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Original Article

Detection of regional low myocardial perfusion helps predict a response to cardiac resynchronization therapy in patients with non-ischemic cardiomyopathy: Results of the Find Index by Nuclear Imaging for Dyssynchrony (FIND) study

Takehiko Keida, MD[a,*], Itsuro Morishima, MD[b], Taketsugu Tsuchiya, MD[c], Kouichi Sagara, MD[d], Kaoru Okishige, MD[e], Kenta Kumagai, MD[f], Yoshiaki Mibiki, MD[g], Kentaro Nakamura, MD[a], Tamon Yamanaka, MD[h], Yukihiko Yoshida, MD[i], Akira Yamamoto, MD[J], Mitsuaki Takami, MD[k]

[a] Department of Cardiology, Edogawa Hospital, 2-24-18 Higashikoiwa, Edogawa-ku, Tokyo 133-0052, Japan
[b] Department of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan
[c] Department of Cardiology, Kanazawa Cardiovascular Hospital, Kanazawa, Japan
[d] Department of Cardiology, The Cardiovascular Institute, Tokyo, Japan
[e] Department of Cardiology, Yokohama City Minato Red Cross Hospital, Yokohama, Japan
[f] Department of Cardiology, Odawara Cardiovascular Hospital, Odawara, Japan
[g] Department of Cardiology, Miyagi Cardiovascular Respiratory Center, Kurihara, Japan
[h] Department of Cardiology, Tohoku Welfare Pension Hospital, Sendai, Japan
[i] Department of Cardiology, Nagoya Daini Red Cross Hospital, Nagoya, Japan
[j] Department of Radiology, Nippon Medical School Tama Nagayama Hospital, Tama, Japan
[k] Cardiac Rhythm Disease Management, Medtronic Japan, Tokyo, Japan

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ABSTRACT

Background: The aim of this study was to investigate the use of imaging techniques to predict the response to cardiac resynchronization therapy (CRT) in patients with non-ischemic cardiomyopathy (NICM) by simultaneous assessment of left ventricular (LV) dyssynchrony and myocardial perfusion in a single nuclear scan of the heart.
Methods: Patients indicated for CRT device implantation underwent a resting myocardial perfusion assessment with single photon emission computed tomography (MP-SPECT) examination using technetium-99 m methoxyisobutylisonitrile prior to device implantation. CardioGRAF and cardioBull software (FUJIFILM RI Pharma, Tokyo, Japan) were used to analyze the LV mechanical dyssynchrony and myocardial viability, respectively. Patient follow-ups were performed at 6 months after device implantation. CRT response was defined as a $\geq$10% decrease in the LV end systolic volume.
Results: A total of 43 patients with NICM were analyzed. Using the cutoff points of 6.2 for the dyssynchrony index and 66% for LV myocardial perfusion, the combined indices predicted CRT response with a sensitivity of 77.8% and specificity of 91.2%.
Conclusion: Combined assessment of MP-SPECT and a measure of LV mechanical dyssynchrony showed good predictive ability in patients with non-ischemic heart failure.

1. Introduction

Cardiac resynchronization therapy (CRT) has been demonstrated to improve symptoms, quality of life, functional status, and reduce mortality and heart failure-related hospitalizations in patients with New York Heart Association (NYHA) class III or IV heart failure and electrocardiographic evidence of ventricular dyssynchrony (QRS duration $\geq$120 ms) [1–3]. However, approximately one-third of patients receiving CRT fail to respond to treatment [4]. Analyses that accounted for the placebo effect and the use of remodeling rather than functional endpoints found an even higher non-response rate [5]. Given the number of device and/or procedure-related adverse events as well as the economic burden of CRT, numerous efforts have been made to identify parameters that could be used to improve patient selection and reduce the incidence of non-response.

Recently, it has been shown that the presence of posterolateral scar burden can predict CRT non-response [10,11]. Birnie et al.

* Corresponding author. Tel.: +81 3 3673 1221; fax: +81 3 3673 1229.
E-mail address: keida@edogawa.or.jp (T. Keida).

