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(results from the CSONGRAD Registry and MAGYAR-Path Study)

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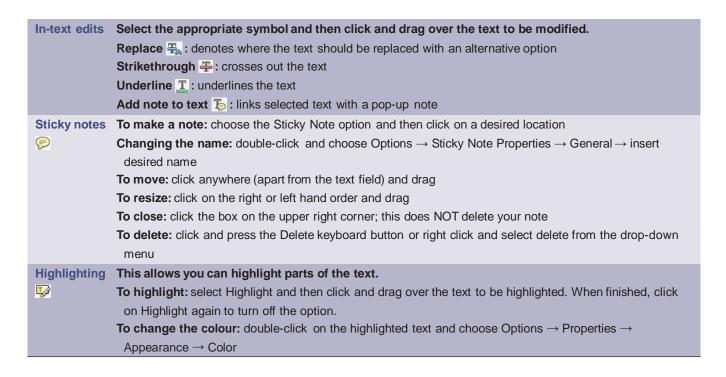
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Tricuspid annular abnormalities following different surgical strategies in adults with corrected tetralogy of Fallot (results from the CSONGRAD Registry and MAGYAR-Path Study)

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Background: Although there is an increasing number of patients with corrected tetralogy of Fallot (cTOF), who reach adulthood due to these successful surgical procedures, some of them suffers from late complications, including functional tricuspid regurgitation (FTR). The purpose of the present study was to examine tricuspid annular (TA) abnormalities in adult cTOF patients and their relationship right atrial (RA) volumes respecting the cardiac cycle assessed by three-dimensional speckle-tracking echocardiography (3DSTE). Moreover, the effect of different surgical procedures on TA morphologic and functional parameters was examined as well.

Methods: The study comprised 24 cTOF patients (32.8±13.5 years, 9 males) in which early palliative surgery and late total correction were performed in 12 cases (pcTOF), while early total reconstruction was performed in 12 subjects (etrTOF). Their results were compared to those of 33 matched healthy adults (36.7±7.2 years, 15 males).

Results: Dilated end-systolic and end-diastolic TA morphologic parameters and their BSA-indexed counterpart could be detected in cTOF patients as compared to that of controls. These parameters were similar in TOF-early total reconstruction (etrTOF) and TOF-early palliation, late correction (pcTOF) patients. TA fractional area change (TAFAC) and fractional shortening (TAFS) proved to be reduced in cTOF patients as well as in etrTOF and pcTOF patients compared to controls. None of the TA morphologic and functional parameters showed any differences between etrTOF and pcTOF patients. Increased maximum preatrial contraction and minimum RA volumes could be detected in cTOF patients compared to controls, which correlated with TA dimensions.

Conclusions: TA is dilated with reduced function in adult patients with cTOF. TA dilation is related to RA volumes. etrTOF and pcTOF patients have similar TA dimensions and TA functional properties.

Keywords: Fallot; tricuspid annulus; three-dimensional (3D); speckle-tracking; echocardiography

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Introduction

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Tetralogy of Fallot (TOF) is a conotruncal malformation characterized by the presence of a multilevel right ventricular (RV) outflow tract obstruction, leading to RV hypertrophy, and a malalignment ventricular septal defect (VSD) with aortic override (1,2). TOF is the most common congenital heart defect (CHD) accounting for 10% of the cases and in unrepaired patients, cyanosis could develop due to right-toleft shunt. Two surgical strategies are used in TOF patients in general: early palliation by creating artificial left-to-right shunts to provide adequate pulmonary blood flow followed by a late total reconstruction (pcTOF), or an early total reconstruction is performed (etrTOF) (3). Although there is an increasing number of patients with corrected TOF (cTOF), who reach adulthood due to these successful surgical procedures, some of them suffer from late complications like functional tricuspid regurgitation (FTR) (4).

Three-dimensional speckle-tracking echocardiography (3DSTE) can be used not only for detailed volumetric and functional assessment of certain cardiac chambers at the same time using the same virtually acquired 3D echocardiographic datasets, but to determine annular dimensions and functional properties as well (5-7). The purpose of the present study was to examine tricuspid annular (TA) abnormalities in adult cTOF patients and their relationship right atrial (RA) volumes respecting the cardiac cycle assessed by 3DSTE. Moreover, the effect of different surgical procedures on TA morphologic and functional parameters was also examined. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/cdt-21-256).

