Role of Dobutamine Stress Echocardiography for Left Ventricular Reverse Remodeling Prediction in Newly Diagnosed Idiopathic Dilated Cardiomyopathy

Hyun-Min Choi

The Graduate School

Yonsei University

Department of Medicine

Role of Dobutamine Stress Echocardiography for Left Ventricular Reverse Remodeling Prediction in Newly Diagnosed Idiopathic Dilated Cardiomyopathy

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Hyun-Min Choi

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This certifies that the dissertation of

Hyun-Min Choi is approved.

Thesis Supervisor: Junghan Yoon

Thesis Committee Member: Chang Mann Ko

Thesis Committee Member: In Deok Kong

Thesis Committee Member: Byung-Su Yoo

Thesis Committee Member: Seung-Hwan Lee

The Graduate School

Yonsei University

June 2019

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Role of Dobutamine Stress Echocardiography for Left Ventricular Reverse Remodeling Prediction in Newly Diagnosed Idiopathic Dilated Cardiomyopathy

Hyun-Min, Choi

Department of Medicine

The Graduate School

Yonsei University

Left ventricular reverse remodelling (LVRR) means spontaneous recovery from substantial degeneration of myocardium in patients with idiopathic dilated cardiomyopathy (IDCM). The aim of study was to evaluate the potential of the positive contractile reserve on dobutamine stress echocardiography [CR-DSE (+)] for LVRR prediction, as a predictive power of CR-DSE (+) for LVRR compared with negative late gadolinium enhancement on cardiac magnetic resonance [LGE-CMR (-)], and clinical outcomes of CR-DSE (+) during follow-up (FU) periods. We prospectively included patients with newly diagnosed IDCM from March

2012 to May 2014. There were 45 patients with IDCM who were assigned to this study and had planned essential echocardiographic studies at baseline and at a 6-months FU. CR-DSE (+) was defined as an increase of LV ejection fraction (LVEF) ≥ 4 units on DSE. CMR studies to detect LGE-CMR were performed. Definition of LVRR was increase of LVEF ≥ 10 units with a decreased LV end-diastolic diameter ≥ 10% at 6-months FU echocardiography. We enrolled 38 patients who underwent 6-months FU echocardiography were enrolled. At baseline, 22 (57.9 %) patients had CR-DSE (+). There were 14 patients (36.8 %) who experienced LVRR at 6-months FU echocardiography. There were 25 patients underwent CMR; however, LGE-CMR (-) was not significant predictor for LVRR at 6-months FU echocardiography. In multivariate logistic regression analysis, CR-DSE (+) was an independent predictor for LVRR (odds ratio: 1.82 [95 % confidence interval: 1.06 to 3.11]; p = 0.029). Receiver operating characteristic curve analysis, delta LVEF on DSE was a meaningful predictor for LVRR (AUC = 0.765, p = 0.007). Using cutoff value of 4 % LVEF increase on DSE, we obtained the negative predictive value of 93.8 % to predict LVRR. Over a mean FU of 28.0 ± 14.0 months, the incidences of major adverse cardiac event were significantly lower in the CR-DSE (+) group. CR-DSE (+) is significant predictor for LVRR and CR-DSE (-) helps exclude LVRR at 6-months FU echocardiography in newly diagnosed IDCM patients. Meanwhile, LGE-CMR (-)

fails to be meaningful predictor for LVRR through a lack of CMR study population. And the CR-DSE (+) group have an excellent prognosis during FU periods.

Keywords: Dobutamine, Idiopathic dilated cardiomyopathy, Remodeling, Stress echocardiography

I. INTRODUCTION

Left ventricular reverse remodeling (LVRR) is a favorable phenomenon that implies functional and structural improvement of the denatured myocardium in patients with idiopathic dilated cardiomyopathy (IDCM). It reflects a good prognosis for the future, so that the efforts for discovering prediction factors for LVRR should be stepping up to choose therapeutic options to reduce the progression of end-stage heart failure.[1-3] Considering the etiologic background of IDCM, irreversible or reversible degeneration in contractile protein of diseased myocardium are thought to be responsible for beta-1 adrenergic receptor (B1AR) downregulation and desensitization.[4,5] Therefore, several modalities assessing biomarker, structural and functional viabilities including the low level of B-type natriuretic peptide (BNP), the negative late gadolinium enhancement on cardiac magnetic resonance [LGE-CMR (-)] and the positive contractile reserve on dobutamine stress echocardiography [CR-DSE (+)] have been suggested as significant predictors of LVRR or good clinical outcomes in patients with IDCM.[6,7]

However, it is not easy to recommend these modalities as LVRR predictors confidently because there are several controversies and differences between

studies. Although recent CMR studies have been describing an important role of LGE-CMR in prediction of LVRR in patients with IDCM, another studies about the association between LGE-CMR and LVRR show negative results.[8,9] Like CMR studies, DSE has been used to assess viable myocardium that can be a potential background for LVRR or good outcomes in patients with IDCM.[10] However, DSE has been underappreciated for non-invasive work-up tool in IDCM patients because of technical factors such as differences in protocol and physician's familiarity.

