International Journal of Cardiology 159 (2012) 220–224

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Increased microvolt T-wave alternans in patients with repaired tetralogy of Fallot ☆

Shuenn-Nan Chiu, Hsin-Hui Chiu, Jou-Kou Wang, Ming-Tai Lin, Chun-An Chen, En-Ting Wu, Chun-Wei Lu, Mei-Hwan Wu *

Department of Pediatrics, National Taiwan University Hospital and Medical College, National Taiwan University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 13 October 2010
Received in revised form 19 January 2011
Accepted 25 February 2011
Available online 21 March 2011

Keywords:
Tetralogy of Fallot
Microvolt T wave alternans
Treadmill
EKG

ABSTRACT

Background: Microvolt T wave alternans (MTWA) is an indicator of repolarization heterogeneity and a predictor of ventricular arrhythmia in adults with ischemic or dilated cardiomyopathy. Its implication in patients with repaired tetralogy of Fallot (TOF) is still unclear. This study sought to define the changes and the clinical implication of MTWA in these patients.

Methods: Treadmill examination with modified moving average beat analysis (MMA) for MTWA was performed in 101 repaired TOF patients (60.4% male). Data from 103 age- and sex-matched subjects with normal hearts served as controls.

Results: The age at latest follow-up was 20.0 ± 10.6 years. Total repair (60.4% received a transannular right ventricular outflow patch) was performed at a mean age of 4.8(± 5.8) years. After excluding 11 patients with indeterminate data, the MTWA data in 90 TOF patients revealed higher values than those in the control (25.1 ± 14.0 vs. 17.6 ± 9.2 μV, $p<0.001$). The values were best correlated to the presence of severe pulmonary regurgitation ($p=0.006$). Ten (9.9%) patients experienced late ventricular arrhythmic events. They tended to have higher MTWA values than those without (34.0 ± 16.5 vs. 24.2 ± 13.5 and $p=0.053$). Although the MTWA per se would not predict the late arrhythmia events better than QRS duration alone, the positive and negative predictive values increased slightly after adding the MTWA to QRS duration.

Conclusions: MTWA, as measured by MMA, increased in repaired TOF patients particularly in those with severe pulmonary regurgitation and late arrhythmia events. To predict late ventricular arrhythmia, MTWA however was not superior to QRS duration alone.

1. Introduction

With advances in cardiac interventions, the outcome of patients with tetralogy of Fallot (TOF) has been much improved. Long-term follow-up, however, revealed that repaired TOF patients were still at risk of ventricular arrhythmia and sudden cardiac death [1,2]. The proposed mechanism of ventricular arrhythmia included macro-reentry tachycardia and repolarization heterogeneity [3–5]. Because of the patch repair of the ventricular septal defect and right ventricular incision during the corrective surgery, patients with repaired TOF frequently have complete right bundle branch block (RBBB). Such prolonged depolarization and repolarization may increase the risks of arrhythmia [5,6]. The electrocardiographic parameters, such as QRS duration, QTc interval and QT dispersion, are important predictors of late arrhythmias [1,2,7–9]. However, there were still some controversies when applying these parameters to risk stratification [9].

Microvolt T wave alternans (MTWA) was introduced in 1980s [10] and is now regarded as an important independent risk factor for sudden cardiac death and ventricular arrhythmia in several large-scale studies [11–15]. However, the effectiveness of MTWA in risk prediction in patients with repaired congenital heart disease, such as TOF patients, was still unclear [16]. MTWA was initially measured by the spectral method. Recently, time domain analysis by the modified moving average beat analysis (MMA) method has been introduced and validated in the risk stratification for ventricular arrhythmia in adult population [17,18]. This study, based on a repaired TOF patient cohort with long-term follow-up, sought to delineate the changes of MTWA and the predictive value of MTWA for risk stratification in these patients.

2. Methods

The study conformed to the ethical guidelines of the Declaration of Helsinki in 1975 and was approved by the Institutional Review Board of National Taiwan University Hospital. Signed informed consent was collected from all the patients or their parents if the patients were younger than 18 years old. Patients who received total repair for TOF between 1970 and 2002 and received electrophysiological

☆ This study is supported by National Science Council in Taiwan (grant 97-2314-B-002-070-MY2).

