Original Article

Evaluation of Effects of Cardiac Resynchronization on Coronary Blood Flow by Coronary Flow Reserve and in Patients with İdiopathic Dilated Cardiomyopathy: Does it Predict the Response?

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Abstract

Background: The results of previous studies evaluating the effects of cardiac resynchronization therapy (CRT) on myocardial blood flow (MBF) and their relation with the response to CRT are conflicting. **Materials and Methods:** Sixty-one patients diagnosed with idiopathic dilated cardiomyopathy (IDC), a functional capacity (New York Heart Association [NYHA]) Class II or III, and left bundle branch block (LBBB) (QRS width >150 ms) were enrolled in the study. We aimed to evaluate the effects of CRT on MBF in patients with IDC and LBBB by coronary flow reserve (CFR) measurements and thereby tried to predict the responders. **Results:** Sixty-one patients with IDC were enrolled. CFR and hyperemic fractional flow reserve (FFR) increased after CRT. The only parameter affecting the increase in CFR was the change in FFR after CRT. Then, 44 patients who responded to the CRT treatment at 6 months were compared with 17 patients who did not. Left ventricle outflow tract time-velocity integral (LVOT-TVI), stroke volume (SV) and cardiac output index (COi) was detected significantly higher also left ventricular end-diastolic pressure (LVEDP) was lower in the CRT responders. However, there were no significant differences in coronary flow velocity measurements between the two groups. Moreover the regression analysis revealed that the baseline NYHA class, LVOT TVI, SV, COi, and LVEDP, which were changed due to increased blood flow after CRT implantation, is not associated with response to CRT. **Conclusions:** Our results suggest that MBF increased after CRT in patients with IDC probably by improving microvascular functions. However, the response to CRT treatment is not related to the changes in the coronary blood flow velocities after CRT.

Keywords: Cardiac resynchronization, coronary blood flow, idiopathic dilated cardiomyopathy

Introduction

Cardiac resynchronization therapy (CRT) has been accepted as a beneficial treatment strategy for a subgroup of patients with heart failure and an asynchronous contraction pattern.[1] It has been shown that CRT improves hemodynamic function,[2] heart failure symptoms, and exercise capacity; moreover, it reduces morbidity and mortality.[3] It is suggested that CRT implantation in patients with left bundle branch block (LBBB) improves coronary blood flow by reducing left ventricular

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filling pressure, wall tension, and septal blood flow[4,5]. However, the results of previous studies evaluating the effects of CRT on myocardial blood flow (MBF) and their effects on the response to CRT are conflicting. In this study, we aimed to evaluate the effects of CRT on MBF in patients with idiopathic dilated cardiomyopathy (IDC) and LBBB by coronary flow reserve (CFR) measurements. Second, we tried to find the factors affecting the changes in CFR after CRT. Third, we searched any effects of the changes in coronary artery flow after CRT on the clinical outcomes and the therapeutic response.

Materials and Methods

Patients with a left ventricular ejection fraction (LVEF) <35% and LBBB (QRS width >150 ms), diagnosed as IDC with functional capacity (New York Heart Association [NYHA]) Class II or III despite optimized medical treatment, who applied consecutively to our clinic were included in the study. All the patients who underwent coronary angiography and patients with coronary artery disease were excluded. Coronary flow velocity measurements were applied to the patients without coronary artery disease. Furthermore, patients with congenital and valvular heart disease, hypertrophic cardiomyopathy, chronic systemic disease or cor pulmonale, and atrial fibrillation were excluded. At the time of enrollment, all the patients were in a clinically stable condition on standard heart failure medication. Medication was kept constant during the study. Informed consent of each subject and the approval of the local ethics committee were obtained. The study protocol conforms to the Declaration of Helsinki (Rickham, 1964).

