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Abnormal Vasomotor Function of the Epicardial Coronary Arteries in Children Five to Eight Years After Arterial Switch Operation

An Angiographic and Intracoronary Doppler Flow Wire Study

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OBJECTIVES This study sought to test the vasoreactivity of the translocated coronary arteries after arterial switch operation (ASO) using quantitative angiographic analysis and intracoronary Doppler flow wire velocimetry.

BACKGROUND Late coronary artery events occur in 3% to 8% of patients after the ASO. Previous studies of coronary flow reserve have yielded disparate results.

METHODS Nineteen children previously underwent ASO (13 boys, age 5.4 ± 3.2 years, weight 22.3 ± 10.6 kg), and six control patients were enrolled in the study. Each patient underwent quantitative angiographic assessment of the epicardial coronary arteries before and after administration of nitroglycerin and coronary blood flow volume assessment before and after administration of adenosine and acetylcholine. The results were compared between groups.

RESULTS Epicardial coronary artery dilation in response to intracoronary nitroglycerin was significantly less in the ASO group than in the control group (left anterior descending [LAD], 5.0 ± 0.05% vs. 18.0 ± 4.5%, p = 0.0009; right coronary artery [RCA], 4.0 ± 0.07% vs. 32.7 ± 12.7%, p = 0.006). Moreover, the coronary blood flow volume reserve was reduced in ASO patients compared with control patients after intracoronary infusion of acetylcholine (2.3 ± 0.9 vs. 4.9 ± 1.7, p = 0.0003) or adenosine (2.7 ± 1.5 vs. 5 ± 0.5, p = 0.002).

CONCLUSIONS Epicardial coronary arteries fail to dilate normally in children after ASO, and the calculated coronary flow volume reserve is consequently reduced. (J Am Coll Cardiol 2005;46: 1565–72) © 2005 by the American College of Cardiology Foundation

The arterial switch operation (ASO) has become the treatment of choice for transposition of great arteries. This procedure includes transection of the great arteries and translocation of the coronary arteries to the opposite arterial root, and it is associated with injury of the sympathetic nerves supplying the coronary arteries (1).

Although the medium-term results of this operation are good (2), especially when compared with the atrial switch operation, its success is still affected by late coronary artery complications. Large studies (3,4) have shown a prevalence of coronary events, including sudden death and myocardial infarction, between 3% and 8% during follow-up periods up to 15 years. Children rarely report symptoms, and noninvasive methods have not been predictive of coronary abnormalities. The functional capacity of the coronary arteries after ASO remains unresolved. Some studies (5–8) performed with positron emission tomography (PET) have shown impaired global coronary flow volume reserve (CFR). More recently, Oskarsson et al. (9) have investigated coronary flow reserve using an intracoronary Doppler flow wire. Their data showed normal coronary flow velocity reserve (CVFR) in children after ASO. These apparently disparate results are likely related to the fact that those techniques measure different things. The PET uses an indicator dilution principle to measure volume flow. The coronary flow velocity measured by Doppler wire is related to volume flow by the cross-sectional area of the coronary artery. Normally, a decrease in coronary vascular resistance results in an increase in flow velocity in the epicardial vessel with a flow-induced increase in diameter (10). Consequently, a normal increase in flow volume depends not only on an increase in flow velocity in the epicardial vessels but also on dilation of the vessel. In the absence of normal dilation of the epicardial vessel, the increase in flow volume will be reduced despite a normal increase in flow velocity. Reduced or absent vasoreactivity of the epicardial vessel could explain the disparate results of the PET and Doppler wire studies.

The goal of this study was to assess the vasoreactivity of the translocated epicardial coronary arteries after ASO and to estimate CFR using quantitative angiographic analysis and intracoronary Doppler flow wire.

METHODS

ASO patients. A total of 19 consecutive asymptomatic children (13 boys and 6 girls; mean age, 5.4 ± 3.2 years; mean weight, 22.3 ± 10.6 kg) who had undergone an ASO in infancy were enrolled in the study. All patients had a normal standard electrocardiogram (ECG), and serial echocardiography showed normal left ventricular function, no right or left ventricular hypertrophy, and absence of supra-

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Abbreviations and Acronyms

APV = average peak velocity
ASO = arterial switch operation
CFR = coronary volume flow reserve
CSA = cross-sectional area
CVFR = coronary velocity flow reserve
LAD = left anterior descending artery
LAO = left anterior oblique
LCA = left coronary artery
PET = positron emission tomography
RAO = right anterior oblique
RCA = right coronary artery

valvular pulmonary and/or aortic stenosis. The study protocol included selective coronary angiography as a first step to exclude significant stenosis of the epicardial vessels. Patients with no stenosis or other abnormality of the epicardial coronary arteries underwent functional assessment.

