Relationship between ventricular function assessed by tissue Doppler imaging and exercise capacity in patients after repair of tetralogy of Fallot: an observational study

Tam düzeltme ameliyatı yapılan Fallot tetralojili hastalarda doku Doppler ekokardiyografisi ile değerlendirilen ventrikül fonksiyonlarının egzersiz kapasitesi ile ilişkisi: Gözlemeli bir çalışma

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ABSTRACT

Objective: The present study aims to study the relationship between tissue Doppler echocardiography (TDE) indices of right ventricle and exercise capacity in patients after total correction for tetralogy of Fallot (ToF).

Methods: This cross-sectional observational study included 20 patients, after undergoing total correction procedure for ToF diagnosed with mild/moderate pulmonary regurgitation and 30 age-matched healthy children. In the postoperative period, patients were invited to hospital for evaluation of the ventricular functions by 2D, M-mode, Doppler (DE) echocardiography and TDE and exercise testing to evaluate the effort capacity. Statistical analysis was performed using Mann-Whitney U and Chi-square tests, and Pearson correlation analysis.

Results: Compared with the controls; the mitral annular peak systolic flow velocity (Sm) value was significantly lower, while isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT) and myocardial performance index (MPI) values obtained at the tricuspid and mitral (MV) valves were significantly higher (p<0.05 for all) in patients after ToF repair. There was a negative correlation between the exercise period and the total correction age (r=-0.20, p=0.015) and the same negative correlation existed between the exercise period and METS (r=-0.25, p=0.010). Left ventricular MPI was found to be correlated with maximum heart rate (r=-0.20, p=0.03). MV IVCT with DE and TDE was found to be correlated with METS (r=-0.45, p=0.04). Left ventricular MPI was found to be correlated with maximum heart rate (r=-0.15, p<0.01).

Conclusion: Even if patients, undergone total correction surgery for ToF were asymptomatic or had minimal clinical symptoms, MPI index assessed by pulse wave TDE and exercise testing may allow early diagnosis of right ventricle dysfunction.

(Anadolu Kardiyol Derg 2012; 12: 490-7)

Key words: Echocardiography, exercise test, tetralogy of Fallot, cardiovascular surgical procedures, ventricular function

ÖZET

Amaç: Tam düzeltme ameliyatı yapılan Fallot tetralojili hastalarda doku Doppler yöntemli ile elde edilen sağ ventrikül fonksiyonları ve egzersiz kapasitesi arasındaki ilişkiyi çalışmayı amaçlamaktayız.


Bulgular: Kontrol grubu ile karşılaştırıldığında, Fallot tetralojili hasta grubunda mitral annüler pik sistolik hız (Sm) değeri belirgin olarak düşük, trikuspid ve mitral (MV) kapaktan elde edilen izovolümik relaksasyon zamanı (IVRT), izovolümik kontraksiyon zamanı (IVCT) ve miyokart performans indeksi (MPI) değerleri daha yüksek idi (tümü için p<0.05). Egzersiz süresi ile total düzeltme yaşını araştırarak negatif korelasyon saptandı (r=-0.20, p=0.015), aynı korelasyon egzersiz süresi ile METS arasında da mevcut idi (r=-0.25, p=0.010). Pulse ve doku Doppler ile elde
Introduction

Tetralogy of Fallot (ToF) is a cyanotic congenital heart disease characterized by an underdeveloped right ventricular outflow tract (RVOT), RVOT stenosis (caused by the anterolateral displacement of the infundibular septum), large malalignment type ventricular septal defect and overriding of the aorta (1). Total correction of ToF refers to the closure of the ventricular septal defect with a patch and correction of the RV outflow tract stenosis (2-4).

The patients with ToF usually have left ventricular (LV) dysfunction before surgery and there is no further deterioration after surgery (5-8). On the other hand, right ventricular (RV) volume increases and ejection fraction decreases after surgery. These post-operative alterations have been attributed to pulmonary insufficiency, pre-operative hypoxia and ventriculotomy (8-12). Restrictive physiology is defined as antegrade blood flow to the pulmonary artery during late diastole. It has been proposed that this physiology protects against RV dilation after total correction of ToF (9-14).

