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Peripheral endothelial function may predict the effectiveness of beta-blocker therapy in patients with idiopathic dilated cardiomyopathy☆

Xudong Xie *, Bifeng Wu, Yao Chen, Wenyuan Li, Xiaosheng Hu, Junzhu Chen

Department of Cardiology, the First Affiliated Hospital, Medical School of Zhejiang University, Hangzhou, Zhejiang, China

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ABSTRACT

Objectives: Beta-blockers have improved the prognosis of patients with dilated cardiomyopathy as they improve left ventricular (LV) systolic function and structure, which are crucial for myocardial recovery. However, to date, no accurate methods can predict the effectiveness of β-blocker therapy. Our goal was to evaluate whether peripheral endothelial function could be a useful predictor for β-blocker responses and related LV reverse remodeling (LVRR) in patients with idiopathic dilated cardiomyopathy (IDC).

Methods: Fifty-two IDC patients were recruited and underwent brachial artery flow-mediated dilation (FMD). Beta-blockers were titrated to doses tolerable for each patient. LV function and structure were measured by echocardiography. A positive response to β-blockers was defined as an increase of ≥10% in LV ejection fraction (LVEF). LVRR was defined as an increase of ≥10% in LVEF and a decrease of ≥15% in LV end-systolic volume (LVESV).

Results: Baseline FMD was 8.4 ± 3.0% in IDC patients and significantly lower than healthy controls. At three-month follow-up, 54% of patients had a positive β-blocker response and 40% achieved LVRR. Patients with a positive response to β-blockers or with LVRR had significantly higher baseline FMD values than those without. FMD was the most significant predictor of changes in LVEF and LVESV. The sensitivity and specificity of baseline FMD to predict β-blocker responses was 64.3% and 83.3%, respectively, and to predict LVRR was 61.9% and 80.6%, respectively. Beta-blockers themselves did not influence FMD values.

Conclusions: FMD could serve as an independent predictor for monitoring β-blocker therapy effectiveness in IDC patients.

1. Introduction

Dilated cardiomyopathy (DCM) is characterized by progressive left ventricular (LV) dilation and systolic dysfunction, which commonly results in heart failure (HF). In the majority of patients, an etiological basis cannot be identified, and the patients are traditionally labeled as idiopathic dilated cardiomyopathy (IDC) [1]. Despite recent developments in clinical management, IDC still remains the major cause for heart transplantation in adults and children [2,3].

Endothelial dysfunction has long been associated with various cardiovascular diseases, and is well-known to accompany HF [4,5]. Flow-mediated dilation (FMD) of the brachial artery is commonly used to quantify peripheral endothelial function. Thus, impaired FMD mirrors endothelial dysfunction and is thought to be of significant prognostic value in predicting cardiovascular outcomes [6,7], although controversies exist regarding its precise predictive value [8]. Meta-analysis studies demonstrated that a 1% increase in FMD is associated with a 13% reduction in cardiovascular events [9]. Recent studies demonstrated that FMD can serve as a marker for the systemic response to cardiac resynchronization therapy in HF [10,11]. To our knowledge, there is limited data on the value of FMD in predicting the effectiveness of HF drugs used for therapy.

Beta-blockers contribute to better prognosis of HF in patients, especially those harboring DCM, with improvements in left ventricular (LV) systolic function and reverse remodeling (LVRR) generally thought to produce a favorable prognosis [11–13]. However, the prognosis of patients in whom β-blockers are ineffective is poor [14,15]. Moreover, β-blockers may worsen HF in severe cases, and thus caution must be exercised in prescribing them [16]. Thus, predicting the effectiveness of β-blockers at the initial stages of diagnosis is of prognostic significance. To date, no reliable clinical predictors have been identified to predict β-blocker responses. Recently, convincing evidence suggests that endothelial dysfunction plays an essential role in the pathophysiology of β-adrenoreceptor activation [17–19], providing a link between

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* Corresponding author.
E-mail address: Dongdong2001xl@163.com (X. Xie).

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endothelial dysfunction and β-adrenoreceptor responsiveness. Accordingly, we designed a study to evaluate whether FMD could be used as a sensitive marker to predict the IDC patient's response to β-blocker therapy and LV reverse remodeling.

2. Methods

2.1. Study population

A population of 52 consecutive patients with newly diagnosed IDC were recruited for the study, all of whom met inclusion criteria standards. Inclusion criteria included: (1) patients with cardiac enlargement, reduced LV systolic function, with or without clinical congestive heart failure; (2) echocardiographic evidence for cardiac enlargement, with LV dilation defined as LV end-diastolic diameter (LVDd) > 55 mm, LV ejection fraction (LVEF) < 50%, and globally reduced ventricular wall motion; and (3) patients with no prior exposure to β-blocker treatment. Otherwise, medications, such as oral digitalis, diuretics, and anticoagulants remained unchanged during the course of the study. Exclusion criteria included: (1) patients with secondary causes of cardiomyopathy, such as ischemic dilated cardiomyopathy, perinatal cardiomyopathy, valvular disease, acute myocarditis, alcoholic cardiomyopathy and others caused by metabolic or autoimmune diseases; (2) patients that were treated with RAS blockade therapies in order to avoid negative drug interactions; (3) patients with a history or evidence of diabetes, hypercholesterolemia, habitual drinking, tobacco use, hypertension, and chronic renal failure because these conditions could independently influence endothelial function; and (4) patients with New York Heart Association (NYHA) functional class IV, clinically significant ventricular arrhythmias, stroke or other major systemic diseases due to safety concerns. A group of 36 age- and sex-matched healthy individuals were used as controls to determine baseline FMD values from individuals in the Chinese Hans population. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Zhejiang University. The rationale and potential risks of the study were explained to all subjects and all subjects gave written informed consent.

