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ORIGINAL ARTICLE

Effects of Pulmonary Regurgitation on Distensibility and Flow of the Branch Pulmonary Arteries in Tetralogy of Fallot

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Abstract Significant pulmonary regurgitation (PR) after repair of tetralogy of Fallot (TOF) may affect flow in the pulmonary artery (PA) side branches. We sought to assess flow changes and distensibility of the PA side branches *in vivo* and test correlation with the degree of PR and right-ventricular (RV) dilatation. Thirty patients after TOF repair and 16 controls underwent cardiovascular magnetic resonance for quantification of RV volumes and measurement of flow in the PA side branches. RV volumes and function, blood flow volumes, and cross-sectional area of the main, left (LPA), and right (RPA) PA were measured and regurgitant volumes and distensibility calculated. Results were compared between the LPA and the RPA and between patients and controls. Median regurgitation fraction of PR was 41 % (range 22–60 %). Regurgitant fraction was greater in the LPA (40 %) than in the RPA (29 %), resulting in lower net flow into the LPA ($p < 0.001$). LPA area was significantly greater than that of the RPA (303.9 vs. 232.7 mm^2/m^2) ($p < 0.0001$). The LPA showed lower distensibility than the RPA (39 vs. 44 %). PA side branch distensibility correlated with MPA regurgitant volume ($p = 0.001$), MPA regurgitant fraction ($p = 0.001$), and RV end-diastolic volume ($p = 0.03$). PA side branches have greater distensibility in patients with PR than in normal subjects. Significant PR leads to changes in flow profile and distensibility of the PA side branches. The LPA shows greater regurgitant volume and greater area but lower distensibility than the RPA.

Keywords Tetralogy of Fallot · Pulmonary regurgitation · Pulmonary arteries · Distensibility

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Background

Pulmonary regurgitation (PR) is a frequent finding in patients after repair of tetralogy of Fallot (TOF). Disruption of the pulmonary valve annulus or transannular patch enlargement at the time of surgery has been identified as the most common reason for PR [9, 18]. Although PR is usually well tolerated in the short term, long-term sequelae often start in young adulthood and may lead to right-ventricular (RV) dysfunction, exercise intolerance, and ventricular arrhythmias associated with sudden cardiac death [6, 8, 9, 17, 18, 25].

In the presence of significant PR, flow changes may extend into the right (RPA) and left (LPA) branches of the pulmonary artery (PA). Distensibility of the PAs has been investigated by cardiovascular magnetic resonance (CMR) in healthy adults [2, 20]. The use of velocity-encoded phase contrast cine CMR (PC cine CMR) has been extensively validated for overall vascular flow quantification, for quantitative assessment of PR in patients after TOF repair [11, 22], as well as for characterising blood flow in the PA side branches [24]. To the best of our knowledge, no data exist on distensibility of the PA side branches in the presence of PR. Because distensibility and flow volume within a vessel can be simultaneously measured by PC cine CMR, we used this technique for investigating

characteristics and correlation between both entities *in vivo* and noninvasively. We hypothesized that the increased flow volume associated with PR alters distensibility of the LPA and the RPA. The aim of this study was to describe and correlate flow patterns and distensibility of the PA side branches in the presence of significant PR using PC cine CMR.

Methods

Subjects

Thirty patients with significant PR who underwent CMR examination in our institution were included in the study (PR group). Significant PR was defined as regurgitation fraction >20 % as measured in the MPA by PC cine CMR. Exclusion criteria were anatomical narrowing of the main, RPA, or LPA and/or asymmetric lung perfusion, which was defined as a blood flow ratio between the RPA and the LPA >60–40 %. Sixteen patients undergoing CMR examination for other reasons, in whom right heart pathology and anomalies of the PAs had been excluded, formed the control group. Informed written consent was obtained from the patients or their legal guardian. Our Institutional Research Board approved the study.

Technique

CMR examinations were performed using a 1.5-Tesla scanner (SignaHDx; GE Medical Systems, Milwaukee, WI) with an eight-channel phased-array cardiac coil. After obtaining coronal, axial, and sagittal localizers, cine steady-state free precession images were acquired in horizontal and vertical long-axis planes of the right and the left ventricle as well as in short-axis plane covering both ventricles as previously described [4]. PC cine images were acquired perpendicularly (through-plane) to the MPA, LPA, and RPA. Blood flow was measured in the MPA midway between the pulmonary valve and the bifurcation and in the RPA and LPA midway between the bifurcation and the origin of the first segmental branch of each vessel. PC cine CMR was acquired with the following parameters: echo time 4.2 ms, repetition time 7.7 ms, flip angle 15°, slice thickness 4 mm, velocity encoding 200 cm/s (if aliasing occurred it was increased to 250 cm/s), number of averages (NEX) 1, views/segment four to six depending on the heart rate, retrospective gating, and 20 reconstructed cardiac phases. Each set of images was acquired during one breath hold of 10- to 12-s duration. Potential phase offset errors were corrected by using a static phantom; by repeating each PC cine CMR acquisition with the same acquisition parameters at exactly the same location within the magnet; and with equivalent simulated heart rate [14].