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showed that lateral wall scarring/fibrosis is important in determining CRT response in non-ischemic cardiomyopathy patients [10]. Bleeker et al. found that the patients most likely to improve after CRT were those without transmural scar tissue in the posterolateral wall and severe left ventricular mechanical dyssynchrony (LVMD) at baseline [11]. These findings were attributed to ineffective pacing due to nonviable scar tissue in the region of the LV pacing lead. This observation supports combined assessment of both LVMD and scar burden prior to CRT implantation to verify the characteristics of the area targeted for LV pacing. Given these findings, there has been increased interest in the use of nuclear imaging for predicting CRT response [12,13]. Myocardial perfusion assessment with single photon computed tomography (MP-SPECT) provides information regarding LV myocardial viability and could enable evaluation of LV scar burden. A software tool that enables the simultaneous estimation of regional LV function and wall motion synchrony in combination with MP-SPECT has been validated [14–16]. Since the phase analysis tool is largely automatic, it is less prone to inter observer errors than echocardiography. Additionally, it does not require the considerable specialized expertise required to perform these assessments by echocardiography.

2. Methods

2.1. Patients and study procedures

A total of 53 patients who had heart failure, were scheduled for implantation of their first CRT device, and had agreed to undergo nuclear imaging at 10 centers were prospectively studied. The Medical Ethics Committee at each participating center approved the study protocol, and all patients provided written informed consent. Patients were selected for CRT implantation based on the Japanese Circulation Society Guideline [17,18]. The basic criteria were as follows: NYHA class III or IV, QRS duration ≥ 130 ms, LV ejection fraction (LVEF) $\leq 35\%$, and non-ischemic heart failure as documented by exclusion of coronary artery disease by using angiography. Based on the QRS duration, LVEF, and prior history of heart failure hospitalizations, NYHA class I and II patients could be included at the physician's discretion. Patients who had a life expectancy < 6 months; were scheduled for heart surgery, including percutaneous coronary intervention; and/or who could not be followed for 6 months were excluded from the study.

The study was conducted as follows: prior to CRT implantation, all patients underwent a resting MP-SPECT examination using technetium-99 m methoxyisobutylisonitrile (TcMIBI). Scanning procedures were performed according to the guidelines of the Japanese Society of Nuclear Medicine Technology working group [19], which are comparable with the American Society of Nuclear Cardiology [20] and European Association of Nuclear Medicine/European Society of Cardiology [21] guidelines. Free computer software, that is, cardioGRAF and cardioBull (FUJIFILM RI Pharma, Tokyo, Japan), were used to assess LVMD and LV myocardial perfusion, respectively. These programs have been validated and assessed in previous studies [16,36] with respect to the performance level of quantitative assessment for LV dyssynchrony. These software programs have been described in further detail in the sections on assessment measures. The MP-SPECT examination was repeated 6 months after CRT implantation, and the patients' clinical status and nuclear cardiographic findings were reassessed. All analyses of data derived from using the cardioGRAF and cardioBull were performed at a core lab in Edogawa Hospital, Tokyo, Japan.

2.2. Assessment of left ventricular mechanical dyssynchrony

Regional contraction timing in the LV was computed and visualized with cardioGRAF software, which processes imaging data acquired by gated MP-SPECT, as described previously by Takahashi et al. [22]. Briefly, the LV was divided into 17 volume segments [23] and the regional wall motion and change in myocardial wall thickening of each segment were estimated [24–26]. The time-based variation in volume was measured for each segment. The onset of a cardiac rhythm was triggered at the peak of the R-wave, and end systole was determined based on the detection of the bottom of the third-derivative of the time–volume curve (i.e., the contraction velocity) (Fig. 1). End systole of the whole LV was estimated as the instant at which the sum of all of the segments was minimal (Fig. 2) [16]. The cardioGRAF software has been validated by Yamamoto et al. [16] and