The complex geometry of the right ventricle, limits the usefulness of conventional echocardiography (14, 15). Magnetic resonance imaging (MRI) and radionuclide ventriculography are the reference methods to evaluate the ventricle functions, but they are costly, and time-consuming (16, 17). Measurement of myocardial velocities by tissue Doppler imaging (TDI) is useful for assessing LV and RV function (17, 18). Pulsed TDI of the tricuspid annulus is non-invasive and has recently been shown to be a reliable method of assessing RV function compared to the gold standard of magnetic resonance imaging (19). Since diastolic dysfunction starts before systolic dysfunction, early diagnosis of diastolic dysfunction by tissue Doppler echocardiography may be helpful (20, 21).

The determination of exercise capacity would indicate the necessity of surgical intervention, catheter angiography or re-evaluation in congenital heart diseases (20). However, exercise test (ET) is subjective and it cannot be performed at every age group. In patients with ToF, any increase in end-diastolic volume can cause deterioration of right heart functions, which may even worsen during exercise (22, 23).

The present study aims to study the relationship between tissue Doppler indices of right ventricular function and exercise capacity in patients after TOF repair.

Methods

Study design

This cross-sectional observational study was approved by the local Ethics Committee of Dr. Behçet Uz Pediatrics and Pediatric Surgery Research and Education Hospital, where the study was conducted. Written informed consent was obtained from the participants and their parents.

Study population

Between the years 2009-2010, 20 patients who were diagnosed with mild or moderate pulmonary regurgitation in the department of tertiary pediatric cardiology unit after undergoing total correction procedure for ToF and 30 age-matched healthy children were included in the present study. Four children with ToF (20%) received palliative treatment before total correction procedure, which was performed after an average period of 2.8±0.5 years. All of the participants were clinically evaluated by physical examination, telecardiography and electrocardiography.

Variables

Baseline demographic, clinical and laboratory parameters are; gender, age, heart rate, tension arterial, and hemoglobin; primary outcome variables are tissue Doppler RV and LV function parameters, secondary outcome variable is exercise capacity.

Study protocol

The follow-up period of the patients was mean 4.5±2.7 years (range: 1.0-13.0 years). All children underwent clinical evaluation, electrocardiographic, echocardiographic and exercise test study.

Echocardiography

All of the patients and healthy controls were assessed by a Vivid 3 echocardiography device with 3 and 5 mHz probes (General Electric, NE, USA) under electrocardiographic monitoring. The same pediatric cardiologist performed two-dimensional echocardiography, color Doppler, pulse wave Doppler, continuous wave Doppler and pulse wave tissue Doppler examinations.

Two-dimensional echocardiograms of the parasternal short-axis view at the level of the aortic root were obtained and the RVOT was visualized. M-mode recordings of the RVOT were obtained and dimensions were measured at end- diastole (onset of the Q wave) and end-systole (end of T-wave) using endocardial leading edge methodology. RV fractional shortening was calculated as the percentage fall in RVOT diameter in systole with respect to that in diastole. RV long -axis function was recorded from the apical four-chamber view with the M-mode cursor positioned at the free wall angle of the tricuspid valve annulus. Total RV long -axis excursion amplitude was taken from end-systole to end-diastole (13).

RVOT SF: [(RVOTd-RVOTs)/RVOTd]x100

edilen MV IVCT, METS ile korele bulundu (r=-0.45, p<0.04). Sol ventrikül MPI maksimum kalp hızı ile korele bulundu (r=-0.20, p<0.03). Triküspit kapak deselerasyon zamanı ve doku Doppler Sm değeri METS ile korele (siraya; r=-0.30, p<0.04; r=-0.25, p=0.005); doku Doppler MPI, maksimum kalp hızı ile korele (r=-0.15, p<0.01) bulundu.

