Reproducibility of Microvolt T-Wave Alternans in Patients with Coronary Artery Disease

Therese Fuchs MD[1], Marina Leitman MD[1], Itzhak Zysman MD[1], Tal Amini[1] and Amram Torjman Msc[2]

[1]Arrhythmia Service, Assaf Harofeh Medical Center, Zerifin, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[2]College of Management, Rishon Lezion, Israel

ABSTRACT: **Background:** Microvolt T-wave alternans (MTWA) measures subtle beat-to-beat fluctuations in the T-wave amplitude. It was found to be associated with cardiac electrical instability in patients with ischemic and dilated cardiomyopathy.
Objectives: To investigate the reproducibility of the MTWA test results in patients with ischemic heart disease.
Methods: The study group comprised patients with ischemic heart disease who participated in a rehabilitation program at the Assaf Harofeh Medical Center. MTWA was measured during a bicycle exercise test at the first encounter and repeated after one week.
Results: Of the 40 study patients with coronary artery disease, 4 had an indeterminate result and were excluded from the data analysis; 5 had a positive MTWA in the first and second study (14%), 27 had a negative MTWA in the first and second study (75%), and 4 had a negative MTWA in the first study and a positive MTWA in the second study (11%). Overall, there was a correlation between the results of the first and the second study in 89% of the patients (kappa = 0.652, $P = 0.0001$).
Conclusions: MTWA measurements are reproducible in the short term in patients with coronary artery disease.

IMAJ 2012; 14: 359-362

KEY WORDS: T-wave alternans (TWA), reproducibility, ischemic heart disease

Microvolt T-wave alternans is a non-invasive method for identifying patients at increased risk of sudden cardiac death from ventricular arrhythmias [1-4]. It measures subtle beat-to-beat fluctuations in the T-wave amplitude. MTWA is heart rate-dependent and can be measured during an exercise stress test, during pharmacologic stress or during cardiac pacing [5,6]. A few studies have investigated the reproducibility of TWA measurements. These studies enrolled patients with heart disease of different etiologies including coronary artery disease, dilated cardiomyopathy and hypertrophic cardiomyopathy. The aim of the present study was to investigate the reproducibility of TWA measurement during a bicycle exercise test in a more homogenous group of patients with coronary artery disease enrolled in a cardiac rehabilitation program.

MTWA = microvolt T-wave alternans

PATIENTS AND METHODS

PATIENT POPULATION

The study group consisted of 40 patients with ischemic heart disease referred to the Assaf Harofeh Medical Center rehabilitation program during the period April 2008 to July 2010. Patients on anti-arrhythmic agents and beta blockers were also included and were tested while on their chronic medications. The study complies with the Declaration of Helsinki and the research protocol was approved by the hospital ethics committee. Informed consent was obtained from all study subjects.

MEASUREMENT OF MTWA

All patients exercised on a bicycle. The HearTwave™ system was used (Cambridge Heart Inc., Bedford, MA, USA). This system uses the spectral method described by Smith et al. [4], where, after careful skin preparation, seven standard electrodes are placed in the standard 12-lead position and seven multisegment special electrodes are arranged in a Frank orthogonal (XYZ) configuration.

The MTWA test was automatically interpreted within the HearTwave system and reviewed by a physician. The test was considered positive if the alternans voltage was ≥ 1.9 V and the alternans ratio ≥ 3 for a period of > 1 minute in VM, X, Y, Z, or two adjacent precordial leads. Alternans was measured at a heart rate of 100–110 and 110–120 beats/min. The test was considered negative if alternans was absent during a sustained interval of exercise at a heart rate ≥ 105 beats/min. If the result did not meet the positive or negative criteria, it was considered indeterminate. The test was repeated after one week.

STATISTICAL ANALYSIS

We compared the MTWA results of the first and the second study. We used the chi-square test for the categorical variables and the independent sample *t*-test for the continuous

variables. Results are presented as mean ± standard deviation. Concordance of MTWA test results during the first and second MTWA measurements was calculated using the Cohen Kappa test and the Bonferroni post-hoc analysis. Statistical analysis was performed using an SPSS version 13 software. A P value < 0.05 was considered statistically significant.

RESULTS

The study group included 40 patients with coronary artery disease. Four patients were unable to increase their heart rate during the exercise test and had an indeterminate result. These patients were excluded from the data analysis. Five patients had a positive MTWA in the first and second study (14%) [Figure 1], 27 patients had a negative MTWA in the first and second study (75%) and 4 patients had a negative MTWA in the first study and a positive MTWA in the second study (11%). Overall, there was a correlation between the results of the first and the second study in 89% of the patients (kappa = 0.652, P = 0.0001) [Table 1]. None of the variables was predictive of a non-reproducible MTWA result [Table 2].

