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The effect of right ventricular myocardial remodeling on ventricular function as assessed by two-dimensional speckle tracking echocardiography in patients with tetralogy of Fallot: A single center experience from China

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ABSTRACT

Background: Published correlations between histological abnormalities and right ventricular (RV) function, as evaluated by speckle tracking echocardiography (STE), are scarce in patients with tetralogy of Fallot (TOF). The purpose of the study is to assess age-associated differences in the effect of RV myocardial remodeling on ventricular function in patients with TOF.

Methods: Operatively resected crista supraventricularis muscle from 30 patients (median age 12 months) undergoing intracardiac repair of TOF were studied by light microscopy. The patients were divided into younger (age at surgery ≤12 months) and older (age at surgery >12 months) subgroups. The RV global longitudinal peak systolic strain (GLS), strain rate (GLSRs) and early diastolic strain rate (GLSRe) were measured by two-dimensional STE before and 6 months after repair.

Results: The histopathological data revealed hypertrophy of the cardiomyocytes, a thickened endocardium, and increased interstitial and perivascular collagen in RV, which were associated with older age at the time of repair. The RV global systolic and diastolic functions in patients with repaired TOF were increased compared with the preoperative values. The RV cardiomyocyte diameter and collagen volume fraction (CVF) correlated with the preoperative GLS, GLSRs and GLSRe, respectively, in the younger patients ($r_1 = -0.566$, $P_1 = 0.018$; $r_2 = -0.493$, $P_2 = 0.004$; $r_3 = -0.504$, $P_3 = 0.039$). The RV cardiomyocyte diameter and CVF correlated with preoperative GLS, GLSRs and GLSRe, respectively, in the older patients ($r_1 = -737$, $P_1 = 0.004$; $r_2 = -0.588$, $P_2 = 0.035$; $r_3 = -0.812$, $P_3 = 0.001$). The correlation of the RV cardiomyocyte diameter with the postoperative GLS and GLSRe ($r_1 = -665$, $P_1 = 0.036$; $r_2 = -0.787$, $P_2 = 0.007$) and the CVF with the postoperative GLSRs and GLSRe ($r_1 = -762$, $P_1 = 0.002$; $r_2 = -0.713$, $P_2 = 0.004$) were identified only in the older patients. Multivariate analysis indicated that the age at repair was an independent predictor of postoperative GLSRs and GLSRe in all of the patients ($\beta = -0.449$, $P = 0.041$; $\beta = -0.607$, $P = 0.004$).

Conclusions: The effect of RV myocardial remodeling on preoperative RV function was more pronounced in the older patients with TOF than in the younger ones. Preoperative myocardial remodeling affected the postoperative RV function in the older but not in the younger patients. The age at the time of surgical repair was the independent determinant of the postoperative RV myocardial function.

1. Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease. Early repair of TOF is advised to minimize the effect of long-standing hypoxia and pressure overload. The optimal timing for surgical correction in children is less than 1 year of age in developed countries. In China, children operated on for TOF are typically older than 1 year because of poor socioeconomic conditions; sometimes

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surgery for TOF was even deferred till adulthood. A late repair might cause additional myocardial remodeling that would affect postoperative outcome.

Most patients with TOF have an uneventful postoperative course; however, a small number of patients experience a problematic postoperative recovery. Identifying the major predisposing risk factors for postoperative RV myocardial dysfunction is crucial to the clinical decision-making process. A small number of studies have demonstrated right ventricular (RV) histopathological abnormalities in TOF patients, including cardiomyocyte hypertrophy, fibrosis, edema, and degenerative changes. These changes might explain postoperative ventricular dysfunction and arrhythmias [1–4]. However, in a prior RV function study, the parameters were obtained from conventional two-dimensional echocardiography, which depends on geometric assumptions [3]. Owing to the complex geometry of the right ventricle, the conventional two-dimensional quantification of RV performance might be considered less accurate. Farah et al. [4] observed the relationship between the preexisting myocardial histopathological findings and postoperative ventricular function, as determined by tissue Doppler imaging (TDI). TDI has an intrinsic limitation of angle-dependence; the angle-dependent method could less accurately assess myocardial performance. Farah et al. [4] did not study children younger than 12 months. The effect of patient's age at the time of surgical repair and its consequences on myocardial remodeling warrant further investigation.

Recently, two-dimensional speckle tracking echocardiography (STE) has emerged as a novel method to assess myocardial performance. This technique does not depend on ventricular geometry and has no angle-dependence. The STE-derived strain and strain rate have been described as more sensitive markers for detecting changes in myocardial performance than conventional echocardiographic parameters of RV function [5]. This approach could be widely used in the evaluation of RV regional and global function [6–8]. To the best of our knowledge, no studies have been performed to determine the correlation between these histopathological abnormalities and RV dysfunction, as assessed by STE, in patients with TOF.

The purpose of our study was to analyze RV myocardial remodeling in younger and older patients with TOF, to evaluate the age-associated differences in the effect of RV myocardial remodeling on ventricular function assessed by STE in patients with TOF, and to explore the possible factors that might predict postoperative RV myocardial dysfunction, including the age at the time of surgical repair, the histopathological abnormalities, the systemic arterial oxygen saturation, the hematocrit, and the pressure gradient across the RV outflow tract.