To provide for better prognosis, we need to evaluate both the structural and functional status of denatured myocardium as soon as possible. Assembly of CMR and DSE may serve as a clue for restoration of B1AR downregulation and desensitization in involved myocardium. Also, the combined effect of DSE and CMR for LVRR prediction in newly diagnosed IDCM has been poorly studied. Therefore, we investigated 1) the relationship between CR-DSE (+) and LVRR, 2) the predicting power of CR-DSE (+) for LVRR compared with that of conventional modalities including LGE-CMR (-), the low level of BNP and other clinical parameters, and 3) the clinical outcomes of CR-DSE (+) over follow-up (FU) periods.

II. MATERIALS AND METHODS

1. Materials

Our study was a prospective case-control study conducted in 45 consecutive patients who were newly diagnosed IDCM. In serial order, DSE, two conventional echocardiographic studies at baseline and 6-months FU and CMR studies had been planned at cardiovascular center of Wonju Severance Hospital (Wonju, Korea) between March 2012 and May 2014. All enrolled patients were admitted to our hospital for clinical and laboratory assessment to confirm the IDCM. All patients had never been hospitalized for heart failure before the time of first admission at our hospital, because we intended to minimize the bias of clinical factors. According to the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies, we enrolled patients who presenting globally reduced LV systolic function [ejection fraction (EF) ≤ 45 %] with absence of significant coronary artery disease (≥ 50 % diameter stenosis) at conventional coronary angiography.[10] Also, we excluded patients who had severe valvular heart disease, atrial fibrillation, left bundle branch block, history of heavy alcohol use (> 100 g/day), chemotherapy-induced or peripartum cardiomyopathy, BNP level < 150 pg/ml, the evidence of bacterial or viral myocarditis, prior use of heart failure treatments including beta-blockers (BB),

angiotensin-receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEI), spironolactone and furosemide therapy, high basal heart rate > 100 bpm by ECG, and uncontrolled hypertension. The study protocol was approved by our institution's committee on human investigation, and written informed consent was obtained from all patients before we began the study.

2. Study flow

At the time of enrollment, all patients were received basic clinical examination, initial blood sampling for BNP, 12-lead electrocardiography, transthoracic echocardiography and conventional coronary angiography. Baseline measurement of BNP level was collected by venipuncture into EDTA tubes within 1hr of the scheduled clinical examination and baseline echocardiography. BNP was assessed by a chemiluminescent immunoanalysis (Triage BNP Test, Biosite Inc, USA). Standard medical treatments including ARB, ACEI, spironolactone and furosemide for acute heart failure were appropriately used according to the recommendations of the European Society Cardiology guidelines.[11] When the patients showed improved functional status (New York Heart Association Class ≤ II) after optimal heart failure treatment, CMR and DES were performed in order. After CMR, we did DSE separately within 3 days without BB therapy according to standard protocols in all patients. Six-months FU transthoracic

echocardiography was done by cardiologists blinded to the results data previously obtained from CMR and DSE.

3. Two-dimensional echocardiography

We did two-dimensional transthoracic echocardiography in all patients according to the recommendations of the American Society of Echocardiography at the onset of study.[12] All transthoracic echocardiographic exams were performed in the lateral decubitus position using a commercially available echocardiography machine (Vivid E9, General Electric, Milwaukee, WI, USA). Images were recorded with a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and four-chamber images). We measured LV end-systolic diameter and LV end-diastolic diameter (LVEDD) using M-mode, and calculated the LVEF from apical two- and four-chamber views by using Simpson's biplane method.

We evaluated regional wall motion of the LV using the division of the LV in 17 segments with reference to the recommendations of the American Society of Echocardiography. Regional mobility is represented as: normal (scored as 1 point); hypokinesia, significantly reduced mobility (2 points); akinesia, the absence of systolic wall thickening (3 points); and dyskinesia, paradoxical movement of segments of the LV in systole (4 points). We documented the sum of the points

obtained by scoring separate segments and defined it as the wall motion score index.

4. Low-dose dobutamine stress echocardiography

We used a low-dose dobutamine protocol to assess the presence of CR. Dobutamine was infused in 10-minute dose increment, starting from 5 μg/kg/min and increasing to 10 with monitoring of electrocardiogram and noninvasive blood pressure.[13] DSE was terminated when one of the following preset end-points was reached: onset of atrial fibrillation, more than 3 consecutive premature ventricular complexes, persistent hemodynamic compromise (drop in the systolic blood pressure of > 20 mmHg), angina, or unbearable dyspnea. An absolute increase in LVEF ≥ 4 points relative to baseline LVEF was considered CR-DSE (+).[14,15] All oral medications except BB were continued before DSE, and BB was started after end of DSE.

5. CMR protocol and analysis

CMR was performed on day 7 (median, day 7; range, days 5 to 11) using a 3-T magnetic resonance imaging system (Achieva Release 2.1, Philips Medical Systems, Eindhoven, the Netherlands) equipped with a dedicated cardiac software package, cardiac coil, and vectorcardiogram. After acquiring localizing images,

we obtained long- and short-axis cine images using retrospectively gated breath-hold true-fast imaging with a steady-state free precession technique. We used the short-axis cine scans of 10-mm slices to measure the left ventricular mass, volume, and function. We injected a bolus of contrast medium (gadolinium diethylenetriamine pentaacetic acid) at a dose of 0.1 mmol/kg, and acquired images for 60 heart beats immediately after contrast infusion. The obtained CMR images were analyzed by a radiologist experienced in LGE-CMR and blinded to all clinical and invasive physiological data. We performed regional analyses of LGE images using the 17-segments model. Initially, LGE was visually detected and was defined when the signal intensity exceeded 3 standard deviation (SD) of normal myocardium.