Methods

Patient population

The present study comprised 24 adult patients with cTOF [mean age 32.8±13.5 years, 15 males (62%)]. Data of these patients origin from a special registry for CHD patients treated and/or operated on at the Department of Pediatrics, Department of Heart Surgery, and 2nd Department of Medicine and Cardiology Center at the University of Szeged, Hungary since 1961. This registry is called as Registry of C(S)ONGenital cardiac Disease patients at the University of Szeged (CSONGRAD Registry) including data of more than 3000 CHD patients (8). In 12 cTOF patients, early palliative surgery and late total correction

were performed (pcTOF), while early total reconstruction

was performed in 12 cTOF patients (etrTOF). Their results were compared with those of 33 age- and gender-matched healthy volunteers, who had no known disorders, diseases or other pathological conditions, risk factors, did not receive any drugs and showed negative echocardiographic and electrocardiographic findings. All cTOF patients and healthy controls underwent transthoracic 2-dimensional (2D) Doppler echocardiography and 3DSTE. The present study serves as a part of the Motion Analysis of the heart and Great vessels by 3DSTE in Pathological cases (MAGYAR-Path) Study. Myocardial mechanics and valvular abnormalities were examined extensively in cTOF patients in this study among others. Informed consent was given by all cTOF patients and healthy controls. Institutional human research committee of the University of Szeged approved the study under the registration number 71/2011 (and updated versions). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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M-mode and 2D Doppler echocardiography

Toshiba ArtidaTM cardiac ultrasound tool (Toshiba Medical Systems, Tokyo, Japan) attached with 1-5 MHz PST-30SBP phased-array transducer was used for 2D Doppler echocardiographic examinations. Left ventricular dimensions and volumes, ejection fraction and left atrial diameter were measured according to the guidelines (9). Doppler echocardiography was used for quantification of valvular regurgitations and stenoses and for measurement of left ventricular (LV) transmitral E and A wave as features of LV diastolic function. Tricuspid annular plane systolic excursion (TAPSE) was also determined by M-mode echocardiography (MME) as a quantitative feature of longitudinal movement of the TA and RV function (10,11).

3DSTE

3DSTE analysis was carried out using the same Toshiba ArtidaTM cardiac ultrasound equipment (Toshiba Medical Systems, Tokyo, Japan) attached to a 1–4 MHz matrix phased-array PST-25SX transducer (6). Two-step analysis was performed, first data acquisition was made of six wedge-shaped subvolumes within a single breath-hold from the transthoracic apical window, then the software created a full volume pyramid-shaped 3D dataset. The second step proved to be the data analysis, when using 3D Wall Motion Tracking software version 2.7 (Toshiba Medical Systems, Tokyo, Japan), data were presented in apical two- (AP2CH)

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and four-chamber (AP4CH) views.

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3DSTE-derived analysis of the tricuspid annulus

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For analysis of TA parameters, planes were optimized on these long-axis views to create an 'en-face' view of the TA on C7 short-axis view (12). End-diastolic (just before tricuspid valve closure) and end-systolic (just before tricuspid valve opening) measurements were performed:

TA morphological parameters

- TA diameter (TAD) = perpendicular line drawn from the peak of MA curvature to the middle of the straight MA border;
- TA area (TAA), measured by planimetry;
- (III) TA perimeter (TAP), measured by planimetry; TA functional features
- TA fractional shortening (TAFS) = [(end-diastolic TAD - end-systolic TAD)/end-diastolic TAD] ×100;
- TA fractional area change (TAFAC) = [(enddiastolic TAA - end-systolic TAA)/end-diastolic TAA] ×100.

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3DSTE-derived measurement of RA volumes

For measurement of RA volumetric parameters, a 3D 123 124 125 126 127

model of the RA was created by using the same software demonstrated in recent studies (13). Shortly, following image optimizations, edges of the TA and the endocardial side of the superior RA region were defined and then the endocardial RA surface was reconstructed. Using the 3D cast of the RA, the following volumetric RA parameters were calculated:

- V_{max}: end-systolic RA volume [largest left atrium (LA) volume before tricuspid valve opening];
- (II) V_{preA}: early diastolic RA volume (detected on ECG before atrial contraction at time of P wave);
- (III) V_{min}: late diastolic RA volume (smallest RA volume before tricuspid valve closure).