The anatomy of the coronary arteries was described according to the classification proposed by Yacoub (11). The right and left coronary ostia arose from the middle of the right and left septal sinuses (type A) in 14 patients, and in 3 patients the right coronary artery (RCA) gave origin to the circumflex coronary artery (type D). A single left coronary artery (LCA) (type B) was found in one case. The two coronary orifices originated close to each other near the facing commissure, with an intramural course of the RCA in the remaining case (type C) (Table 1).

Control group. Six additional patients (four boys and two girls; mean age, 6.25 ± 2.9 years; mean weight, 22.2 ± 4.5 kg) with normal coronary arteries who were undergoing cardiac catheterization for other reasons served as the control group. The reasons for the catheterization were dilation of the aortic root (one patient), mitral valve prolapse and mitral regurgitation (two patients) and patent ductus arteriosus (three patients). Echocardiography excluded ventricular hypertrophy and outflow tract obstruction and showed a normal ejection fraction in all cases. No coronary artery anomaly was identified during aortography. For patients with patent ductus arteriosus, the Qp/Qs was <1.5, and catheterization was performed for device closure. The quantitative angiography and the intracoronary Doppler study in this subgroup of patients were conducted approximately 1 h after successful closure of the ductus arteriosus and restoration of normal hemodynamic conditions.

Table 1. Patient Characteristics

	ASO Patients n = 19	Control Group n = 6
Gender	13 M; 6 F	4 M; 2 F
Age, yrs (mean)	5.4 ± 3.2	6.25 ± 2.9
Weight, kg (mean)	22.3 ± 10.6	22.2 ± 4.5
Time from intervention, yrs	5.5 ± 3.3	—
Coronary pattern	Type A: 14 Type B: 1 Type C: 1 Type D: 3	Normal

The scientific and ethical committee of the Bambino Gesù Hospital approved the protocol, and the parents gave their consent.

Study protocol. All patients were anesthetized, intubated, and mechanically ventilated during cardiac catheterization. Atropine was not administered at the time of premedication. Anesthesia was induced by inhalation of sevoflurane in 100% oxygen by mask and 2 γ/kg of remifentanil, 3 γ/kg of cisatracurium besylate, and 0.2 mg/kg of midazolam were administered intravenously. Anesthesia was maintained with 2 γ/kg/min of remifentanil, 0.1 mg/kg/h of cisatracurium besylate, and 0.1 mg/kg/h of midazolam. The Fio_2 was 0.21 throughout the catheterization study. All patients received an intravenous bolus injection of heparin (100 IU/kg) after vascular access was obtained. Each patient underwent a routine cardiac catheterization including right and left ventriculography, pulmonary angiography, and aortography. Then selective coronary angiography was performed to evaluate possible macroscopic abnormalities of the coronary arteries and to serve as a baseline for quantitative angiographic assessment of the epicardial coronary arteries.

Quantitative coronary angiography. We performed selective coronary angiography of both epicardial arteries (i.e., left and right) in all cases. Because of the anterior position of the translocated ostia, selective angiograms were performed exclusively with right coronary catheters. After the coronary artery ostium was cannulated, coronary angiography was performed by manual injection. High-resolution digital angiograms (resolution, 0.2 mm) were recorded of the RCA (right anterior oblique [RAO], 30°; left anterior oblique [LAO], 20°) and of the LCA (RAO, 20°; LAO, 90°) before and after an intracoronary bolus of nitroglycerin. To obtain maximal coronary dilation, we choose the dose of nitroglycerin based on data validated in adult patients. The recommended dose in the literature (12) is 200 μg for adults. Assuming an adult weight of 70 kg, we administered 3 μg/kg (≃200 μg /70 kg). We used the LAO 20° for the RCA and the RAO 20° for the LCA to measure the diameter of the proximal, mid, and distal epicardial portions (13) of the left anterior descending artery (LAD) or RCA during diastole using commercially available quantitative digital system software (BICOR PLUS/TOP, Siemens, Munich, Germany). Two independent and blinded observers measured the vessel and calculated the change in diameter in response to nitroglycerin. Nitroglycerin infusion was performed in only one coronary artery in each child, the RCA in 10 ASO patients and 2 control patients, and the LCA in 9 ASO patients (including the child with a single LCA orifice) and 4 control patients.