Then, to estimate LGE semi-quantitatively, we scored each LV segment using a 5-point scoring system (0 = no LGE, 1 = 1 – 25 % of trans-mural extent of LGE, 2 = 26 – 50 %, 3 = 51 – 75 %, 4 = 76 – 100 %).[16] As described in the results section, the patients were assigned to three groups based on LGE distribution: none, localized, and extensive. We defined localized LGE as when LGE existed at only the interventricular septum, and defined extensive LGE as when LGE spread into anterior and/or inferior segments beyond the inter-ventricular septum.[17] The intra- and inter-observer concordance rates for the estimation of LGE score were

89 % and 87 %, respectively.

6. Clinical outcome parameters

We assessed the changes of LVEF and LVEDD at 6-months FU compared to baseline echocardiographic data. We identified LVRR as an increase in ≥ 10 % of LVEF concomitant with a decrease in ≥ 10 % of the LVEDD compared to the baseline echocardiographic data.[18] Also, we evaluated major adverse cardiac events (MACE) such as rehospitalization because of heart failure and cardiac death during FU periods depending on CR-DSE (+).

7. Statistical analyses

All continuous variables are presented as mean ± SD and were analyzed using the Student's *t*-test or analysis of variance. Categorical variables are presented as frequencies (percentage) and were analyzed using the chi-square test or Fisher's exact test. Baseline clinical, echocardiographic, and LGE-CMR results were compared according to the presence of CR-DSE. We did the univariate logistic regression analyses to investigate the correlations between LVRR, clinical and laboratory parameters, the CR-DSE (+) and LGE-CMR (-). Also, we used multivariate logistic regression analysis to assess the correlations of LVRR from variables on the basis of the best results of the univariate regression analyses at

the significance level of $p < 0.05$. We performed a receiver operating characteristic curve (ROC) analysis to determine the optimal cutoff value for predicting LVRR with respect to the change of LVEF. All analyses were carried out using Statistical Package for the Social Sciences 20.0 (SPSS Inc., Chicago, IL, USA).

III. RESULTS

1. Baseline characteristics according to CR-DSE

A total of 38 newly diagnosed IDCM patients were enrolled in this study and underwent 6-months FU echocardiography. Among them, 25 patients agreed to CMR study at baseline (Figure 1). We divided the patients into 2 groups: the CR-DSE (+) and the CR-DSE (-) group. Baseline characteristics, clinical and echocardiographic data of 2 groups are shown in Table 1. As the reference criteria for the presence of CR-DSE, 22 patients showed preserved CR-DSE (57.9 %). There were no significant differences in clinical and echocardiographic data between 2 groups except the proportion of NYHA class.

The results of DSE were summarized in Table 2. Interestingly, there were no significant echocardiographic differences between patients with CR-DSE (+) and those with (-) at rest. However, CR-DSE (-) group showed not only a lack of LVEF improvement but also too high rise of HR on DSE. Index changes of LVEF (delta LVEF) is significant higher in the CR-DSE (+) than in the (-) group on DSE. Also, index changes of HR (delta HR) is significant lower in the CR-DSE (+) than in the (-) group.

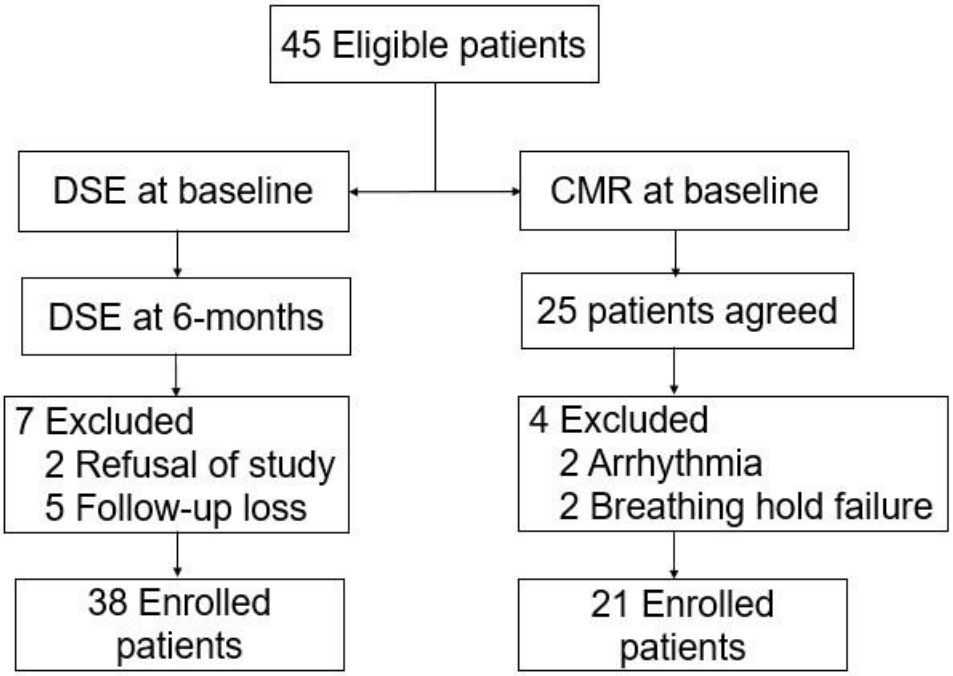

Figure 1. Study flow and enrollment of patients.

