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ORIGINAL ARTICLE

Assessment of coronary flow reserve predicts long-term outcome of responders to cardiac resynchronization therapy

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Abstract
Cardiac resynchronization therapy (CRT) has been established as a treatment for patients with chronic heart failure (HF). We tested the hypothesis that assessment of coronary flow reserve (CFR) predicts the long-term outcome of CRT. The study consisted of 114 HF patients implanted with a CRT device for the treatment of advanced HF between April 2010 and April 2018. After excluding patients that withdrew from long-term follow-up and patients missing a baseline CFR measurement, we enrolled 53 eligible patients. CFR was determined non-invasively by transthoracic echocardiography. Based on the ROC curve for predicting the appearance of major adverse cerebral and cardiovascular events (MACCE), the level of preserved CFR was set at >1.35 in responders. Accurate follow-up information (mean 873 ± 498 days) was obtained in 23 patients with a preserved CFR (16 females; mean age 71 ± 7.9 years) and 11 patients with a depressed CFR (5 females; mean age, 73 ± 7.6 years) in responders. Kaplan–Meier survival analysis demonstrated that the depressed CFR group had a higher prevalence of MACCE than the preserved CFR group (log rank, 9.83; $p = 0.0021$). Multivariate analysis revealed that depressed CFR was associated with MACCE (hazard ratio 4.88, 95% confidence interval 1.13–26.5, $p = 0.0329$). Our results suggest that the assessment of CFR predicts the outcome in responders to CRT. Preservation of coronary circulation flow might underlie one of the mechanisms for a better response to CRT in responders.

Keywords Coronary flow reserve · Cardiac resynchronization therapy · Long-term outcome · Responder

Introduction

Coronary flow reserve (CFR) is the magnitude of increase in coronary flow that can be achieved from basal coronary perfusion to maximal vasodilation. CFR reflects the ability of the microvasculature to respond to a stimulus and likely represents the function of the small vessels as well [1]. CFR is determined by measuring coronary or myocardial blood flow at baseline and following myocardial hyperemia[1]. CFR determined by transthoracic Doppler echocardiography (TTDE) is useful in the non-invasive assessment of significant left anterior descending coronary artery (LAD) stenosis [2] and accurately reflects invasive measurement of CFR using the Doppler guide wire method [3].

In patients with severe heart failure (HF), cardiac resynchronization therapy (CRT) is a therapeutic modality for improving symptoms, exercise capacity, cardiac function, and prognosis [4–7]; however, little is known about the relationship between the outcome of responders to CRT and the baseline coronary circulation assessed by CFR. The purpose of this study was to test the hypothesis that assessment of coronary flow reserve (CFR) is associated with the long-term outcome of CRT responders.

Materials and methods

Patient selection

The study consisted of 114 HF patients who had a CRT device implanted for the treatment of advanced HF between

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April 2010 and April 2018. The inclusion criteria were as follows: New York Heart Association (NYHA) class III–IV; left ventricular ejection fraction (LVEF) < 0.35; and a QRS duration ≥130 ms. After excluding the patients who were withdrawn for a lack of long-term follow-up and did not have a baseline CFR measurement, we enrolled 53 eligible patients (Fig. 1). Patients with significant stenosis of the LAD were excluded because stenosis of the LAD may have an impact on measurement of the CFR.

The CFR could not be assessed in 38 patients for the following reasons: 5 bronchial asthma (adenosine triphosphate [ATP] was unavailable); 5 significant coronary artery stenosis; 2 treatment with any intravenous vasoconstrictor or vasodepressor agents within the 14 days prior to device implantation (due to the impact on the measurement of CFR), 6 unstable HF, 7 bradyarrhythmia, 3 tachyarrhythmia, 1 unobservable of LAD by TTDE, and 9 missing the timing to carry out CRF measurement before operation.