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Statistical analysis

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Continuous and categorical variables are presented as mean values ± standard deviation and frequencies and percentages, respectively. Levene's test was used to assess homogeneity of variances. Student's t-test was used in normally distributed data, while Mann-Whitney Wilcoxon test was used in case of not normally distributed data. Chi-squared test and Fisher's exact test were used for statistical analysis of categorical variables. All tests proved to be 2-sided and P<0.05 was considered to be statistically significant. Medcalc software package was used for statistical analysis (MedCalc, Mariakerke, Belgium).

Results

Clinical data

From the 24 adult cTOF patients, 12 had palliative surgery first [modified Blalock-Taussig (n=9), Waterston-Cooley (n=1) shunts, or Brock procedure (n=2)] (mean age at the palliation: 2.4±2.1 years, median age: 1.4 years, interquartile range: 3.5 years) followed by a late total correction (mean age at the total correction: 6.9±6.7 years, median age: 5.5 years, interquartile range: 6.5 years) (pcTOF group). Early total correction was performed in another 12 TOF patients (mean age at the repair: 3.9±3.1 years, median age: 5.0 years, interquartile range: 5.0 years) (etrTOF group). Demographic data and risk factors and their distribution in the cTOF group and subgroups and in controls are presented in Table 1.

2D echocardiographic data

Left atrial and left ventricular dimensions in controls and in patients with cTOF and in subgroups are presented in Table 1. TAPSE proved to be 18.7±3.2 mm in cTOF patients, which did not differ between TOF-early total reconstruction (etrTOF) and TOF-early palliation, late correction (pcTOF) patients (18.8±2.0 vs. 18.6±4.1 mm, P=ns). Valvular regurgitations and their severity expressed in grades are presented in Table 1. Mean RV pressure was 14.3±2.1 mmHg without residual pulmonary stenosis or narrowing of a pulmonary artery branch.

3DSTE

Dilated end-systolic and end-diastolic TA morphologic parameters and their BSA-indexed counterpart could be detected in cTOF patients as compared to controls (Table 2). TAFAC and TAFS proved to be reduced in cTOF patients as well as in etrTOF and pcTOF patients compared to controls. None of TA morphologic and functional parameter showed any differences between etrTOF and pcTOF patients. Increased maximum (64.0±32.1 vs. 36.9±9.5 mL, P<0.05), preatrial contraction (56.2±30.9 vs. 30.5±9.3 mL, P<0.05) and minimum (48.6±31.9 vs. 24.0±8.4 mL,

Table 1 Baseline demographic and 2D Doppler echocardiographic data in patients with tetralogy of Fallot and controls

Parameters	Controls (n=33)	All cTOF patients (n=24)	EtrTOF patients (n=12)	PcTOF patients (n=12)
Risk factors				
Age (years)	36.7±7.2	32.8±13.5	32.6±14.5	33.7±15.0
Male gender [%]	15 [45]	9 [41]	7 [58]	3 [25]
Hypertension [%]	0 [0]	5 [22]	2 [17]*	4 [33]*
Diabetes mellitus [%]	0 [0]	0 [0]	0 [0]	0 [0]
Hypercholesterolaemia [%]	0 [0]	1 [4]	0 [0]	1 [8]
Two-dimensional echocardiography				
LA diameter (mm)	38.4±3.2	41.3±6.5	41.2±7.2	41.3±6.0
LV end-diastolic diameter (mm)	48.5±2.8	50.1±14.1	47.3±5.6	47.9±5.6
LV end-diastolic volume (mL)	108.7±19.4	106.8±30.3	107.8±29.9	107.8±29.9
LV end-systolic diameter (mm)	32.1±2.1	30.7±5.7	30.7±5.1	30.7±6.4
LV end-systolic volume (mL)	37.9±7.0	38.0±19.9	37.7±20.0	38.4±20.6
Interventricular septum (mm)	9.2±1.0	9.8±1.5	9.5±1.1	10.1±1.9
LV posterior wall (mm)	8.9±1.0	9.5±1.4	9.3±1.4	9.8±1.4
LV ejection fraction (%)	65.1±2.4	65.5±8.7	65.5±6.3	65.5±10.9
Mitral regurgitation [%]				
Grade 1	0 [0]	13 [54]*	5 [41]*	8 [75]*
Grade 2	0 [0]	2 [8]	1 [8]	1 [8]
Tricuspid regurgitation [%]				
Grade 1	0 [0]	9 [37]*	6 [50]*	3 [25]*
Grade 2	0 [0]	11 [46]*	5 [42]*	6 [50]*
Grade 3	0 [0]	1 [4]	1 [8]	0 [0]
Grade 4	0 [0]	2 [8]	0 [0]	2 [16]*