DSE: dobutamine stress echocardiography; CMR: cardiac magnetic resonance.

	Total (n = 38)	CR-DSE (+) (n = 22)	CR-DSE (-) (n = 16)
Age (years)	63.2 ± 12.9	61.6 ± 14.3	65.6 ± 10.8
Male, n (%)	18 (47)	13 (59.1)	5 (31.3)
BMI, kg/m^2	23.7 ± 3.6	24.3 ± 3.9	22.9 ± 2.7
NYHA class*	2.26 ± 0.9	2.14 ± 0.8	2.44 ± 0.9
Hypertension, n (%)	13 (34)	7 (31.8)	6 (37.5)
Diabetes, n (%)	6 (16)	3 (13.6)	3 (18.8)
Smoking, n (%)	14 (37)	11 (50)	3 (18.8)
SBP, mmHg	126.9 ± 17.0	130.5 ± 18.7	122.0 ± 13.4
DBP, mmHg	81.3 ± 14.8	84.1 ± 15.4	77.3 ± 13.4
HR, bpm	87.5 ± 18.8	90.7 ± 20.7	85.4 ± 13.3
BNP, pg/ml	1025.1 ± 920.7	855.3 ± 639.8	1274.2 ± 1205.8
LVEDD, mm	68.0 ± 6.6	67.2 ± 5.9	69.1 ± 7.5
LVESD, mm	57.4 ± 6.3	56.3 ± 5.3	58.8 ± 7.4
LVEF, %	33.2 ± 5.5	34.1 ± 5.3	31.9 ± 5.8
E/E´	23.3 ± 8.5	22.2 ± 7.9	25.0 ± 9.4
RVSP, mmHg	45.1 ± 12.3	45.4 ± 12.7	44.8 ± 12.6

LAVI, ml/m^2	57.5 ± 15.6	58.6 ± 15.4	56.2 ± 16.4

Table 1. Baseline characteristics according to CR-DSE. [* $p < 0.05$, CR-DSE (+) vs. (-)] CR, contractile reserve; DSE, dobutamine stress echocardiography; BMI, body mass index; NYHA, New York Heart association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BNP, B-type natriuretic peptide; LVEDD, left ventricle end diastolic dimension; LVESD, left ventricle end systolic dimension; LVEF, left ventricle ejection fraction; RVSP, right ventricular systolic pressure; LAVI, left atrial volume index.

	Total (n =38)	CR-DSE (+) (n = 22)	CR-DSE (-) (n = 16)
HR, bpm			
At rest	74.0 ± 12.6	13 (59.1)	5 (31.3)
At peak	93.4 ± 23.5	24.3 ± 4.1	22.9 ± 2.5
SBP, mmHg			
At rest	120.1 ± 24.6	127.3 ± 25.6	108.5 ± 18.2
At peak	136.1 ± 36.6	142.7 ± 39.5	125.3 ± 29.6
DBP, mmHg			
At rest	70.1 ± 16.4	74.4 ± 17.9	63.2 ± 10.9
At peak	77.5 ± 14.9	79.2 ± 17.9	74.6 ± 7.8
LVEF, %			
At rest	29.4 ± 7.6	29.1 ± 8.5	29.1 ± 6.3
At peak*	35.8 ± 8.5	38.9 ± 7.6	31.6 ± 7.8
Delta HR*	19.4 ± 23.3	12.2 ± 15.1	31.1 ± 29.7
Delta SBP	17.8 ± 28.0	18.4 ± 31.5	16.8 ± 22.7
Delta DBP	7.7 ± 14.1	5.4 ± 14.8	11.5 ± 11.4
Delta LVEF	4.9 ± 5.2	8.1 ± 4.2	0.5 ± 2.7

Table 2. Variations of vital sign and LVEF during DSE according to CR-DSE. [* $p < 0.05$, CR-DSE (+) vs. (-)] HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction.

2. Incidence and types of LGE-CMR according to CR-DSE

The imaging analysis of LGE-CMR is described in Table 3. There were only 9 LGE-CMR (+) patients in this study. There was no difference in the prevalence of LGE-CMR (+) between the CR-DSE (+) and (-) group. In LGE distribution pattern, an extensive type was frequent than a localized type in the CR-DSE (-) group. Although our 3-T scanner shortens scan time and increases image resolution via high signal to noise ratio, image acquisition of 4 patients were not of optimal quality, because of respiratory hold failure and arrhythmia.

