Comparison of Long-Term Postoperative Sequelae in Patients With Tetralogy of Fallot Versus Isolated Pulmonic Stenosis

Michael J. Zdradzinski, BA[a,b], Athar M. Qureshi, MD[c], Robert Stewart, MD[d], Gosta Pettersson, MD, PhD[d], and Richard A. Krasuski, MD[a,*]

Patients with tetralogy of Fallot (TOF) after complete repair and pulmonic stenosis (PS) after surgical valvotomy often develop significant pulmonic regurgitation (PR) that eventually requires valve replacement. Although criteria exist for the timing of pulmonary valve replacement in TOF, it remains less clear when to intervene in valvotomy patients and whether TOF recommendations can be applied. Our aim was to compare the structural and functional sequelae of valvotomy for PS with complete repair for TOF. We compared the clinical characteristics, electrocardiograms, echocardiograms, cardiac magnetic resonance imaging (MRI), and invasive hemodynamics of 109 adults (34 PS and 75 TOF) newly referred to a congenital heart disease center for evaluation of PR between 2005 and 2012. Both cohorts were similar in terms of baseline demographics and presenting New York Heart Association function class. Valvotomy patients had a slightly greater degree of PR by echocardiogram, although it was similar by cardiac MRI. Electrocardiography QRS width was greater in patients with TOF (114 ± 27 vs 150 ± 28 ms, p <0.001). MRI right ventricular ejection fraction (49 ± 8 vs 41 ± 11%, p = 0.001) and left ventricular ejection fraction (59 ± 7 vs 52 ± 10%, p = 0.002) were lower in patients with TOF. Pacemaker or defibrillator implantation was significantly greater in patients with TOF (3% vs 23%, p = 0.011). In conclusion, patients postvalvotomy and complete repair present with similar degrees of PR and severity of symptoms. Biventricular systolic function and electrocardiography QRS width appear less affected, suggesting morphologic changes in TOF and its repair that extend beyond the effects of PR. These findings suggest the need for developing disease-specific guidelines for patients with PR postvalvotomy. © 2014 Elsevier Inc. All rights reserved. **(Am J Cardiol 2014;114:300−304)**

Tetralogy of Fallot (TOF) and isolated pulmonic stenosis (PS) are common congenital disorders that often require early corrective intervention.[1−4] Traditional corrective surgery for TOF ("complete repair") and surgical valvotomy for PS frequently have resulted in significant pulmonic regurgitation (PR).[5−9] In both populations, the resultant PR places patients at risk for right ventricular (RV) dysfunction, arrhythmias, and sudden death.[10−13] Pulmonary valve replacement (PVR) is the gold standard therapeutic option because medical management is often ineffective.[14−16] The timing of PVR is controversial, with early replacement limited by long-term prosthetic valve degeneration and delayed replacement risking the development of irreversible RV damage.[17] For this reason, the timing of PVR after TOF repair has been well-studied, and specific guidelines exist to determine the appropriate timing of intervention.[18−23] Unfortunately, few studies exist to guide the timing of PVR in the PS population.[18] Many providers, therefore, apply the TOF guidelines to valvotomy patients despite the fundamentally different anatomy, pathophysiology, and surgical corrections of these conditions. To assess whether the two populations are truly comparable, we examined the structural, functional, and symptomatic sequelae of patients with PR resulting from TOF repair and valvotomy referred for initial assessment at an adult congenital heart disease center.

Methods

In this retrospective, incipient cohort study, we identified 109 patients from the Cleveland Clinic Adult Congenital Heart Disease Database who were newly referred between July 2005 and June 2012 for evaluation of moderate or greater native valve PR (as quantified by echocardiography) related to previous surgical repair of PS or TOF. All patients underwent an electrocardiogram and an echocardiogram at the initial clinic visit, with cardiac magnetic resonance imaging (MRI) and heart catheterization subsequently performed in appropriately selected patients. Patients with left bundle branch block, previous PVR, or those with greater mild RV outflow narrowing evident on imaging were excluded. In addition, those with other major additional cardiac malformations (i.e., double-chambered right ventricle, transposition of great vessels, atrioventricular

[a]Department of Cardiovascular Medicine, The Cleveland Clinic, Cleveland, Ohio; [b]Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, Ohio; [c]Department of Pediatric Cardiology, The Cleveland Clinic, Cleveland, Ohio; and [d]Department of Pediatric and Congenital Heart Surgery, The Cleveland Clinic, Cleveland, Ohio. Manuscript received February 14, 2014; revised manuscript received and accepted April 24, 2014.