* Corresponding author at: Department of Pediatrics, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan. Fax: +886 2 23412601.
E-mail address: wumh@ntu.edu.tw (M.-H. Wu).

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.02.063

follow-up including treadmill examination at this hospital between Jan 2007 and Dec 2009 were enrolled. Their medical charts were reviewed, and their hemodynamic and electrocardiographic data were obtained. We also enrolled 103 consecutive subjects who received a treadmill examination for chest pain or other reasons in the same study period. They, after proven to have no arrhythmia, coronary artery disease or other structural heart disease by subsequent examinations, served as normal controls.

The Bruce protocol was used for the treadmill exercise test. The test would be stopped when the target heart rate was reached or the patients could no longer tolerate the study. All repaired TOF patients had accomplished the exercise. Among them, 70.4% reached the target heart rate (which is defined as 85% maximal predicted heart rate, i.e. 85%×(220-age) beats per minute), and another 27.6% achieved working heart rate for MTWA analysis (which is defined as below). Patients, who have inadequate exercise strength (defined as not reaching the working heart rate for MTWA analysis or not increasing heart rate during the test) were defined as indeterminate group. We used the MMA method (GE Systems, Milwaukee, WI) for MTWA analysis as previously described [17]. In brief, it separated odd from even beats, and the average morphologies of both odd and even beats were calculated separately and continuously updated which results in continued moving averages of the odd and even beats. The MTWA was defined as the maximal difference in amplitude between the odd-beat and the even-beat average complexes. The data were counted valid only if the noise level was less than 10 μV. In patients who were older than 15 years of age, a recording of MTWA at heart rates less than 125 beats per minute (which is defined as working heart rate) was considered valid [19,20]. In those younger than 15 years of age, we used 60% of the predicted maximal heart rate as the working heart rate [21].

In addition to automatic noise elimination by software, we also double checked the curve of the MTWA vs. time manually. Both the MTWA data derived from exercise phase and recovery phase were included in our study. The MTWA value was derived from the maximal MTWA among 12 lead surface EKG. For those patients with heart rate below the working heart rate less than 2 min, their MTWA was categorized as indeterminate to avoid false positive due to noise contamination. Those with too much noise without countable MTWA were categorized as indeterminate too. Although previous data by spectral method showed that indeterminate MTWA might still have some predictive value, it was not demonstrated by MMA method [19,20]. Therefore, we excluded those patients from subsequent MTWA analysis. In addition to the treadmill examination, all the patients received echocardiography, EKG, and the 24-hour Holter examination. We recorded videotape in each echocardiography evaluation. The pulmonary regurgitation (PR) was graded as moderate degree if regurgitated flow was from distal half main pulmonary artery, and graded as severe degree if regurgitated flow was from branch pulmonary artery [22]. The right ventricular outflow tract (RVOT) and pulmonary stenosis were graded as severe if the pressure gradient across RVOT and main pulmonary artery was greater than 60 mm Hg. Severe peripheral pulmonary stenosis was defined if the pressure gradient across one branch pulmonary artery was greater than 50 mm Hg, or evidence of marked preferential pulmonary flow to one lung or estimated right ventricular pressure greater than 60 mm Hg.

Student's *T* test and one way ANOVA test were used for numerical data comparison. Non-parametric Wilcoxon Rank sum test was used if the case number in either group to be compared was less than 30 or normality test revealed not normal distribution. Chi square test or Fisher's exact test was used for categorical data comparison. For evaluating the cut-off point of MTWA in ventricular arrhythmia events prediction, we used the receiver operating characteristic (ROC) curve analysis. Logistic and linear regressions were used for multivariate risk factor analysis. Clinical significance was defined as a p value less than 0.05.