Echocardiography

Each patient underwent M-mode and two-dimensional (2D) echocardiography, followed by color flow imaging and pulsed- and continuous wave Doppler ultrasound. Transthoracic echocardiographic studies were performed using a commercially available ultrasound machine (iE33; Philips Medical Systems, Andover, MA) equipped with a 2.5-–3.5-MHz phased-array sector scan probe (S3). Left ventricle (LV) end-systolic volume, LVEF, left ventricular dimensions, left ventricle outflow tract time-velocity integral area (LVOT-TVI), and stroke volume (SV) were determined according to the recommendations of the American Society of Echocardiography.[6] An index for cardiac output index (COi) was calculated from the CW aortic outflow spectrum: LV outflow tract diameter was measured from a 2D parasternal long-axis view. The measurements repeated after pacemaker implantation and optimization.

Biventricular pacemaker leads were inserted through the left subclavian vein, 1 in the atrial appendage, 1 in the right ventricular apex, and 3 in the coronary sinus (90% in posterolateral vein). After pacemaker implantation, the atriobiventricular delay was optimized individually based on Doppler echocardiographic measurements.[7]

Coronary flow velocity measurements

A 0.014-inch, 15-Mhz Doppler guidewire was advanced through the catheter to the proximal portion of the left anterior descending (LAD) artery. Frequency analysis of the Doppler signals was carried out in real time by fast Fourier transform using a velocimeter. Once baseline flow-velocity data had been obtained, a bolus injection of intracoronary 18 mg adenosine was given to obtain data during hyperemia. To confirm that maximal hyperemia had been achieved, coronary blood flow velocity was recorded during the administration of an additional larger dose of adenosine. This was repeated until a plateau in flow velocity was reached. Time-averaged peak coronary flow velocity (APV) was measured for each vessel. CFR was determined as the ratio of APV at maximal hyperemia (h-APV) to APV at baseline (b-APV) as described before.[6] All measurements were made at a constant heart rate of 90 beats/min to exclude the influence of variant heart rate. This was accomplished by the dual chamber and biventricular pacing. Recordings were repeated 5 min after CRT. Afterward, a pressure guidewire was propagated through the LAD artery. Basal and hyperemic pressure measurements were performed at proximal 1/3 and distal 1/3 of the LAD artery. And, in this way, we determined a fractional flow reserve (FFR).

Clinical evaluation of improved cardiac function

Clinical improvement at 6 months was defined as reduction by ≥1 functional class in the NYHA classification and an increase in the 6-min walk test by ≥20%.

Statistical analysis

The numerical variables before and after CRT were compared using a paired *t*-test. The correlation between variables was tested by Pearson's correlation analysis. The independent factors affecting CFR after CRT was defined using linear logistic regression analysis. The numerical and continuous variables were compared Student's *t*-test and Mann–Whitney *U*-test between "responders" and "nonresponders." The factors affecting the response were evaluated by regression analysis.

Results

Sixty-one patients (mean age: 57.8 ± 12.3 years), 24 females and 37 males with IDC, were enrolled in the study. The average LVEF was 26.9% ± 7.5%. The majority of the patients (82%) have NYHA class III symptoms. COi, LVOT-TVI area, and SV increased and left ventricular end-diastolic pressure (LVEDP) decreased significantly after CRT. Time-b-APV before and after CRT was similar. However, time-h-APV increased remarkably after CRT. Due to this increased hyperemic coronary flow, CFR after CRT also increased. Basal FFR before and after CRT was similar. However, after adenosine injection, hyperemic FFR was found to be significantly higher after CRT compared to before [Table 1].

Correlation analysis revealed that CFR before and after CRT was not correlated with SV, COi, LVOT-TVI area, and systolic and diastolic blood pressures before and after CRT. However, the changes in CFR after CRT (ΔCFR) were correlated with the changes in LVEDP (Δ LVEDP) ($r = -0.4$, $P = 0.03$) and the changes in FFR (Δ FAR_{basal}; $r = 0.6$, $P = 0.06$ and Δ $FAR_{adenosine}$; $r = 0.7$, $P = 0.02$).

Linear logistic regression analysis revealed that the only parameter affecting the increase in CFR after CRT was the change in FFR after CRT [Table 2].