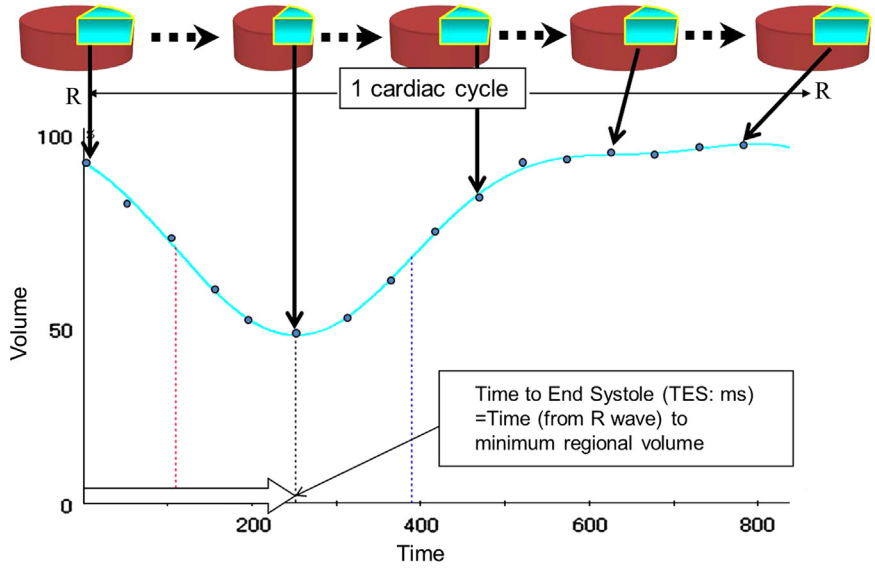

Fig. 1. Change in the regional LV chamber volume. Global and regional time–volume curves were generated from the data obtained by Fourier curve-fitting analysis with 3 harmonics; the first derivative curve was simultaneously created from the time–volume curve. The global and regional parameters were obtained from the time–volume curves and the first derivative curves.

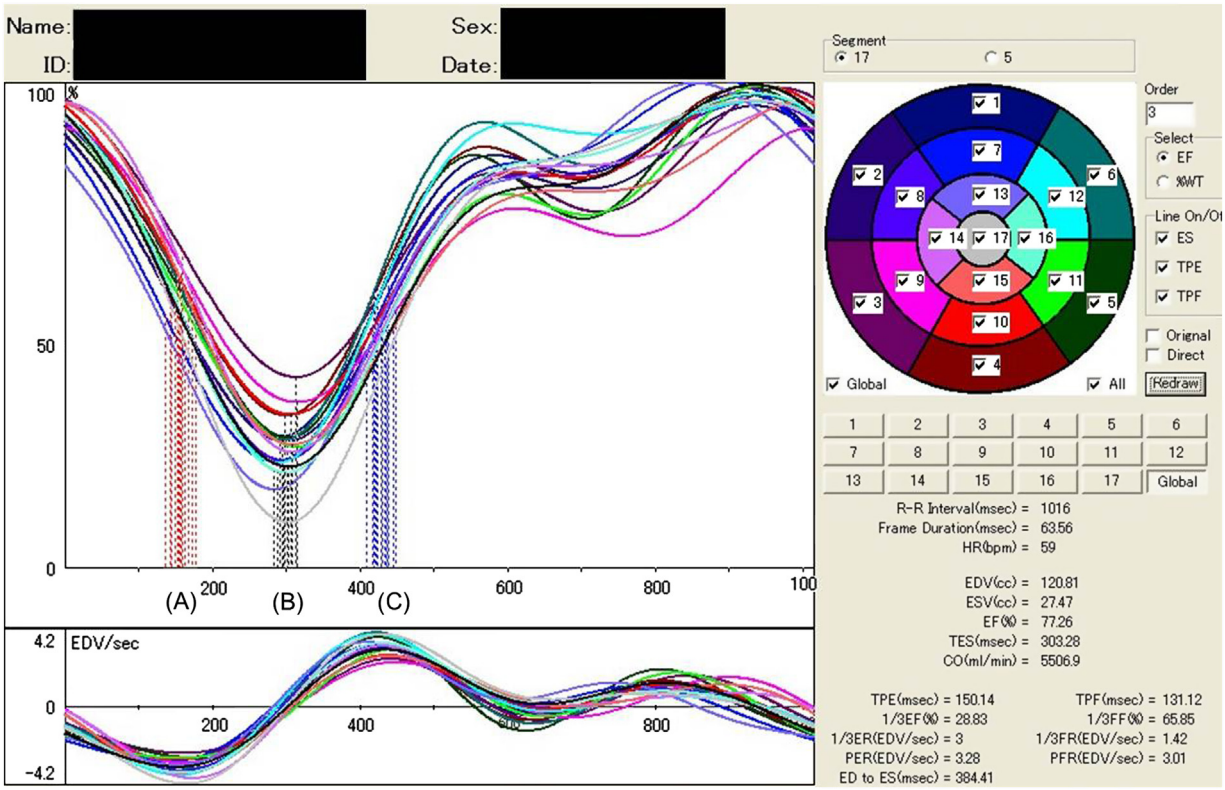

Fig. 2. Main window of the cardioGRAF Software. CardioGRAF plots regional left ventricular (LV) time–volume curves. The dashed lines indicate the "time to peak ejections" (A), "time to end systoles" (TES; B), and "time to peak fillings" (C) for each of the LV segments.

