Incremental Value of Cardiac Magnetic Resonance for Assessing Pulmonic Valve Regurgitation

Michael Zdradzinski[2], Rachel Elkin[2], Stephen Hart[3], Scott Flamm[1], Richard Krasuski[4]

[1]Cleveland Clinic Foundation, Cleveland, Ohio, [2]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, [3]Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, [4]Duke University Medical Center, Durham, USA

Background and aim of the study: **Cardiac magnetic resonance (CMR) is the 'gold standard' for quantifying pulmonic regurgitation (PR) in adults with congenital heart disease, but remains costly and is less readily available than echocardiography. Qualitative echocardiographic assessment of PR is challenging, and guiding criteria are limited. It is unknown if echocardiography is sufficient to screen for significant PR. The study aim was to determine whether cardiac MRI provides additional benefit in the assessment of PR in adults with congenital heart disease.**

Methods: **Patients with repaired tetralogy of Fallot or congenital pulmonic stenosis after valvotomy undergoing transthoracic echocardiography and CMR with no interval intervention were identified from a prospective registry. Patients with greater than mild pulmonic stenosis, residual ventricular septal defect or poor echocardiographic windows were excluded. Whole-cohort and subgroup (tetralogy of Fallot versus pulmonic stenosis) analyses for inter-modality agreement were performed.**

Results: **A total of 48 patients (24 men, 24 women; mean age 43 ± 12 years) was included in the analysis. The unweighted kappa value for the two modalities was 0.30, suggesting 'fair' agreement, though only 52% had matching PR assessments. The indexed right ventricular end-systolic volume (RVESVi) correlated closely with cardiac MRI-monitored PR (p = 0.011 by analysis of variance), but not with that monitored with echocardiography (p = 0.081). Subgroup analysis demonstrated less inter-modality agreement in the tetralogy of Fallot population (kappa 0.25) than in the pulmonic stenosis population (kappa 0.35).**

Conclusion: **CMR measurement of PR correlates closely with the RVESVi, and appears superior to echocardiography when assessing patients at risk for PR. The study results suggest a vital role for CMR whenever significant PR is suspected in the adult congenital heart disease population.**

The Journal of Heart Valve Disease 2015;24:

Advances in the surgical, catheter-based, and medical management of congenital heart disease have led to a dramatic increase in the prevalence of adults with repaired congenital heart disease (1,2). This unique population requires regular follow up and surveillance imaging to monitor for and treat the long-term sequelae of their diseases and subsequent repairs. Both, tetralogy of Fallot repair and valvotomy for pulmonic stenosis often lead to pulmonic regurgitation (PR), which can result in progressive right heart dilatation and failure (3-10). Cardiac magnetic resonance (CMR) is considered the 'gold standard' for quantifying PR in adults with congenital heart disease (5,6,11-14). Additionally, CMR is employed to assess residual conduits, ventricular size and function, regional wall motion abnormalities, and myocardial scar and fibrosis in the repaired tetralogy of Fallot population (15-21). Despite these clear benefits, CMR is considered to be more costly and less available than echocardiography, and for these reasons echocardiography is often employed in lieu of CMR to monitor for PR and other consequences of tetralogy of Fallot repair. The qualitative echocardiographic assessment of PR is challenging and operator-dependent, and guiding criteria are limited. The reliability of echocardiography as a longitudinal screening tool for this population is controversial,

Address for correspondence:
Richard A. Krasuski MD, DUMC 3012, Duke University Medical Center, Durham, NC 27710, USA
e-mail: Richard.krasuski@duke.edu

with conflicting results in previous studies (22-26). The aim of the present study was to determine whether echocardiography alone is sufficient to screen for PR in adults with prior surgical interventions to the right ventricular outflow tract.

Clinical material and methods

Patients

In this observational cohort study, candidates were identified from a prospective database of patients who were newly referred between July 2005 and June 2012 for the evaluation of PR involving their native valve after prior surgical repair of tetralogy of Fallot or congenital pulmonic stenosis. This database excluded patients with greater than mild pulmonic stenosis or residual ventricular septal defects. Additionally, patients with major cardiac malformations, including double-chambered right ventricle, transposition of the great vessels, atrioventricular canal-type defects, or anomalous pulmonary venous return were excluded.