Sonuç: Tam düzeltme operasyonu olan hastalar asemptomatik veya klinik bulguları çok az bile olsa doku Doppler ekokardiografi ile ölçülen MPI değeri ile egzersiz testi sağ ventrikül disfonksiyonunun erken tanısında kullanılabılır. (Anadolu Kardiyol Derg 2012; 12: 490-7)

Anahtar kelimeler: Ekokardiografi, egzersiz testi, Fallot tetralojisi, kardiyovasküler cerrahileri, ventriküller fonksiyon
For assessment of the degree of enlargement of the RV, the RV end-diastolic diameter (RVEDD) was indexed to the LV end-diastolic diameter (LVEDD), finally given as RV dilatation index (RVDI=RVEDD/LVEDD). RV size was classified as normal when RVDI was equal or less than 0.5 (24).

Tricuspid regurgitation (TR) was assessed on a scale from 1 to 3, grade 1 for trivial, grade 2 for mild, and grade 3 for severe.

To evaluate LV mass index, Devereux Formula is used (25)

\[ \text{LV mass} = 1.04 \times (\text{LVID} + \text{PWT} + \text{IVST})^3 - (\text{LVID})^3 - 13.6 \text{ g} \]

The tricuspid valve Doppler signals were recorded in the apical 4-chamber view, with the Doppler sample volume placed at the tip of the valve. Peak early filling velocity (E wave), peak atrial systolic velocity (A wave), early-to-late diastolic flow ratio (E/A), deceleration time (dTE), isovolumic relaxation time (IVRT) and isovolumic contraction time (IVCT) were measured for the tricuspid valve (26). Tricuspid annular plane systolic excursion (TAPSE) was calculated with 2-dimensional echocardiography-guided M-mode recordings from the apical 4-chamber view with the cursor placed at the free wall of the tricuspid annulus (27). Care was taken in aligning the sample volume as vertical as possible with respect to the cardiac apex. Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the lowest point of descent during ventricular systole.

Tissue Doppler echocardiography (TDE) was performed from the apical four-chamber view. Myocardial velocity profiles of the lateral tricuspid annulus were obtained by placing the sample volume at the junction of the tricuspid annulus and the RV free wall, respectively. With this modality, the values recorded were the early (Em) and late (Am) diastolic mitral annular velocity, and the ratio of Em/Am (28).

The myocardial performance index (MPI) was calculated according to the following equation: \( \text{MPI} = (\text{IVCT + IVRT})/\text{ET} \).

The mean values were recorded by averaging the results of five consecutive measurements.

**Exercise test**

Exercise Test (ET) was performed on a treadmill (LE 200 CE, h/p.Cosmos sports&medical GmbH, Nussdorf-Traunstein, Germany) according to modified Bruce protocol. The heart rate and electrocardiographic changes were monitored continuously; blood pressure was measured every minute with an indirect automatic manometer throughout the test. ST elevation or depression, negative T-waves, maximum blood pressure, heart rate, and if present, symptoms were noted, QRS duration and QTc were calculated during exercise.

Treadmill test depends on the principle of walking or running on either a speed and slope adjustable rolling band. In compliance with modified Bruce protocol, treadmill test was terminated whenever target heart rate was achieved and/or there was exhaustion, shortness of breath or serious ventricular arrhythmia. Maximum heart rate, maximum blood pressure, metabolic equivalents (METs) and exercise period were recorded. The test was regarded as suboptimal for patients in whom target heart rate was not achieved.

**Statistical analysis**

Collected data were analyzed by Statistical Package for Social Sciences version 12.0 (SPSS Inc, Chicago, IL, USA). All variables are presented as mean±standard deviation; and minimum-maximum values. Comparison between patients and controls was performed using Mann-Whitney U and Chi-square tests, while Pearson test was utilized to specify the correlations. A p<0.05 was accepted to be statistically significant.

**Results**

**Baseline characteristics (Table 1)**

The present study included 20 patients (8 females, 12 males) and 30 healthy controls (13 females, 17 males). Both the patients and controls were statistically similar in aspect of mean age, body weight, systolic blood pressure and diastolic blood pressure.