DISCUSSION

Clinical studies have shown a good correlation between MTWA and the results of electrophysiologic studies in patients with ischemic heart disease [4]. More recent studies

Figure 1. TWA measurements of the VM, X, Y and Z leads during the first **(A1)** and second study **(A2)** and the precordial leads during the first **(B1)** and second study **(B2)**. Both studies showed a positive MTWA measurement

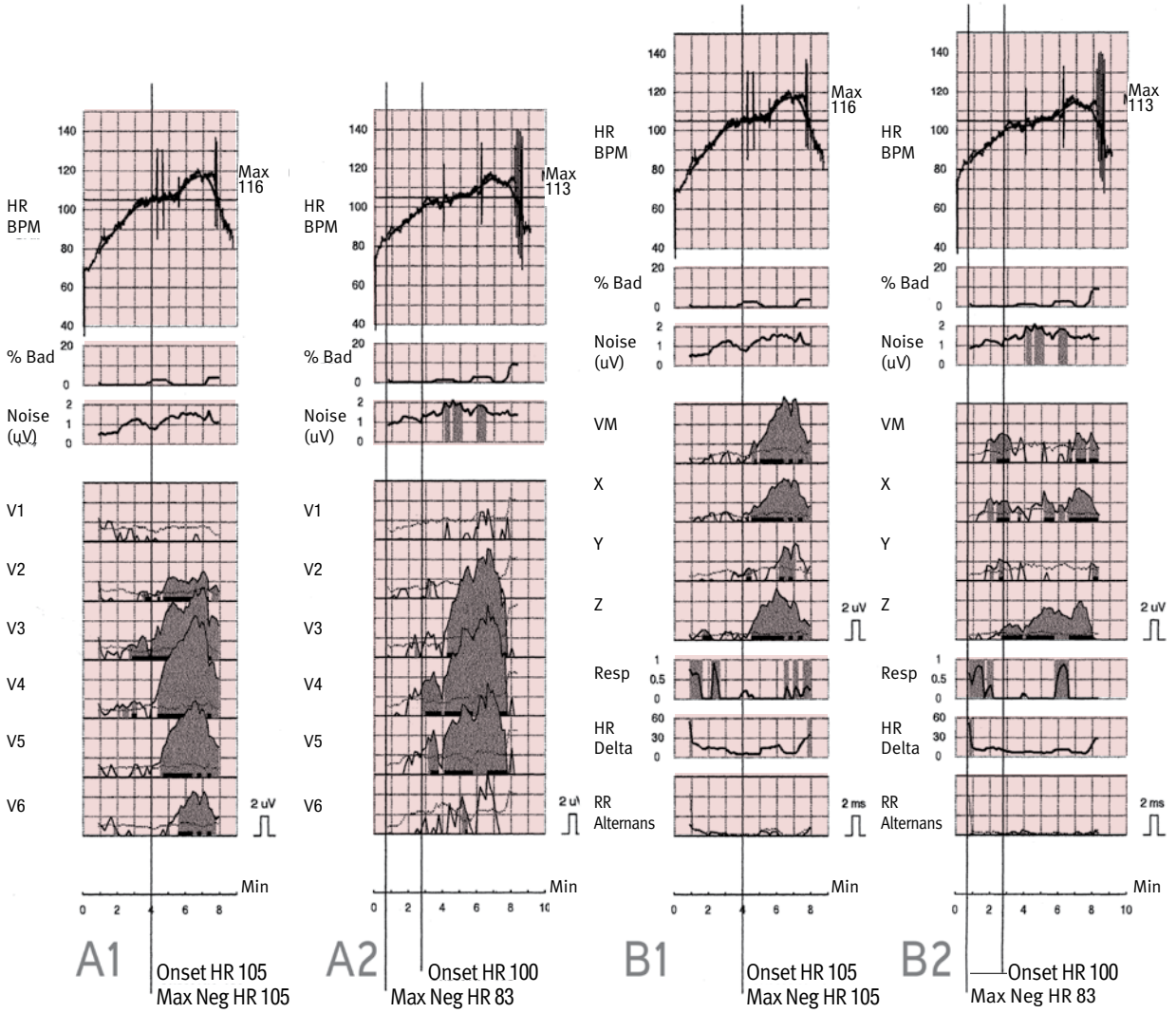

Table 1. Reproducibility of MTWA: comparison of the results of the first and second studies