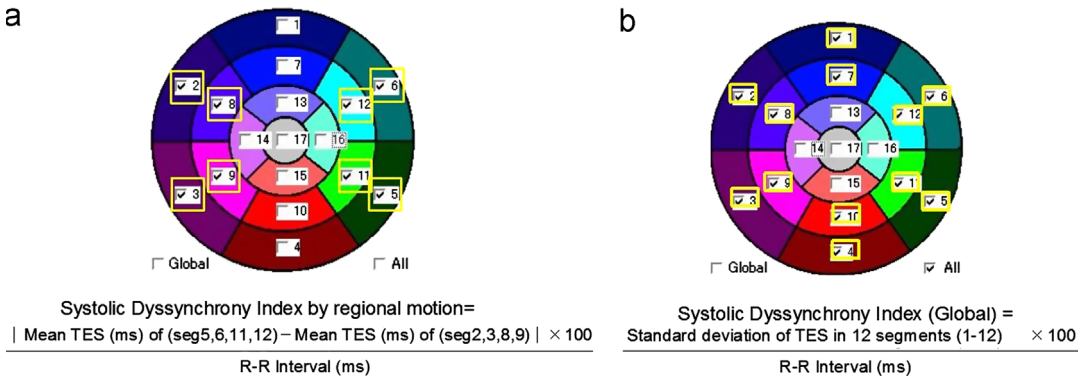

Fig. 3. Definition of the dyssynchrony index. (a) SDI:LVMD-SL was defined as the value obtained on subtracting the mean of the time to end systole (TES) of the left ventricular (LV) septum (4 segments) from the mean of the TES of the LV lateral wall (4 segments), dividing the resultant value by the R–R interval (ms), and multiplying the final value by 100. (b) SDI:LVMD-GL was defined as the value obtained on determining the standard deviation of TES in 12 segments excluding the apical segments, dividing this standard deviation value by the R–R interval (ms), and multiplying the final value by 100.

Takahashi et al. [22]. The cardioBull software has been validated by Nakajima et al. [27].

2.3. Development and evaluation of the systolic dyssynchrony index

We developed 2 types of systolic dyssynchrony indices (SDIs) in order to assess the quantitative measure of LVMD. One was used to quantify the LVMD between the LV septum and LV lateral wall (SDI:LVMD-SL), and the other was used to quantify the global LVMD (SDI:LVMD-GL). SDI:LVMD-SL was defined as the value obtained on subtracting the mean of the time to end systole (TES; Fig. 1) of the LV septum (4 segments) from the mean of the TES of the LV lateral wall (4 segments), dividing the resultant value by the R–R interval (ms), and multiplying the final value by 100 (Fig. 3a).

SDI: LVMD-GL was defined as the value obtained on determining the standard deviation of TES in 12 segments excluding the apical segments, dividing this standard deviation value by the R–R interval (ms), and multiplying the final value by 100 (Fig. 3b). It was assumed that measurements in the apex area did not contribute to the SDI:LVMD-GL.

2.4. Assessment of regional left ventricular myocardial perfusion

LV myocardial perfusion was assessed by the uptake rate in each of the 17 segments of the LV, as calculated by the software and displayed in the form of a bull's eye map. Toyota et al. [28] reported that bull's eye mapping with this software tool provided a simple and useful numerical parameter for diagnosing myocardial viability with high specificity and high sensitivity.

Table 1
Baseline patient characteristics and medications used.

	CRT responder (*N*=34, 79%)	CRT non-responder (*N*=9, 21%)	*P*-value*
Age (years)	68.1 ± 10.8	69.4 ± 8.6	0.93
Gender (M/F)	24/10	8/1	0.26
NYHA Class (I, II, III, IV)	2/8/17/7	0/0/9/0	0.65
QRS duration (ms)	155.6 ± 3 5.2	156.9 ± 27.6	0.92
LBBB/RBBB/IVCD/narrow	20/5/4/5	4/2/3/0	0.28
Rhythm (SR/AF/paced/other)	23/5/4/2	5/2/2/0	0.68
LVEF (%)	23.9 ± 8.9	26.6 ± 11.7	0.47
LVEDV (mL)	298.0 ± 121.3	278.1 ± 136.5	0.67
LVESV (mL)	231.3 ± 105.4	209.1 ± 119.6	0.60
BNP (pg/mL)	680 (292–1085)	401 (246–778)	0.24
6-minute hall walk distance (m)	325 (240–415)	340 (280–400)	0.95
% V pacing	96.9 ± 8.4	96.9 ± 3.5	0.98
Inotropic agents (iv)	5 (14.7%)	0 (0%)	0.22
Beta-blocker	25 (73.5%)	9 (100%)	0.08
ACE inhibitor	13 (38.2%)	4 (44%)	0.74
ARB	11 (32.4%)	2 (22.2%)	0.56
Spironolactone	16 (47.1%)	5 (55.6%)	0.65
Loop diuretic	27 (79.4%)	9 (100%)	0.14
Digitalis	1 (2.9%)	3 (33.3%)	0.005
Statin	6 (17.6%)	1 (11.1%)	0.61