The follow-up period of the patients was 4.5±2.7 years in average (range: 1.0-13.0 years). Four children with ToF (20%) received palliative treatment before total correction procedure was performed after an average period of 2.8±0.5 years. The mean age was 3.5±1.5 years (range: 1.0-7.0) at the time of total correction. Two patients with ToF had transatrial surgery whereas transventricular surgery was preferred in 18 patients. Transannular patch was placed in four patients in whom transventricular intervention was accomplished. The mean duration of intensive care unit stay and hospitalization were respectively 3.0±3.1 days and 9.5±7.1 days. All patients’ electrocardiographic evaluation showed sinus rhythm with QRS time increase (the mean QRS time was 145±15 msec) and right bundle block accompanied by right axis deviation. Mean cardiothoracic index on telecardiography was 0.50±0.05.

**Echocardiography (Tables 2-4)**

The patient and control groups were statistically significantly different in the following aspects: LVEDD was lower...
(p=0.008), RVOT fraction shortening (SRVOT) and LV mass were decreased (p<0.0001 and p=0.049), while tricuspid ring diameter (TR diameter), RV diastolic long-axis diameter, RV systolic long-axis diameter, RV EDV, RV end systolic diameter (RVESD) and RVDI parameters were increased (p<0.001 for all) in patient group. No statistical significance was found in tricuspid annular plain systolic excursion (TAPSE) values. Two patients had tricuspid insufficiency, that the TR velocity was 2.3 and 3.5 m/sec. The RVOT gradient was 26 and 54 mmHg.

Table 3 summarizes the pulse Doppler and pulse tissue Doppler echocardiographic parameters. Accordingly, with pulse wave Doppler echocardiography, the patient and control groups had statistically significant differences in tricuspid valve A velocity, tricuspid valve E/A flow velocity ratio, and IVRT (p<0.001, <0.001, p=0.029, respectively). When compared with the healthy controls; the pulse tissue Doppler parameters such as Sm value was significantly lower while IVCT, IVRT and MPI values were significantly higher in patients with ToF (p=0.007, p=0.035, p=0.004, and p<0.001, respectively).

Table 4 demonstrates the pulse Doppler and pulse tissue Doppler measurements obtained from mitral valve. Compared with the control group; MV deceleration time was lower.
MV A, and MV IVCT were higher group (p=0.049, p<0.001, respectively) in patients after ToF repair. Similarly, tissue Doppler echocardiography MV IVCT, IVRT and MPI values were significantly higher in patients with ToF (p=0.031, p=0.034, p<0.001, respectively) as compared with controls.

Exercise test (Table 5)

Exercise test could not be performed in one patient who was unable to cooperate. Moreover, another patient was unable to complete the exercise test due to exhaustion. The exercise test was regarded to be suboptimal in 12 of 19 patients (63.1%). Maximum heart rate was 132.5±13.3 bpm. METS value was found to be 6.9±1.49. There was negative correlation between the exercise period and the total correction age (r=-0.20, p=0.015) and the same negative correlation existed between the exercise period and METS (r=-0.25, p=0.010).

Correlation between tissue Doppler and exercise test variables (Tables 6, 7)

MV IVCT by pulse Doppler echocardiography was found to be correlated with METS (r=-0.45, p=0.04). Tissue Doppler MV IVCT was correlated with METS (r=-0.45, p=0.04), LV MPI was found to be correlated with maximum heart rate (r=-0.20, p=0.03). Yet by Doppler echocardiography, exercise test parameters especially METS was significantly correlated with tricuspid valve deceleration time (r=-0.30, p=0.04); while MPI calculated with tissue Doppler echocardiography was correlated with maximum heart rate (r=-0.15, p<0.01), and Sm peak flow velocity with METS score (r=-0.25, p=0.005) (Table 7).