	MTWA positive (2nd study)	MTWA negative (2nd study)	MTWA indeterminate (2nd study)
MTWA positive (1st study)	5	0	0
MTWA negative (1st study)	4	27	0
MTWA indeterminate (1st study)	0	0	4

Table 2. Baseline characteristics of the patients according to the MTWA results during the first and second exercise test

	MTWA positive	MTWA negative	1st study negative/2nd study positive	*P* value
	N=5	N=27	N=4	
Age (yrs)	57.4 ± 6.7	54.1 ± 7.9	60 ± 7.3	0.255
Gender, male	5 (100%)	25 (92.6%)	4 (100%)	0.703
History of myocardial infarction	5 (100%)	21 (77.8%)	4 (100%)	0.301
Coronary artery bypass graft	2 (40%)	6 (22.2%)	1 (25%)	0.701
Percutaneous coronary intervention	4 (80%)	21 (77.8%)	3 (75%)	0.984
Left ventricular ejection fraction (%)	43.0 ± 6.71	49.26 ± 12.38	45.0 ± 14.72	0.505
Neg T wave	2 (40%)	7 (25.9%)	3 (75%)	0.143
Blood-brain barrier	0	1 (3.7%)	0	0.843
Beta blocker	5 (100%)	24 (88.9%)	3 (75%)	0.495
Calcium blocker	0	4 (14.8%)	0	0.472
Angiotensin-converting enzyme inhibitor	5 (100%)	14 (51.9%)	3 (75%)	0.106
Statins	5 (100%)	27 (100%)	3 (75%)	0.016
Plavix	3 (60%)	12 (44%)	2 (50%)	0.809
Aspirin	4 (80%)	27 (100%)	4 (100%)	0.041

Values given are number of patients (%)

have shown mixed results with regard to the capacity of MTWA to predict sudden death, sustained ventricular arrhythmias or appropriate implantable cardioverter defibrillator discharges [7-10]. There are a few studies to date on the reproducibility of MTWA testing. Oliviera et al. [11] studied 51 patients post-myocardial infarction who underwent percutaneous coronary intervention. They had an MTWA measured 1 month before and 6 months after revascularization. The MTWA test results were concordant in 36 patients (70.6%) and discordant in 15 (29.4%).

Turitto and colleagues [12] enrolled 42 patients who had two bicycle stress tests within 4 hours of each other. The MTWA results were concordant in 93% of the cases. MTWA was positive in 23 patients and negative in 16. Patients with hypertrophic cardiomyopathy were also included in their study [12]. Bloomfield et al. [13] enrolled 35 patients with congestive heart failure who had two sequential bicycle exercise tests. The MTWA results were concordant in 82% of the cases. The study patients had ischemic, idiopathic valvular and alcoholic cardiomyopathies [13]. Wierzbowski et al. [14] studied 22 patients with heart disease. MTWA was measured during an exercise test or during pacing via an implantable defibrillator. The results were concordant in 76% of the tests. This study included patients with ischemic cardiomyopathy, patients with non-ischemic cardiomyopathy and patients with an implantable defibrillator [14]. In the study of Fuchs et al. [15], 21 patients with hypertrophic cardiomyopathy underwent MTWA testing at baseline, and at 6 months and 12 months follow-up. Three patients with a negative MTWA study had a positive study during follow-up and two patients with a positive study had a negative study during follow-up. Overall the MTWA results were concordant in 77% of patients.

In the present study the test was performed twice within one week in a population of patients with coronary artery disease enrolled in a cardiac rehabilitation program. The results were concordant in 89% of the cases.

CONCLUSIONS

MTWA measurements are reproducible in the short term in patients with coronary artery disease.

Corresponding author:
Dr. T. Fuchs
Arrhythmia Service, Assaf Harofeh Medical Center, Zerifin 71300, Israel
Phone: (972-3) 616-4042
Fax: (972-77) 328-0001
email: therese@fuchs.org