This study was supported by the National Heart, Lung, and Blood Institute at the National Institutes of Health (NIH T35 HL082544).

See page 303 for disclosure information.

*Corresponding author: Tel: (216) 445-7433; fax: (216) 445-6163.

E-mail address: krasusr@ccf.org (R.A. Krasuski).

0002-9149/14/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2014.04.041

Table 1
Demographic data at presentation

Variable	Pulmonic Stenosis (n = 34)	Tetralogy of Fallot (n = 75)	p Value
Age, years	47.0 ± 13.5	43.9 ± 13.3	0.260
Male	17 (50%)	43 (58%)	0.536
Body mass index, kg/m^2	28.6 ± 7.1	27.4 ± 6.8	0.388
Age at first repair, years	6.8 ± 8.5	8.5 ± 10.3	0.411
Time from repair to presentation, years	37.5 ± 10.5	32.3 ± 10.6	0.023
Shunt	1 (3%)	30 (40%)	<0.001
Pacer/implantable cardiac defibrillator	1 (3%)	17 (23%)	0.011
New York heart Association functional class	1.7 ± 0.7	1.6 ± 0.6	0.506
Hypertension	11 (32%)	19 (25%)	0.491
Pulmonary hypertension	1 (3%)	11 (15%)	0.100
Diabetes mellitus	2 (6%)	4 (5%)	1.000
Hyperlipidemia	3 (9%)	12 (16%)	0.383
Smoker	8 (24%)	18 (24%)	1.000

Data given as mean ± SD.

Table 2
EKG and echocardiogram data

Variable	Pulmonic Stenosis	Tetralogy of Fallot	p Value
PR interval, ms	177 ± 32	177 ± 55	0.946
QRS width, ms	114 ± 27	150 ± 28	<0.001
QTc, ms	421 ± 51	420 ± 53	0.888
Right atrium volume, ml	25.1 ± 10.6	27.0 ± 10.6	0.560
Right ventricle volume†	1.5 ± 1.0	1.5 ± 1.0	0.761
Right ventricle function*†	1 (0,2)	1 (0,2)	0.512
Left ventricle diastolic width, cm	4.4 ± 0.5	4.5 ± 0.8	0.457
Left ventricle systolic width, cm	2.9 ± 0.5	3.1 ± 0.6	0.289
Left ventricle function*†	0 (0,0)	0 (0,0)	0.163
Aortic regurgitation*‡	0 (0,0)	0.5 (0,2)	0.021
Pulmonic regurgitation‡	3.2 ± 0.9	2.4 ± 1.6	0.004
Mitral regurgitation‡	0.9 ± 0.6	0.9 ± 0.9	0.869
Tricuspid regurgitation‡	1.5 ± 1.0	1.5 ± 0.9	0.853
Pulmonic gradient, mm Hg	8.2 ± 3.1	13.9 ± 8.2	0.007
Right ventricular systolic pressure, mm Hg	35 ± 13	46 ± 20	0.007
Left ventricle ejection fraction, %	56 ± 5	54 ± 8	0.166

Data given as mean ± SD.
EKG = electrocardiogram; PR = pulmonic regurgitation; QTc = corrected QT interval.
* Data given as median (IQ range).
† Volume/function graded from 0 (normal) to 3 (severely dilated/decreased).
‡ Valvular regurgitation graded as 0 (none), 1 (mild) to 4 (severe).

canal type defect or anomalous pulmonary venous return) were excluded. Other cardiac comorbidities, including residual atrial and ventricular septal defects and peripheral pulmonic stenosis, were individually reviewed by a committee of investigators for their contribution to cardiac structure and risk of arrhythmia before possible exclusion. The study was approved by the Institutional Review Board of the Cleveland Clinic.

