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Novel Heart Failure Biomarkers Predict Improvement of Mitral Regurgitation in Patients Receiving Cardiac Resynchronization Therapy—The BIOCRT Study

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Abstract

Background—Cardiac resynchronization therapy (CRT) improves mitral regurgitation (MR) in a subset of patients. We hypothesized that biomarkers (amino-terminal pro-B type natriuretic peptide [NT-proBNP], high-sensitivity troponin [hsTnI], galectin-3 [gal-3] and soluble ST-2 [sST2]) may predict MR response post-CRT.

Methods—We measured levels of biomarkers during CRT implantation in 132 patients with subsequent 2 years follow-up. MR was graded as no-trace, mild, moderate or severe at baseline and 6 months.

Results—In patients with baseline at least mild MR, 56% had improvement at 6 months, with lower two-year mortality vs patients without improvement (0% vs 18%, $p=0.002$). At baseline, patients with MR improvement had lower hsTnI and gal-3 levels compared to those without improvement (19 vs 40 pg/L, $p=0.01$; 14 vs 18 ng/mL, $p=0.007$). In multivariable analyses, higher log-transformed gal-3 (OR 0.15, 95% CI 0.04 - 0.65, $p=0.01$) remained independent predictor for MR non-improvement. Levels of NT-proBNP and sST2 were lower at follow-up in patients with MR improvement (potentially reflecting reduced myocardial stretch and stress) without reaching statistical significance.

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Conclusion—Higher galectin levels at the time of CRT implantation are associated with MR non-response.

Keywords

Biomarker; mitral regurgitation; Cardiac resynchronization therapy

Functional mitral regurgitation (MR) is an important factor of adverse outcomes and decreased survival in heart failure (HF)(1). Mechanisms are related to left ventricular (LV) enlargement and secondary restriction of valve closure(2). Decrease in functional MR severity has been reported following cardiac resynchronization therapy (CRT) device implantation (3-6), with subsequent improvement in survival (3, 7-10). Mechanisms of MR reduction after CRT have been related acutely to reduced dyssynchrony and increased closing forces, while later improvement has been linked to LV reverse remodeling (5, 6, 11, 12). However, not every patient will benefit from MR reduction following CRT. Various predictors of MR response based on echocardiography have been previously studied, with variable results (6, 8, 13, 14).

LV reverse remodeling is a process starting at the molecular level and ultimately reflected by changes of heart size and function, with the potential to influence functional MR severity. Galectin-3 (gal-3) is a protein (lectin family) involved in fibrogenesis; it is upregulated in heart failure and induces fibroblast proliferation and collagen production. ST2 is part of the interleukin receptor family, expressed by cardiomyocytes and fibroblasts when strained. The soluble form (sST2) binds interleukin-33 and prevents antifibrotic signaling. Both gal-3 and sST2 have been associated with adverse prognosis in HF from ischemic and non-ischemic causes. These markers of fibrotic remodeling, in conjunction with known markers of myonecrosis (high-sensitivity troponin [hsTnI]) have the potential to identify individuals less likely to have reverse remodeling and therefore less likely to improve MR. Biomarkers of myocardial stretch and stress (amino-terminal pro-B type natriuretic peptide [NT-proBNP] and sST2) could also be helpful to monitor overtime the effects of volume overload variations in patients improving or not improving MR. These biomarkers can predict clinical non-response and MACE in heart failure and after CRT(15-19). Since MR improvement with CRT relates at least in part to LV reverse remodeling, we hypothesized that pro-fibrotic biomarkers could predict MR response after CRT.

Methods

This is an analysis of Biomarkers to Predict CRT Response in Patients With HF (BIOCRT; Clinical Trials.gov # NCT01949246), a prospective observational study consisting of New York Heart Association (NYHA) Functional Class II-IV patients undergoing CRT device implantation from a single tertiary hospital, from whom peripheral venous (PV) and coronary sinus (CS) blood was drawn at the time of device implantation and PV samples serially at 1 and 6 months. Inclusion criteria consisted of patients with an approved indication for a CRT or CRT-D system (NYHA Class II-IV HF unresponsive to drug therapy, ejection fraction (EF) <35% and QRS>120 ms). Specific inclusion and exclusion criteria have been published previously (17).

