Vascular Function in Children With Repaired Tetralogy of Fallot

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We compared the endothelial function and vascular wall characteristics of 11 children with tetralogy of Fallot (TOF) (age 13 ± 3 years) with the characteristics of 17 age-matched peers (12 ± 2 years). Echocardiographic Doppler measurements were performed under standardized conditions to assess (1) the carotid and femoral artery diameter and intima–media thickness, (2) brachial artery endothelial function using flow-mediated dilation, and (3) central and peripheral compliance using pulsewave velocity. In addition, the physical activity level was assessed using a validated questionnaire. We found that the physical activity level of the children with TOF was lower than that of the controls, but the difference did not reach statistical significance (4.5 vs 5.9 h/wk, p = 0.087). A significantly larger femoral artery intima–media thickness was observed in those with TOF, and the carotid and brachial artery diameter and intima–media thickness were comparable between groups. The children with TOF demonstrated a significantly lower brachial artery flow-mediated dilation than that of the controls. The central and peripheral compliance did not differ between the 2 groups. In conclusion, children with TOF demonstrated an impaired brachial artery endothelial function and increased intima–media thickness of the femoral artery compared to their healthy peers. In conclusion, our findings have, therefore, indicated that children with TOF, already at a young age, have changes in vascular function and structure. **(Am J Cardiol 2010;106:851–855)**

Endothelial dysfunction is an early marker for the development of atherosclerosis, which occurs before the clinical presentation of atherosclerosis. Also, artery wall thickening[1] and reduced compliance of the large and middle-size conduit arteries[2] are associated with an increased risk of developing cardiovascular disease. Previous studies have demonstrated that these vascular abnormalities can be present in children with comprised cardiovascular risk profiles, including children with familial hypercholesterolemia, renal disease, type 1 diabetes mellitus, and obesity.[3–8] To date, little is known about whether children with tetralogy of Fallot (TOF) demonstrate such changes in vascular function and structure. Because of the hemodynamic abnormalities and lower physical fitness evident in children with TOF,[9–11] we hypothesized that they would demonstrate impaired vascular function and structural adaptations in the artery wall.

Methods

The children eligible for participation in the study were selected from a database of the Department of Pediatric Cardiology and included patients with TOF who had undergone surgery from 1990 to 1999 at the Radboud University Nijmegen Medical Centre (Nijmegen, The Netherlands; Table 1). Patients with metabolic, neurologic, muscular, or orthopedic anomalies were excluded from the present study. Also, patients with syndromes with congenital heart defects as one of their features (including 22q11 microdeletions), heart failure (New York Heart Association class I or greater), resting cyanosis (oxygen saturation <90%), and familial hypercholesterolemia were excluded. Patients taking medication that affect vascular function were excluded (e.g., statins, diuretics). The siblings of these children were included as the control group. A total of 11 children with TOF and 17 control subjects were included. The local ethical committee approved the study, and the children and their parents provided written informed consent.

Vascular function assessments were conducted in a quiet, temperature-controlled environment. All children were requested to fast for 4 hours, abstain from caffeine, chocolate, dairy products, vitamin C supplements, and kiwi for 12 hours, and to avoid exercise for 24 hours. All tests were conducted by the same investigator with the subjects in the supine position. First, anthropometric measurements, including height, weight, and waist circumference, were collected. After a resting period of ≥10 minutes, the blood pressure was measured manually, and the oxygen saturation was measured. Subsequently, the vascular assessment was performed.

The vessel diameter and intima–media thickness (IMT) of the carotid artery (CA) and common femoral artery (CFA) were measured using ultrasonography with a high-resolution, 5- to 10-MHz linear array transducer (Picus, Esaote, Genoa, Italy). Images for the CA were obtained ~1.5 cm proximal to the bifurcation of the external and internal CA, and CFA measurements were performed ~2

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Table 1
Patient characteristics