^{*,} P<0.05 vs. controls. 2D, two-dimensional; cTOF, corrected tetralogy of Fallot; etrTOF, TOF-early total reconstruction; pcTOF, TOF-early palliation, late correction; LA, left atrial; LV, left ventricular.

P<0.05) RA volumes could be detected in cTOF patients

195 compared to controls.

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Correlations

End-diastolic TAD and TAA correlated with Vmax (r=0.58, P=0.05 and r=0.63, P=0.04, respectively), VpreA (r=0.50, P=0.05 and r=0.57, P=0.04, respectively) and Vmin (r=0.76,

P=0.03 and r=0.76, P=0.05, respectively). Similarly, end-

203 systolic TAD and TAA correlated with Vmax (r=0.57,

P=0.05 and r=0.63, P=0.05, respectively), VpreA (r=0.59,
 P=0.03 and r=0.55, P=0.05, respectively) and Vmin (r=0.76,

P=0.04 and r=0.73, P=0.05, respectively), as well. End-

diastolic and end-systolic TAP showed correlations with V_{min} only (r=0.56, P=0.05 and r=0.66, P=0.04, respectively). Only TAFS correlated with V_{min} (r=-0.45, P=0.05), other correlations between TA functional properties and RA volumes could not be detected. No correlations could be demonstrated between TAPSE and 3DSTE-derived TA dimensions and functional properties (TAFAC, TAFS) in cTOF patients.

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Discussion

To the best of the authors' knowledge, this is the first time to examine 3DSTE-derived TA abnormalities in adult

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Table 2 Comparison of 3D speckle-tracking echocardiography-derived TA morphological and functional parameters between adult patients with TOF and controls

Data	Controls (n=33)	Controls (n=33) All cTOF patients (n=24) EtrTOF patients (n=12) PcTOF patients		PcTOF patients (n=12)	
Morphological parameters					
TAD-D (cm)	2.15±0.23	2.74±0.45*	2.77±0.52*	2.71±0.38*	
TAD-D/BSA (cm/m²)	1.18±0.16	1.54±0.31*	1.47±0.24*	1.61±0.37*	
TAA-D (cm ²)	6.91±1.20	9.82±3.14*	9.86±3.76*	9.78±2.53*	
TAA-D/BSA (cm/m²)	3.78±0.74	5.51±1.70*	5.21±1.63*	5.81±1.79*	
TAP-D (cm)	10.17±1.51	12.26±1.72*	12.15±2.11*	12.38±1.31*	
TAP-D/BSA (cm/m²)	5.58±1.01	6.90±1.30*	6.48±1.00*	7.33±1.45*	
TAD-S (cm)	1.78±0.16	2.45±0.48*	2.48±0.56*	2.41±0.39*	
TAD-S/BSA (cm/m²)	0.98±0.11	1.38±0.31*	1.32±0.26*	1.43±0.35*	
TAA-S (cm ²)	5.25±1.21	7.98±2.62*	8.16±3.20*	7.80±2.02*	
TAA-S/BSA (cm/m²)	2.87±0.69	4.48±1.43*	4.30±1.37*	4.66±1.53*	
TAP-S (cm)	8.93±0.97	10.88±1.55*	10.78±1.90*	10.98±1.20*	
TAP-S/BSA (cm/m²)	4.91±0.78	6.12±1.19*	5.75±0.92*	6.50±1.34*	
Functional parameters (%)					
TAFAC	24.08±16.72	18.72±6.99*	17.52±6.85*	19.93±7.21	
TAFS	16.72±6.46	10.93±5.68*	10.65±6.09*	11.21±5.50*	