Patients had pre-implant, 1- and 6-month follow-up evaluations consisting of medical history, NYHA Class, Minnesota Living with HF quality of Life (QOL) score, 6-minute walk distance and 2D transthoracic echocardiography. MR severity at baseline and follow-up was assessed by Level 3 readers blinded to clinical and biochemical patient characteristics. MR was graded as none/trace (0/1), mild (2), moderate (3) or severe (4) using the integrated approach detailed in the American Society of Echocardiography Guidelines(20). Decrease of at least one grade of MR at follow-up was considered an improvement. LV volumes and derived EF were calculated by the Simpson's method of disks. Patients were followed for up to 2 years for major adverse cardiac events (death, transplantation, left ventricular assistance, hospitalization for HF).

Blood samples were sent to independent laboratories (Siemens Healthcare Diagnostics Inc., BG Medicine, and Critical Diagnostics) for analysis. Plasma gal-3 measurements (BGM Galectin-3, BG Medicine, Inc.) were performed by ELISA (interassay CV 2.2%; intraassay CV 3.0%). Plasma sST2 measurements (Presage® ST2 assay, Critical Diagnostics) were performed using highly sensitive ELISA (interassay CV<12%; intraassay CV 2.3%). An outcome panel (two cardiologists) blinded to biomarker results and MR grade determined the clinical response of each subject based on medical records, with disagreement resolved by consensus with a third cardiologist. MACE was defined as the composite endpoint of death, cardiac transplant, left ventricular assist device (LVAD), and HF hospitalization. Our institutional review board approved the study protocol, and all patients provided written informed consent.

Descriptive statistics were expressed as mean±standard deviation (SD) or median with interquartile range for continuous variables and as frequency and percentages for nominal variables, as appropriate based on their distribution. Patients were stratified according to the presence of MR. Patients with grade 2 MR were classified according to MR response following CRT. Baseline variables were compared between patients improving and not improving their MR at follow-up. Predictors of MR improvement were tested with receiver operating characteristic (ROC) curves. Clinical outcomes were compared with Kaplan-Meier curves and log-rank test. For each biomarker with $p<0.05$ to predict MR regression in univariate analysis, we performed separate stepwise multivariable logistic regressions. A model including all significant biomarkers at baseline was also performed. Variables included in models were those with $p<0.10$ in univariate analysis while $p<0.05$ was required to remain in the final model. Statistics were performed with SAS version 9.4 (Cary, NC).

Results

A total of 133 patients were studied (Table 1). Most patients (127/133; 95%) received CRT-defibrillators; 6 had CRT-pacemakers. Baseline MR was grade 0-1 for 28 (21%) patients, grade 2 for 43 patients (33%), and grade 3-4 in 62 (47%) patients. Patients with more than grade 2 MR at baseline had larger LV dimensions, lower LVEF, increased left atrial size and right ventricle systolic pressure (all $p < 0.01$, Table 1). Lower BMI, higher use of diuretic and worse renal function was also noted in patients with MR. Median NT-proBNP and sST2 levels were higher in patients with grade 3 or 4 MR vs grade 0-2 MR (2671 vs 926 pg/mL, $p<0.001$; 50 vs 39 ng/mL, $p=0.03$), while baseline hsTnI and gal-3 were not different (Table

2). Patients with grade 3-4 MR at baseline had a significant increase in adverse clinical outcomes at 2 years follow-up (Figure 1).