Image Analysis

The acquired images were postprocessed on a separate workstation (SUN Microsystems, Mountainview, CA) using cardiac-dedicated software (Advantage Window, MASS Plus and FLOW, version 4.0; Medis Medical Imaging Systems, Leiden, Netherlands).

Ventricular volumes were calculated by using the MASS+ software package (Magnetic Resonance Analytical Software System, version 4.0; Medis) as previously described [4, 15].

Blood flow measurements were performed using flow analysis software (FLOW, version 4.0; Medical Imaging Systems). The area of each vessel was first outlined using semiautomatic contour detection on the anatomical and flow images in all cardiac phases. The generated contours were then thoroughly checked for any errors and manually corrected according to the vessel border visualized on the magnitude image, particularly in cases in which a close additional vascular structure needed to be excluded from the region of interest. The flow volume was then calculated by multiplying the outlined cross-sectional area of each phase by the mean velocity of each pixel contained in the area [21, 22].

From the obtained velocity-time curves, the following parameters were calculated for the MPA, RPA and LPA: positive forward flow volume, regurgitant flow volume, net forward flow volume (positive forward flow volume − regurgitant flow volume), RPA/LPA flow ratio [net forward flow volume/(net forward flow volume LPA + net forward flow volume RPA)], and regurgitant fraction (regurgitant flow volume/forward flow volume). LPA and RPA maximum and minimum cross-sectional areas were outlined, and fractional area change ($A_{max} - A_{min}$)/A_{max}, which represents distensibility, was calculated.

Intraobserver and interobserver variability was calculated for 10 subjects of the PR group. Intraobserver variability was determined by comparison of blood flow volume measurements by one observer (E. M. V.) on two separate occasions at least 3 months apart. Interobserver variability was assessed by comparing the results of two independent observers (E. M. V. and E. R. V.).

Statistical Analysis

All haemodynamic parameters were normalized to body surface area (BSA). Continuous data are expressed as median (range) values. Nonparametric tests were used because not all parameters were normally distributed. The significance of differences between paired variables within the patient or the control group was analyzed using Wilcoxon signed rank test; significance of differences between unpaired variables was tested using Mann–Whitney *U*-test. Spearman correlation was used for assessing the

Table 1 Cardiac diagnosis and technique of surgical repair

Diagnosis	*N*
TOF	25
Pulmonary valve stenosis	3
Double-outlet right ventricle	1
Ventricular septal defect	1
Surgical procedure	**N**
Transannular patch enlargement	13
Comissurotomy with RVOT patch or infundibulectomy	8
Homograft monocusp	5
Ventricular septal defect closure	1
RV–PA graft	1
Unknown procedure	1

RVOT RV outflow tract

relationship between distensibility of the PAs and the regurgitant volume and regurgitant fraction. Linear regression was the best model fitting the correlation between distensibility and regurgitant volume or regurgitant fraction. A p-value <0.05 was considered to be statistically significant. A regression model was defined to be best by analysis of r^2.

Intraobserver and interobserver variability was determined by calculating the mean difference (SD) and the limits of agreement between measurements [1]. Sensitivity and specificity of RPA and LPA measurements for predicting PR severity was calculated by receiver operator curve analysis. Statistical analysis was performed with Prism software (version 4.03 [2005] GraphPad Software, San Diego, CA) and SPSS for Windows (release 16.0.1.2007; SPSS, Chicago, IL).

Results

Thirty patients (17 male) and 16 controls (8 male) were enrolled in the study. The median age in the PR group was 18.1 years (range 0.7–64.0); the median weight was 56.5 kg

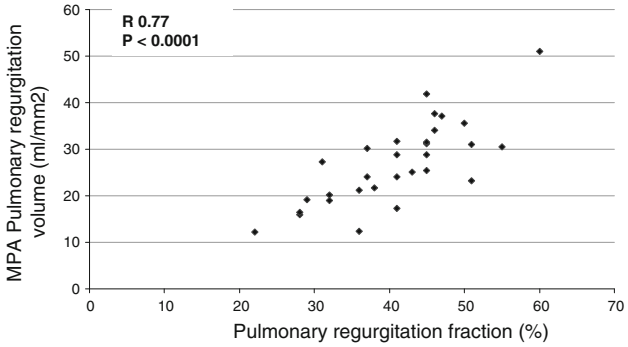

Fig. 1 Correlation between regurgitant volume and regurgitant fraction in the MPA