NYHA=New York Heart Association, LBBB=left branch bundle block, RBBB=right branch bundle block, IVCD=interventricular conduction delay, SR=sinus rhythm, AF=atrial fibrillation, LVEF=left ventricular ejection fraction, LVEDV=left ventricular end diastolic volume, LVESV=left ventricular end systolic volume, BNP=brain natriuretic protein, ACE=angiotensin-converting enzyme, ARB=angiotensin receptor blocker.

* Results have been expressed as mean ± standard deviation values. The Student-*t* test was applied for absolute values and the chi-square test was applied for proportional values. The *p*-value represents the comparison between the responder and non-responder groups.

2.5. CRT device implantation

Patients received commercially available CRT devices with and without a defibrillator (*N*=39 and 4, respectively) with implantation of a standard active-fixation pacing lead in the right atrium and a high-voltage lead in or near the right ventricular apex. A transvenous LV lead was positioned in a lateral or posterolateral branch of the coronary vein. The atrioventricular and interventricular delays were optimized using Doppler echocardiography by the method chosen at the physicians' discretion.

2.6. Definition of a CRT responder

CRT response was defined as a ≥10% decrease in the LV end-systolic volume (LVESV) at 6 months after CRT implantation, as measured by the cardioGRAF software. The definition of CRT response was based on the results of a study conducted by Yu et al., who found that LV reverse remodeling was the best predictor of long-term survival after CRT [29]. A ≥10% improvement in LVESV was predictive of long-term survival and is an objective measure of CRT response.

2.7. Statistical analysis

Using the indicators obtained by cardioGRAF and cardioBull as independent variables, the odds ratio (OR) and the 95% confidence interval (CI) were calculated with the multivariable logistic regression model. After correction for the confounding explanatory variables, the degree of CRT response prediction of each independent cardioGRAF and cardioBull indicator was evaluated. The hazard ratio (HR) was calculated using the multivariate Cox proportional hazards model. When the predictive factors obtained from the aforementioned model were in the form of continuous data, the cutoff points for LVMD and LV scar burden were examined using the receiver-operating characteristic (ROC) curves.

Table 2
Uptake rate of Tc-MIBI (%) in all patients, responders, and non-responders.

	Total (*N*=43)	Responders (*N*=34)	Non-responders (*N*=9)	*p*-value*
Uptake at the mid-inferolateral wall	71 ± 11	74 ± 10	61 ± 10	<0.001

* The p-value represents the comparison between the responder and non-responder groups.

3. Results

3.1. Study population

Of the 53 patients enrolled in the study, 3 patients died and 7 were lost to follow-up prior to 6 months; 43 patients completed the 6-month follow-up. Thus, a total of 43 heart failure patients with no angiographic evidence of coronary artery disease were included in the analysis. According to the predefined definition of CRT response as a ≥10% decrease in LVESV at 6 months, there were 34 responders and 9 non-responders. The baseline characteristics of the study population and baseline medications are shown in Table 1. There were no baseline differences between the CRT responders and non-responders, with the exception of digitalis use in non-responders (Table 2).

3.2. Predicting CRT response

3.2.1. LVMD index (cardioGRAF)

Using cardioGRAF, we found that SDI:LVMD-SL is a better predictor of systolic dyssynchrony than SDI:LVMD-GL (crude OR: 1.12, 95% CI: 1.02 − 1.23, $p=0.018$) (Fig. 4a). ROC analysis showed that the area under the curve (AUC) was 0.737. Using a DI cutoff point of 6.2 resulted in 77.8% sensitivity and 64.7% specificity for the prediction of CRT response (Fig. 4b).

3.2.2. Regional LV myocardial perfusion score (cardioBull)

Using the % uptake values in the 17 segments as independent variables, the ORs and 95% CIs were calculated with the multivariate logistic regression model. The decrease in the % uptake in the basal inferolateral, middle inferolateral, and middle anterolateral segments was a significant ($p<0.05$) predictor of CRT response (Fig. 5a). Among these 3 regions, the middle inferolateral region is usually most adjacent to or corresponds with the position of the LV lead placement, and showed the highest OR of 0.89 (95% CI: 0.81–0.97), thus it was a segment of particular interest. ROC analysis of this segment showed that the AUC was 0.858. Using a % uptake cutoff point of 66% provided a 77.8% sensitivity and 76.5% specificity for the prediction of CRT response (Fig. 5b).