Association of Biomarkers and MR regression after CRT

Within patients with mild MR at baseline, 50 (56%) patients had MR reduction at 6 months (16 patients excluded for unavailable MR data at follow-up). MR reduction was already seen at 1 month for 76% of these patients, while 37% had MR reduction between 1 and 6 months. MR reduction was associated with smaller LV ESV and right ventricular systolic pressure at follow-up, without significant relation with clinical CRT response (Table 3). Patients not improving their MR (n=39) had a significantly reduced survival compared with patients improving their MR grade at follow-up (18% vs 0% mortality, $p=0.002$; Figure 3). Patients improving their MR grade had significantly lower concentration of hsTnI and gal-3 at baseline (PV hsTnI: 19 vs 40 pg/mL, $p=0.01$; CS hsTnI: 42 vs 86 pg/mL, $p=0.04$; PV gal-3: 14 vs 18 ng/mL, $p=0.007$; CS gal-3: 13 vs 18 ng/mL, $p=0.048$; Figure 2), without significant difference for baseline NT-proBNP, sST2 (both PV and CS), LV volume or LVEF. Use of aldosterone antagonists ($p=0.05$), digoxin ($p=0.02$) and QRS duration ($p=0.02$) were other significant predictors of MR response in univariate analyses (Supplemental Table 1). In multivariable stepwise analyses, log-transformed gal-3 and use of aldosterone antagonists remained independent predictors for MR improvement at 6 months (Table 4). Patients improving MR had a statistically nonsignificant decrease in Median NT-proBNP and sST2 levels at follow-up. Median galectin-3 and hsTnI levels were no different from baseline to follow up in both groups (Table 3).

Discussion

In this study, we show that baseline gal-3 levels can help predict MR evolution after CRT. Functional MR in HF is clearly related to adverse prognosis, but the treatment of this condition remains elusive. CRT for eligible patients emerges as a possible solution: significant MR reduction has been shown for a subset of patients in previous and current data (4, 6, 21-23). Since surgical or catheter treatment of secondary MR can sometime be considered in selected patients, identification of those likely or unlikely to improve their MR after CRT becomes clinically relevant. Our cohort is consistent with previous literature demonstrating the prognostic implication of functional MR in HF, variable improvement after CRT with better outcomes in patients with MR reduction. MR improvement was associated with smaller LV size, lower pulmonary pressure and decreased mortality.

The capacity for LV to change its size and shape following CRT (with subsequent improvement in functional MR) is related to various factors including the myocardial substrate and fibrosis at the cellular/molecular levels, which can be explored with gal-3. Levels of gal-3 and hsTnI were not different between patients with vs without MR at baseline, without significant changes overtime, even in patients improving their MR. Stability of gal-3 despite differences in loading conditions is consistent with previous literature(24), and low serial variations for troponin measurements have also been shown(19). Our results are consistent with previous data (including analyses from CARE-HF and MADIT-CRT) in which high values of gal-3 have been associated with adverse

remodeling, worse clinical outcomes and lack of response to CRT(25, 26). However, these studies did not specifically focused on MR. Levels of NT-proBNP and sST2 behave differently than gal-3 and hsTnI: these markers correlate with baseline MR levels (increased stretch/volume overload), but such baseline measures do not predict MR regression. Serial measurement of these biomarkers appeared to trend with MR improvement (reflecting reduced stretch/stress) but without statistical significance; possibly by lack of power since prior work demonstrated that serial measurements of these markers can predicts LV remodeling, and parallel change in MR(16, 19, 27, 28).

Although the use of aldosterone antagonists was relatively low, their use was independently associated with MR reduction. The effects of aldosterone antagonists on LV remodeling are well known and our data reemphasize the importance of these agents in this population. Conversely, we are not aware of a biological rationale to support the univariate association of digoxin with MR reduction; heart rate (influenced by digoxin) was not related to MR. Digoxin was not significant in multivariable models when gal-3 was included.