Doppler flow wire technique. After coronary angiography, a 0.014-inch Doppler guide wire, with a 12-MHz piezoelectric transducer (FlowWire, Volcano Therapeutics

Inc., Rancho Cordova, California) mounted on the tip was advanced into the proximal third of the LAD or of the RCA. The position of the wire was adjusted to obtain the highest-quality coronary Doppler flow signal. The ECG and arterial blood pressure, recorded invasively through a radial artery cannula, were continuously monitored and recorded on a magnetic tape recorder and played back for recording on paper at the end of each study.

Coronary blood flow velocity was measured by connecting the flow wire to a pulsed Doppler velocimeter. From the Doppler flow velocity spectra, the average peak velocity (APV) was calculated as the time-averaged value of the instantaneous peak velocity over two consecutive cardiac cycles. After obtaining a stable baseline flow velocity signal, acetylcholine (1.8 μg/min) and adenosine (270 μg/min) were alternately infused (1 ml/min) into the coronary artery ostium for a period of 3 min each. A washout period of at least five minutes was allowed between the two infusions. Acetylcholine and adenosine were infused at a concentration of 10^{-4} mol/l and 10^{-3} mol/l, respectively. Responses to adenosine and acetylcholine were expressed as the ratio of APV obtained after drug infusion to basal APV. The CVFR was calculated automatically by the Flow Map software based on the recordings of flow velocity at peak effect, after the administration of adenosine and acetylcholine. The CVFR was measured in the same coronary arteries in which the response to nitroglycerin was measured by quantitative angiography.

We estimated the volumetric coronary blood flow before and after administration of vasodilators according to the validated formula (14): cross-sectional area $\times$ APV $\times$ 0.5. For the cross-sectional area (CSA) of the epicardial vessel, we used the luminal diameter of the proximal epicardial vessel before and after nitroglycerin. Similarly, we used the APV at baseline and in response to vasoactive agents, adenosine, and acetylcholine. The CFR was calculated as the ratio of the coronary flow volume before and after hyperemic stimulus.

Data analysis. Continuous data are expressed as mean $\pm$ 1 standard deviation. Coronary blood flow velocity is expressed as average peak velocity throughout the cardiac cycle. The peak-to-baseline ratio of the diameter of the coronary artery before and after nitroglycerin and coronary blood flow velocity before and after adenosine and acetylcholine were calculated. The significance of differences in vessel diameter before and after administration of nitroglycerin and the significance of differences between flow velocity and volume before and after administration of acetylcholine and adenosine were evaluated using a Student *t* test for paired data for both control and ASO patients. The significance of intergroup comparisons was evaluated using a Student *t* test for unpaired data. A p value < 0.05 was considered statistically significant. Intraclass correlation coefficient was computed as a measure of interobserver reliability in the evaluation of results of quantitative coronary angiography.

RESULTS

Selective coronary angiography showed no macroscopic abnormality of any epicardial coronary artery. Consequently, coronary function studies were performed in all 19 patients. All patients remained stable throughout the study protocol with no change in the electrocardiogram suggestive of ischemia.

The study was terminated after the first 19 patients and 6 control patients because an interim analysis showed sufficient power to detect clinically meaningful differences between the study and control groups. This sample provided 80% power to detect a 10% difference in baseline coronary artery diameter between the study and control groups. We analyzed separately the coronary artery arising from the right sinus (RCA) and the one arising from the left sinus (LCA). The analysis of the RCA was conducted in 10 children and of the LCA in 9 children. The results are reported in Tables 2 and 3.

Baseline coronary artery size. The proximal epicardial segments of the LAD (2.3 $\pm$ 0.4 mm vs. 2.3 $\pm$ 0.6 mm, p = 0.92) and RCA (2.2 $\pm$ 0.3 mm vs. 2.0 $\pm$ 0.6 mm, p = 0.29) at baseline did not differ significantly in diameter between the ASO and control groups (Table 2).

Nitroglycerin bolus in the study group. A reduction of arterial blood pressure between 10 and 25 mm Hg (10% to 15% from baseline) was observed after the intracoronary bolus of nitroglycerin, whereas the heart rate increased by <10% from baseline values. The diameter of neither the RCA nor the LAD increased significantly in response to nitroglycerin in the proximal, mid, or distal segments (p = not significant) (Table 3). The value of the intraclass correlation coefficient (average measure intraclass correlation coefficient, 0.98; 95% confidence interval, 0.95 to 0.99) indicated a high level of agreement between observers.