CRT responders were defined as patients with a ≥ 15% reduction in left ventricular end-systolic volume (LVESV) [8] at least 6 months after CRT implantation. Patients who were hospitalized for HF, demonstrated a persistent worsening of the NYHA class at last observation, had persistent moderate or marked worsening of the global assessment score [9] at last observation, permanently discontinued CRT because of or associated with worsening heart failure, or died before the 6-month follow-up were considered non-responders [8].

The study was approved by the Ethics Review Board of our institution and written informed consent was obtained from all subjects. This investigation was conducted according to the principles expressed in the Declaration of Helsinki.

Follow-up

All 53 patients with CFR assessment underwent a full device interrogation and clinical functional status was recorded every 4–6 months after CRT implantation. Accurate follow-up information for 873 ± 498 days was obtained. In 33 out of 53 patients, follow-up CFR data were obtained about 6 months after CRT implantation. The end point was defined as the appearance of major adverse cerebral and cardiovascular events (MACCE), which included cardiovascular mortality, non-fatal myocardial infarction, coronary revascularization through angioplasty, or bypass, stroke, and congestive heart failure requiring admission. Using combined criteria, only the first event was taken into the account for statistical analysis.

Assessment of echocardiography

Complete M-mode, 2-D, and Doppler evaluations were performed using a 1.5–4.0 MHz transducer at an appropriate depth in the parasternal and apical views. Left ventricular end-diastolic volume (LVEDV), LVESV, and LVEF were assessed by echocardiography using the modified biplane Simpson rule.

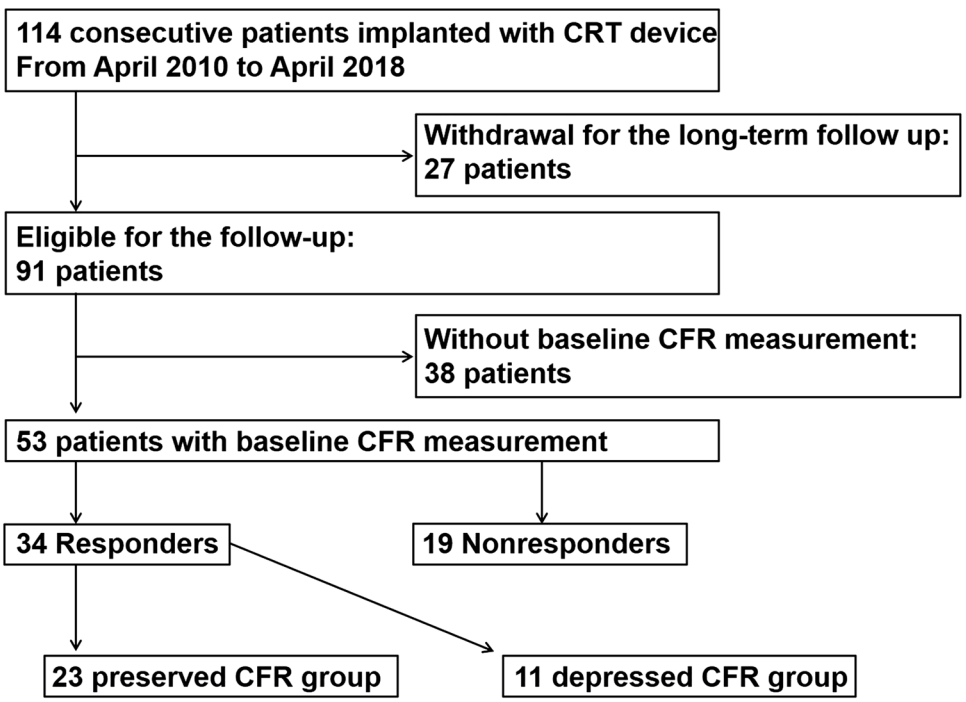

Fig. 1 Flow chart of 114 consecutive patients implanted with a CRT device from April 2010 to April 2018. *CFR* coronary flow reserve, *CRT* cardiac resynchronization therapy

Assessment of CFR by TTDE

TTDE for the measurement of CFR was performed with a Vivid 7 (GE Vingmed, Horten, Norway) with a high-frequency transducer (1.7–3.4 MHz). A modified foreshortened 2-chamber view was applied to explore the flow in the distal portion of the LAD under the guidance of color Doppler flow mapping. Angle correction was performed if the angle between color flow and the Doppler beam was greater than 20 [10 ,11].