Of the 109 patients in the database, 61 were excluded from this analysis, including 14 for poor echocardiographic windows, 12 with contraindication to CMR, and 35 for incomplete data. Each of the 48 candidates included in the study underwent both transthoracic echocardiography (TTE) and CMR without interval intervention, and complete data were available from each imaging modality.

Approval to conduct the study was obtained from the Institutional Review Board of the Cleveland Clinic.

Data acquisition

Information was abstracted from the database and augmented by a thorough review of the electronic and paper medical records. This included baseline demographics, cardiac medical and surgical history, and echocardiographic and CMR data.

Echocardiographic assessment of PR severity was determined by the imaging report listed in the medical record. Echocardiographic PR severity was graded as 0 (none), 1+ (mild), 2+ (moderate), 3+ (moderate-severe) and 4+ (severe) (27). Cardiac MRI assessment of PR severity was based on the reported regurgitant fraction, calculated using a phase-contrast analysis of pulmonary artery flow. Severity was graded by regurgitant fractions: <20% mild, 20-29% moderate, 30-39% moderately severe, and ≥40% severe. In cases of >1 grade of disagreement between the two modalities, the echocardiographic and CMR images were reviewed by the investigators and an independent, blinded observer to ensure that no systemic error or interpreter bias was the cause of disagreement.

Data analysis

Baseline demographic and comorbidity data were described using mean ± SD or median and interquartile range, as appropriate. A table was constructed to analyze the agreement of PR on severity between the two modalities. Inter-modality agreement was assessed by unweighted kappa statistic (28-30). Categorical PR severity by each modality was compared to the indexed right ventricular end-systolic volume (RVESVi), using an analysis of variance. The pulmonary regurgitant fraction by CMR was then compared to the RVESVi using linear regression modeling.

Finally, data were stratified into subgroups based on congenital diagnosis (tetralogy of Fallot or pulmonic stenosis). Kappa statistic and comparisons between PR severity and RVESVi were repeated for each subgroup and compared.

Statistical analysis

Comparison statistics were performed using Student's *t*-test, Fisher's exact test and Wilcoxon rank-sum test, as appropriate. For all tests, a p-value <0.05 was considered to be statistically significant. Data analysis was performed using JMP Pro software (SAS Institute Inc.; version 10.0.2).

Results

A total of 48 patients (26 tetralogy of Fallot, 22 pulmonic stenosis) was included in the study. There were 25 unique echocardiographic interpreters and four CMR interpreters. The patient population characteristics are summarized in Table I. Patients underwent imaging and evaluation at an average of 34.4 ± 9.8 years after corrective surgery. The group demonstrated, on average, moderately severe PR by both echocardiogram and CMR (pulmonic regurgitant fraction 35.2 ± 20.6%). The RVESVi, monitored by CMR, was elevated at 79.3 ± 41.2 ml/m^2 (Table II).

The agreement between the two modalities is examined in Table III. Inter-modality agreement of PR severity occurred 52% of the time. Of the 23 instances where inter-modality disagreement existed, echocardiographic assessment underestimated PR severity in 35%, and overestimated in 65%. The unweighted kappa value was 0.30 (95% confidence interval (CI) 0.12, 0.48).

A comparison of PR severity with right ventricular volumes showed significant correlation between RVESVi and categorical PR severity by cardiac MRI ($p = 0.011$), while the RVESVi did not correlate with PR severity by echocardiography ($p = 0.081$) (Fig. 1). On secondary analysis, the CMR-assessed regurgitant fraction strongly correlated with the RVESVi, by linear regression ($r^2 = 0.40$, $p < 0.001$; Fig. 2).

Table I: Patient population characteristics.