Nitroglycerin bolus in the control group. After nitroglycerin, a similar decrease in blood pressure was observed and the heart rate increased by <10% from baseline values. The diameters of both the RCA and the LAD increased significantly from baseline after injection of nitroglycerin (RCA, p = 0.044; LCA, p = 0.002) (Tables 2 and 3, Figs. 1 and 2). The percent change in coronary artery diameter for the proximal segment after nitroglycerin was significantly lower in patients than in control patients for both the RCA and the LAD (RCA, 4.0 $\pm$ 0.07% vs. 32.7 $\pm$ 12.7%, p = 0.006; LAD, 5.0 $\pm$ 0.05% vs. 18 $\pm$ 4.5%, p = 0.0009) (Table 2).

Acetylcholine infusion. No change in heart rate or blood pressure was noted during acetylcholine infusion in either the patient or the control group. Peak APV after acetylcholine increased significantly in both the patient and control groups compared with baseline (Table 4, Fig. 3). Coronary flow volume estimated at baseline tended to be higher in the

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Table 2. Coronary Angiography: Quantitative Analysis of Vessel Diameter

	ASO Group n = 19	Control Group n = 6	
LAD			
Before nitroglycerin, mm	2.3 ± 0.4	2.3 ± 0.6	p = 0.002
After nitroglycerin, mm	2.4 ± 0.4	2.7 ± 0.5	
Percent change, %	5.0 ± 0.05	18 ± 4.5	
RCA			
Before nitroglycerin, mm	2.2 ± 0.3	2.3 ± 0.6	p = 0.044
After nitroglycerin, mm	2.3 ± 0.2	2.7 ± 0.4	
Percent change, %	4.0 ± 0.07	32.7 ± 12.7	

LAD = left anterior descending artery; RCA = right coronary artery.

ASO group (51.4 ± 37. 9 ml/min vs. 26.2 ± 8.7 ml/min, p = 0.13), but this did not reach statistical significance. The peak flow volume (136.2 ± 143.7 ml/min vs. 128.5 ± 49.7 ml/min, p = 0.9) did not differ significantly between the ASO and control groups. The estimated CFR was significantly lower in the ASO group (2.3 ± 0.9 vs. 4.9 ± 1.7; p = 0.0003) (Table 5), principally because of the high baseline volume in the ASO group.

Adenosine infusion. Heart rate and blood pressure did not change significantly after adenosine infusion in either the patient or control group. Peak APV increased significantly from baseline in both the patients and control patients (Table 4, Fig. 4). Estimated coronary flow volume at baseline tended to be higher in the ASO group, but this did not reach statistical significance (57.3 ± 36.3 ml/min vs. 26.7 ± 9.9 ml/min, p = 0.06). The peak CFR did not differ significantly between the groups (181.5 ± 198.1 ml/min vs. 133.6 ± 46.5 ml/min, p = 0.57). As for acetylcholine, the CFR was lower in the ASO patients (2.7 ± 1.5 vs. 5 ± 0.5; p = 0.002) (Table 6) because of the higher baseline values.

DISCUSSION

This study shows for the first time that the epicardial coronary arteries fail to dilate normally in response to an endothelium-independent vasodilator (nitroglycerin) in our young patients after ASO. Vasoreactivity is reduced not only in the proximal segment, but also in the mid and distal segments of the coronary arteries examined.

Table 3. Coronary Angiography: Quantitative Analysis of Vessel Diameter for Each Segment in the ASO Group

	Before Nitroglycerin (mm)	After Nitroglycerin (mm)	Percent Diameter (mean ± SD)	p
LAD				
Basal	2.3 ± 0.4	2.4 ± 0.4	5 ± 0.07	1
Middle	2.0 ± 0.3	2.1 ± 0.3	7 ± 0.10	0.57
Distal	1.9 ± 0.8	2.0 ± 0.1	7 ± 0.08	0.5
RCA				
Basal	2.2 ± 0.3	2.3 ± 0.2	4 ± 0.08	0.46
Middle	2.2 ± 0.4	2.2 ± 0.3	5 ± 0.06	0.79
Distal	1.9 ± 0.2	1.9 ± 0.3	7 ± 0.10	0.91

ASO = arterial switch operation; LAD = left anterior descending artery; RCA = right coronary artery; SD = standard deviation.