We recorded baseline spectral Doppler signals in the distal LAD over five cardiac cycles at end-expiration by TTDE. Intravenous ATP disodium hydrate was administered (0.14 mg/kg/min) to obtain spectral Doppler signals during peak hyperemic conditions. Doppler signals recording during peak hyperemia were recorded over five cardiac cycles at end-expiration by TTDE. Measurements were averaged over three cardiac cycles. CFR was assessed as the ratio of hyperemic-to-basal mean diastolic coronary flow velocity [10, 11].

We obtained cutoff values for the baseline CFR by creating a ROC curve (Fig. 2) in responders. The best CFR value with which to predict MACCE with the highest sensitivity and specificity was 1.35. Therefore, a value ≤1.35 was used to define patients with a depressed CFR. Beginning in 2010, accurate follow-up information was obtained for 11 patients in the depressed CFR group (5 females and 6 males; mean age 73 ± 7.4 years) and 23 patients in the preserved CFR group (11 females and 12 males; mean age 70 ± 8.2 years).

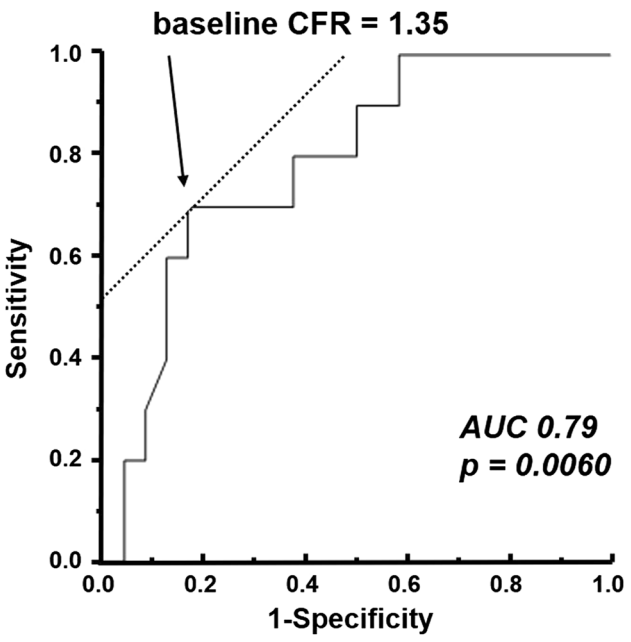

Fig. 2 Receiver-operating characteristic (ROC) curve for the ability of coronary flow reserve (CFR) to predict major adverse cerebral and cardiovascular events (MACCE). *AUC* area under the curve

We also obtained cutoff values for the baseline CFR by creating a ROC curve in the whole study population and non-responders. The best CFR values were 1.37 (AUC = 0.632, $p = 0.128$), and 1.57 (AUC = 0.550, $p = 0.787$), respectively.

Statistical analysis

Data are presented as the mean SD. A Chi-square test was used for categorical variables and analysis of variance (ANOVA) was used for continuous variables. The differences between groups were analyzed by Student's t-test. Kaplan–Meier survival analysis was used to compare MACCE-free times between responders and non-responders, and between the preserved and depressed CFR groups. Univariate Cox proportional hazard regression analysis was performed to identify the predictors of MACCE. Risk factors were entered into the risk model and included age, gender, etiology of dilated cardiomyopathy, QRS duration, blood pressure, heart rate, LVEF, LVEDV, LVESV, serum creatinine, brain natriuretic peptide (BNP), and depressed CFR. The results are given as hazard ratios with 95% confidence intervals. A $p < 0.05$ was considered significant. Multivariate Cox regression analysis was performed only for variables with significant univariate impact. All computations were performed with JMP (version 13.2.0; SAS, Cary, NC, USA) running under Windows 7 (Microsoft, Redmond, WA, USA).