3.2.3. Combined index of LVMD and myocardial perfusion in the middle inferolateral area

The combined indexes of LVMD and myocardial perfusion in the middle inferolateral area for the prediction of CRT response are shown in Fig. 6. When the elements of LVMD and regional myocardial perfusion were combined, the combined AUC was 0.895. Moreover, when the SDI:LVMD-SL calculated by cardioGRAF was

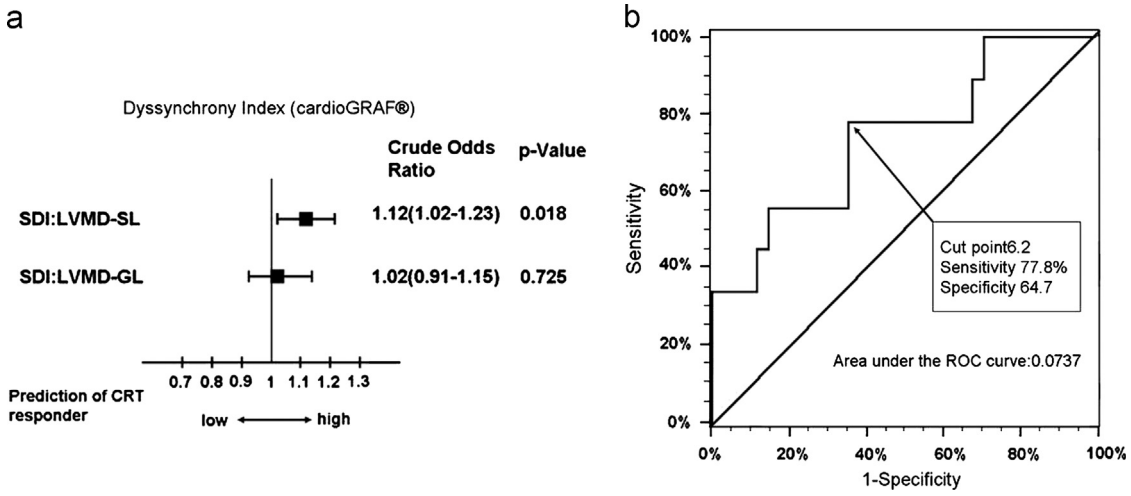

Fig. 4. (a) The dyssynchrony index calculated by the cardioGRAF software for the prediction of response to cardiac resynchronization therapy. (b) Receiver-operating characteristic analysis of left ventricular (LV) mechanical dyssynchrony for the prediction of cardiac resynchronization therapy response.

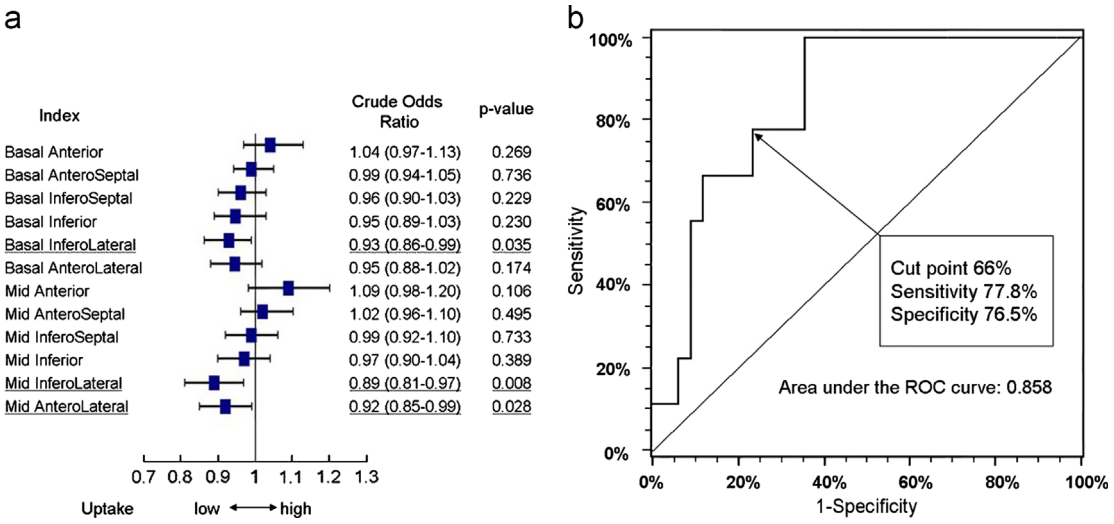

Fig. 5. (a) Regional left ventricular (LV) myocardial perfusion calculated by the cardioBull software for the prediction of response to cardiac resynchronization therapy. (b) Receiver-operating characteristic analysis of regional LV myocardial perfusion for the prediction of cardiac resynchronization therapy response.