Discussion

In this study, we observed that even if patients, undergone total correction surgery for ToF were asymptomatic or had minimal clinical symptoms, MPI index assessed by PW TDE and exercise testing may allow early diagnosis of right ventricular dysfunction. Compared with the controls; the mitral Sm value was significantly lower while IVCT, IVRT and myocardial performance index values obtained at the tricuspid and mitral valves were significantly higher. There was negative correlation between the exercise period and the total correction age and the same negative correlation existed between the exercise period and METS. Transthoracic and tissue Doppler MV IVCT
was found to be correlated with METs. LVMPI was found to be correlated with maximum heart rate. Tricuspid valve deceleration time and Sm peak flow velocity were significantly correlated with METs.

Many patients with TOF following successful operations reach adolescent and adult ages. The overall survival rate of patients with repaired TOF is good, with mortality of less than 6% at 25 years after corrective surgery (29).

RV systolic and diastolic dysfunction commonly occurs after total correction surgery for TOF is performed. It has been hypothesized that the problems encountered during the follow-up of patients who underwent TOF repair are related with the RV physiology. Pre-operative hypoxia and hypertrophy, intra-operative myocardial damage and postoperative pulmonary regurgitation (PR) may participate in the etiopathogenesis of RV dysfunction (22, 23).

Both PR and TR are seen frequently in patients with TOF after repair. The prognosis is good; however, because of long-term volume overload, in patients with moderate or severe regurgitation, progressive RV dysfunction takes place in time (18, 19). It is impossible to assess RV dysfunction according to the clinical findings. PR and TR are well-tolerated by the patients. In the presence of severe regurgitation, especially PR, the risk for arrhythmia, heart failure, and sudden death increases (30). In our study, two patients had severe tricuspid regurgitation that the TR velocity was 2.3-3.5 m/sec. and the RVOT gradient was 26-54 mmHg.

The studies indicate that the Doppler pulse echocardiography usually shows the reduction in tricuspid valve E/A ratio and prolongation of IVRT, which indicate restrictive pattern in the RV. Chaturvedi et al. (31) presented prolonged relaxation time and decreased E/A ratio in these category of patients. In our study, we also found that TV IVRT was significantly higher compared to the control group.

On the other hand, it was shown that age, heart rate, sample volume position, RV preload and function might affect Doppler time intervals (32). Cullen et al. (20) confirmed the existence of restrictive pattern in the RV by showing that tricuspid valve E/A ratio did not vary with inspiration and expiration in TOF patients who had total correction surgery. We also found that TV E/A values were significantly lower when compared with the control group. This result can be explained by increased A wave, and restrictive physiology of the ventricle.

Due to the complex geometry of the RV, the utilization of conventional echocardiographic techniques (such as two-dimensional or M-mode pulse wave Doppler) is insufficient to diagnose RV dysfunction (16).

MPI overall reflects the systolic and diastolic functions of the ventricles. It has been recently reported that MPI can be efficiently used to evaluate the global RV functions in patients who developed valve insufficiency after surgery (33).

Lindqvist et al. (13) reported that the systolic functions of the RV can be assessed by measuring RVOT end-diastolic and end-systolic diameters obtained by two-dimensional M-mode echocardiography throughout the parasternal short-axis. Yauoka et al. (34) stated that MPI assessed by tissue Doppler echocardiography (rather than pulse wave Doppler echocardiography) successfully pointed out the RV functions of the patients who developed PR after total correction of TOF. The present study also showed that LV and RV MPI values obtained by pulse tissue Doppler were significantly increased in the patients with TOF.

Evaluation of the tricuspid valve by pulse Doppler echocardiography resulted in statistically significant differences in tricuspid valve A, tricuspid valve E/A, and IVRT values. When compared with the healthy controls, the patients with TOF had significantly lower Em peak velocity whereas significantly higher IVCT, IVRT and MPI as evaluated by pulse wave tissue Doppler echocardiography.

MRI and radionuclide ventriculography are the reference methods but they are costly, and time-consuming (16, 17). Measurement of myocardial velocities by tissue Doppler imaging is useful for assessing left and RV function (18). Pulsed TDI of the tricuspid annulus is noninvasive and has recently been shown to be a reliable method of assessing RV function compared to the gold standard of MRI (19). The present study also shows significant changes, among TDI parameters such as LV MPI and RV MPI.