Results

Patient characteristics

The baseline characteristics of the responders and non-responders are presented in Table 1. No significant difference was observed in age, gender, underlying etiology of heart failure, duration of QRS, blood pressure, heart rate, echocardiographic findings, blood sample findings, and baseline CFR between the two groups.

No significant difference was observed between responders and non-responders, with respect to biventricular pacing rate (97 ± 7.2%, vs. 98 ± 8.7%), left ventricular pacing position (apical 12%/midventricle 65%/basal 24% vs. apical 11%/midventricle 53%/basal 37%) [12], and rate of patients with previous frequent (>40%) RV pacing [13] before CRT (41% vs. 42%). There was no difference in baseline CFR between 48 non-ischemic cardiomyopathy patients and 5 patients with ischemic cardiomyopathy (1.74 ± 0.49, vs. 1.49 ± 0.28, respectively, $p = 0.25$).

The baseline characteristics of the preserved and depressed CFR groups in responders are presented in Table 2. The heart rate was higher in the depressed CFR group than the preserved CFR group ($p < 0.05$). The

Table 1 Baseline clinical characteristics

	Nonresponders ($n=19$)	Responders ($n=34$)	p value
Age (years)	73 ± 7.6	71 ± 7.9	NS
Gender (female/male)	5/14	16/18	NS
Ischemic cardiomyopathy	2	3	NS
Dilated cardiomyopathy	8	18	NS
Cardiac sarcoidosis	4	6	NS
Others	5	7	NS
QRS duration (ms)	162 ± 27	169 ± 18	NS
Systolic blood pressure (mmHg)	112 ± 13	118 ± 18	NS
Diastolic blood pressure (mmHg)	69 ± 8.4	67 ± 10	NS
Heart rate (beats/min)	66 ± 18	65 ± 10	NS
LVEF (%)	31 ± 8.6	30 ± 7.4	NS
End-diastolic volume (ml)	150 ± 53	159 ± 60	NS
End-systolic volume (ml)	105 ± 41	113 ± 50	NS
Creatinine (mg/dl)	1.1 ± 0.29	1.1 ± 0.45	NS
BNP (pg/ml)	445 ± 360	429 ± 402	NS
CFR	1.78 ± 0.49	1.69 ± 0.47	NS

BNP brain natriuretic peptide, *CFR* coronary flow reserve, *LVEF* left ventricular ejection fraction

Table 2 Baseline clinical characteristics of the patients according to baseline CFR in responders

	Preserved CFR ($n=23$)	Depressed CFR ($n=11$)	p value
Age (years)	70 ± 8.2	73 ± 7.4	NS
Gender (female/male)	11/12	5/6	NS
Ischemic cardiomyopathy	1	2	NS
Dilated cardiomyopathy	14	4	NS
Cardiac sarcoidosis	4	2	NS
Others	4	3	NS
QRS duration (ms)	168 ± 20	171 ± 15	NS
Systolic blood pressure (mmHg)	119 ± 19	118 ± 16	NS
Diastolic blood pressure (mmHg)	66 ± 11	69 ± 8.5	NS
Heart rate (beats/min)	63 ± 8.0	70 ± 11	<0.05
LVEF (%)	31 ± 6.9	28 ± 8.4	NS
End-diastolic volume (ml)	158 ± 61	163 ± 61	NS
End-systolic volume (ml)	112 ± 52	115 ± 49	NS
Creatinine (mg/dl)	1.3 ± 0.56	1.0 ± 0.38	NS
BNP (pg/ml)	398 ± 399	494 ± 423	NS
CFR	1.91 ± 0.41	1.23 ± 0.11	<0.0001

BNP brain natriuretic peptide, *CFR* coronary flow reserve, *LVEF* left ventricular ejection fraction

baseline CFR was higher in the preserved CFR group than the depressed CFR group ($p<0.0001$). No significant difference was observed in age, gender, underlying etiology of heart failure, duration of QRS, blood pressure, measurements assessed by echocardiography, and blood sample findings.