3. Prevalence and predictor of LVRR according to CR-DSE

We observed LVRR in 14 (36.8 %) patients on 6-months FU echocardiography. The prevalence of LVRR was significantly higher in CR-DSE (+) group [12 (54.5) vs. 2 (12.5), *n* (%) $p < 0.05$]. We used univariate and multivariate logistic regression analysis for several covariates to find out predictors for LVRR (Table 4). In univariate logistic regression analyses, delta LVEF was significantly correlated with LVRR. In multivariate logistic regression analysis, delta LVEF was an independent risk factor after adjustment of age and sex (OR: 1.82, 95 % CI: 1.06 – 3.11, $p = 0.029$).

We assessed the ability of delta LVEF on DSE to predict LVRR by using a

ROC curve (Figure 2). The Area Under Curve for the ROC curve with delta LVEF during DSE used to detect LVRR was 0.765 (95 % CI: 0.61 – 0.92, p = 0.007). When the delta LVEF of ≥ 4 % had a sensitivity 82 %, a specificity of 65 %, a negative predictive value of 93.8 %, and a positive predictive value 59.1 % as a prediction for LVRR at 6-months FU (Table 5).

4. Clinical outcomes according to CR-DSE

During FU periods, 5 patients reported cardiac death and 11 patients reported readmission due to heart failure. In Kaplan-Meier survival analysis, the prevalence of MACE was significantly lower in the CR-DSE (+) than in the (-) group during last clinical FU periods (Figure 3).

	CR-DSE (+) (n = 12)	CR-DSE (-) (n = 9)
LGE-CMR		
Positive	3 (25.0)	4 (44.4)
LGE type		
Extensive*	0	3 (33.3)
Localized	3 (25.0)	1 (9.1)
Uninterpretable		
Total	5 (35.7)	4 (36.3)
Motion blurring	2 (40)	3 (75)
Arrhythmia	3 (60)	1 (25)

Table 3. Results of CMR scanning according to CR-DSE. [* $p < 0.05$, CR-DSE (+) vs. (-)] CMR, cardiac magnetic resonance; CR, contractile reserve; DSE, dobutamine stress echocardiography; LGE, late gadolinium enhancement.

	Univariate		Multivariate	
	OR	95 % CI	OR	95 % CI
Age	0.95	0.90 - 1.01	0.96	0.83 - 1.11
Male	0.33	0.09 - 1.31	0.063	0.003 - 1.41
BMI	1.18	0.95 - 1.46		
Hypertension	0.19	0.04 - 1.08		
Diabetes	0.29	0.03 - 2.80		
Smoking	2.05	0.84 - 5.01		
Alcohol	2.39	0.96 - 5.95		
SBP	1.04	0.99 - 1.09		
DBP	1.03	0.99 - 1.07		
HR	1.01	0.98 - 1.05		
BNP	1.00	0.99 - 1.00		
LVEDD	0.99	0.90 - 1.10		
LVESD	0.98	0.88 - 1.10		
LVEF	1.01	0.92 - 1.10		
LAVI	1.01	0.97 - 1.06		
E/E'	0.99	0.91 - 1.07		

RVSP	0.99	0.92 - 1.07		
ACEI/ARB use	1.86	0.17 – 19.8		
Beta-blocker use	0.96	0.00 – 23.5		
DSE				
Delta LVEF*	1.27	1.05 - 1.55	1.82	1.06 - 3.11
Delta SBP	1.00	0.97 - 1.03		
Delta HR	0.95	0.90 - 1.01		
CMR				
LGE (+)	0.50	0.09 - 2.73	0.13	0.01 - 3.33

Table 4. Logistic regression analysis of predictive power for LVRR. (* $p < 0.05$)
LVRR, left ventricular reverse remodeling; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BNP, B-type natriuretic peptide; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DSE, dobutamine stress echocardiography; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

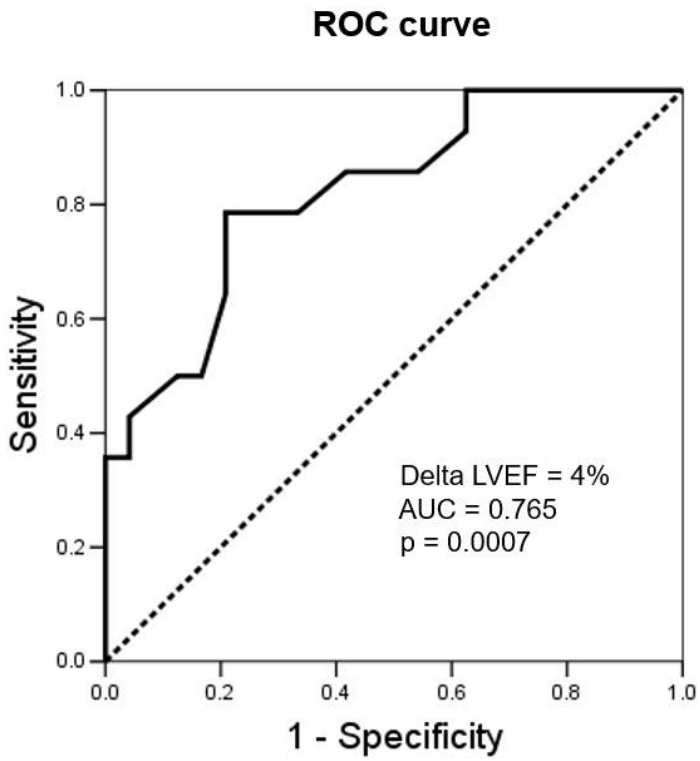

Figure 2. The diagnostic accuracy of the delta LVEF for LVRR prediction in patients with IDCM from ROC curve. ROC, receiver operator characteristics; LVEF, left ventricular ejection fraction; AUC, area under the curve.