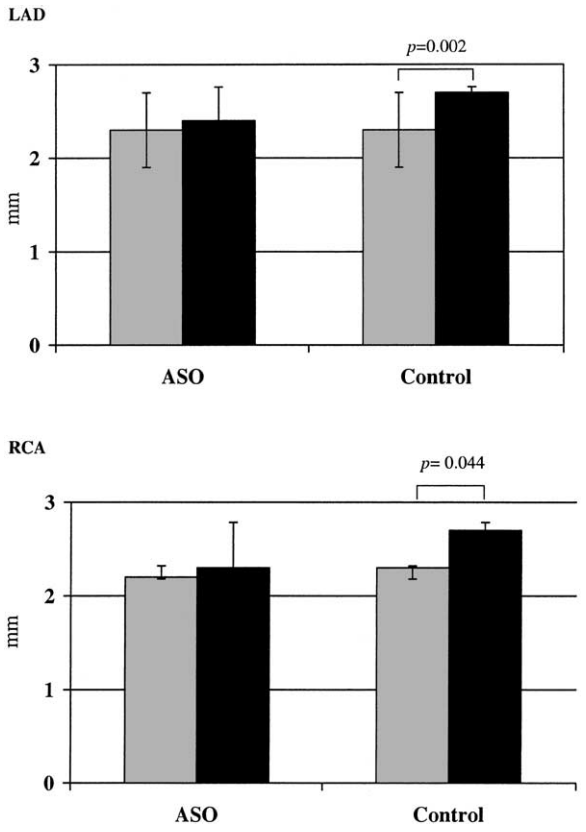

Figure 1. Bar graphs showing the mean diameters of left anterior descending (LAD) coronary artery **(top)** and right coronary artery (RCA) **(bottom)** before and after nitroglycerin in arterial switch operation (ASO) and control patients. **Gray bars** = before nitroglycerin; **black bars** = after nitroglycerin.

On the other hand, coronary flow velocity increased to levels equivalent to those seen in control patients and normal values reported in both pediatric (15) and adults patients (16,17) in response to either an endothelium-dependent or endothelium-independent vasodilator. With failure of normal dilation of the epicardial vessel, a normal increase in flow velocity does not imply a normal increase in

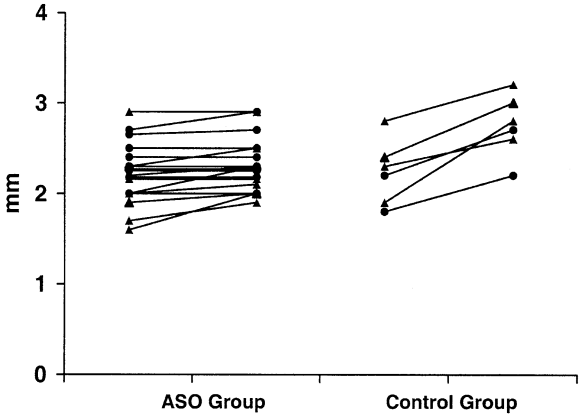

Figure 2. Plot of vessel diameter before and after nitroglycerin administration. The **dots** indicate the individual value of vessel diameter for both the ASO group **(left)** and the control group **(right)**. **Circles** = LCA; **triangles** = RCA.

Table 4. Intracoronary Doppler: Coronary Flow Velocity in ASO and in Control Groups

	ASO Group (n = 19)				Control Group (n = 6)			
	LAD (n = 9)		RCA (n = 10)		LAD (n = 4)		RCA (n = 2)	
Acetylcholine								
APV b (cm/s)	14.0 ± 1.0	p = 0.0001	17.8 ± 5.2	p = 0.004	12.3 ± 2.5	p = 0.011	18.5 ± 2.4	p = 0.043
APV p (cm/s)	36.7 ± 6.1		43.4 ± 4.7		34.4 ± 13.6		41.0 ± 14.0	
Adenosine								
APV b (cm/s)	17.7 ± 4.4	p = 0.0001	19.0 ± 6.4	p = 0.007	14.4 ± 4.4	p = 0.006	19.5 ± 3.9	p = 0.007
APV p (cm/s)	58.8 ± 14.6		55.0 ± 20.5		41.2 ± 13.4		46.8 ± 4.6	

APV = average peak velocity; other abbreviations as in Table 3.

flow volume. In fact, estimates of the CFR were significantly reduced for children after ASO compared with the control group. Thus, normal coronary flow reserve requires normal dilatory function of the epicardial conduit arteries as well as normal capacity of the resistance vessels. Abnormalities of either component can result in impaired CFR.