Variable	Total cohort	TOF	PS	p-value
No. of patients	48	26	22	
Age (years)*	42.7 ± 12.0	40.9 ± 12.1	44.8 ± 11.9	0.266
Male gender	24 (50)	14 (58)	10 (42)	0.772
Time from surgery to first imaging (years)*	34.4 ± 9.8	33.0 ± 9.0	35.9 ± 10.5	0.344
Interval between imaging modalities (days)+	94 (23, 302)	94 (18, 229)	80 (57, 502)	0.431
NYHA class*	1.6 ± 0.6	1.5 ± 0.1	1.6 ± 0.1	0.772
Hypertension	14 (29)	5 (19)	9 (41)	0.122
Diabetes mellitus	3 (6)	2 (8)	1 (5)	1.000
PAH	2 (4)	2 (8)	0 (0)	0.493
Hyperlipidemia	4 (8)	2 (8)	2 (9)	1.000
Smoker	10 (21)	4 (15)	6 (27)	0.478
Atrial fibrillation	5 (10)	4 (15)	1 (5)	0.357

*Values are mean ± SD.
+Values given as median (interquartile range).
Values in parentheses are percentages.
PAH: Pulmonary arterial hypertension; PS: Pulmonary stenosis; TOF: Tetralogy of Fallot.

Table II: Imaging characteristics.

Variable	Total Cohort	TOF	PS	p-value
Echocardiogram PR*	3.0 ± 1.2	2.8 ± 1.4	3.3 ± 1.0	0.168
CMR PR fraction (%)	35.2 ± 20.6	37.6 ± 22.0	32.3 ± 18.9	0.384
RVESVi (ml/m^2)	79.3 ± 41.2	85.0 ± 47.4	72.7 ± 32.5	0.313
RVEDVi (ml/m^2)	146.0 ± 60.0	142.7 ± 60.1	149.7 ± 61.2	0.700
CMR RVEF (%)	45.9 ± 9.5	42.4 ± 10.1	50.0 ± 7.0	0.004
CMR LVEF (%)	56.0 ± 8.7	52.0 ± 8.5	60.0 ± 6.9	0.001

Values are mean ± SD.
*Pulmonic regurgitation by echocardiography graded as: 0 (none), 1+ (mild), 2+ (moderate), 3+ (moderate-severe), and 4+ (severe).
CMR: Cardiac magnetic resonance; LVEF: Left ventricular ejection fraction; PR: Pulmonic regurgitation; RVEDVi: Indexed right ventricular end-diastolic volume; RVEF: Right ventricular ejection fraction; RVESVi: Indexed right ventricular end-systolic volume.

Table III: Echocardiogram versus cardiac magnetic resonance agreement table.

		Cardiac Magnetic Resonance Pulmonic Regurgitation Severity				
		None	Mild	Moderate	Mod-Severe	Severe
Echo Pulmonic Regurgitation Severity	None	0	1	0	1	0
	Mild	1	5	0	0	0
	Moderate	0	2	1	1	3
	Mod-Severe	0	4	0	2	2
	Severe	0	1	3	4	17