(range 7.7–85.0); and the median BSA was 1.6 m^2 (range 0.4–2.1). The median age of the control group was 15.3 years (range 7.4–53.8); the median weight was 53.3 kg (range 21.5–90.0); and the median BSA was 1.5 m^2 (range 0.8–2.1). Age, weight, and BSA did not differ significantly between the two groups. Exact diagnosis and surgical technique used for TOF repair are listed in Table 1. Median age at time of repair was 2 years (range 0–39). Time interval between surgery and the CMR examination was 15 years (range 0–53). One patient had previously undergone catheter-guided valvuloplasty of isolated pulmonary valve stenosis.

Flow Volume

In the patient group, PR was moderate to severe, with a MPA regurgitation fraction of 41 % (range 22–60 %) and regurgitant volume of 26.4 ml/m^2 (range 12.2–51.0) (Fig. 1). Flow volumes in the RPA and LPA are listed in Table 2. In the PR patients, the forward flow volume was symmetrical in the RPA and LPA. In the LPA, the regurgitant volume and fraction were greater and the net flow volume significantly lower than in the RPA. In controls, a significant difference in LPA and RPA forward flow and net flow volume was observed. The differential net LPA/RPA flow ratio was similar and within the normal range in

Table 2 Comparison of flow volumes in the LPA and RPA between patients and controls

Flow volumes (ml/m^2)	Patients		Controls	
	LPA	RPA	LPA	RPA
Forward flow	30.4 (15.6–43.7)$^{\dagger\dagger a}$	31.6 (20.3–49.8)†	20.9 (13.9–31.5)*$^{\dagger\dagger b}$	23.5 (16.1–36.1)*†
Regurgitant flow	12.1 (4.5–22.3)*††	9.0 (4.6–27.8)*††	0.1 (0–0.9)*††	0 (0–0.3)*††
Regurgitant fraction (%)	40.0 (20–59)**††	29.5 (16–59)**††	1.0 (0–4)*††	0.0 (0–1)*††
Net flow	18.8 (11.0–28.0)**	22.2 (13.8–36.1)**	20.6 (13.9–31.3)*	23.3 (16.1–36.1)*
Net flow ratio (%)	45.5 (38–52)**	54.5 (48–62)**	46.5 (36–54)*	53.5 (46–64)*

[a] p-values comparing patients with controls († $p < 0.05$, †† $p \leq 0.001$)

[b] p-values within same group (* $p < 0.05$, ** $p \leq 0.001$)

Table 3 Comparison of area and distensibility of the LPA and RPA between patients and controls

Area (mm/m^2)	Patients		Controls	
	LPA	RPA	LPA	RPA
CSA maximum	303.9 (160.4–501.4)$^{**\dagger\dagger ab}$	232.7 (138.0–431.0)**††	162.0 (133.7–205.2)††	174.6 (113.5–306.7)††
CSA minimum	174.3 (88.1–373.6)**††	125.0 (87.6–282.8)**	112.2 (84.8–153.9)††	118.1 (71.1–212.8)
Distensibility (%)	39.3 (21.0–58.8)*††	43.7 (12.1–58.2)*††	28.2 (15.8–36.6)*††	34.5 (19.1–44.0)*††

CSA cross-sectional area

[a] *p*-values within same group (* $p < 0.05$, ** $p \leq 0.001$)

[b] *p*-values comparing patients with controls († $p < 0.05$, †† $p \leq 0.001$)

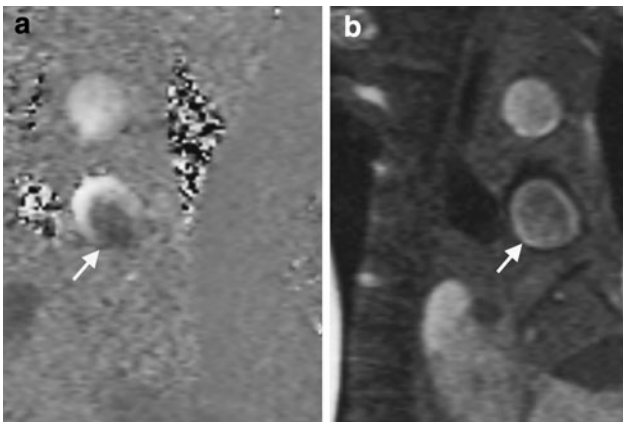

Fig. 2 Phase contrast images of the cross-section of the LPA (*arrow*). The phase image **a** shows an inhomogenous flow distribution within the LPA with forward (*white*) and backward (*black*) flow occurring simultaneously

both groups [24]. Both forward and regurgitant flow were significantly greater in the PR group than in controls; in contrast, net flow volume was similar in both groups.