Then, 44 patients who responded to the CRT treatment at 6 months were compared with 17 patients who did not. Besides the baseline characteristics, early hemodynamic changes after CRT were also compared. Only the NYHA class was higher in the responder group regarding the baseline characteristics. LVOT-TVI, SV, and COi were significantly higher, and LVEDP was lower in the responders. However, there were no significant differences in coronary flow velocity measurements between the two groups [Table 3]. Moreover, the regression analysis revealed that the baseline NYHA class and the changes in LVOT-TVI, SV, COi, and LVEDP after CRT predicted the positive response to CRT treatment [Table 4].

Table 1: Comparison of parameters before and after cardiac resynchronization therapy

	CRT (−)	CRT (+)	*P*
LVOT-TVI (cm/sn)	19.9±2.2	24.9±1.8	1
SV (ml/m^2)	32.8±8.4	40.4±6.3	0.001
COi (L/min)	2.9±0.7	3.7±0.6	0.001
LVEDP (mmHg)	15.6±4.8	13.4±3.9	0.01
b-APV (cm/sn)	20.8±7.7	21.7±6.8	0.2
h-APV (cm/sn)	37.2±11.6	47.4±13.1	0.001
CFR	1.84±0.3	2.3±0.6	0.001
FFR_{basal}	0.92±0.035	0.92±0.032	0.3
$FFR_{adenosine}$	0.85±0.038	0.9±0.03	0.001

LVOT-TVI: Left ventricle outflow tract- time velocity integral, SV: Stroke volume, b-APV: Time-averaged peak coronary flow velocity at baseline, h-APV: time-averaged peak coronary flow velocity at maximal hyperemia, CFR: Coronary flow reserve, FFR: Fractional flow reserve, COi: Cardiac output index, LVEDP: Left ventricle end-diastolic pressure, CRT: Cardiac resynchronization therapy

Table 2: The independent factors affecting the changes in coronary flow reserve after cardiac resynchronization therapy (the changes in coronary flow reserve after cardiac resynchronization therapy)

Variable	β	SE	*t*	*P*
ΔLVOT-TVI	0.03	0.4	0.7	0.5
ΔSV	0.004	0.005	0.8	0.4
ΔCOi	0.02	0.03	0.5	0.2
ΔLVEDP	−0.03	0.3	−0.2	0.1
ΔFFR_{basal}	4.6	2.4	1.9	0.08
$\Delta FFR_{adenosine}$	9.6	4.0	2.4	0.04

CRT: Cardiac resynchronization therapy, ΔLVOT-TVI: The changes in left ventricle outflow tract- time velocity integral, ΔSV: The changes in stroke volume, ΔCOi: The changes in cardiac output index, ΔLVEDP: The changes in left ventricular end-diastolic pressure after CRT, ΔFFR_{basal}: The changes in basal fractional flow reserve of a left anterior descending artery, $\Delta FFR_{adenosine}$: The changes in hyperemic (after adenosine) fractional flow reserve after CRT, SE: Standard error

Discussion

The main finding of our study (1) was an increase in both hyperemic CFR and FFR in the early period in cardiac resynchronization therapy. (2) The increase in FFR was detected as the only independent predictor of the increase in CFR after CRT implantation; The parameters predicting the response to CRT therapy are the increase in cardiac output and SV LVOT-TVI and decrease in LVEDP, but not changes in coronary flow rates.