No patients had complications including exacerbation of HF, arrhythmia, hypotension, and shock during the CFR by TTDE.

Patient outcome

During the mean follow-up period (1042 ± 450 days for the preserved CFR group and 718 ± 345 days for the depressed CFR group), MACCE were evident in 10 patients (29%); specifically, 7 patients in the depressed CFR group developed MACCE (congestive heart failure requiring admission = 5, cardiac death=1, and stroke = 1), while only 3 patients in the preserved CFR group developed MACCE (congestive

heart failure requiring admission=2 and stroke = 1. MACCE was significantly greater in the depressed CFR group than the preserved CFR group (64% vs. 13%, $p < 0.005$).

The change of CFR from baseline to follow-up about 6 months after CRT (ΔCRT) was analyzed between in responders and in non-responders, respectively. However, no significant difference was detected between responders and non-responders (0.103 ± 0.601 vs. -0.129 ± 0.177). ΔCRT showed no correlations with the change of LVEF, LVEDV, LVESV between 6 months.

Kaplan–Meier MACCE-free estimation

The survival rate in all patients without MACCE, as evaluated by Kaplan–Meier analysis, was not different between patients with a CFR ≥ 1.37 and patients with a CFR < 1.37 (log rank = 2.45, $p = 0.118$; and Wilcoxon = 0.886, $p = 0.347$; Fig. 3).

The survival rate in responder patients without MACCE, as evaluated by Kaplan–Meier analysis, was significantly greater in the preserved CFR group than the depressed CFR group (log rank = 9.43, $p = 0.0021$; and Wilcoxon = 8.61, $p = 0.0034$; Fig. 4).

Univariate and multivariate analyzes to predict MACCE

Univariate Cox proportional hazards regression analysis revealed that the etiology of dilated cardiomyopathy and depressed CFR was associated with MACCE in responders, as shown in Table 3. In the following multivariate analysis using risk factors including the etiology of dilated cardiomyopathy and depressed CFR, only depressed CFR independently predicted MACCE (hazard ratio 4.88, 95% confidence interval 1.13–26.5, $p = 0.0329$) (Table 3).

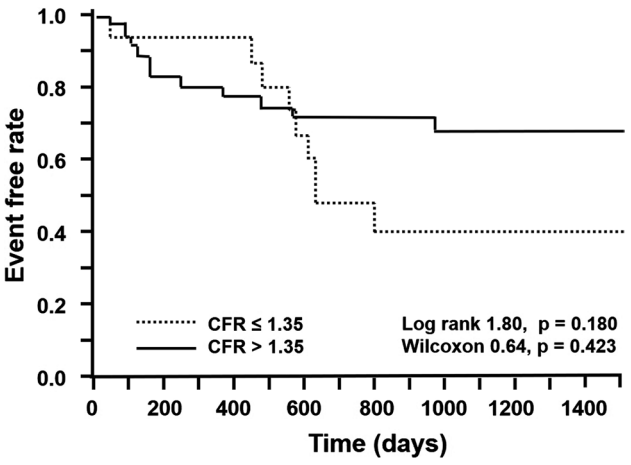

Fig. 3 Kaplan–Meier event-free curves for MACCE between patients with a CFR ≥ 1.37 and a CFR < 1.37. *CFR* coronary flow reserve, *MACCE* major adverse cerebral and cardiovascular events