A prior study using a Doppler flow wire also showed a normal increase in flow velocity in response to vasodilators (9). On the other hand (5–8), CFR after ASO measured using PET scanning has consistently been lower than normal. We believe that our findings explain this apparent discrepancy. Similar to a study of CFR using PET scanning (6), the baseline coronary flow volume in our ASO patients tended to be higher than in control patients, although this difference was not statistically significant. The coronary flow volume, diameter, and velocity did not seem to be related to coronary anatomy. We have no explanation for the trend toward increased baseline flow volume detected in our patients.

Differences in coronary flow reserve between coronary arteries. Previous studies (9,18) have shown differences in coronary flow velocities between the two main coronary arteries under certain circumstances. For example, the RCA flow velocity at rest has been shown to correlate with systolic right ventricular pressure in children and with the extent of right ventricular hypertrophy (9). Also, left ventricular hypertrophy and increased left ventricular diastolic pressure affects the coronary flow velocity and CFR (18). Previous reports in adults with normal coronary arteries (16) found no differences among the three main coronary arteries. Our sample included only patients without ventricular hypertrophy and with normal ventricular filling pressures.

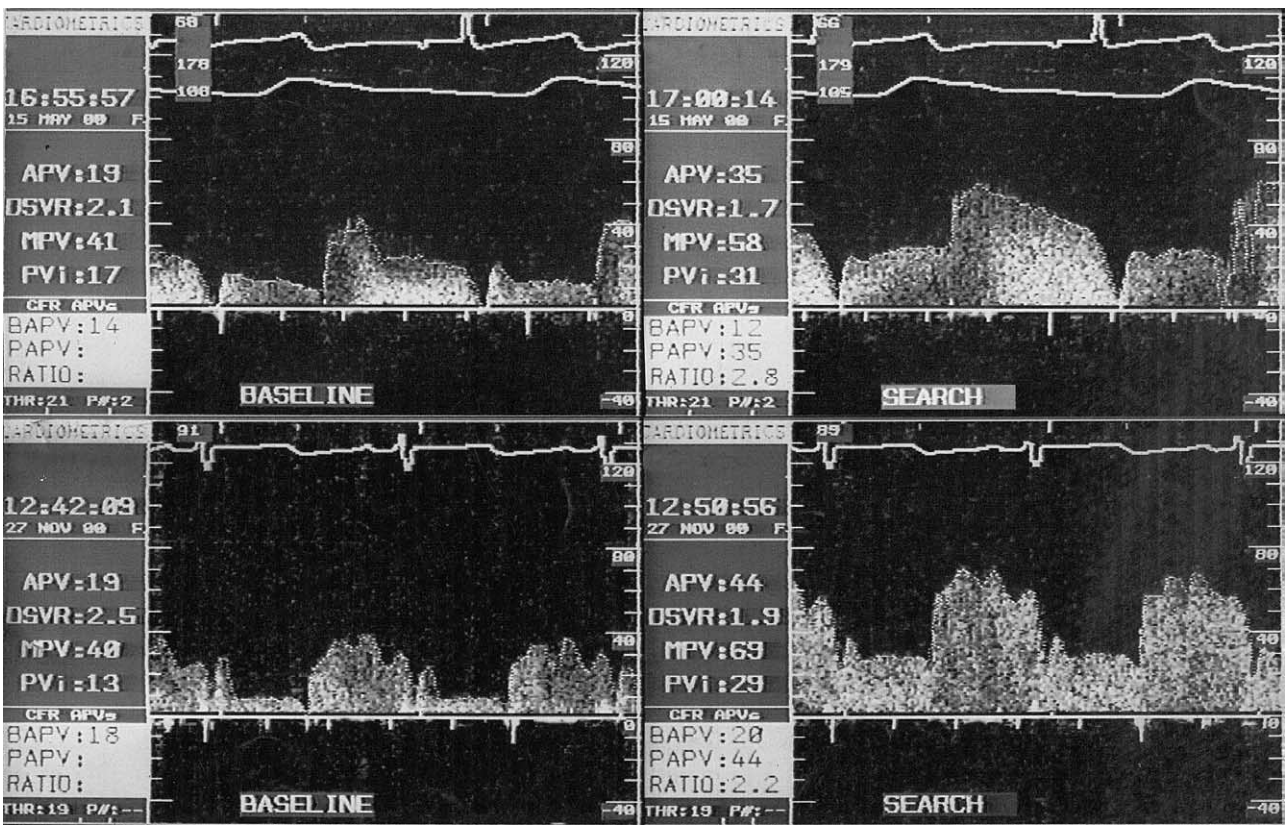

Figure 3. Flow profiles before **(left)** and after **(right)** intracoronary injection of acetylcholine in a patient after the arterial switch operation **(upper)** and in a control patient **(lower)**.