Though providing mechanistic insights to MR improvement after CRT and interface with biomarker testing, our study has limitations. This is a single center study with limited sample size. MR improvement prediction with biomarkers was modest but significant given limited power. Median gal-3 values were overall lower than previous CRT trials(25), but comparable with other heart failure studies(29). Levels of sST2 and hsTnI were overall comparable with previous studies(30). Although supported by previous literature, serial measurement of NT-proBNP and sST2 paralleling MR improvement did not reach statistical significance. MR evaluation was done at 1 and 6 months, therefore the evolution immediately after CRT or after a longer follow-up was not available. Changes of medication, incidence of ischemic events and revascularization during follow-up were not available. Other imaging modalities such as MRI to compute the extent of scar, or 3D echocardiography to explore advanced geometric variables known to influence functional MR were not available. Future studies integrating advanced imaging parameters and biomarkers to predict MR response following CRT would be of interest.

In conclusion, elevated concentrations of gal-3 at the time of CRT device implantation are associated with lack of subsequent MR response after CRT. CRT patients whose MR did not improve by 6 months had worse 2-year survival. Predicting MR response with CRT can potentially influence clinical management; larger studies are therefore needed to confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Survival without major adverse cardiac events curves according to MR grade at baseline.

Figure 2. Receiver operating curves for prediction of MR reduction after CRT for galectin-3 (A) and hsTnI (B). Both markers at baseline are significantly associated with MR response (gal-3: OR=0.16 (0.04–0.66), $p=0.01$, area under the curve=0.69; hsTnI: OR=0.65 (0.45–0.95), $p=0.02$, area under the curve=0.66).

Figure 3.
Survival probability according to MR response after CRT.

Table 1
Patients characteristics according to the presence of MR at baseline

	All patients n=133	No/Mild MR (n=71)	Significant MR (n=62)	p-value
Age	65±13	64±12	66±14	0.27
Male, n (%)	104 (78)	54 (76)	50 (81)	0.54
BMI (kg/m ²)	27.8 [24.8, 32.1]	28.9 [26.0, 32.9]	26.5 [24.1, 31.0]	0.01
Diabetes, n (%)	43 (32)	22 (31)	21 (34)	0.85
Hypertension, n (%)	84 (63)	46 (65)	38 (61)	0.72
Hyperlipemia, n (%)	80 (60)	43 (61)	37 (60)	1.00
Ischemic disease, n (%)	60 (45)	28 (39)	32 (52)	0.17
Atrial fibrillation, n (%)	48 (36)	22 (31)	26 (42)	0.21
Baseline QRS (ms)	160 [141, 178]	164 [148, 178]	156 [136, 176]	0.15
NYHA				0.02
I, n (%)	0 (0)	0 (0)	0 (0)	
II, n (%)	12 (9)	9 (13)	3 (5)	
III, n (%)	113 (85)	61 (86)	52 (84)	
IV, n (%)	8 (6)	1 (1)	7 (11)	
eGFR (ml/min)	60.5 [46.8, 78.7]	67.2 [52.4, 80.0]	54.3 [38.7, 68.4]	<0.01
Medication				
ACEI, n (%)	71 (53)	41 (58)	30 (48)	0.30
ARB, n (%)	33 (25)	16 (23)	17 (27)	0.55
BB, n (%)	111 (83)	61 (86)	50 (81)	0.49
Aldosterone antagonists, n (%)	38 (29)	20 (28)	18 (29)	1.00
Diuretics, n (%)	102 (77)	49 (69)	53 (85)	0.04
Digoxin, n (%)	30 (23)	14 (20)	16 (26)	0.41
Echocardiography				
LV EDV (ml)	220 [180, 284]	205 [173, 280]	228 [197, 293]	0.04
LV EDV index (ml/m ²)	107 [91, 132]	98 [83, 127]	119 [99, 139]	<0.01
LV ESV (ml)	159 [128, 208]	146 [113, 197]	166 [145, 231]	0.04
LV ESV index (ml/m ²)	79 [61, 100]	70.3 [58, 92]	90.8 [70, 112]	<0.01
LVEF (%)	25 [20, 31]	27 [21, 32]	23 [19, 29]	0.01
RVSP (mmHg)	43 [36, 51]	38 [32, 45]	47 [41, 52]	<0.01
LA size (mm)	45 ± 67	43 ± 7	48 ± 7	<0.01
Functional Capacity				
Baseline Minnesota QOL	41.2±24.5	41.1±22.2	41.2±27.3	0.99
Baseline 6 minute walk	960 [650, 1250]	1065 [840, 1300]	800 [600, 1085]	<0.01

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricle ejection fraction; RVSP, right ventricular systolic pressure; LA, left atrium; QOL, quality of life.