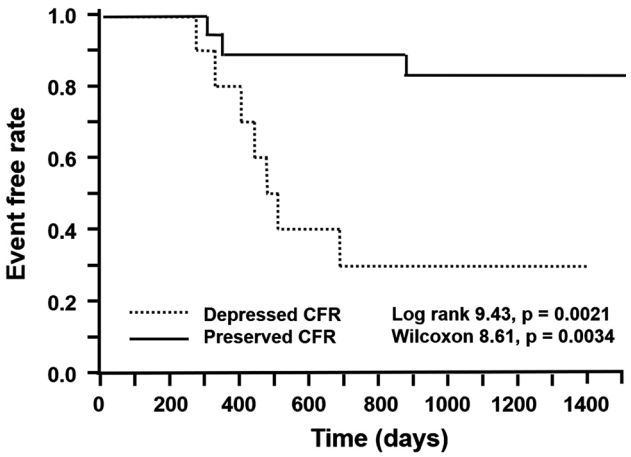

Fig. 4 Kaplan–Meier event-free curves for MACCE in responders between preserved and depressed CFR patients. *CFR* coronary flow reserve, *MACCE* major adverse cerebral and cardiovascular events

Discussion

In the present study, 34 responders who had been implanted with a CRT device for the treatment of advanced HF were followed during a mean of 873 ± 498 days, and MACCE were evident in 10 patients (29%). The MACCE-free ratio, as evaluated by Kaplan–Meier analysis, was significantly lower in the preserved CFR group than the depressed CFR group. The most important finding was that a depressed CFR value accurately predicts MACCE after CRT in responders.

The degree of response to CRT is variable because of different patient characteristics, implantation procedures, and definitions of improvement or normalization [14, 15]. The extent of reverse LV remodeling varies significantly among patients undergoing CRT; 22% are considered super-responders [16]. More extensive LV reverse remodeling is related to greater clinical and functional improvement after 6 months of CRT and more LV reverse remodeling results in better survival and less hospitalization for decompensated heart failure after 6 months of CRT [16].

The primary endpoints (non-fatal HF events or all-cause deaths) occur in 7.8% of patients [17]. All-cause deaths occur in 2.7% of patients and all-cause deaths or ICD therapy for ventricular tachycardia or ventricular fibrillation occur in 11.9% of patients in the responder group approximately 3 years after CRT in MADIT-CRT [17]. Some responders exhibit a short-lived response and LV reverse remodeling effects are brief in 15% of responders [18]. These brief responders show LV reverse remodeling on short-term follow-up; the positive response might not

Table 3 Univariate and multivariate Cox proportional hazards regression analysis of the MACCE in responders

	Univariate *p* value	Multivariate Hazard ratio	95% CI	*p* value
Age (years)	0.0979			
Gender (female)	0.493			
Dilated cardiomyopathy	0.0376*	0.521	0.0969–2.240	0.393
QRS duration (ms)	0.514			
Systolic blood pressure (mmHg)	0.309			
Diastolic blood pressure (mmHg)	0.566			
Heart rate (beats/min)	0.764			
LVEF (%)	0.963			
End-diastolic volume (ml)	0.412			
End-systolic volume (ml)	0.327			
Creatinine (mg/dl)	0.0549			
BNP (pg/ml)	0.446			
Biventricular pacing rate				
Depressed CFR	0.0043**	4.88	1.13–26.5	0.0329*

BNP brain natriuretic peptide, *CFR* coronary flow reserve, *LVEF* left ventricular ejection fraction

*$p < 0.05$, **$p < 0.01$

persist over the long term [18]. Of the responders, 40% had MACCE approximately 1000 days after CRT in the current study. Oka et al. [18] proposed that the mechanism for a brief response was the small amount of viable myocardium, continuation of the disease process, systolic dysfunction due to reasons other than dyssynchrony, and insufficient resynchronization. Ichibori et al. [19] demonstrated that one-third of the responders were transient responders at 2 years after CRT. Poor prognoses were evident in the transient responders during the long-term follow-up [19]. Chronic atrial fibrillation and amiodarone usage were independent predictors of transient responders [19].