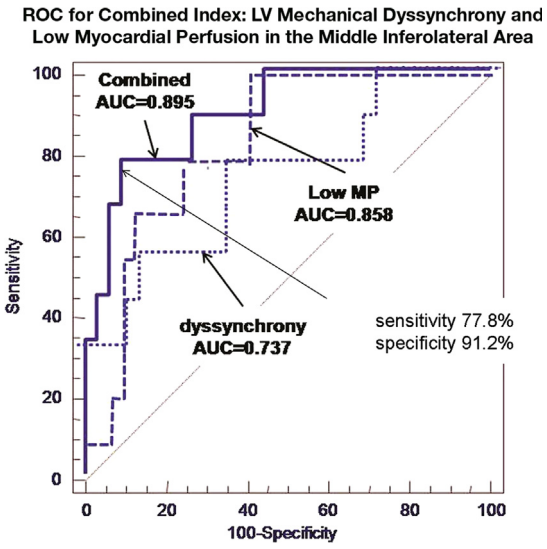

Fig. 6. Receiver-operating characteristic analysis of the combined index of left ventricular (LV) mechanical dyssynchrony and myocardial perfusion in the middle inferolateral area for the prediction of cardiac resynchronization therapy response.

≥6.2 and the % uptake of the middle inferolateral region calculated by cardioBull was ≥66%, CRT response was predicted with sensitivity of 77.8% and specificity of 91.2% (Fig. 6).

4. Discussion

The main findings of this study are as follows. First, the LVMD index calculated by the nuclear imaging analysis with cardioGRAF phase analysis software had a moderate predictive value for 6-month CRT response (defined as >10% reduction in LVESV). Second, regional myocardial perfusion assessment with nuclear imaging analysis using cardioBull software yielded a greater predictive capability for CRT response. In particular, the extent of low perfusion in the middle inferolateral wall indicated by cardioBull was highly relevant to the response. Third, the combined assessment of myocardial perfusion in the middle inferolateral wall and LVMD with nuclear imaging analysis using cardioGRAF and cardioBull, respectively, augmented the predictive capability for CRT response.

As with other phase analysis tools, computing quantified cardiac function parameters with cardioGRAF is largely automatic. Therefore, the considerable level of expertise required

to achieve reproducible results with echocardiography is not required. In an evaluation of the cardioGRAF tool, Takahashi et al. [22] demonstrated that the inter- and intra-observer reproducibility (i.e., coefficient of variation error) for the time to contraction (i.e., time from the onset of the R-wave to end systole) was 4.8% and 3.2%, respectively.

Patients with ischemic cardiomyopathy were not included in this study because of the potential difficulties in accurate depiction of the LV endocardium with gated MP-SPECT due to severe perfusion defects. The results of the present study, however, suggested that there could be severe perfusion defects even in the hearts of patients with non-ischemic cardiomyopathy. The growing numbers of patients eligible for CRT due to an aging population and expanded indications, including mild heart failure [30,31], in combination with evidence that the actual non-responder rate may be even higher than initial estimates [32], underscores the ongoing need for methods to predict the CRT response. Reducing the non-response rate requires identification of appropriate parameters, cutoff values, and assessment techniques. Starting with the early stages of CRT, the use of a wide QRS duration as a patient selection criterion has been questioned; rather, the presence of LVMD was proposed as an important predictor of a firm response to CRT [6]. Direct estimation of LVMD using an imaging modality has been proposed as a method to improve patient selection for CRT and reduce the incidence of non-responses. Multiple small single center studies have demonstrated the application of a variety of echocardiographic measures of LVMD to predict CRT response with a high degree of sensitivity and specificity [6–8]. However, these results have not been duplicated in a large-scale multicenter study. The Predictors of Response to CRT (PROSPECT) trial, a prospective, multicenter study evaluating 12 echocardiographic parameters of LVMD, found only modest sensitivity and specificity in predicting CRT response [9]. Although each of the 53 participating centers was required to obtain accreditation from an echocardiography core laboratory, Chung et al. found that differences in technology platforms, training standards, and measurement analytics limited the reproducibility of the imaging methods in a non-specialized multicenter setting [9]. In Japan, Seo et al. concluded that echocardiographic parameters did not show significant power to detect CRT responders independently [35].

