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Combined prognostic value of peak O_2 uptake and microvolt level T-wave alternans in patients with idiopathic dilated cardiomyopathy

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Abstract

Background: Despite the great improvement in clinical management of patients with idiopathic dilated cardiomyopathy (DCM), sudden cardiac death (SCD) and death due to worsening heart failure (HF) remain a challenging problem. The assessment of oxygen consumption (peakVO_2) has been recognized as an independent marker of mortality. Nevertheless peakVO_2 is not helpful in the risk stratification of SCD. Given this limitation, the association with another non-invasive test able to predict SCD such as microvolt level T-wave alternans (MTWA) would be useful.
Objectives: To determine the combined predictive value of peakVO_2 and MTWA in patients with DCM.
Methods: Seventy consecutive DCM patients were prospectively investigated. PeakVO_2 and MTWA were determined during bicycle exercise testing. Primary composite study end-point was defined as major cardiac events (MCE): total cardiac death or documented sustained VT/VF (including appropriate ICD shock). Secondary end-point was defined as arrhythmic events (AE): SCD or documented sustained VT/VF.
Results: Thirty-nine patients (55%) had a peakVO_2 < 10 ml/kg/min, while 40 patients (57%) showed an abnormal MTWA test. During an average follow-up of 19.2 ± 10.7 months, 11 MCE of which 6 AE have been documented. Among patients with abnormal MTWA and peakVO_2 < 10 ml/kg/min 8 MCE of which 5 AE occurred while among patients with normal MTWA and peakVO_2 ≥ 10 ml/kg/min no event occurred. From multivariate analysis, the combined prognostic value of MTWA and peakVO_2 achieved statistical significance for MCE (p = 0.03, HR 0.28, 95% CI 0.12–0.95) and for AE (p = 0.05, HR 0.39, 95% CI 0.18–0.99) while MTWA alone was a significant predictor of AE (p = 0.04, HR 0.32, 95% CI 0.14–0.93).
Conclusions: Our results suggest that only the association of MTWA and peakVO_2, but not the two single tests, is a significant prognostic marker of both MCE and AE in DCM patients. However, MTWA alone confirms its predictive power as arrhythmic risk stratifier in this population.

Keywords: Microvolt level T-wave alternans; Peak O_2 uptake; Idiopathic dilated cardiomyopathy; Heart failure; Sudden cardiac death

1. Introduction

Despite the great improvement in clinical management of patients with idiopathic dilated cardiomyopathy (DCM), sudden cardiac death (SCD) and death due to worsening heart failure (HF) remain a major health problem in these patients. Recently, improved medical treatment [1] and cardiac resynchronization therapy (CRT), with or without a defibrillator back-up (ICD) [2,3], have significantly reduced mortality in these patients. Nevertheless, the identification of optimal candidate to CRT represents a challenging problem; furthermore only a small percentage of SCD-HeFT [4] population have received appropriate life-saving shocks from ICD with 2.5% absolute reduction in annual mortality [5]. Therefore, since the indiscriminate use of this devices

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would be an economically costly undertaking, a need for stratification with non-invasive tools of patients at highest risk remains a priority.

The non-invasive assessment of oxygen consumption ($peakVO_2$) during cardiopulmonary exercise testing has been recognized as an independent marker of mortality among patients with HF and it is widely performed to evaluate functional status and to stratify this population [6–8].

Studies have demonstrated that $peakVO_2$ is a continuous predictor of mortality in HF population and does not have an absolute cut-off point for risk stratification [9]. However, based on several data, $peakVO_2 < 10$ ml/kg/min identifies high-risk patients whereas $peakVO_2 > 18$ ml/kg/min identifies patients at low risk of death [10].

However $peakVO_2$ is an independent predictor of total death but it is not helpful in the risk stratification of death due to life-threatening arrhythmias [11]. Given this limitation, the association with another non-invasive test able to predict SCD would be useful.