Table 5. Extrapolated Data for CFR Calculated With Administration of Acetylcholine

	CSA (mm^2)		Flow Volumes (ml/min)			
	Before NTG	After NTG	Before Ach	After Ach	CFR	
ASO group	6.4 ± 3.9	6.9 ± 5.2	51.4 ± 37.9	136.2 ± 143.7	2.3 ± 0.9	p = 0.002
Control group	3.8 ± 1.4	6.1 ± 1.4	26.2 ± 8.7	128.5 ± 49.7	4.9 ± 1.7	

Ach = acetylcholine; ASO = arterial switch operation; CFR = coronary flow volume reserve; CSA = cross-sectional area; NTG = nitroglycerin.

Mechanisms. We did not investigate the mechanisms for abnormal epicardial coronary artery function in these patients. However, at least two possible causes are apparent. First, there is denervation of the coronary arteries because they are explanted from the aortic root and re-implanted into the pulmonary root and the aortic root is transacted (1). Second, dissection of the proximal coronary arteries to permit transfer from the aortic root to the pulmonary root might lead to disruption of the blood supply to the vessels with scarring and restriction of dilatory capacity.

Arterial wall fibrosis. During the ASO, the proximal coronary arteries are dissected free from the underlying tissue for some distance along the length of the artery to permit transfer to the opposite arterial root. This could disrupt the vascular supply to the vessel wall with subsequent scarring and fibrosis (19). Even without vascular disruption, simply dissecting the vessel from surrounding tissue is likely to cause scar formation around the vessel. Such changes could explain the abnormal vasomotor function observed in our patients. However, this does not explain the abnormal vasoreactivity seen in the more distal segments of the vessels. One cannot exclude possible indirect effects of proximal scar on the distal portions of the artery, leading to negative remodeling of the epicardial vessels, as recently reported by an intracoronary ultrasound study (20).

Role of shear stress. Normal elastic arteries are constantly subjected to both acute and chronic changes in blood flow. Variation in the forces acting on the endothelium is responsible, in part, for the regulation of vascular tone. Studies by several groups have identified abnormal shear stress as a stimulus for development and progression of atherosclerosis (21–23). We suspect that the impaired vessel wall compliance and vasoreactivity, caused by denervation and/or direct vessel wall injury, alter intravascular hemodynamics producing abnormal patterns of flow and shear stress. Altered shear stress might lead to endothelial layer damage with preco-