2.2. Study design

Based on previous study designs [20], we implemented a patient follow-up time of three months. Thirty-one patients were treated with metoprolol, while 21 patients were treated with bisoprolol, which was administered by the charge physician in our cardiovascular department. The initial recommended starting doses of metoprolol and bisoprolol were 11.875 mg and 2.5 mg daily, respectively. Dosages were gradually increased according to a weekly titration schedule as tolerated to a maintenance dose. Patients subsequently underwent follow-up once every two weeks.

2.3. FMD measurements

Peripheral endothelial function was evaluated by brachial artery FMD at baseline and three months following enrollment. FMD studies were performed as described previously [21]. FMD measurements were performed in the morning, after an overnight fast. All subjects were studied at rest in a supine position and in a quiet room set at a temperature of 25 °C. A high-resolution ultrasound system (Vivid E9 GE) was used to measure FMD. The left brachial artery diameter was measured both at rest and during reactive hyperemia. Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mmHg for 4.5 min, followed by a release. Arterial diameter was measured at end-diastole at a fixed distance from an anatomical marker at rest and 40, 60, and 80 s after cuff release. The ultrasound scan of the vessel diameter after reactive hyperemia was expressed as a percentage relative to the vessel diameter during the resting scan. An average of three measurements were obtained for each time point and then used to derive the maximum FMD (the greatest value between 40 and 80 s). A single reader blinded to the clinical information analyzed all of the ultrasound scans.

2.4. Echocardiography

Standard echocardiography was performed at baseline and at the three-month follow-up time point using commercially available equipment (Vivid E9, GE Vingmed Ultrasound). Specific parameters measured included: left atrial dimension (LAD) as well as left ventricular chamber dimension at end-systole (LVDs) and end-diastole (LVDd). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF were quantified using Simpson's biplane method. Echocardiographic analyses were performed by observers blinded to the clinical data and not involved in the clinical follow-up of the patients.

2.5. Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD), while categorical data were summarized as frequencies and percentages. Comparisons between groups were made by using the 2-sample *t*-testing for continuous data and χ^2 tests and Fisher's exact tests for categorical data. Differences between baseline and end-of-study measurements were assessed by paired *t* tests. Regression analysis was used to examine the relationship between baseline FMD as well as changes in LVEF and LVESV at three months. Regression analysis was used to determine univariate predictors of change in LVEF and LVESV after three months of β-blocker therapy. A multivariate model was developed using the significant univariate predictors. Receiver operating characteristic (ROC) curve analysis was used to assess the prognostic characteristics. Statistical tests with a value of $p < 0.05$ were considered significant. A statistical software package was used for all analyses (SPSS 22.0, Chicago, IL).

3. Results

3.1. Baseline characteristics

All of the patients completed the study with no major complications. Optimal medical therapy with the maximal tolerated dose of metoprolol or bisoprolol was achieved and maintained during the three-month follow-up. Baseline characteristics of the 52 IDC patients are presented in Tables 1 and 2. Thirty-six healthy controls were used to determine baseline FMD values in a population of Chinese Hans nationality from the Zhejiang area. The mean baseline FMD in IDC patients was 8.4 ± 3.0%. This value was significantly lower in IDC patients when compared with healthy controls (8.4 ± 3.0% vs 10.2 ± 3.4%, $p = 0.014$) (Table 3). No significant differences in age, sex, blood pressure, heart rate, body mass index (BMI), and biochemical parameters were observed between IDC patients versus controls (Table 1).

3.2. Response to β-blocker therapy and LV reverse remodeling

After three months of β-blocker therapy, 28 of the 52 IDC patients (54%) responded well to β-blockers, which resulted in an improvement in LVEF of more than 10% as compared with baseline (mean increase, 12.0 ± 9.0%, $p < 0.01$). However, in the remaining 24 subjects, LVEF improvement did not reach at least 10% (mean decrease, 2.7 ± 4.5%, $p = 0.01$). As a result, by definition, the former group of patients were categorized as responders, while the latter group of patients were categorized as non-responders to β-blocker therapy, respectively [16]. Interestingly, we show that baseline LVEF was significantly lower in responders when compared with non-responders (29.2 ± 7.3% vs 35.5 ± 7.4%, $p = 0.003$). No significant differences were observed between responders and non-responders in terms