Group	Gender	Age (y)	BMI (kg/m^2)	Waist (cm)	MAP (mm Hg)	SO_2 (%)	Surgery Type							Age at Surgery (mo)	Complications				
							TC	TPC	TAP	PV	LPA	BT	RVOT		RBBB	PI	TVI	LAD	PVS
TOF	Male	8	16.1	56	74	90	+	0	+	0	0	0	0	3	0	+	0	0	0
TOF	Male	9	15.6	60	71	100	+	0	+	0	0	0	0	2–8	+	+	+	0	0
TOF	Male	11	20.8	73	83	100	+	0	+	+	0	0	0	5–182	+	0	+	0	0
TOF	Male	12	16.6	65	83	99	0	+	0	0	0	0	0	7	+	0	0	+	0
TOF	Male	12	17.3	67	79	99	+	0	0	0	+	0	0	21–150	+	+	0	0	+
TOF	Male	15	17.2	66	79	99	+	0	+	0	0	+	0	5	+	+	0	+	0
TOF	Male	16	21.7	76	91	100	+	0	0	0	0	0	0	15	+	+	0	0	0
TOF	Male	17	19.2	74	81	100	0	+	0	0	0	0	+	5–70	+	0	0	0	+
TOF	Female	9	18.8	63	81	100	+	0	0	0	0	0	+	14	+	0	0	0	0
TOF	Female	14	21.9	71	85	98	+	0	+	0	0	0	0	13	+	+	0	0	0
TOF	Female	18	22.6	73	83	99	+	0	+	0	0	0	0	6	+	+	0	0	0
Control	Male	8	16.3	57.75	71	99													
Control	Male	9	17.9	65.75	79	100													
Control	Male	10	15.5	66	69	98													
Control	Male	11	15.7	59	71	100													
Control	Male	12	16.0	59	75	97													
Control	Male	14	19.3	67	73	98													
Control	Female	11	13.7	52.5	77	99													
Control	Female	11	15.6	55.75	71	100													
Control	Female	11	16.0	57	79	98													
Control	Female	11	20.7	71	81	100													
Control	Female	11	21.1	68.75	73	100													
Control	Female	12	16.5	56	76	100													
Control	Female	12	16.6	61.75	75	98													
Control	Female	13	16.5	60	75	100													
Control	Female	13	21.1	68	78	100													
Control	Female	14	20.2	67.5	83	100													
Control	Female	15	18.8	62.5	92	99													

BMI = body mass index; BT = Blalock-Taussig-shunt; MAP = mean arterial pressure; LAD = left anterior descending coronary artery; LPA = left pulmonary artery; PI = pulmonary insufficiency; RBBB = right bundle branch block; RVOT = right ventricle outflow tract; SO_2 = oxygen saturation; TAP = transannular patch; TC = total correction; TPC = transarterial/ transpulmonal correction; TVI = tricuspid valve insufficiency; PV = pulmonary homograft valve; PVS = pulmonary valve stenosis.

cm proximal of the bifurcation of the deep and superficial femoral arteries. The IMT and vessel diameter were analyzed using a custom-designed edge detection and wall tracking system that is independent of investigator bias. From each artery, 2 images were stored that contained 6 measurements of the IMT and diameter. IMT is expressed in absolute values and as the IMT/diameter ratio. In our laboratory, the measurement of the diameter and IMT has a coefficient of variation of 1% to 3% and 9% to 14%, respectively.[12]

The clinical evaluation of the endothelial function was performed using flow-mediated dilation (FMD), a nitric oxide-mediated endothelium-dependent vasodilation.[13,14] For the measurement of FMD of the superficial femoral artery and brachial artery, a rapid inflation/deflation pneumatic cuff was placed around the upper thigh and forearm, respectively, and inflated for 5 minutes to 220 mm Hg to block the arterial inflow. The reactive hyperemic response provides a measure of endothelial function.

When an optimal image was obtained, the probe was held stable, and the ultrasound parameters were set to optimize the images of the lumen–arterial wall interface (Terason 3000, Burlington, Massachusetts). A continuous Doppler velocity assessment was obtained simultaneously using the ultrasound machine and the lowest possible insonation angle (always $<60°$). The baseline scans of the vessel diameter and red blood cell velocity (1 minute) were followed by cuff inflation. Recordings of the diameter and velocity were obtained 30 seconds before cuff deflation and continued for 5 minutes (superficial femoral artery) and 3 minutes (brachial artery) thereafter.