J Heart Valve Dis
Vol. 24. No. 4
July 2015

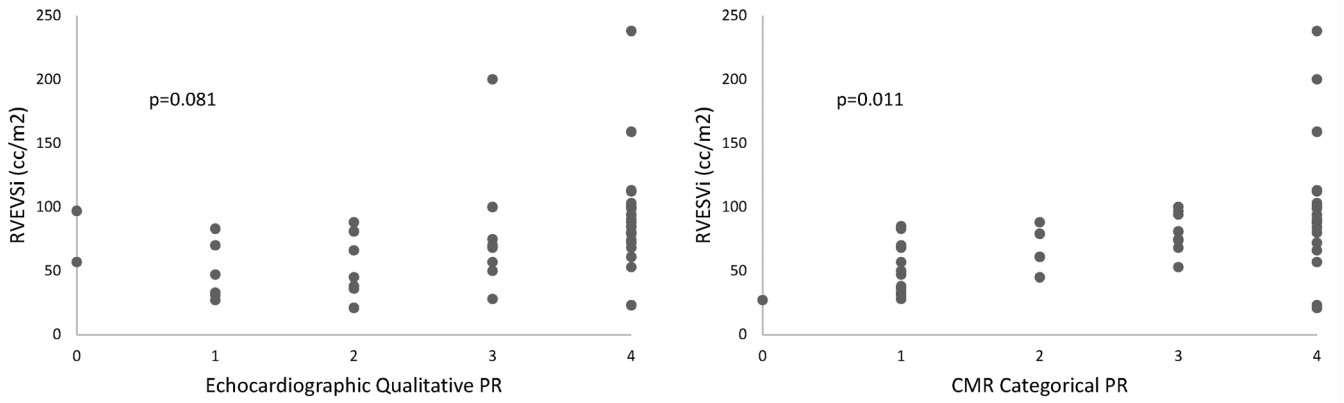

Figure 1: Analysis of variance comparing indexed right ventricular end-systolic volume (RVESVi) and categorical pulmonic regurgitation (PR) by cardiac MRI and echocardiography. Note the correlation between right ventricular dilatation and PR severity determined by cardiac MRI (p = 0.011). PR severity by echocardiography did not demonstrate significant correlation (p = 0.081).

The tetralogy of Fallot and pulmonic stenosis subgroups demonstrated similar severity of PR by both imaging modalities (Table II). Demographic characteristics and comorbidities were similar in the two subgroups, although the right and left ventricular ejection fractions by CMR were significantly lower in the tetralogy of Fallot population. The tetralogy of Fallot subgroup kappa value was 0.25 (95% CI 0.01, 0.50), with 50% agreement, while the kappa for the pulmonic stenosis subgroup was 0.35 (95% CI 0.11, 0.59), with 55% agreement.

A comparison of categorical PR severity with RVESVi demonstrated a significant correlation between CMR categorical PR severity and ventricular volume for the pulmonic stenosis subgroup (p = 0.026), but not for the tetralogy of Fallot subgroup (p = 0.291). No significant trends were found when comparing echocardiographic PR and RVESVi (p = 0.105 for tetralogy of Fallot, p = 0.121 for pulmonic stenosis). On secondary analysis, the CMR regurgitant fraction correlated with the RVESVi in both the tetralogy of Fallot subgroup (r^2 = 0.424, p <0.001) and the pulmonic stenosis group (r^2 = 0.369, p = 0.003).

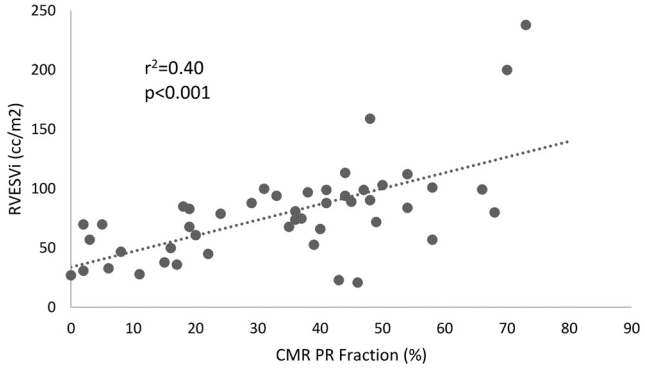

Figure 2: Indexed right ventricular end-systolic volume (RVESVi) versus regurgitant fraction by cardiac MRI. Note the correlation between the pulmonary regurgitant (PR) fraction and right ventricular dilatation. Linear regression analysis demonstrated significant correlation (p <0.001).

Discussion

Among a cohort of patients with tetralogy of Fallot after complete repair and pulmonic stenosis following valvotomy, CMR appeared to provide more accurate assessment of PR severity than did echocardiography. Intermodality agreement occurred only half of the time, and the unweighted kappa statistic indicated 'fair' agreement.

Disagreement by greater than one degree of severity between the two modalities occurred in 12 of the cases, in eight of which echocardiography overestimated the degree of PR, while underestimating the severity in the remaining four patients.