Data were abstracted from the database and augmented by review of the electronic and paper medical records, which included baseline demographics, cardiac medical and surgical history, comorbidities, symptom severity as measured by New York Heart Association functional class, electrocardiographic and imaging data, and hemodynamic tracings.

Table 3
Invasive hemodynamic data

Variable	Pulmonic Stenosis (n = 18)	Tetralogy of Fallot (n = 38)	p Value
Right atrial mean, mm Hg	10.1 ± 5.4	11.4 ± 6.5	0.487
Systolic pulmonary artery, mm Hg	35.4 ± 11.6	42.2 ± 22.2	0.159
Diastolic pulmonary artery, mm Hg	12.6 ± 5.1	13.8 ± 10.5	0.584
Mean pulmonary artery, mm Hg	21.0 ± 5.2	23.9 ± 14.2	0.348
Systolic right ventricle, mm Hg	41.2 ± 12.9	50.3 ± 20.5	0.102
Diastolic right ventricle,* mm Hg	10 (5, 14)	10 (6, 13.5)	0.767
Mean pulmonary capillary wedge pressure, mm Hg	12.5 ± 4.9	13.0 ± 5.4	0.737
Fick cardiac index, l/min/m^2	2.4 ± 0.5	2.4 ± 0.9	0.963

Data given as mean ± SD.
* Data given as median (interquartile range).

Table 4
MRI subgroup analysis

Variable	Pulmonic Stenosis (n = 24)	Tetralogy of Fallot (n = 39)	p Value
Age, years	45.9 ± 13.3	46.2 ± 11.7	0.304
Male	11 (46%)	23 (59%)	0.435
Body mass index, kg/m^2	27.5 ± 6.3	27.1 ± 6.3	0.783
Time from surgery to MRI, years	36 ± 11	32 ± 9	0.152
Shunt	4%	46%	<0.001
New York Heart Association class	1.6 ± 0.6	1.5 ± 0.6	0.786
Body surface area, m^2	1.96 ± 0.28	1.91 ± 0.24	0.489
Right ventricular end-diastolic volume, ml	267.1 ± 77.7	256.3 ± 112.0	0.691
Right ventricular end-diastolic volume indexed, ml/m^2	147.9 ± 58.8	139.2 ± 61.7	0.592
Right ventricular end-systolic volume, ml	134.5 ± 52.7	151.8 ± 97.0	0.394
Right ventricular end-systolic volume indexed, ml/m^2	73.3 ± 31.2	82.5 ± 49.7	0.389
Right ventricular ejection fraction, %	49.1 ± 7.7	40.8 ± 11.0	0.001
Left ventricular end-diastolic volume, ml	150.5 ± 34.4	158.1 ± 48.1	0.584
Left ventricular end-diastolic volume index, ml/m^2	79.3 ± 14.8	83.3 ± 24.6	0.466
Left ventricular end-systolic volume, ml	61.8 ± 15.7	78.4 ± 36.3	0.028
Left ventricular end-systolic volume index, ml/m^2	31.7 ± 7.9	41.3 ± 19.0	0.015
Left ventricular ejection fraction, %	59.3 ± 7.1	52.1 ± 9.6	0.002
Pulmonic regurgitation, %	32.3 ± 18.9	37.3 ± 21.6	0.394
Aortic regurgitation, %	2.8 ± 6.4	4.3 ± 4.5	0.341
Root diameter, cm	3.1 ± 0.3	4.0 ± 0.6	<0.001
Ascending diameter, cm	3.0 ± 0.6	3.6 ± 0.8	0.054

Data given as mean ± SD; Values indexed by body surface area.
MRI = magnetic resonance imaging.

Electrocardiogram analysis was limited to nonpaced tracings. Blinded, qualitative assessments of cardiac chamber sizes by echocardiography were quantified as: 0 = normal, 1 = mild, 2 = moderate, 3 = moderate to severe, and 4 = severe enlargement. Similarly, RV function by echocardiogram was quantified as: 0 = normal, 1 = mild, 2 = moderate, 3 = moderate to severe, and 4 = severe dysfunction. Cardiac catheterization data included right heart pressures, cardiac index calculated by Fick method, and the presence and severity of coronary artery disease. Cardiac MRI data included chamber sizes and function, quantified valvular regurgitation, and aortic dimensions. Volumetric data by MRI was indexed using body surface area.