3. Results

There were 101 TOF patients (male/female ratio, 61/40) enrolled at a mean age of 20.0 (±10.6) years. They received total cardiac repair at age 4.8±5.8 years: 61 (60.4%) received a transannular patch, 6 (5.9%) received Rastelli conduit surgery (a direct connection between right ventricle and pulmonary artery through an artificial conduit), and 34 (33.7%) received valve sparing surgery for right ventricular outflow reconstruction. In 14 patients with extreme form of TOF (TOF with pulmonary atresia), transannular patch or Rastelli conduit was performed in all. The mean follow-up period after total cardiac repair was 15.7±7.3 years. Severe pulmonary regurgitation was noted in 14 (13.9%) patients. Nine (8.9%) patients had severe pulmonary or peripheral pulmonary stenosis. All except one had normal cardiac function. The patient who had impaired left ventricular function also had moderate aortic regurgitation and severe pulmonary regurgitation by echocardiographic evaluation. He had symptoms of heart failure and the brain natriuretic peptide level was 222 pg/ml.

In the control group, no subject had any documented arrhythmias. None of them received any medication one month before and during the examination. There was no significant difference in the age, gender and heart rate between the control and TOF patients. All of our TOF patients showed complete RBBB at surface EKG. The QRS duration, QTc interval, but not JTc interval (JT interval divided by square root of RR interval) was longer in TOF patients. None in the control group had abnormal EKG parameters (Table 1). Four TOF patients experienced ventricular premature beats during pre-exercise and recovery phase, but none had ventricular tachycardia or ventricular couplets during the exercise phase.

3.1. MTWA study

Eleven (10.6%) TOF patients and 18 (17.5%) control subjects had indeterminate MTWA results and were excluded from subsequent analysis. In the normal controls, the mean MTWA was 17.6±9.2 μV, and 62.4% of them had a MTWA below 20 μV. To define the age-related difference, the MTWA were further studied in the normal controls by dividing them into four subgroups according to age: subgroup younger than 10 years (n=26), 10–20 years (n=41), 20–30 years (n=24), and 30–40 years (n=12). We found no significant differences in the MTWA among these four age groups (p=0.207). The mean MTWA value was 20.4±10.7, 17.1±8.3, 17.5±9.3 and 13.0±7.0 μV, respectively (Fig. 1A). Linear regression analysis in the normal control revealed that the age, sex, QRS duration, QTc interval and heart rate were not associated with the value of MTWA.

The values of MTWA in repaired TOF patients were significantly higher than those in the control (25.1±14.0 μV in TOF vs. 17.6±9.2 μV in control and p<0.001) (Fig. 1B). In the TOF group, the MTWA value was even higher in patients with severe pulmonary regurgitation (34.8±16.6 vs. 23.3±12.8 μV and p=0.016), prolonged QRS duration (≧180 ms) (32.5±12.8 vs. 24.0±13.9 ms and p=0.015), and those receiving transannular patch for right ventricular outflow tract reconstruction (26.6±12.9 vs. 22.7±15.1 and p=0.031). By multivariate regression analysis on the above factors in addition to operation age and follow-up period, we found that MTWA was best correlated to severe pulmonary regurgitation (p=0.006).

Ten TOF patients had late arrhythmic events (9.9%), which included clinical ventricular tachycardia in five, and unexplained syncope episodes with significant ventricular arrhythmia (defined as more than ventricular couplets at the 24 h Holter examination) in another five. MTWA values tended to be higher in these patients as compared to those without late arrhythmic events (34.0±16.5 vs. 24.2±13.5 μV and p=0.053). However, multivariate logistic regression analysis on the factors, including age at operation, gender, follow-up period, operative method, extreme form of TOF, severity of pulmonary regurgitation, QRS duration,

Table 1
Comparisons of EKG and clinical parameters between tetralogy of Fallot patients and control groups.

Parameters	TOF (n=101)	Normal control (n=103)	P value
Age (mean±SD)	20.0±10.6	17.8±8.3	0.09
Gender (male, %)	61 (60.4%)	65 (63.1%)	0.77
Resting heart rate (bpm)	77.9±13.0	76.7±12.4	0.48
Maximal/predicted maximal heart rate (%)	84.9±7.1	88.3±5.0	**0.001**
QRS duration (ms)	151.6±22.7	88.6±13.5	<**0.001**
QTc interval (ms)	487.5±32.3	419.0±24.4	<**0.001**
JTc interval (ms)	315.7±25.4	319.5±24.6	0.28
Indeterminate (n, %)	11 (10.6%)	18 (17.5%)	0.23

Abbreviation: TOF — tetralogy of Fallot.
P value less than 0.05 was marked as bold.