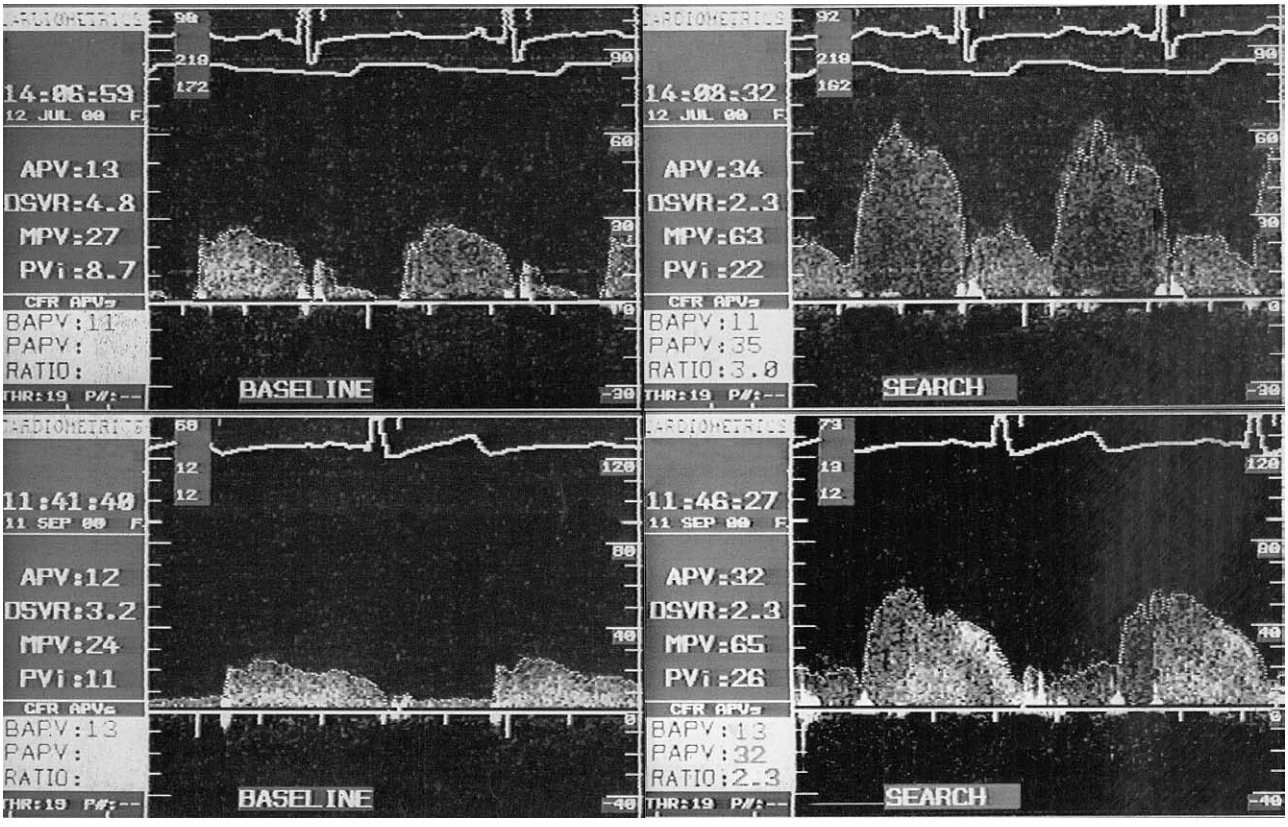

Figure 4. Flow profiles before **(left)** and after **(right)** intracoronary injection of adenosine in a patient after the arterial switch operation **(upper)** and in a control patient **(lower)**.

Table 6. Extrapolated Data for CFR Calculated With Administration of Adenosine

	CSA (mm^2)		Flow Volumes (ml/min)			
	Before NTG	After NTG	Before Adn	After Adn	CFR	
ASO group	6.4 ± 3.9	6.9 ± 5.2	57.3 ± 36.3	181.5 ± 198.1	2.7 ± 1.5	p = 0.0003
Control group	3.8 ± 1.4	6.1 ± 1.4	26.7 ± 9.9	133.6 ± 46.5	5 ± 0.5	

Adn = adenosine; other abbreviations as in Table 5.

cious development of intimal thickening (24) and negative remodeling (20).

Study limitations. The small number of cases constituting our control group is a limitation of the study. However, the data are tightly clustered and in agreement with previous studies in children (15,25) and adults (9,12). It would be difficult to justify extending this group because the intracoronary Doppler study in these children presents some risks.

Although our data showed impairment of dilation of the epicardial coronaries in the ASO group, there was some heterogeneity in the response to nitroglycerin. A small subset of the ASO group showed an increase in diameter similar to the control group, whereas the rest had essentially no change in diameter. There were no obvious differences between these two subsets, but the number of patients is small. Moreover, we did not investigate the morphology of vessel wall and further studies are needed to show the structure of the vessel wall.

The calculation of CFR was based on the assumption that different vasodilators produce similar changes in diameter. We calculated the baseline and post-dilation cross-sectional area of the vessel using the proximal luminal diameter before and after nitroglycerin, but we used the APV measured before and after adenosine and acetylcholine. Nitroglycerin is a more potent vasodilator then either acetylcholine or adenosine, so the CFR may have been overestimated.

All examinations were performed during general anesthesia, so the baseline coronary flow velocity could have been lower than under physiological conditions, with a consequent overestimation of the CFR by Doppler technique.

In addition, several limitations of measurement of CFR by intracoronary Doppler wire should be pointed out (26). It is unclear how closely administration of vasodilator drugs mimics physiological stress. This technique measures total flow reserve for each coronary vessel and does not reflect regional heterogeneity of flow reserve or differences between the subendocardial and subepicardial layers.

CONCLUSIONS

We have shown that after ASO the epicardial coronary arteries fail to dilate normally, even in response to a powerful stimulus such as nitroglycerin. Further studies are needed to explore mechanisms for the lack of vasodilatation using other vasodilators such as acetylcholine and verapamil. Also, intracoronary ultrasound would better define the morphologic aspects of the coronary wall.

This population of patients deserves close follow-up and more extensive investigation to understand the mechanisms involved in epicardial coronary artery dysfunction, the potential risks that it imposes, and methods for avoiding or treating this complication of the ASO.

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