Area and Distensibility

Cross-sectional areas and distensibility of the RPA and LPA are listed in Table 3. The RPA and LPA were larger in PR patients than in controls, except for the minimal cross-sectional area of the RPA, which was similar in both groups. LPA and RPA distensibility was significantly greater in the PR group than in the control group.

In the PR group, the LPA maximal and minimal cross-sectional areas were significantly greater than those in the RPA. RPA distensibility was greater than LPA distensibility in both groups.

RV Volumes

RV volumes were significantly greater in the PR group, with a median RV end-diastolic volume of 157.9 (range 87.4–254.7) versus 86.8 ml/m^2 (range 63.4–118.7) in the control group ($p < 0.001$). RV end-systolic volume was 78.3 (43.3–154.7) versus 36.0 ml/m^2 (15.1–59.2) ($p < 0.001$), with the latter being within previously published normal values [15].

Correlation

LPA distensibility correlated with LPA regurgitant volume ($r = 0.56$, $p = 0.001$), LPA regurgitant fraction ($r = 0.57$, $p = 0.001$), MPA regurgitant volume ($r = 0.53$, $p = 0.002$), MPA regurgitant fraction ($r = 0.45$, $p = 0.01$), and RV end-diastolic volume ($r = 0.40$, $p = 0.03$). Similarly, RPA distensibility showed a positive correlation with RPA regurgitant volume ($r = 0.57$, $p = 0.001$), RPA regurgitant fraction ($r = 0.46$, $p = 0.01$), MPA regurgitant volume ($r = 0.48$, $p = 0.007$), and RV end-diastolic volume ($r = 0.57$, $p < 0.001$).

Prediction of PR

An LPA pulsation >36 % was predictive for significant PR (MPA regurgitant volume >20 ml/m^2) with a sensitivity of 74 % and a specificity of 94 %. RPA pulsation >41 %

Table 4 Interobserver and intraobserver variability of area measurements

Interobserver variability				Intraobserver variability		
Area (mm^2/m^2)	Mean difference	Limits of agreement	Coefficient of variability	Mean difference	Limits of agreement	Coefficient of variability
LPA	−5.6	−55.6 ± 44.4	0.074	−0.6	−23.2 ± 22.1	0.032
RPA	−3.1	−46.2 ± 39.9	0.075	4.9	−9.7 ± 19.6	0.025

predicted significant PR with a sensitivity of 61 % and a specificity of 94 %.

Reproducibility

Intraobserver and interobserver variability of the area measurements is listed in Table 4. Intraobserver variability had a coefficient of variability of 3.2 % for the LPA and 2.5 % for the RPA. The coefficient of variability for interobserver variability was 7.4 % for the LPA and 7.5 % for the RPA.

Discussion

Long-term PR causes RV dilatation, RV dysfunction, and associated comorbidities, such as arrhythmias, which may lead to a cardiac event or even sudden death [8, 9]. In addition to the detrimental effects of PR on RV function, some changes of flow properties occurring in PA side branches have been also reported [12, 13, 27]. This study provides new information on flow characteristics, size, and distensibility of the PA side branches in the presence of PR as measured accurately and reproducibly *in vivo*. We could demonstrate a correlation between PA side branch distensibility and the degree of PR and RV dilatation. Our data provide advanced pathophysiological understanding of these complex mechanisms. In addition, values of cross-sectional area and distensibility, because they can be measured for the RPA in the suprasternal view, may have the potential to be used as an additional echocardiographic parameter for estimation of the severity of PR.

Regurgitant flow volume is determined by the function of the pulmonary valve, the pulmonary vascular resistance, the diastolic RV compliance, and the diastolic filling time [23]. Subtle pressure changes in the pulmonary circulation may have significant effects on the amount of PR volume [23]. It has been shown that late after surgery, RV diastolic dysfunction is related to a smaller amount of pulmonary regurgitant flow volume and may protect against the secondary effects of long-lasting PR [7]. Thus RV dilatation may not necessarily always correlate with the severity of PR [3]. The relationship between PR fraction and absolute regurgitant volume is variable; in fact, patients with relatively normal RV volume and relatively modest absolute volume of regurgitation may have identical regurgitant fraction compared with patients having a dilated RV, greater stroke volume, and greater regurgitant volume [26]. We found a similar relationship between regurgitation fraction and regurgitant volume (Fig. 1), not only in the MPA, but also in the side branches, where our data show a better correlation between distensibility and regurgitant volume than with regurgitant fraction.