Delta LVEF (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
6	57	75	73.8	53.3
5	64	69	80	55.6
4	82	65	93.8	59.1
3	93	52	90.9	48.1

Table 5. Sensitivity, specificity, negative and positive predictive value of various cut points of delta LVEF for LVRR prediction. LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling; NPV, negative predictive value; PPV, positive predictive value.

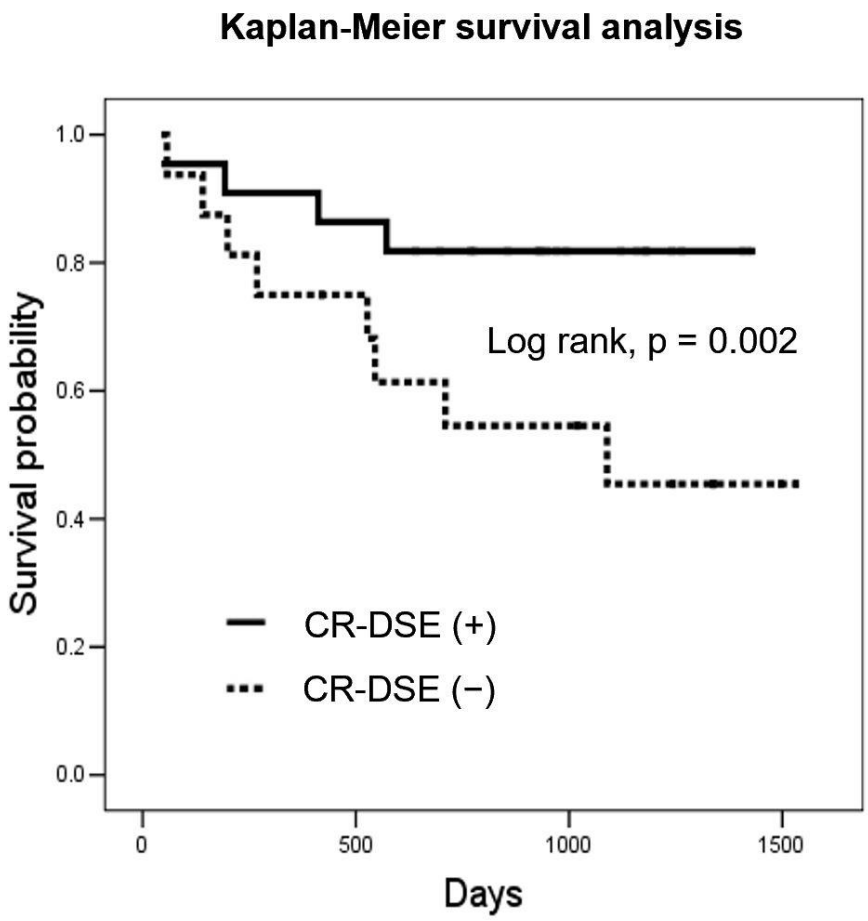

Figure 3. Kaplan-Meier survival analysis for MACE according to CR-DSE. CR-DSE: contractile reserve on dobutamine stress echocardiography.

IV. DISCUSSION

This study was the first to assess the predictive power of the CR-DSE (+) for LVRR in patients with IDCM compared with structural predictor of LVRR such as LGE-CMR (-). Our novel findings this study are as follows: 1) the CR-DSE (+) can predict LVRR in patients with IDCM; 2) the CR-DSE (-) may mean no forecast of LVRR during FU periods; 3) the CR-DSE (+) is significantly associated with good prognosis during clinical FU periods; 4) clinical application of LGE-CMR has some limitations such as motion artifact and arrhythmia during scanning. These data suggest that early identification of functional reversible factors, such as the CR-DSE (+) might be valuable in the clinical field.

B1AR downregulation or desensitization in myocardium, the consequence of anti-B1AR antibody, has been demonstrated in development of IDCM.[19] This B1AR downregulation or desensitization facilitates norepinephrine synthesis, which is thought to be involved in acceleration of heart failure.[20] This increased adrenergic activity may attenuate or block the myocardial responsiveness to beta adrenergic stimuli.[21] The selective B1AR agonist, dobutamine has been playing an important role for evaluation in B1AR status in patients with IDCM or ischemic heart failure.[7] Temporarily, DSE may improve contractile capacity by various degrees in denatured myocardium, and the results of DSE can be utilized for