^{*,} P<0.05 vs. controls. 3D, three-dimensional TA, tricuspid annular; TOF, tetralogy of Fallot; cTOF, corrected tetralogy of Fallot; etrTOF, TOF-early total reconstruction; pcTOF, TOF-early palliation, late correction; TAD-D, end-diastolic tricuspid annular diameter; TAA-D, end-diastolic tricuspid annular area; TAP-D, end-diastolic tricuspid annular perimeter; TAD-S, end-systolic tricuspid annular diameter; TAA-S, end-systolic tricuspid annular area; TAP-S, end-systolic tricuspid annular perimeter; TAFAC, tricuspid annular fractional area change; TAFS, tricuspid annular fractional shortening.

cTOF patients and their relationship with RA volumes. Several disorders like cTOF itself may lead to FTR through TA dilation. In patients with atrial fibrillation, RA dilation were more important than RV dilation to determine TA dilation and subsequent FTR development. Minimum RA volume and TA area were directly correlated to FTR severity (14). Moreover, RA volume was found to be a major determinant of TA area, and RA enlargement is an important mechanism of TA dilation in FTR irrespective of the cardiac rhythm and RV loading conditions (15). In a recent 3DSTE study, detailed analysis showed increased RA volumes with reduced RA emptying fractions together with unchanged RA stroke volumes respecting the cardiac cycle in cTOF patients (5). In the present study, FTR was significantly common in cTOF patients with more pronounced presence in pcTOF cases. Both enddiastolic and end-systolic TA dimensions were found to be dilated in cTOF as compared to those of controls, and were accompanied with TA functional impairment.

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No differences could be demonstrated, however, in TA morphological and functional properties according to the surgical procedure performed. Moreover, strong correlations could be demonstrated between RA volumes and TA dimensions in cTOF suggesting a determinative relationship between these parameters.

Old-fashioned MME and the most recent 3DSTE together allows complex spatial analysis of the TA movement thought the cardiac cycle. Vertical movement of the TA represented by TAPSE and decreased horizontal 'sphincter-like' TA motion represented by TAFAC and TAFS did not correlate with each other in cTOF in this study. These results could suggest complexity of deterioration of TA functions in cTOF, which requires further examinations on the right heart function.

According to the surgical procedures used for TOF corrections, beneficial results could be demonstrated in recent studies related to LV contractility represented by LV strains (16) and LV rotational mechanics (17) and MA

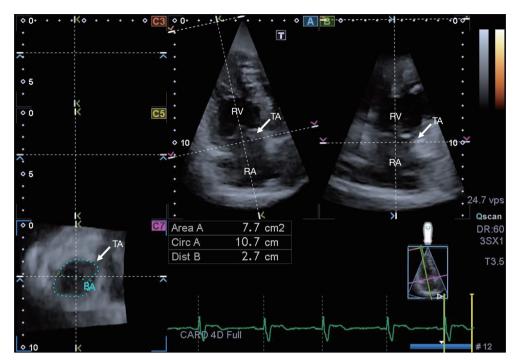


Figure 1 Images from a 3D echocardiographic full-volume dataset in a patient with repaired: (A) apical four-chamber view; (B) apical two-chamber view and a cross sectional view at the level of the tricuspid annulus; (C7) optimized on apical four- and two-chamber views. The arrow represents the TA plane on the long- (A,B) and short-axis (C7) images. 3D, three-dimensional; RA, right atrium; RV, right ventricle; TA, tricuspid annular.

morphology and function (18) in etrTOF patients compared to pcTOF patients. Similar findings could not be detected in TA parameters between the subgroups examined. These results could suggest fixed clinical situation on the right heart, but further studies are warranted to confirm our findings.

Limitation section

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The following important limitations were present:

- (I) 2D echocardiography has higher temporal and spatial resolution than 3DSTE, which could affect the results;
- (II) Interchamber and atrio-ventricular interactions could affect TA function, more detailed analysis would have strengthened the results;
- (III) Although TOF has a prevalence of 3–6 per 10,000 births, only limited number (n=24) of adult patients with cTOF were involved into the present study, which could affect the results;
- (IV) The normal reference values of 3DSTE-derived TA parameters are not available in the literature at this moment.

Conclusions

TA is dilated in cTOF with reduced function in adult patients with cTOF. TA dilation is related to RA volumes. etrTOF and pcTOF patients have similar TA dimensions and TA functional properties.

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Footnote

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Ethical Statement: the authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Informed consent was given by all cTOF patients and healthy controls. Institutional human research committee of the University of Szeged approved the study under the registration number 71/2011 (and updated versions). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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