An analysis of the pre- and postdeflation diameter and velocity signals was performed using custom-designed edge-detection and wall-tracking software that is largely independent of investigator bias.[15] Detailed descriptions of this analysis approach have been recently published.[16,17] From this synchronized diameter and velocity data, blood flow (the product of lumen cross-sectional area and Doppler velocity) were calculated at 30 Hz. The shear rate (an estimate of shear stress without viscosity) was calculated as 4 times the mean blood velocity/vessel diameter.[18] The baseline diameter and blood flow were calculated as the mean of the data acquired across the 1 minute preceding cuff inflation. The patterns of shear rate were also assessed by calculating the area under the curve for all the anterograde blood flow and shear and the area under the retrograde blood flow and shear recordings.

Table 2
Femoral, brachial, and carotid artery (CA) diameter

Variable	TOF	Controls	p Value
Central pulse wave velocity (m/s)	4.8 ± 0.8	4.6 ± 0.6	0.65
Peripheral pulse wave velocity (m/s)	6.7 ± 0.9	6.1 ± 1.1	0.20
Carotid artery			
Diameter (mm)	6.1 ± 0.5	6.0 ± 0.5	0.60
Intima–media thickness (mm)	0.45 ± 0.07	0.42 ± 0.05	0.15
Wall/lumen ratio	0.075 ± 0.011	0.071 ± 0.008	0.27
Femoral artery			
Diameter (mm)	6.4 ± 1.1	6.5 ± 0.6	0.79
Intima–media thickness (mm)	0.48 ± 0.09	0.41 ± 0.07	0.052
Wall/lumen ratio	0.075 ± 0.014	0.062 ± 0.011	0.027*
Brachial artery diameter (mm)	2.8 ± 0.4	2.9 ± 0.4	0.62

* Statistically significant.

FMD is expressed as the relative and percentage of increase from the baseline diameter. The interval to the peak diameter (in seconds) was calculated from the point of cuff deflation to the maximum diameter. In accordance with recent findings,[19,20] the shear rate stimulus responsible for endothelium-dependent FMD after cuff deflation is expressed as the area under the shear rate curve up to the point of maximum diameter for each subject using the trapezoid rule. The reproducibility of the FMD using this semiautomated software has a coefficient of variation of 6.7% to 10.5%.[21]

Pulsewave velocity: To assess the pulsewave velocity, the heart rhythm was recorded using a 3-lead electrocardiogram, and a Doppler waveform (Waki Loki, Atys Medical, Soucieu en Jarrest, France) was obtained in the CA, radial artery, and CFA. The distances were measured from the sternal notch to the site of measurement for the CA and radial artery and the CFA by way of the navel.[22,23] At least 10 cardiac cycles were recorded for analyses. From the interval between the R-wave on the electrocardiogram and the onset of the Doppler waveform of the arteries under investigation, the central and peripheral pulsewave velocities were calculated in a customized software program (Matlab, MathWorks, Natick, Massachusetts).

Questionnaire: After the vascular function assessment, the participating children were instructed to complete a comprehensive questionnaire on their physical activity level, physical fitness, and sports participation at home (modified Hemophilia and Physical fitness questionnaire for children 8 to 18 years).[24] We focused on the physical activity level (number of hours weekly that the children participated in sports activities and gymnastics, including the walking/biking time from home to school) and the rating of self-perceived fitness and health of the subjects (scale from 1 to 10).

Statistical analysis: Statistical analysis was performed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, Illinois). The data are reported as the mean ± SD. Student's *t* test was used to compare the differences between groups for characteristics, vascular parameters, and questionnaire results. Fisher's exact test was used to compare the gender distribution between the 2 groups. Statistical significance level was set at $p \leq 0.05$.