2. Methods

2.1. Study population

From March 2008 to May 2010, 30 consecutive patients with TOF who were scheduled for intracardiac repair in our hospital (23 males, 7 females; median age = 12 months, mean = 63.2 months, range 4–384 months) were enrolled in our study. The inclusion criteria included also the following: concomitant small atrial septal defects or patent foramen ovale. Patients with pulmonary atresia or atrioventricular septal defect were excluded from our study. The patients were divided into younger (age at surgery ≤12 months, 16 cases) and older (age at surgery >12 months, 14 cases) subgroups. All of the patients were in sinus rhythm. The study was approved by our institutional review ethics board.

2.2. Clinical assessment

The arterial oxygen saturation (SaO_2) and hematocrit were assessed using standard laboratory techniques in all the patients. All of the patients received a 12-lead electrocardiogram. The QRS duration was measured from the onset of the Q wave to the end of the S wave on the standard 12-lead ECG. The clinical data were thoroughly assessed before surgery.

2.3. Echocardiography

The echocardiogram was performed using a commercially available ultrasound transducer and equipment (M3S and M7S probes, Vivid 7; GE Medical Systems, Horten, Norway). The RV end-diastolic diameter (RVEDD) and right atrial diameter (RA) were determined from the apical four-chamber view [9]. The left ventricular end-diastolic diameter (LVEDD) was obtained from the parasternal long-axis view. The gradient across the RV outflow tract (RVOT) was measured using continuous-wave Doppler. For the conventional RV function assessment, the tricuspid annular peak systolic velocity (Sm), early diastolic velocity (Em) and late diastolic velocity (Am) assessed by TDI, and tricuspid annular peak systolic excursion (TAPSE) assessed by M-mode echocardiography were measured from the apical four-chamber view at the RV free wall level [9]. The left ventricular ejection fraction (LVEF) was assessed according to the biplane Simpson's rule.

Two-dimensional grayscale images of the subjects were obtained by using the apical four-chamber view at frame rates of 60 to 90 per second. All of the images were digitally stored for off-line analysis (EchoPAC, version BT06; GE-Vingmed, Norway). For the speckle tacking analysis, the RV endocardial border was manually traced in the end-systolic frame. The region of interest (ROI) in each image was automatically generated. The position of the ROI and its width was adjusted manually when the speckle tracking appeared to be poor. The software automatically tracked and accepted segments of good tracking quality. When all the segments of the RV were accepted, the RV global longitudinal strain and strain rate curves were automatically generated. The RV global longitudinal strain and strain rate were based on the average of the six RV segments (the basal, mid, and apical segments of the RV free wall and septum). Representative examples of the global longitudinal strain and strain rate curves taken from the right ventricle in the patients with TOF by STE are shown in Fig. 1.

All of the echocardiographic parameters were measured three times, and the mean value was used for the analysis. The echocardiographic studies were performed by the same investigator before surgery and 6 months after surgery.

2.4. Histopathological analyses

The resected crista supraventricularis muscle during intracardiac repair of TOF was subjected to histopathological evaluation by light microscopy. Tissue samples were processed routinely for histology as follows: 5-μm thick sections were stained by hematoxylin and eosin. Masson's trichrome staining was performed for the collagen quantification. The morphometric measurements were performed with an interactive computerized system of image analysis (Leica Qwin version 2.2, Leica Imaging Systems, Inc.).

2.4.1. Cardiomyocyte diameter

The smallest transverse cardiomyocyte diameter was measured along a line that intercepted the respective nucleus at 400× magnification, and 60 cells per section were measured in at least 10 different fields. The results were compared with normal values as published in the literature [1,10]. Mean cardiomyocyte diameter values higher than the normal value plus two standard deviations were considered histological hypertrophy. The degenerative changes observed as incontractile elements of cardiac myocytes are known as myocytolysis (cellular vacuolization).

2.4.2. Endocardial thickness

Based on the varying degrees of endocardial thickening, the endocardial thickness was measured at magnifications of 40×, 100× and 200×. At least 10 microscopic fields were evaluated per section.

2.4.3. Interstitial collagen content analysis

Interstitial collagen content was obtained in at least 10 microscopic fields at 200× magnification. For collagen quantification, the collagen volume fraction (CVF) was described as a percentage of the positively stained area relative to the total area of the myocardium. Replacement fibrosis and perivascular fibrous tissue more than 30 μm in diameter were excluded from the analysis. The results obtained were compared with the reference values in the literature [11,12].

2.5. Statistical analysis

The statistical analysis was performed with an SPSS software package (SPSS for Windows 11.5). The continuous data were expressed as the mean value, standard deviation and medians. The TOF and control groups were compared using a Mann–Whitney U test. The preoperative and postoperative RV functions were compared using a paired-samples t-test. The correlations between the histopathological parameters and the RV function were calculated as Pearson's or Spearman's correlation coefficients, depending on the data distribution. The independent determinants of the echocardiographic RV function in the patients with TOF were examined using a multivariate stepwise linear regression analysis. The intra-observer and inter-observer variability was assessed in 10 randomly selected subjects. The intra-observer and inter-observer reproducibility was evaluated using the intra-class correlation coefficient (ICC). For all the analyses, a value of $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics

The patient characteristics of our study are listed in Table 1. The mean SaO_2 was 83.74% (median 89.0%, ranging from 64% to 99%).The mean hematocrit was 41.28% (median 41.45%, ranging from 30% to