Comparisons of dichotomous variables between groups were performed using the Pearson chi-square test, Fisher's exact test, or Wilcoxon rank-sum test where appropriate. Comparisons of continuous variables were performed using two-sided t-tests. For all tests, a $p < 0.05$ was considered statistically significant. Data analyses were performed using JMP Pro software version 9.0.0 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 109 patients (34 PS valvotomy and 75 TOF complete repair) were included in the final analysis (Table 1). Basic demographic data, including age, gender, and body mass index, were similar between groups. There was no difference in mean age at corrective surgery. Patients with PS presented to the Adult Congenital Heart Disease Center an average of 37.5 ± 10.5 years after surgery compared with 32.3 ± 10.6 years in patients with TOF ($p = 0.023$). Not surprisingly, because of anatomic limitations, patients with repaired TOF were significantly more likely to have required palliative shunting and eventual placement of a pacemaker or cardiac defibrillator. Cardiovascular and noncardiovascular comorbidities were otherwise similar. At presentation, the PS group reported a greater prevalence of chest pain (29% vs 12%, $p = 0.026$) and shortness of breath at rest (32% vs 15%, $p = 0.033$). All other symptoms—including fatigue, cyanosis, orthopnea, palpitations, dyspnea on exertion, home oxygen supplementation and edema—were similar in prevalence between the two groups. Severity of symptoms at presentation also was similar as determined by New York Heart Association function class. Complete operative records were available for 23% of the cohort. Of the TOF subset, 33% of the repairs included known use of a transannular patch.

Nonpaced electrocardiographic data were obtained from 95 patients (31 valvotomy and 64 complete repair). PR and corrected QT intervals were similar in both groups (Table 2). QRS duration, however, was significantly greater in the TOF group.

Echocardiographically assessed RV size (mildly to moderately enlarged) and function (mildly decreased) was similar in the 2 groups (Table 2). PR, assessed qualitatively, was slightly more severe in the postvalvotomy group, whereas aortic regurgitation was worse in TOF. RV systolic pressure and pulmonic outflow gradient were both slightly greater in the TOF cohort.

Complete cardiac catheterization data were available in 56 patients (18 PS and 38 TOF). These data demonstrated similar hemodynamics, including right atrial pressure, pulmonary artery pressure, and cardiac indexes in both groups (Table 3).

A total of 63 patients (24 PS and 39 TOF) had complete and technically adequate cardiac MRI data (mean 2.2 ± 2.7 months from the initial evaluation; Table 4). To ensure similarity of this selected cohort to the entire study population, baseline demographic data were recompared, with no significant differences observed. As with the entire cohort, patients with TOF in this subgroup were substantially more likely to have a pervious history of palliative shunt placement.

Both groups experienced similar degrees of RV dilation, including indexed RV end-diastolic and end-systolic volumes. RV ejection fraction was significantly greater postvalvotomy. Although left ventricular (LV) volumes fell within normal range for patients with PS, they were mildly increased in the TOF group, and the LV ejection fraction was also lower in the TOF group.

Flow measurements demonstrated similar degrees of pulmonic and aortic regurgitation in both groups. There was no significant difference in pulmonic valve regurgitant fraction, which was increased in both groups. Although aortic regurgitant fractions were similarly small in both groups, aortas were larger in patients with TOF, including larger root and mid-ascending aorta diameters.

Discussion

In a similarly symptomatic cohort of patients with PS after valvotomy and TOF after complete repair, we found that structural and functional sequelae were significantly more evident with TOF. Although valvotomy patients appeared to have a greater degree of PR by echocardiography, MRI quantification was similar. This finding likely reflects the greater accuracy of cardiac MRI in the quantification of PR. Alternatively, the exclusion of patients with pacemaker and defibrillators (still considered a contraindication to MRI scanning) may have altered the TOF cohort. Comparison of the full cohort and those undergoing MRI scanning, however, did not suggest any major differences. Furthermore, it should be suspected that patients with previously placed defibrillators would have wider QRS durations, more dilated right ventricles, and thus greater PR. Excluding these patients would therefore be expected to reduce the degree of PR observed in the TOF cohort and widen the observed difference, contrary to what was seen.