Pulmonic regurgitation severity, as determined by CMR, demonstrated a strong correlation with right ventricular volumes, supporting the validity of CMR phase-contrast analysis to determine the regurgitant fraction. Pulmonic regurgitation severity by echocardiography demonstrated a non-significant trend towards increasing the RVESVi, with greater severities of PR. This suggests that CMR is more accurate in its assessment of physiologically significant PR, particularly when it is moderate in severity. In two similar cohorts separated by congenital diagnosis, the tetralogy of Fallot subgroup experienced a lower level of agreement than did the pulmonic stenosis group. Although both subgroups' kappa statistics indicated fair agreement in inter-modality interpretation of PR, the difference in agreement values suggests that patients with more complex congenital heart disease may experience a greater variability and less reliability in their echocardiographic assessments. This may

reflect difficulty in obtaining optimal acoustic access following complex congenital repairs. Similar to the whole group analysis, the end-systolic ventricular size correlated with PR severity by CMR in the subgroups of tetralogy of Fallot and pulmonic stenosis. Pulmonic regurgitation by echocardiography did not demonstrate a correlation in either group.

Guidelines for the use of CMR in adults with congenital heart disease from the European Society of Cardiology currently recommend its use in cases where the echocardiographic study is suboptimal or provides ambiguous echocardiographic measurements (12). Cardiac magnetic resonance is particularly suited for the quantification of right ventricular volumes, ejection fractions, PR and shunt flow, as well as the evaluation of myocardial fibrosis, coronary anomalies and aortic anatomy. The results of the present and other studies suggest that CMR use should not be solely restricted to instances when echocardiographic evaluation is suboptimal or ambiguous (15,16,23,26). In the present authors' experience, the use of CMR is often limited to the initial assessment of symptomatic disease or when evaluating for surgical intervention, most likely due to its more limited availability and perceived greater expense. However, it is suggested that the use of CMR in patients with complex congenital heart disease be expanded to include routine assessment every three to five years, as the increased accuracy and quantification of anatomic and functional abnormalities can provide valuable information about the progression of disease.

It is important to note that while the use of CMR for anatomical and functional assessment should be expanded, echocardiography also has several distinct advantages. Doppler studies allow for the qualitative assessment of regurgitant jets, including their direction and duration. Additionally, diastolic dysfunction can be diagnosed using tissue Doppler techniques. Valve leaflet morphology and pathology is more easily determined with echocardiography, including the presence of vegetations. Finally, the use of agitated saline contrast ('bubble') studies allows for the identification of small degrees of right-to-left shunting which is often missed when using CMR. Whilst the regular use of CMR is advocated in this population, the two modalities are each important and provide complementary information.

Study limitations

The main limitation of the study was the selective nature of the prospective database, which included patients with congenital pulmonic stenosis or tetralogy of Fallot. Hence, the conclusions drawn may not apply to those patients with other types of congenital heart disease. Nonetheless, the study results raise interesting questions about the validity of echocardiographic PR measurements in adults with congenital heart disease. Future studies may wish to focus on further delineating the ideal timing intervals for routine CMR in this patient population.

In conclusion, CMR measurement of PR appears superior for the assessment of patients at risk for PR when compared to echocardiography, as PR severity by CMR correlates closely with the RVESVi, while echocardiographic assessment of PR does not. Inter-modality disagreement occurred more often in the tetralogy of Fallot population, suggesting that complex congenital heart disease and its subsequent surgical interventions increase the likelihood of suboptimal echocardiographic analysis. It is recommended that CMR be regularly used as a surveillance instrument for adults with congenital heart disease, particularly when the anatomy is complex.

Acknowledgements

The authors would like to thank Paul Schoenhagen MD for his insightful review and feedback on this manuscript.

References

1. Perloff JK, Warnes CA. Challenges posed by adults with repaired congenital heart disease. Circulation 2001;103:2637-2643
2. Dearani JA, Connolly HM, Martinez R, Fontanet H, Webb GD. Caring for adults with congenital cardiac disease: Successes and challenges for 2007 and beyond. Cardiol Young 2007;17(Suppl.2):87-96
3. Eyskens B, Brown SC, Claus P, et al. The influence of pulmonary regurgitation on regional right ventricular function in children after surgical repair of tetralogy of Fallot. Eur J Echocardiogr 2010;11:341-345
4. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: A multicentre study. Lancet 2000;356:975-981
5. Rajiah P, Nazarian J, Vogelius E, Gilkeson RC. CT and MRI of pulmonary valvular abnormalities. Clin Radiol 2014;69:630-638
6. Geva T. Repaired tetralogy of Fallot: The roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson 2011;13:9
7. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. Lancet 2009;374:1462-1471
8. Gregg D, Foster E. Pulmonary insufficiency is the nexus of late complications in tetralogy of Fallot. Curr Cardiol Rep 2007;9:315-322

