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Original article

Myocardial contractile reserve predicts left ventricular reverse remodeling and cardiac events in dilated cardiomyopathy

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ABSTRACT

Background: Catecholamine sensitivity estimated using a dobutamine stress test (DST) is recognized as a measure of the beta-adrenergic myocardial contractile reserve, which is involved with left ventricular reverse remodeling (LV-RR). We investigated whether the prognostic ability of the DST for LV-RR could predict cardiac events.

Methods: There was a total of 192 enrolled patients with dilated cardiomyopathy (DCM). DCM was defined as a LV ejection fraction (LV-EF) $\leq$45% and LV end-diastolic dimension (LVDd) $\geq$55 mm. One hundred patients were subjected to micromanometer-based measurement of the maximal first derivative of LV pressure ($LVdP/dt_{max}$), an index of LV contractility, at baseline and following the infusion of dobutamine (10 μg/kg/min) via a pigtail catheter. Percentage changes in $LVdP/dt_{max}$ from the baseline to peak values under dobutamine stress ($\Delta LVdP/dt_{max}$) were also calculated. After excluding 17 patients who received cardiac resynchronization therapy within 3 months of undergoing DST (n = 15) and who did not receive follow-up echocardiography (n = 2), 83 patients were enrolled (52.5 ± 12.3 years).

Results: During the follow-up period (4.7 ± 2.6 years), LV-RR was recognized in 49 of 83 patients (59.0%). A multivariate logistic regression analysis revealed that $\Delta LVdP/dt_{max}$ (hazard ratio: 1.024, p = 0.007) and the symptom duration (hazard ratio: 0.977, p = 0.003) were independent predictors of LV-RR. A receiver operating characteristic curve analysis revealed a $\Delta LVdP/dt_{max}$ cut-off value of 75.1% for LV-RR and a significantly lower cardiac event rate in the $\Delta LVdP/dt_{max} \geq 75.1\%$ group (p = 0.045).

Conclusions: $\Delta LVdP/dt_{max}$ estimated using DST was a useful predictor of LV-RR and cardiac events in patients with DCM.

Introduction

Dilated cardiomyopathy (DCM) is characterized by a reduction in ventricular myocardial contractility and an increase in left ventricular (LV) volume [1]. The prognosis of patients with DCM has improved during the past few decades as a result of advances in pharmacotherapy, various modalities such as implantable cardioverter–defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices, and cardiac transplantation [2–4]. However, precise prognostic prediction is difficult because lethal cardiac events may be observed during the follow-up of patients with DCM. Despite the prognostic challenges, optimal medical therapy [5,6], and mechanical support can ameliorate cardiac dysfunction in patients with DCM. This outcome may be attributable to the phenomenon known as LV reverse remodeling (LV-RR), which is characterized by an increase in the pump function and a decrease in the LV dimension [7]. LV-RR predicts heart failure staging, exercise performance, and independently, the long-term prognosis of patients with idiopathic DCM [8–12]. Therefore, the predicted LV-RR could be used to stratify patients with latent myocardial damage. The dobutamine stress test (DST), which is based on an echocardiographic estimation, predicts late spontaneous

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improvements in the cardiac function of patients with DCM [13–16]. In addition, the biventricular contractile reserve, which is another measure estimated using echocardiography, is an important determinant of cardiovascular outcomes in patients with DCM [17]. It is difficult to confirm the intra- and inter-observer variability of these measurements in clinical settings [18]. Our group recently determined that DST with a pigtail catheter yielded clear determinations of myocardial contractile reserve and facilitated the observance of an association of the adrenergic myocardial functional reserve with cardiac hemodynamics [19–22]. However, the exact efficacy of DST as a prognostic tool for LV-RR remains to be identified. Therefore, the present study aimed to confirm the efficacy of DST with a pigtail catheter as a prognostic tool for LV-RR and determine whether DST for LV-RR could also predict cardiac events.

Methods

Study population

A total of 192 patients were diagnosed with DCM, and100 patients were subjected to DST at Nagoya University Hospital between July 2001 and February 2015. All patients underwent laboratory measurement, echocardiography, and cardiac catheterization to facilitate estimations of their general conditions. A diagnosis of DCM was made on the basis of the echocardiographic measures and/or left ventriculography of LV function [LV ejection fraction (LV-EF) $\leq$45% and LV end-diastolic dimension (LVDd) $\geq$55 mm] and lack of significant coronary artery stenosis requiring therapeutic intervention [17] and having no prior evidence of primary valvular disease and cardiac hypertrophy due to essential or secondary hypertension. At the time of registration, patients were excluded if they (1) had undergone CRT device implantation within 3 months of undergoing DST (n = 15); and (2) had not received follow-up echocardiography (n = 2). Finally, 83 patients underwent follow-up echocardiography and received optimal medical treatment (Fig. 1). Symptom duration was defined as the interval from the date of abnormal symptom and/or data emergence to the date of cardiac catheterization.