RV volumes were similarly increased in both groups, although the RV ejection fraction was considerably lower in patients with TOF. This measure is more sensitive to changes, and it reflects the effect of slightly smaller end-diastolic volumes and larger end-systolic volumes in TOF. LV end-systolic volume was larger and ejection fraction lower in patients with TOF. LV dysfunction recently has been characterized in the TOF population.[24] It appears from our data that PS patients are spared this effect and suggests a pathologic effect in TOF beyond longstanding right-sided volume overload from PR. It is important to note that the decrease in LV function was seen in a cohort of patients with TOF who did not have implantable devices, thus excluding the potentially detrimental effect of pacing, which

previously has been reported in other cohorts of patients. Also important to note is that invasive hemodynamics suggest no difference in pulmonary capillary wedge pressure, suggesting a smaller role of LV involvement on the presence of symptoms in these patient populations.

Aortic sizes tended to be larger in patients with TOF. This finding is not surprising because TOF is a conotruncal abnormality with aortic override being a major component. Aortic dissection has been reported in patients with TOF; fortunately, it does not appear that the PS population is prone to this problem.

Sudden death is a well-described phenomenon in patients with congenital heart disease, particularly in TOF, and risk in the latter appears to be mitigated by RV size and function.[24] QRS complex width has been proposed as an effective marker for predicting future risk in TOF and a cut-off of 180 ms has been proposed for defining patients at particularly high risk.[10,25] Many clinicians regularly track this value to help decide when to intervene operatively for PR. Interestingly, QRS width was considerably less in patients with PS and only mildly abnormal in these patients despite similarly, significantly enlarged right ventricles. Complete repair in TOF is known to produce right bundle branch block, and our data suggest that physicians should ideally not apply the cut-offs derived from TOF to the PS population. Further studies should investigate sudden death risk in the postvalvotomy population and whether a lower cutpoint or change in QRS width over time is a helpful screening tool.

Current guidelines and indicators for PVR in patients with TOF include criteria for RV size, QRS width, and symptomatic impairment.[10,18] This study suggests that postvalvotomy patients with PR become symptomatic despite fewer structural changes and functional deficits than do patients with TOF. Therefore, the guidelines developed for PVR in the TOF population do not appear to apply to the postvalvotomy population.

This study is limited by the very selective nature of the patient cohort. All patients were referred to an adult congenital heart disease center based on the presence of PR and/or symptoms of heart failure. As such, we are capturing patients who have developed complications or are otherwise unable to be managed by their general cardiologist. Therefore, one cannot be certain that these findings apply to all patients with PS and previous valvotomy or tetralogy with prior complete repair. Nonetheless, it is a comparison that has not been previously made, and its findings have the potential to change clinical practice if confirmed in other populations. Because of the retrospective nature of data collection, the details of previous surgeries were not always available. In such cases, the patients were the sole source of clinical information, a common situation in adults with congenital heart disease. We also did not attempt to examine the impact of valvular interventions in this patient population. Future studies should aim to determine the effect of pre-PVR structure and function on the functional, structural, and symptomatic improvement after valve replacement in the postvalvotomy population. This would further facilitate the development of population-specific guidelines.

Disclosures

The authors have no conflicts of interest to disclose.