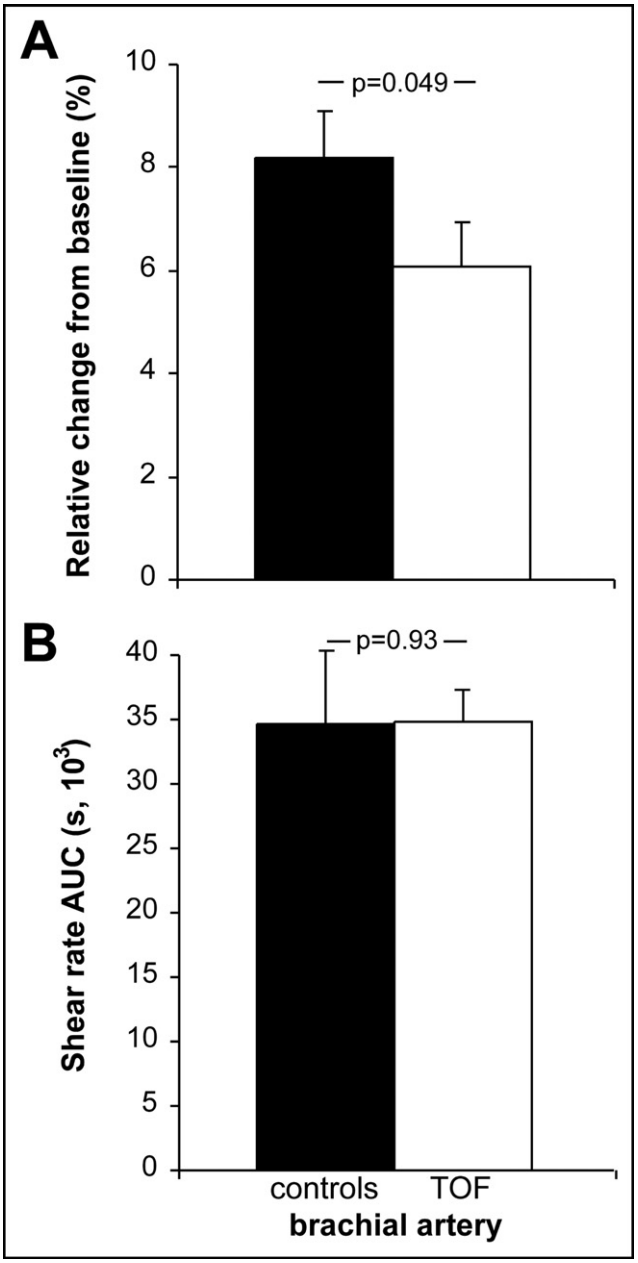

Figure 1. Brachial artery FMD in children with TOF and their age-matched controls. FMD presented as *(A)* relative change from baseline. *(B)* Shear rate area under the curve (SR-AUC) (i.e., eliciting stimulus for conduit artery dilation). Error bars represent SE.

Results

No differences were found between the children with TOF and the controls for age (12.8 ± 3.4 vs 11.6 ± 1.8 years, p = 0.25), body mass index (18.9 ± 2.5 vs 17.5 ± 2.3 kg/m^2, p = 0.14), gender (8 males and 3 females vs 5 males and 11 females; Fisher's exact test, p = 0.12), and oxygen saturation (98 ± 3% vs 99 ± 1%, p = 0.39; Table 1). Children with TOF had a larger waist circumference (68 ±

6 vs 62 ± 6 cm, p = 0.024), and greater blood pressure (81 ± 6 vs 76 ± 6 mm Hg, p = 0.037) than did the controls. In addition, children with TOF were less physically active than the controls (4.5 ± 1.6 hours/week vs 5.9 ± 2.4 hours/week; p = 0.087). Self-perceived fitness (7.5 ± 1.0 vs 7.8 ± 1.5; p = 0.5) and health (8.3 ± 1.1 vs 8.4 ± 1.2, p = 0.7) were similar between the children with TOF and the controls. The central and peripheral pulsewave velocity did not differ between the 2 groups (Table 2).

No differences between groups were found for the femoral, brachial, and CA diameter (Table 2). The femoral artery wall thickness was larger in those with TOF than in the controls, but this did not reach statistical significance (p = 0.052, Table 2). The CA wall thickness was similar between 2 groups (Table 2). The CA wall/lumen ratio was not different between the 2 groups, but the patients with TOF demonstrated a significantly larger femoral artery wall: lumen ratio (p = 0.027, Table 2).

Children with TOF had a significantly lower brachial artery FMD than did the controls (p = 0.049), and the eliciting shear rate stimulus for the FMD was similar between the 2 groups (p = 0.93; Figure 1).