Kang et al. [13] assessed the contribution of each individual PA to total regurgitant flow and found that regurgitation from the LPA is far more significant than regurgitation from the RPA, in some cases accounting for $\leq$90 % of the total regurgitant volume. Our data confirm this important observation and show that the slightly lower net flow in the LPA than in the RPA is determined by a greater regurgitant flow volume and not by decreased forward flow volume into the LPA. Possible explanations for this observation can be the peculiar geometry of the PA bifurcation and the smaller left lung volume with greater LPA impedance. Chaturvedi and Redington postulated that delicate changes in vascular impedance by an enlarged right ventricle may lead to increased vascular resistance in the left lung and cause increased backward flow [5, 12, 23].

Flow Profiles

Analysis of PA side branch flow volumes and velocities suggests the presence of a different flow profile in the RPA and LPA in patients with reconstructed RV outflow tract and PR. We found significantly greater peak velocities in the LPA than in the RPA. Moreover, qualitative analysis of the flow-encoded PC cine images showed a more laminar flow profile in the RPA and a more inhomogeneous flow profile with forward and backward flow occurring simultaneously in the same cross-sectional area of the LPA (Fig. 2). These findings are suggestive for the presence of vortex flow in the LPA. The peculiar geometry of pulmonary bifurcation with a steeper angle of the LPA, in combination with the increased RV stroke volume in the presence of PR, could be the logical explanation for such turbulent flow. Recent investigations using four-dimensional (4D)-MR flow analysis helped to demonstrate such complex flow characteristic of the pulmonary bifurcation [10]. Upcoming CMR techniques, such as 4D-MR flow, and larger studies in TOF patients may better elucidate this particular aspect in the future [16].

Turbulent flow may be an additional cause for LPA enlargement. Interestingly, similarly to Kang et al. [13], our data confirm that the size of the PA side branches is not predictive of net forward flow volume.

Distensibility

Distensibility of a vessel is determined by wall elasticity and by changes in loading and pressure conditions. The increased distensibility of the RPA and of the LPA in presence of significant PR results mainly from intravascular volume changes. If the wall properties are normal during systole, the vessel enlarges (maximal area) to accommodate the increased stroke volume. At end diastole, i.e., at the end of the regurgitant period, no significant size

difference (minimum area) is expected between patients and controls as it was observed for the RPA. In contrast, the LPA remained enlarged throughout the cardiac cycle, i.e., also at the end of diastole, suggesting that the LPA may not be instantaneously stretched during systole but that LPA dilatation may result from different vessel growth. Although in normal subjects the dimension of the LPA and RPA are similar, in patients with long-standing PR the chronic increased intravascular pendel volume/cardiac cycle and the turbulent flow, both more marked in the LPA, may represent an additional stimulus for vascular growth.

The increased maximum and minimum areas of the LPA coincide with a lower distensibility compared with the RPA. An equal absolute distension (area change) of LPA and RPA (p 0.09), despite significantly greater regurgitation volume and regurgitant fraction in the LPA, is an additional indicator of decreased compliance. This is in accordance with the findings of Patel et al. [19], who described that the more the arterial wall is stretched from its natural size, the stiffer the vessel and the lower its distensibility becomes. Such a model suggests that with increasing vessel enlargement, pulsation strives toward a boundary.

Limitations

The retrospective character of the study did not allow optimization of some sequence parameters, such as temporal resolution. Improved temporal resolution may have enabled more detailed information about flow/time curves in the PAs.

The size of the patient group was limited by the fact that all patients who presented with peripheral PA stenosis or PA hypoplasia and asymmetrical lung perfusion were excluded from the study. In fact, it is well known that presence of peripheral narrowing in a PA tends to increase the amount of regurgitant volume from the same vessel [5, 12]. Future prospective studies may help to test the utility of our observations and their potential for translation into the echocardiographic assessment of patients with PR.

Conclusion

In the presence of significant PR, flow velocity and volume profiles are altered in the PA side branches. Regurgitant volume is significantly greater in the LPA than in the RPA. Distensibility of both PA side branches is increased compared with that of normal controls. LPA shows greater size but lower distensibility than does the RPA. In both PA side branches, distensibility correlates with the degree of regurgitant fraction and regurgitant flow volume through the pulmonary valve as well as RV dilatation.

Conflict of interest The authors declare that they have no competing interests.

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