1. Bashore TM. Adult congenital heart disease: right ventricular outflow tract lesions. *Circulation* 2007;115:1933−1947.
2. Jassal DS, Thakrar A, Schaffer SA, Fang T, Kirkpatrick I, Tam JW, Kashour T. Percutaneous balloon valvuloplasty for pulmonic stenosis: the role of multimodality imaging. *Echocardiography* 2008;25: 231−235.
3. Fitzgerald KP, Lim MJ. The pulmonary valve. *Cardiol Clin* 2011;29: 223−227.
4. Laks H, Plunkett MD. Right ventricular outflow tract obstruction with intact ventricular septum. In: Gardner T, Spray T, eds. Operative Cardiac Surgery. 5th ed. New York: Oxford University Press, 2004: 721−724.
5. Erdem S, Ozbarlas N, Küçükosmanoğlu O, Poyrazoğlu H, Salih OK. Mid-term results of patients following total surgical correction of tetralogy of Fallot. *Turk J Pediatr* 2012;54:393−402.
6. Bautista-Hernandez V, Cardenas I, Martinez-Bendayan I, Loyola H, Rueda F, Portela F. Valve-sparing tetralogy of Fallot repair with intraoperative dilation of the pulmonary valve. *Pediatr Cardiol* 2013;34:918−923.
7. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. *Br Heart J* 1992;67: 470−473.
8. Polansky DB, Clark EB, Doty DB. Pulmonary stenosis in infants and young children. *Ann Thorac Surg* 1985;39:159−164.
9. Kirklin JW, Blackstone EH, Pacifico AD, Kirklin JK, Bargeron LM. Risk factors for early and late failure after repair of tetralogy of Fallot, and their neutralization. *Thorac Cardiovasc Surg* 1984;32:208−214.
10. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 2000;356: 975−981.
11. Shimazaki Y, Blackstone EH, Kirklin JW. The natural history of isolated congenital pulmonary valve incompetence: surgical implications. *Thorac Cardiovasc Surg* 1984;32:257−259.
12. Hill G. Repair and follow-up of Tetralogy of Fallot with pulmonary stenosis. *Congenit Heart Dis* 2013;8:174−177.
13. Yoo BW, Park HK. Pulmonary stenosis and pulmonary regurgitation: both ends of the spectrum in residual hemodynamic impairment after tetralogy of Fallot repair. *Korean J Pediatr* 2013;56:235−241.
14. Kogon B, Plattner C, Kirshbom P, Kanter K, Leong T, Lyle T, Jennings S, McConnell M, Book W. Risk factors for early pulmonary valve replacement after valve disruption in congenital pulmonary stenosis and tetralogy of Fallot. *J Thorac Cardiovasc Surg* 2009;138: 103−108.
15. Karagoz T, Asoh K, Hickey E, Chaturvedi R, Lee K-J, Nykanen D, Benson L. Balloon dilation of pulmonary valve stenosis in infants less than 3 kg: A 20-year experience. *Catheter Cardiovasc Interv* 2009;74: 753−761.
16. Kogon B, Patel M, Leong T, McConnell M, Book W. Management of moderate functional tricuspid valve regurgitation at the time of pulmonary valve replacement: Is concomitant tricuspid valve repair necessary? *Pediatr Cardiol* 2010;31:843−848.
17. Lurz P, Bonhoeffer P, Taylor AM. Percutaneous pulmonary valve implantation: an update. *Expert Rev Cardiovasc Ther* 2009;7: 823−833.
18. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation* 2008;118:e714−e833.
19. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *Am J Cardiol* 2005;95:779−782.
20. Oosterhof T, van Straten A, Vliegen HW, Meijboom FJ, van Dijk APJ, Spijkerboer AM, Bouma BJ, Zwinderman AH, Hazekamp

MG, de Roos A, Mulder BJM. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. *Circulation* 2007;116:545−551.
21. Ammash NM, Dearani JA, Burkhart HM, Connolly HM. Pulmonary regurgitation after tetralogy of Fallot repair: clinical features, sequelae, and timing of pulmonary valve replacement. *Congenit Heart Dis* 2007;2:386−403.
22. Piazza L, Chessa M, Giamberti A, Bussadori CM, Butera G, Negura DG, Micheletti A, Callus E, Carminati M. Timing of pulmonary valve replacement after tetralogy of Fallot repair. *Expert Rev Cardiovasc Ther* 2012;10:917−923.
23. Geva T. Indications and timing of pulmonary valve replacement after tetralogy of Fallot repair. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2006:11−22.
24. Broberg CS, Aboulhosn J, Mongeon F-P, Kay J, Valente AM, Khairy P, Earing MG, Opotowsky AR, Lui G, Gersony DR, Cook S, Ting JG, Webb G, Gurvitz MZ. Alliance for Adult Research in Congenital Cardiology (AARCC). Prevalence of left ventricular systolic dysfunction in adults with repaired tetralogy of Fallot. *Am J Cardiol* 2011;107:1215−1220.
25. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W, Zwinderman AH, Van Gelder IC, Mulder BJM. Sudden cardiac death in adult congenital heart disease. *Circulation* 2012;126: 1944−1954.