The patients who have total correction surgery for TOF should undergo annual exercise test in order to determine the maximum heart rate, blood pressure response and any arrhythmias provoked during physical stress.

D’Andrea reported that Em flow rate values less than 0.13 msec (as measured at the tricuspid annulus by pulse wave tissue Doppler echocardiography) can predict submaximal exercise test with 90% sensitivity and 93% specificity (35). The present study showed that exercise test was suboptimal in twelve patients and two of these patients had Em flow velocity rate less than 0.13 msec (0.10-0.11 m/sec). Moreover, there were statistically significant correlations between tricuspid valve Em/Am flow velocity ratio, deceleration time, MPI and IVCT parameters. The exercise test parameters were found to be unrelated with the measurements obtained by two-dimensional echocardiography. In addition, these parameters did not correlate with the systolic and diastolic measurements of the LV obtained by either pulse Doppler or pulse tissue Doppler echocardiography except IVRT and IVCT. There was no correlation between left and RV MPI values.
Harada et al. (36) reported that an insufficient increase in Sm suggests impaired response to exercise of RV in patients with ToF. We found a negative correlation between Sm and METS index ($r=-0.25$). Cheung reported that RV MPI correlated inversely with exercise duration ($r=-0.45$, $p=0.013$) and peak oxygen consumption ($r=-0.56$, $p=0.001$). Increased MPI is a reflection of reduced exercise capacity in patients after TOF repair (37). In our study, we observed negative correlation between TV deceleration time, RV Sm peak velocity and METS ($r=-0.30$, $-0.25$, respectively). After the examination of LV, we found negative correlation between IVCT, both measured with pulse Doppler and pulse tissue Doppler, and METS ($r=-0.45$, $-0.30$)

**Study limitations**

The limitation is the number of the study group. These patients were all operated just in one pediatric cardiac surgery unit and follow-up made by only our department to minimize the observer variability. That is why these results may not indicate a satisfactory answer, we thought this study as a midterm result and we will continue to evaluate new ToF patients.

**Conclusion**

Pulse wave tissue Doppler echocardiography can be used to determine the left and RV dysfunction in patients who has undergone total correction surgery for ToF within a short-to-moderate postoperative period. Even if these patients were asymptomatic, MPI index assessed by pulse wave tissue Doppler echocardiography may allow early diagnosis of RV dysfunction. For further diagnostic workup; tricuspid deceleration time, Sm peak velocity, Em/Am flow velocity ratio, MPI and IVCT parameters can be considered whenever the evaluation of exercise capacity is a necessity and exercise test cannot be performed.

**Conflict of interest:** None declared.

**Authorship contributions.** Concept - VT, B.Ş.; Design - B.Ş.; Supervision - VT; Resource - VT; Materials - VT; Data collection&/ or Processing - B.Ş.; Analysis &/or interpretation - A.Ç.; Literature search - A.Ç.; Writing - B.Ş., A.Ç.; Critical review - A.Ç., B.Ş.

**References**

9. Lange PE, Onnasch DG, Bernhard A, Heintzen PH. Left and right ventricular adaptation to right ventricular overload before and after surgical repair of tetralogy of Fallot. Am J Cardiol 1982; 50: 786-94. [CrossRef]
19. Harada K, Tamura M, Toyono M, Yasuoka K. Comparison of right ventricular Tei index by tissue Doppler imaging to that obtained by pulsed Doppler in children without heart disease. Am J Cardiol 2002; 90: 566-9. [CrossRef]


27. Caplin JL. The difficulties in assessing right ventricular function. Heart 1996; 75: 322. [CrossRef]


32. Serwer GA, Cougle AG, Eckerd JM, Armstrong BE. Factors affecting use of the Doppler-determined time from flow onset to maximal pulmonary artery velocity for measurement of pulmonary artery pressure in children. Am J Cardiol 1986; 58: 352-6. [CrossRef]