prognostic stratification. In clinical implications, it is hard to differentiate cardiac B1AR dysfunction at molecular level whether absolute reduction of B1AR density at the plasma level, called downregulation or uncoupling of the remaining membrane B1AR from G proteins, called desensitization.[4] Inotropic effects of dobutamine can be increased through the degree of myocardial neurohormonal status, including signal coupling and function of G proteins in viable myocardium.[22,23] If dobutamine increases in the inotropic and chronotropic reserve of the heart at the early diagnosis stage, it may lead to a good prognosis by improving cardiac B1AR density, called upregulation and restoration of signaling and function, called resensitization in the future. The CR-DSE (+) in a denatured myocardium reflects not only up to 50 % of viable myocytes but also an acceptable integrity of the myocardial adrenergic system.[24] However, it should be emphasized that the CR-DSE (+) is a functional marker of B1AR responsiveness and does not provide past mechanistic etiologies including B1AR downregulation or desensitization. Also, CR-DSE (+) may be influenced by complex circumstances, including myocardial fibrosis, myocardial blood flow and the level of myocardial norepinephrine.[25] Thus, we chose newly diagnosed IDCM patients in order to minimize the influence of these complex circumstances and to obtain a reliable information-inferring capacity and density of B1AR in the myocardium.

CMR studies in IDCM have shown that the LGE-CMR (+) can predict an

increased prevalence of MACE and a larger extent of mid-wall LGE reflect the bare chance of LVRR during FU periods.[6,26,27] Contrary to previous CMR studies for LVRR prediction, our study results revealed no association between LGE-CMR (-) and LVRR during FU periods. The prevalence of extensive type of LGE-CMR was significantly higher in the CR-DSE (-) group in this study. The LGE-CMR (+) may be linked to contractile impairment that is thought to reflect the changes from reversible to irreversible myocardial damage. However, there is possibility that a localized type of LGE-CMR (+) can result from other forms of interstitial expansion. Also, one study showed that the presence of localized type of LGE-CMR (+) was more related to microscopic findings of inflammation rather than to fibrosis in endomyocardial biopsy.[28] This might be why LGE-CMR (+) does not always represent current myocardial fibrosis in patients with IDCM. It remains unclear whether early detection of LGE-CMR (+) reflects continuous myocardial damage that bring about poor prognosis in the future.

The percentage of detection of LGE-CMR (+) in newly diagnosed IDCM differs significantly across the studies, ranging from 12 to 67 % with different enhancement protocols probably because of the lack of standardized image acquisition protocols using 1.5-T or 3-T scan systems and the subjective bias of different operators.[26] There is no consensus on the type and dose of contrast agent, nor on the timing in acquisition of LGE sequences after contrast infusion.

Although we hoped our 3-T MR scanner might bring better resolution through fast scanning speed, high signal-to-noise ratio and contrast-to-noise ratio, the imaging analysis of some patients was impossible because of several artifacts generated from patient factors, such as motion blurring, respiratory hold failure and arrhythmia. These artifacts might reduce the validation power of the LGE-CMR (-) for LVRR prediction by hindering reliable analysis in our study. To reduce these artifacts, an image-acquisition protocol for LGE-CMR will need standardization of method and improvement of breathing hold and heart rate control during scanning.

Although clinical availability of BNP in IDCM is well accepted in clinical fields, a predicting power for LVRR was not significant in this study. According to previous studies which evaluated predictors of LVRR in IDCM patients, we also evaluated plasma BNP at baseline and 6-months FU, NYHA class, SBP, LVEDV, LAVI and ACEI use for predictor of LVRR.[29] None of these variables were the significant predictors for LVRR on multivariable logistic regression analysis in this study. Some studies reported that elevated biomarkers, including BNP level showed significant long-term prognostic significance that might provide that the structural and functional information about the denatured myocardium in patients with IDCM.[6,8] However, this surrogate marker needs serial measurements, and the

level of BNP might reflect the degree of wall stress rather than functional ventricular dysfunction indirectly, so we ought to integrate quantitative value and clinical factors.

In this study, we hypothesized that initial inotropic and chronotropic reserve of myocardium by using DSE could assess the desensitization and downregulation of B1AR which might imply the reversibility of a diseased myocardium and unrevealed intact myocardium. Compared with LGE-CMR (-) and other biomarkers, DSE is very logical candidates for forecasting LVRR in newly diagnosed IDCM. Moreover, DSE was shown to be safe and well tolerated in patients with IDCM. The rationale of low-dose DSE is to avoid confounding effects of high-dose DSE, such as ischemia like myocardial contractile responses on DSE.[30] As far as we know, our study would be the first to evaluate the LVRR prediction power between DSE and CMR in newly diagnosed IDCM patients. One study reported that changes in LV systolic performance on low-dose DSE are useful marker to predict the outcome of LV systolic function in patients with IDCM.[31] Although it was the first study to mention the DSE as a predictor for functional recovery in diseased myocardium, total number of enrolled patients were very small. Although DSE has rarely been used in IDCM patients who need to quantify the likelihood of LV functional improvement, the role of DSE might

be salutary modality for both functional and structural recovery of a deranged myocardium. It is not clear that the CR-DSE (+) fully translates into upregulation and resensitization of B1AR and subsequent LVRR in patients with IDCM. However, DSE can be the promised modality to dig for an intact or unbroken myocardium inferring LVRR at least. The application of DSE for IDCM patients to find out whether it predicts LVRR doesn't take a long time or danger. In addition, the identification of poor responsiveness of the denatured myocardium during DSE could provide the physician with optimal timing for heart transplantation.