Therefore, other imaging techniques and tools have been evaluated. The results of this study add to the body of evidence demonstrating the value of SPECT and the need for a multifactorial approach to patient selection for CRT and in evaluating potential predictors of CRT response in non-ischemic patients. Bleeker et al. [11] used magnetic resonance imaging (MRI) to assess the extent of myocardial scar tissue. In addition to the automaticity provided by software analysis tools, SPECT offers the additional advantages of accessibility and usability in patients with pacemakers and/or other non-MRI conditional implantable medical devices.

With regard to the specific measures used in this study, a wide QRS has been associated with ventricular dyssynchrony and used as a patient selection criterion for CRT since its development. However, since large-scale, prospective, randomized studies have demonstrated that approximately one-third of patients with electrographic evidence of ventricular dyssynchrony fail to respond to CRT, attempts have been made to refine patient selection criteria. The results of this study suggest that not only measurement of mechanical dyssynchrony but also assessment of myocardial viability is an important factor in patient selection for CRT. Therefore, the Find Index by Nuclear Imaging for Dyssynchrony (FIND) study is unique in terms of evaluating a non-ischemic population and using the cardioGRAF and cardioBull software tools simultaneously.

In studies on the effect of posterolateral scar tissue on CRT response, Bleeker et al. [11] demonstrated that patients with transmural scar tissue in the posterolateral wall do not respond to CRT even in the presence of extensive mechanical dyssynchrony. Birnie et al. [10] reported that the location of scar tissue (lateral wall versus global or septal scar tissue) was a predictor of CRT response. To assess the relevance of the results of the FIND study in comparison to these studies, it is helpful to review the results of Udelson et al. [33] who compared SPECT imaging with 201Tl and MIBI for the determination of reversible and irreversible myocardial dysfunction after revascularization. The study found that both agents comparably predicted reversibility of contractile dysfunction after revascularization and that an arbitrary cutoff point of 60% of peak activity separated the regions of reversible and irreversible myocardial function. The cutoff value of 66% in this study was close to this value, demonstrating the potential value of the methods used to determine scar burden.

A recent large-scale study conducted by Adelstein et al. that used SPECT to evaluate the effect of scar burden from prior myocardial infarction on outcomes following CRT is also notable [34]. The study, which included patients with both non-ischemic and ischemic heart failure etiologies found that a high scar burden was associated with reduced survival and a lack of LV functional improvement, whereas baseline dyssynchrony did not predict CRT outcomes. The study suggests a possible utility of both cardioGRAF and cardioBull in an ischemic population. Further evaluation of the methods and software tools used in this study should be performed in a larger-scale prospective study involving a prescriptive protocol for conducting SPECT imaging in a broader population of patients eligible for CRT device implantation.

Our results demonstrated a relatively higher response rate as compared to other studies. Several studies have been published on response rates in CRT. For example, the Japan Cardiac Resynchronization Therapy Registry Trial (J-CRT) trial [35] reported that 63% of patients in the CRT group responded to the therapy as volume responders. Comparing this result to that of our study, we demonstrated a higher response rate. One of the reasons for this is likely patient population differences, particularly with regard to etiology. Our patient population solely included non-ischemic patients, and it is well known that ischemic patients do not respond well to CRT compared to non-ischemic patients [29]. Furthermore, we defined responders as patients demonstrating $\geq 10\%$ reduction of LVESV after CRT. This definition might classify a larger proportion of patients as responders compared to the standard definition of volume responders (i.e., $> 15\%$ reduction of LVESV after CRT).

5. Limitations

The limitations of this study are the small total sample size, lack of enrollment of consecutive patients, and the inclusion of patients who did not meet the inclusion criteria (i.e., QRS duration and NYHA classification). The included patients may, therefore, represent selection bias. Another limitation is that, although data analysis using SPECT software was performed at a core lab and scanning procedure was performed as per the guidelines, the scanning environment, including the gamma camera, pixel size, and technetium dose, varied between sites. Therefore, imaging quality varied between centers. In addition, the temporal resolution of cardioGRAF is not high (16 points/cardiac cycle). This may explain why the dyssynchrony predictive accuracy alone was not definitive (AUC = 0.737).

6. Conclusions

Low myocardial perfusion of the lateral wall is an important factor in determining the response to CRT in patients with non-ischemic cardiomyopathy, and the detection of low perfusion with SPECT analysis is a powerful tool to predict CRT response. The combined assessment of low myocardial perfusion and LVMD using automated software for SPECT analysis may augment the predictive capability of CRT response.

Disclosures

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