During follow-up, patients were classified into two groups according to the presence or absence of LV-RR. Daily doses of beta-blocker were reported as carvedilol equivalents (carvedilol-equivalent doses: bisoprolol, 0.2 and metoprolol, 2) [23,24]. The study protocol was approved by the Ethics Review Board of Nagoya University School of Medicine, and written informed consent was obtained from all study subjects.

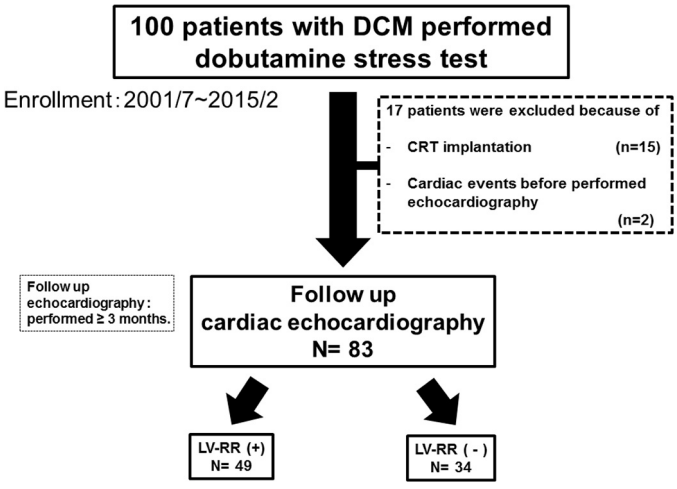

Fig. 1. Diagram of dobutamine stress test. A total of 100 patients with DCM underwent DST between July 2001 and February 2015. Seventeen patients who underwent CRT device implantation within 3 months of undergoing DST (n = 15), or those who were did not receive follow-up echocardiography (n = 2) were excluded. DCM, dilated cardiomyopathy; DST, dobutamine stress test; CRT, cardiac resynchronization therapy; LV-RR, left ventricular reverse remodeling.

Echocardiography

Standard M-mode and two-dimensional echocardiography, Doppler blood flow, and tissue Doppler imaging measurements were obtained using a Vivid 7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) and formula approved by the American Society of Echocardiography (ASE) [25].

Definition of LV-RR

LV-RR was defined as an increase in LV-EF from $\geq$10% to a final value of >35% accompanied by a decrease in LVDd of $\geq$10%. These values were determined via echocardiography during the follow-up period [12].

Cardiac catheterization

All patients initially underwent biventricular cardiac catheterization analyses. Right heart catheterization was primarily performed using a 7-Fr triple-lumen Swan–Ganz thermodilution pulmonary artery catheter (Edwards Life Science Co., Irvine, CA, USA) when the patient was at rest. After collecting baseline hemodynamic data, coronary angiography was performed using a 4-Fr catheter via the transradial or brachial approach to avoid ischemic cardiomyopathy. After collecting baseline angiographic data, a 6-Fr fluid-filled pigtail catheter fitted with a high-fidelity micromanometer (CA-61000-PLB pressure-tip catheter; CD Leycom, Zoetermeer, Netherlands) was inserted into the LV cavity to measure LV pressure (LVP).

Micromanometer pressure signals and standard electrocardiograms were recorded online using a multichannel recorder. LVP signals were digitized at 3-ms intervals and analyzed using a 32-bit microcomputer system equipped with software developed in-house. LVP and heart rate were determined as the average values of at least 13 consecutive beats. The maximum first derivative of LVP ($LVdP/dt_{max}$), an index of contractility, and the half-time LVP ($T_{1/2}$), an index of LV isovolumic relaxation, were measured both at baseline and following an intravenous infusion of dobutamine (10 μg/kg/min), as previously described [26]. $\Delta LVdP/dt_{max}$ was defined as the percent change in the maximal first derivative of LVP during dobutamine infusion (10 μg/kg/min) compared with the baseline value. $\Delta T_{1/2}$ was also defined as the percent change in the $T_{1/2}$ during dobutamine infusion (10 μg/kg/min) compared with the baseline value.

Clinical follow-up

The follow-up duration was calculated from the date of catheterization to the date of the last clinical visit. For follow-up medications, electrocardiogram, echocardiography and LV-RR data were included: initial data indicative of LV-RR for the LV-RR(+) group and most recent data for the LV-RR(−) group. Composite cardiac events were defined as sudden cardiac death (SCD), ventricular tachycardia (VT), or admission because of worsening heart failure (HF).

Statistical analysis

All statistical analyses were performed using the SPSS 18.0 software package (SPSS/IBM Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviations or as

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