Coronary blood flow in patients with IDC has been evaluated previously using different methods. The decrease in CFR in these patients; Vanderhayden *et al*.,[8] Santagata *et al*.,[9] Rigo *et al*.[10] by echocardiography, Skalidis *et al*.[11] by intracoronary Doppler measurements has been demonstrated. In patients with IDC, MBF decreases, especially when a metabolic[12] and pharmacologic vasodilator[13] agent is used. Similar to our results, Skalidis *et al*.[11] showed that coronary blood flow is normal at rest but significantly reduced at maximal hyperemia, as well as the reduced CFR. These changes in MBF are first suggested to be caused by left ventricular hypertrophy and dilatation and/or increased end-diastolic pressures.[14] However, later, structural and/or functional alterations of the small coronary vessels (microcirculation) have been implicated in pathogenesis. Capillaries offer the most resistance to coronary blood flow during hyperemia,[15] and since IDC is associated with areas of interstitial and perivascular fibrosis causing loss of ceiling effects of capillaries to hyperemic blood flow,[16,17] functional and/or structural changes in microcirculation in IDC may explain reduced coronary flow during hyperemia. Recently, Gulati *et al*.[18] showed that patients with IDC exhibit microvascular dysfunction and the severity of which is associated with the degree of LV impairment. If microvascular dysfunction contributes to the pathogenesis of dilated cardiomyopathy (DCM), the underlying mechanism is more likely to involve stress-induced repetitive stunning rather than chronic myocardial hypoperfusion.

Accordantly, the abnormalities in endothelium-independent coronary flow regulation in conjunction with the abnormal microvascular endothelial function are frequently observed in these patients.[19-21] The clinical significance of this finding disclosed. Rigo *et al*. found that the decreased coronary blood flow during a vasodilator stimulation is a poor prognosis in the patients with IDCM[10] and Santagata *et al*.[9] showed that the decrease in CFR is associated with a worsening in the functional status of these patients. Endothelial dysfunction occurs in IDC patients, and also, there is a positive correlation with NHYA class in DCM.[22] Patients with DCM and LBBB show more severe forms of microvascular dysfunction, which is related to worse left ventricular function and lack of contractile reserve. Ciampi *et al*. claimed that therapeutic interventions to restore microvascular function may improve left ventricular function parameters in patients with DCM.[5] Moreover, coronary endothelial dysfunction is involved in myocardial fibrosis and worsening heart failure concomitant with DCM.

In previous studies, it was reported that there was no improvement in MBF after CRT, but improved myocardial

Table 3: Comparison of baseline characteristics and the early hemodynamic changes after cardiac resynchronization therapy in the patients with responders and nonresponders

	Nonresponders (*n*=17)	Responders (*n*=44)	*P*
Age (years)	58.3±13.8	56.6±12.6	0.3
Female (%)	42	38	0.2
HT (%)	82	80	0.4
DM (%)	24	21	0.3
EF (%)	25.8±6.3	24.8±6.8	0.3
NYHA class			
II	41	10	0.01
III	59	90	
Medications (%)			
Furosemide	82	80	0.6
Spironolactone	76	72	0.4
Beta-blockers	77	76	0.7
Digoxin	35	32	0.4
ACE-I	71	75	0.5
LVOT-TVI (cm/sn)	21.2±0.8	23.9±0.7	0.01
SV (ml/m^2)	36.8±5.4	40.1±4.3	0.001
COi (L/min)	3.1±0.7	3.6±0.6	0.001
LVEDP (mmHg)	15.4±2.8	13.6±3.4	0.01
b-APV (cm/sn)	20.4±5.7	21.5±4.9	0.2
h-APV (cm/sn)	45.2±10.6	47.1±11.1	0.1
CFR	2.1±0.4	2.2±0.5	0.1
FFR_{basal}	0.92±0.034	0.92±0.033	0.7
$FFR_{adenosine}$	0.89±0.03	0.90±0.03	0.1

LVOT-TVI: Left ventricle outflow tract- time velocity integral, SV: Stroke volume, b-APV: Time-averaged peak coronary flow velocity at baseline, h-APV: time-averaged peak coronary flow velocity at maximal hyperemia, CFR: Coronary flow reserve, FFR: Fractional flow reserve, COi: Cardiac output index, LVEDP: Left ventricle end-diastolic pressure, CRT: Cardiac resynchronization therapy, EF: Ejection fraction, ACE-I: Angiotensin-converting enzyme-I, NYHA: New York Heart Association

Table 4: The independent factors affecting the response after cardiac resynchronization therapy

