgroups of different ages to identify trends which may be influenced by age. Although there are ethical constraints concerning the investigation of normal children, age-matched groups of children with TGA, but without surgical coronary manipulation, and of children with nonsurgically treated congenital heart disease may be used in the future as control groups for further determination of the factors underlying altered coronary flow in children after ASO.

Second, invasive coronary angiographic data were not obtained in this study. Selective coronary angiography has been proven to be useful not only for detection of coronary stenosis or occlusion, but also for detection of coronary artery stretching after ASO (8), and thus would be desirable to unmask macroscopic coronary abnormalities as a reason for the observed flow alterations. To validate findings derived from noninvasive PET, it is planned in the future to perform coronary angiography at least in the subgroup of children in whom stress-induced defects were detectable visually. Stress echocardiography has also been shown to be useful for the detection of wall motion abnormalities associated with perfusion abnormalities (27), and may be a useful noninvasive tool for longitudinal follow-up of the present study group.

**Conclusions.** Quantitative measurements of MBF by PET suggest decreased coronary reserve in the absence of ischemic symptoms in children late after anatomical correction of TGA. The global impairment of stress flow dynamics may indicate altered vasoreactivity. The prognostic significance of these findings, however, needs to be defined.

The excellent technical assistance of Coletta Kruschke, Claudia Kolligs and Sylvia Fuurst during PET measurements was appreciated. In addition, the authors thank the cyclotron staff of the Klinikum rechts der Isar for reliable production of N-13 ammonia.

**References**