CFR depends on epicardial coronary stenosis and microvascular function. If there is no epicardial coronary stenosis, CFR is associated only to microvascular function. Previous reports suggest that a marked decrease in myocardial capillary density existed in DCM patients, which correlated with a decrease in CFR [20, 21]. The mechanisms underlying the reduction in blood flow in DCM patients are as follows: decreased myocardial capillary density [20]; anatomic disturbance of microcirculation due to areas of interstitial and perivascular fibrosis [22]; endothelial dysfunction [23, 24]; and extravascular compressive forces due to elevated LVEDP [25]. In a previous study [26], CRT was associated with increased CFR in the LAD and this effect was observed almost immediately after switching from right ventricular to biventricular pacing. The effect might contribute to the beneficial action of CRT in the failing heart [26]. In another study, a preserved CFR predicts a positive response and LV improvement after CRT in patients with dilated non-ischemic cardiomyopathy [27]. Higher hyperemic flow before CRT is associated with improvement in ejection fraction after CRT, thus indicating increased preserved microcirculation in responders [27].

The presence of global contractile reserve at baseline, as assessed by dobutamine stress echocardiography, was associated with a higher likelihood of a CRT response [28]. If one of the mechanisms underlying the reduction in CFR in HF patients was an anatomic disturbance of microcirculation due to myocardial fibrosis, CFR might represent the same functional property as the contractile reserve. Future studies should focus on CFR as a reliable physiologic test associated with contractile reserve.

In this study, CFR could predict the outcome after CRT only in responders, and not in the whole study population including non-responders. CRT exerts a beneficial effect on coronary flow circulation through the reduction of microvascular resistance [29]. Non-responder patients could not obtain the beneficial effect of CRT. Therefore, the prediction ability of CFR might be significantly reduced in non-responders.

Our analysis included only responders. We excluded non-responders for the following reasons. There were many heterogeneous unfavorable backgrounds for non-responders, including large scar tissue, the absence of echocardiographically identified dyssynchrony before CRT, the absence of echocardiographically identified improvement of dyssynchrony after CRT, inappropriate placement of the LV lead, and inappropriate device programming. In fact, our analyzes, including non-responders, demonstrated no association between the value of CFR and MACCE (data not shown) because of heterogeneous backgrounds. Our observation that CFR did not predict long-term outcomes in the entire cohort

of CRT patients might be explained by the heterogeneous backgrounds of the studied patients.

The difference in survival between the preserved CFR group and the depressed CFR group occurred about 1 year after CRT implantation, not immediately. That event might be based on the time adverse events occurred in the responders. Initial responders may later become non-responders due to, possibly, diminishing beneficial effects of CRT over time. In the previous study, sixteen percent of the responders in 6 months after CRT turned into non-responders after 14 months of CRT [30].

Several limitations should be considered in the present study. First, we evaluated a small number of patients in a single center in this study, which might make it difficult to analyze the data. Therefore, future studies with larger patient populations are necessary to determine the effect of CRT on the coronary microcirculation. Second, because the analysis was retrospective, there was a potential for sampling bias and incomplete data. The retrospective nature of the study and the small sample size make the results difficult to generalize to all patients. Therefore, future prospective studies are warranted to determine the effect of CFR in responders to CRT. Third, 80 of 114 patients were excluded from responder group for various reasons, including a lack of long-term follow-up, lack of CFR measurement, and non-responder status, thus potentially contributing to significant bias. Fourth, the follow-up data regarding CFR after implantation could be obtained in only 33 patients out of 53 patients. Therefore, we could not accurately evaluate the serial data of ΔCRT.

Conclusion

Our results suggest that the assessment of endothelial function predicts the long-term outcome of CRT. Preservation of coronary circulation flow might underlie one of the mechanisms for a better response to CRT in responders.

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Compliance with ethical standards

Conflict of interest The authors have no financial conflicts of interest to disclose.

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