Much attention has recently been focused on microvolt level T-wave alternans (MTWA), a new spectral method to determine the presence of beat-to-beat minimal changes in T-wave morphology on the surface ECG. Several clinical and experimental studies [12–14] have shown that MTWA is strictly correlated with presence of inducible and spontaneous ventricular tachycardia/fibrillation (VT/VF). Therefore, MTWA has been proposed as a new non-invasive tool for stratification of patients with DCM at high risk of SCD and malignant arrhythmias [15–22].

The present study aims to assess the combined predictive value of $peakVO_2$ and MTWA for total major cardiac and arrhythmic events in patients with DCM.

2. Methods and patients

The study population included 70 consecutive patients with DCM referred to our Department between January 2003 and December 2005. Patients were eligible for participation in the present prospective study if the inclusion and exclusion diagnostic criteria of DCM were met, as previously described by the World Health Organization [23]. Exclusion criteria included also prior VT/VF, permanent atrial flutter/fibrillation and pace-maker dependency. All patients were on stable (>3 months) medical treatment for HF. All patients were submitted to cardiopulmonary exercise testing and MTWA determination during bicycle exercise stress testing.

Our institutional committee on human research approved the study protocol and a regular informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.1. Cardiopulmonary exercise testing

All patients underwent a symptom-limited bicycle $peakVO_2$ testing using V-max Series 229 (Sensormedics, Yorba Linda, CA, USA). Our testing protocol consisted of a 2 min rest period followed by 1 min of free pedaling and by 10 W/min step increases at a constant pedal speed of 60 rpm. The exercise tests were performed on a bicycle ergometer in the upright position (Lode-I Ergometer; Lode; Groningen, The Netherlands). During the test patients breathed through a mouthpiece attached to a low dead space and low resistance flow meter. Respired gas was continuously sampled and analysed for O_2 and CO_2 using rapidly responding sensors. Breath-by-breath gas exchange analysis allowed on-line determination of ventilation (VE), oxygen consumption (VO_2) and carbon dioxide production (VCO_2). $PeakVO_2$ was defined as the average VO_2 over the last 15 s of exercise. Both anaerobic threshold (VO_2 AT) and ventilatory efficiency (VE vs. VCO_2 slope) were also determined. A 12-lead electrocardiogram was performed in each patient for determination of heart rate and ST segment changes. Blood pressure was measured at 2 min intervals throughout the test.

2.2. Micro T-wave alternans measurements

MTWA was measured by the spectral analysis method during bicycle exercise using commercially available software (Cambridge Heart, Bedford, MA), as previously described [14,24,25]. The spectral method measures MTWA in terms of alternans voltage (Valt) and determines the ratio of the alternans voltage and the noise voltage (Ralt) [25]. The MTWA was considered as positive if alternans longer than 1 min (sustained) occurred at onset heart rate < 110 beats/min with the Valt > 1.8 microV and a Ralt < 3. The MTWA was defined as negative if there was 1 min of artefact-free ECG without sustained alternans with a heart rate > 105 beats /min. Alternatively MTWA was defined as indeterminate. MTWA positive or indeterminate was summarised as abnormal result. According to our protocol, after obtaining a 3-min resting ECG, bicycle exercise began and the workload gradually increased 10 W every minute. Care should be taken to elevate the heart rate gradually as close as possible to target of 110 b/min for at least 1 min. The heart rate and blood pressure were measured at rest and during each stage of exercise.

MTWA test was performed on the same day or 24 h before cardiopulmonary testing.

2.3. End-points

The primary composite study end-point was defined as total major cardiac events: deaths due to worsening HF, SCD and documented sustained VT/VF (including appropriate ICD shock). Secondary end-point was defined as arrhythmic events: SCD or documented sustained VT/VF.

Deaths due to worsening HF have been defined as acute deaths due to pulmonary oedema or progressive and refractory pump failures.

SCD has been defined as death occurring instantaneously, within 60 min of a change in symptoms or unexpectedly