References

1. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. *N Engl J Med* 1994; 330: 235-41.
2. Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. *Circulation* 1999; 99: 1385-94.
3. Armoundas AA, Tomaselli GF, Esperer HD. Pathophysiological basis and clinical application of T-wave alternans. *J Am Coll Cardiol* 2002; 40: 207-17.
4. Smith JM, Clancy EA, Valeri CR, Ruskin JN, Cohen RJ. Electrical alternans and cardiac electrical instability. *Circulation* 1988; 77: 110-21.
5. Hohnloser SH, Klingenheben T, Zabel M, Li YG, Albrecht P, Cohen RJ. T-wave alternans during exercise and atrial pacing in humans. *J Cardiovasc Electrophysiol* 1997; 8: 987-93.
6. Shalaby AA, Voigt A, El-Saed A, Mains M, Shusterman V. Microvolt T-wave alternans during atrial and ventricular pacing. *PACE* 2007; 30: S178-82.
7. Chow T, Kereiakes DJ, Bartone C, et al. Microvolt T-wave alternans identifies patients with ischemic cardiomyopathy who benefit from implantable cardioverter-defibrillator therapy. *J Am Coll Cardiol* 2007; 49: 50-8.
8. Salerno-Uriarte JA, De Ferrari GM, Klersy C, et al. ALPHA Study Group Investigators. Prognostic value of T-wave alternans in patients with heart failure due to nonischemic cardiomyopathy: results of the ALPHA study. *J Am Coll Cardiol* 2007; 50 (19): 1896-904.
9. Hohnloser SH, Klingenheben T, Li YG, Zabel M, Peetermans J, Cohen RJ. T wave alternans as a predictor of recurrent ventricular tachyarrythmias in ICD recipients: prospective comparison with conventional risk markers. *J Cardiovasc Electrophysiol* 1998; 9: 1258-68.
10. Costantini O, Hohnloser SH, Kirk MM, et al. ABCD Trial Investigators. The ABCD (Alternans Before Cardioverter Defibrillator) Trial: strategies using T-wave alternans to improve efficiency of sudden cardiac death prevention. *J Am Coll Cardiol* 2009; 53: 471-9.
11. Oliviera MM, Fiarresga A, Pelicano N, et al. Temporal variations in microvolt T-wave alternans testing after acute myocardial infarction. *Ann Noninvasive Electrocardiol* 2007; 12 (2): 98-103.
12. Turitto G, Mirandi AP, Pedalino RP, Uretsky S, El-Sherif N. Short term reproducibility of T wave alternans measurement. *J Cardiovasc Electrophysiol* 2002; 13 (7): 641-4.
13. Bloomfield DM, Ritvo BS, Parides MK, Kim MH. The immediate reproducibility of T wave alternans during bicycle exercise. *Pacing Clin Electrophysiol* 2002; 25 (8): 1185-91.
14. Wierzbowski R, Michalkiewicz D, Marowski K, et al. Long term reproducibility of microvolt T-wave alternans in patients after cardioverter-defibrillator implantation. *Cardiol J* 2007; 14 (6): 561-7.
15. Fuchs T, Torjman A. The usefulness of microvolt T-wave alternans in the risk stratification of patients with hypertrophic cardiomyopathy. *IMAJ Isr Med Assoc J* 2009: 11 (10): 606-10.

Capsule

Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets

Highly pathogenic avian H5N1 influenza A viruses occasionally infect humans, but currently do not transmit efficiently among humans. The viral hemagglutinin (HA) protein is a known host-range determinant as it mediates virus binding to host-specific cellular receptors. Imai et al. assessed the molecular changes in HA that would allow a virus possessing subtype H5 HA to be transmissible among mammals. The authors identified a reassortant H5 HA/H1N1 virus – comprising H5 HA (from an H5N1 virus) with four mutations and the remaining seven gene segments from a 2009 pandemic H1N1 virus – that was capable of droplet transmission in a ferret model. The transmissible H5 reassortant virus preferentially recognized human-type receptors, replicated efficiently in ferrets, caused lung lesions and weight loss, but was not highly pathogenic and did not cause mortality. These results indicate that H5 HA can convert to an HA that supports efficient viral transmission in mammals; however, the authors do not know whether the four mutations in the H5 HA identified here would render a wholly avian H5N1 virus transmissible. The genetic origin of the remaining seven viral gene segments may also critically contribute to transmissibility in mammals. Nevertheless, as H5N1 viruses continue to evolve and infect humans, receptor-binding variants of H5N1 viruses with pandemic potential, including avian-human reassortant viruses as tested here, may emerge. These findings emphasize the need to prepare for potential pandemics caused by influenza viruses possessing H5 HA, and will help individuals conducting surveillance in regions with circulating H5N1 viruses to recognize key residues that predict the pandemic potential of isolates, which will inform the development, production and distribution of effective countermeasures.

Nature 2012; doi:10.1038/nature10831

Eitan Israeli

It was in my heart to help a little because I was helped much

Kalil Gibran (1883-1931), Lebanese-American artist, poet and writer. He is chiefly known in the English-speaking world for his 1923 book *The Prophet*, an early example of inspirational fiction including a series of philosophical essays that became extremely popular in the 1960s counterculture. Gibran is the third best-selling poet of all time, behind Shakespeare and Lao-Tzu