Variable	β	SE	*t*	*P*
NYHA class	1.1	1.4	0.7	0.02
ΔLVOT-TVI	3.3	2.4	1.7	0.03
ΔSV	2.4	1.8	0.8	0.04
ΔCOi	2.2	2.3	2.5	0.01
ΔLVEDP	−2.3	2.3	−2.2	0.01
ΔFFR_{basal}	0.4	0.2	0.9	0.5
$\Delta FFR_{adenosine}$	0.9	0.3	0.4	0.2

NYHA: New York Heart Association, ΔLVOT-TVI: The changes in left ventricle outflow tract- time velocity integral, ΔSV: The changes in stroke volume, ΔCOi: The changes in cardiac output index, ΔLVEDP: The changes in left ventricular end-diastolic pressure after CRT, ΔFFR_{basal}: The changes in basal fractional flow reserve of a left anterior descending artery, $\Delta FFR_{adenosine}$: The changes in hyperemic (after adenosine) fractional flow reserve after CRT, SE: Standard error

glucose metabolism or provided a more homogeneous blood flow.[23-26] Knaapen *et al*.[27] showed that MBF does not change after CRT, but hyperemic MBF increases significantly by positron emission tomography. Similarly, Flevari *et al*. also demonstrated increased hyperemic MBF after CRT by transesophageal echocardiography.[28] The septal blood flow is reduced in patients with LBBB.[5] Thus, just the disappearance of LBBB by CRT may explain the improvement of MBF in these patients. Blanc *et al*.[29] reported the normalization of left ventricular function after the disappearance of LBBB that may contribute to improved systolic functions after CRT. Knaapen *et al*.[27] suggested that an increase in hyperemic MBF and CFR in the early period after CRT is related to the reduction in left ventricular filling pressures and wall stress. However, Flevari *et al*.[28] found that hyperemic forearm blood flow is also increased after CRT which is widely used as an index of endothelial function.[30] Similar to previous reports,[27,28] we found that hyperemic blood flow increases after CRT by CFR measurement. We also found that the increase in FFR after hyperemia is the only parameter affecting the increase in CFR.

Kaźmierczak *et al*. showed that CFR increased significantly in LAD is a predictor for a clinical improvement after CRT.[31] Valzania *et al*. stated that an increase in LAD flow is observed in CRT responders with IDC. They claimed that the increase in LAD flow is associated with an improvement in regional myocardial contraction and a decrease in intraventricular dyssynchrony.[30] Yildirim *et al*.[32] also showed that the increase in LAD flow velocities by successful CRT is concordant for improving the systolic and diastolic echocardiographic parameters, such as diastolic filling time, dP/dT, and ejection fraction %. However, they said that the changes in the coronary blood flow velocities by CRT are not directly linked to the changes in conventional echocardiographic parameters. Moreover, 2 nonresponder patients in their study had no significant change in the coronary velocities after CRT. Similarly, our results also showed that the response to CRT was not associated with the changes in coronary blood flow velocities after CRT.

Primary outcome of this study was the improvement in coronary blood flow after CRT implantation and this improvement may likely because of the endothelial functions although cannot be proved. However, this improvement in coronary blood flow was not correlated with the response to CRT treatment in contrary to other previous reports. Although abnormal microvascular endothelial function is frequently observed in these patients, the efforts to improve endothelial functions may not effective in clinical outcomes. Future researches are needed to define how endothelial functions are affected by CRT treatment and their role in therapy.

Conclusions

Our results suggest that the main pathophysiologic mechanism affecting MBF in the microvascular dysfunction is the patients with IDC and cardiac resynchronization causes an increase in hyperemic MBF by improving microvascular functions. However, the response to CRT treatment is not related to the changes in the coronary blood flow velocities after CRT.

Study limitations

The number of patients with DCM in the present study was relatively small, which was related to a complex invasive protocol of the study. We did not compare DCM patients with or without LBBB, as we intended to evaluate patients selected for CRT.

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Conflicts of interest

There are no conflicts of interest.

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