9 Fox D, Devendra GP, Hart SA, Krasuski RA. When 'blue babies' grow up: What you need to know about tetralogy of Fallot. Cleve Clin J Med 2010;77:821-828
10. Burchill LJ, Wald RM, Harris L, Colman JM, Silversides CK. Pulmonary valve replacement in adults with repaired tetralogy of Fallot. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2011;14:92-97
11. Villafañe J, Feinstein JA, Jenkins KJ, et al. Hot topics in tetralogy of Fallot. J Am Coll Cardiol 2013;62:2155-2166
12. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitter J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. Eur Heart J 2010;31:794-805
13. Wald RM, Redington AN, Pereira A, et al. Refining the assessment of pulmonary regurgitation in adults after tetralogy of Fallot repair: Should we be measuring regurgitant fraction or regurgitant volume? Eur Heart J 2009;30:356-361
14. Helbing WA, de Roos A. Clinical applications of cardiac magnetic resonance imaging after repair of tetralogy of Fallot. Pediatr Cardiol 2000;21:70-79
15. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J 2004;147:218-223
16. Mooij CF, de Wit CJ, Graham DA, Powell AJ, Geva T. Reproducibility of MRI measurements of right ventricular size and function in patients with normal and dilated ventricles. J Magn Reson Imaging 2008;28:67-73
17. Wald RM, Haber I, Wald R, Valente AM, Powell AJ, Geva T. Effects of regional dysfunction and late gadolinium enhancement on global right ventricular function and exercise capacity in patients with repaired tetralogy of Fallot. Circulation 2009;119:1370-1377
18. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of Fallot and its relationship to adverse markers of clinical outcome. Circulation 2006;113:405-413
19. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: Volumetric evaluation by magnetic resonance velocity mapping. J Am Coll Cardiol 1996;28: 1827-1835
20. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: Detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-2052
21. Samyn MM, Powell AJ, Garg R, Sena L, Geva T. Range of ventricular dimensions and function by steady-state free precession cine MRI in repaired tetralogy of Fallot: Right ventricular outflow tract patch vs. conduit repair. J Magn Reson Imaging 2007;26:934-940
22. Renella P, Aboulhosn J, Lohan DG, et al. Two-dimensional and Doppler echocardiography reliably predict severe pulmonary regurgitation as quantified by cardiac magnetic resonance. J Am Soc Echocardiogr. 2010;23:880-886
23. Greenberg SB, Crisci KL, Koenig P, Robinson B, Anisman P, Russo P. Magnetic resonance imaging compared with echocardiography in the evaluation of pulmonary artery abnormalities in children with tetralogy of Fallot following palliative and corrective surgery. Pediatr Radiol 1997;27:932-935
24. Frigiola A, Redington AN, Cullen S, Vogel M. Pulmonary regurgitation is an important determinant of right ventricular contractile dysfunction in patients with surgically repaired tetralogy of Fallot. Circulation 2004;110 (11 Suppl.1):II153-II157
25. Crean AM, Maredia N, Ballard G, et al. 3D Echo systematically underestimates right ventricular volumes compared to cardiovascular magnetic resonance in adult congenital heart disease patients with moderate or severe RV dilatation. J Cardiovasc Magn Reson 2011;13:78
26. Mercer-Rosa L, Yang W, Kutty S, Rychik J, Fogel M, Goldmuntz E. Quantifying pulmonary regurgitation and right ventricular function in surgically repaired tetralogy of Fallot: A comparative analysis of echocardiography and magnetic resonance imaging. Circ Cardiovasc Imaging 2012;5:637-643
27. Lancellotti P, Tribouilloy C, Hagendorff A, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: Aortic and pulmonary regurgitation (native valve disease). Eur Heart J Cardiovasc Imaging 2010;11:223-244
28. Cohen JA. A coefficient of agreement for nominal scales. Educ Psychol Meas 1960;20:37-46
29. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med 2005;37:360-363
30. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-174