This study has some limitations as follows: 1) Although this study launched with 45 patients with newly diagnosed IDCM, unavoidable FU loss of 7 patients and the refusal of CMR scanning of 20 patients resulted from their lack of understanding study and of the need for compliance. 2) Image acquisition and validation of LGE-CMR was affected by unexpected motion artifact and arrhythmia, so the CMR data of 4 patients were excluded and uninterpretable in this study. Thus, the analysis of LGE-CMR for LVRR in this study might have been underpowered. 3) This study was not designed to estimate the effect of pharmacologic therapies according to guidelines, so that the targeting dose of ACEI, ARB and BB differed case by case. 4) Because we did not perform CMR at

6-months FU, interval changes of LGE-CMR (+) were not validated in this study. Nevertheless, this study showed highly effective value of DSE for LVRR prediction in spite of the reduced sample size and difficulty in imaging interpretation because of artifacts.

V. CONCLUSION

This prospective case control study showed that the early application of DSE is more valuable method for predicting LVRR than CMR and biomarker in patients with IDCM. If a standardized image protocol for LGE-CMR is developed, the combination of CR-DSE (+) and LGE-CMR (-) at initial diagnosis may be available predictor for future LVRR in patients with IDCM.

VI. REFERENCES

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국문 요약

처음 진단된 특발성 확장형 심근병증 환자에서 좌심실 역방향 재형성 예측을 위한 도부타민 스트레스 심장 초음파 검사의 역할

최현민

연세대학교 대학원

의학과

좌심실 역방향 재형성은 특발성 확장형 심근병증 환자에서 변형된 심근의 자발적 회복을 의미한다. 본 연구의 목적은 도부타민 스트레스 심장 초음파에서 관찰된 수축 예비능의 보존이 좌심실 역방향 재형성 예측에 있어 어떤 잠재력을 갖는지 평가하고, 심장 자기공명 영상 검사에서의 후기 gadolinium 조영 증강 부재와 함께 좌심실 역방향 재형성 예측력을 비교하고, 마지막으로 추적 관찰 기간 동안 수축 예비능 보존 여부에 따라 임상 예후를 평가하는 것이다. 우리는 2012년 3월부터 2014년 5월까지 처음 진단된 특발성 확장형 심근병증 환자들을 대상으

로 하였다. 이 연구에 총 45명이 배정되어 초기 및 6개월 후 심장 초음파 검사를 계획하였다. 수축 예비능의 보존은 도부타민 투여 후 좌심실 구혈율이 투여 전 보다 4점 이상 증가된 경우로 정의되었다. 후기 gadolinium 조영 증강을 평가하기 위한 심장 자기 공명 영상도 함께 시행되었다. 좌심실 역방향 재형성의 정의는 초기 심장 초음파 검사 결과와 비교해서 6개월 추적 심장 초음파 검사 결과에서 좌심실 구혈율 10 % 이상의 증가와 좌심실 이완기 말 직경의 10 % 이상 감소로 정의하였다. 배정된 환자 중 총 38명이 6개월 후 추적 심장 초음파검사를 마쳤다. 초기 22명 (57.9 %)의 도부타민 스트레스 심장 초음파 검사에서 보존된 수축 예비능이 관찰되었다. 6개월 추적 심장 초음파 검사에서 좌심실 역방향 재형성은 총 14명 (36.8 %)에게서 관찰되었다. 심장 자기 공명 영상 검사에서의 후기 gadolinium 조영 증강의 부재는 좌심실 역방향 재형성의 예측 요소가 되지 못했다. 다변량 로지스틱 회귀 분석에서 수축 예비능의 보존은 좌심실 역방향 재형성에 대한 독립적인 예측 인자였다 (승산비: 1.82 [95 % 신뢰 구간: 1.06 대 3.11]; p = 0.029). 수신기 작동 특성 곡선 분석에서 도부타민 스트레스 심장 초음파 검사에서의

좌심실 구혈율의 변화량은 좌심실 역방향 재형성에 의미 있는 예측 인자였다 (곡선하 면적 = 0.765, p = 0.007). 도부타민 스트레스 심장 초음파 검사에서 4 %의 좌심실 구혈율 증가 한계치를 사용한 좌심실 역방향 재형성을 음성 예측 값은 93.8 % 였다. 28 ± 14 개월의 평균 추적 관찰 기간 동안 수축 예비능이 보존된 군은 주요 심장 이상 증상의 발병률이 현저히 낮았다. 수축 예비능의 보존은 좌심실 역방향 재형성의 중요한 예측 인자이며 수축 예비능이 없었던 군은 6개월 추적관찰 심초음파에서 좌심실 역방향 재형성의 발생하지 않을 가능성이 높다. 반면, 심장 자기 공명 영상의 후기 gadolinium 조영 증강의 부재는 연구 참여 인수가 부족하여 좌심실 역방향 재형성에 대한 유의한 예측 인자가 되지 못했다. 그리고 수축 예비능이 보전된 군은 추적 관찰 기간 동안 좋은 예후를 보여주었다.

핵심되는 말: 도부타민, 특발성 확장형 심근병증, 재형성, 스트레스 심장 초음파