Discussion

Children with TOF have impaired brachial artery endothelial function, greater blood pressure, larger waist circumference, and an increased wall/lumen ratio for the femoral artery compared to the age-matched controls. These adaptations in vascular function and structure are commonly associated with the development of atherosclerosis and future cardiovascular disease. A potential limitation of our report was the small group size. Also, our groups were not matched for gender. Although the findings from a subgroup of 8 age- and gender-matched pairs from our data set have confirmed our primary finding, future studies should examine further whether children with TOF develop cardiovascular disease at a younger age than their healthy peers.

Previous studies of children with a compromised cardiovascular risk profile, such as obesity, diabetes, or familial hypercholesterolemia, have found brachial artery endothelial dysfunction.[3,4] Impaired endothelial function is regarded as an integrative part of the atherosclerotic process and is predictive of future cardiovascular events.[25] The decrease in brachial artery endothelial function in children with TOF, therefore, suggests that these children have an increased risk of future cardiovascular disease. In addition, increased conduit artery wall thickness is related to increased cardiovascular risk.[1] We found that the femoral artery wall/lumen ratio is increased in those with TOF. Moreover, blood pressure and waist circumference, 2 established cardiovascular risk factors, were significantly greater in the TOF group than in the controls. Taken together, these differences in vascular function and physical characteristics suggest that children with TOF, already at an early age, have an increased risk of developing cardiovascular disease later in life.

The marked differences in vascular function between the 2 groups in our study raise questions about the potential mechanisms. Previous studies have demonstrated that exercise training is a potent stimulus to improve endothelial function in various groups (e.g., childhood obesity),[5,26] thereby reducing the risk of cardiovascular disease.[27] We found that children with TOF reported a lower physical activity level than their peers. Although the difference between the 2 groups did not reach statistical significance, this observation parallels unpublished data from our laboratory. Using an activity monitor, a lower physical activity level was found for 19 children with TOF compared to 18 age- and gender-matched controls (4.1 vs 4.5 METs, respectively, p = 0.01). The A decreased physical activity level might explain the impaired vascular function in children with TOF. The endothelial dysfunction in those with TOF might also relate to postoperative hemodynamic abnormalities, such as changes in transmural pressure,[28] flow patterns,[21,29] and oxidative stress.[30] The exact consequences of TOF on the hemodynamic characteristics of central and peripheral arteries, however, is unclear. Finally, a recent study found endothelial dysfunction in obese, but not lean, children after an arterial switch operation.[31] Endothelial dysfunction might therefore relate to differences in body composition. However, the body mass index was not different between the 2 groups, and we found no relation between the body mass index (or waist circumference) and endothelial function. This suggests that the lower FMD in children with TOF is not related to differences in body composition.

In contrast to the femoral artery, no differences were found for the CA wall/lumen ratio between the 2 groups. This suggests that thickening of the artery wall in those with TOF was site specific and that the arteries differ in their vulnerability to develop atherosclerosis. Also, older women have increased femoral artery wall thickness, with preserved CA wall thickness, compared to younger women.[27] A recent study found that endothelial dysfunction predicts the 6-year progression in wall thickness.[32] This might explain why we and others (in children with familial hypercholesterolemia[26]), found impaired endothelial function but preserved artery wall thickness. This suggests that site-specific changes in wall thickness occur, irrespective of changes in endothelial function.

Central and peripheral vascular compliance was preserved in children with TOF. This finding can be explained by the order of events that eventually lead to the clinical manifestation of atherosclerosis. Advanced age leads to impaired brachial artery endothelial function[33] and increased femoral artery wall thickness in women,[29] but the peripheral compliance in older women is preserved.[34] Children with Fabry's disease (i.e., a lysosomal storage disorder associated with low physical fitness)[35] also show impaired brachial artery endothelial function but preserved central arterial compliance.[36]

A growing number of children with TOF reach adulthood and will face problems unrelated to the anatomic abnormalities. The impaired vascular function suggests the presence of increased cardiovascular risk in children with TOF. This should be realized in the clinical management, especially when children with TOF reach adulthood. Moreover, this observation raises questions about treatment strategies to improve endothelial function. Exercise training has various beneficial effects on endothelial function and cardiovascular risk.[37,38] Although decisions should be made on

an individual basis, the lower physical activity level in children with TOF suggests that exercise training and an active lifestyle can be effective to improving and/or preserving vascular function.

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