Table 2
Biomarkers levels at baseline and odds ratio for MR improvement

	Baseline				Follow-up	
	All patients n=133	No/Mild MR n=71	Significant MR n=62	p-value	OR for MR improvement	p-value
HsTnI	20.5 [11.1, 43.5]	19.4 [10.3, 35.3]	22.5 [12.0, 64.1]	0.28	0.65 (0.45-0.95)	0.02
Galectin-3	16.5 [13.1, 22.5]	16.0 [12.4, 20.9]	17.4 [13.7, 24.0]	0.39	0.16 (0.04-0.66)	0.01
NT-proBNP	1592 [590, 3143]	926 [416, 1869]	2671 [1019, 5482]	<0.01	0.75 (0.51-1.1)	0.14
Soluble ST2	43.1 [29.4, 58.7]	38.8 [26.1, 51.6]	50.0 [32.0, 68.7]	0.03	0.89 (0.36-2.2)	0.81

HsTnI indicates high Sensitivity Troponin I, NT-proBNP, amino-terminal pro-B type natriuretic peptide; MR, mitral regurgitation; OR, odds ratio. Biomarkers values were log-transformed for odds ratio calculation.

Table 3
Evolution of clinical and echocardiographic variables in patients with and without MR improvement

Decrease of at least one grade of MR after CRT	MR better with CRT (n=50)	MR not better (n=39)	p-value
Baseline			
LV EDV index (ml/m ²)	118 [99, 130]	114 [91, 163]	0.82
LV ESV index (ml/m ²)	85 [70, 99]	83 [61, 129]	0.73
LVEF (%)	25 [20, 29]	23 [18, 32]	0.90
RVSP (mmHg)	41.5 [37.0, 50.0]	45.5 [36.5, 60.5]	0.62
LA size (mm)	46.1 ±7.7	45.6±6.3	0.74
QRS duration (ms)	160 [150, 180]	150 [134, 172]	0.04
MR			0.32
Grade 2	17 (34)	19 (49)	
Grade 3	24 (48)	16 (41)	
Grade 4	9 (18)	4 (10)	
Minnesota QOL	36 [15, 57]	48 [27, 66]	0.63
6 minute walk test	1037±411	913±363	0.23
6-months follow-up			
LV EDV index (ml/m ²)	104±30	119±41	0.06
LV ESV index (ml/m ²)	70±28	87±39	0.04
LVEF (%)	33±10	30±11	0.16
RVSP (mmHg)	35.0 [31.0, 40.0]	42.0 [35.0, 53.0]	0.004
LA size (mm)	43.5 [39.0, 47.0]	47.0 [41.0, 50.0]	0.10
QRS change (ms)	-12 [-26, 7]	6 [-18, 16]	0.09
Minnesota QOL	25 [10, 46]	30 [11, 57]	0.58
6 minute walk	1200 [1040, 1503]	1140 [720, 1320]	0.08
CRT responder	33 (66)	22 (56)	0.39
Change in biomarkers			
ST2	-5.0 [-22.5, 4.7]	0.6 [-2.2, 10.5]	0.07
NT-proBNP	-613 [-1312, -3]	-163.5 [-634, 197]	0.11
hsTnI	-3.6 [-14.4, 0.2]	-3.2 [-46.8, 1.3]	0.78
Galectin-3	-0.3 [-2.0, 2.3]	0.3 [-0.8, 3.3]	0.33

LV indicates left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricle ejection fraction; RVSP, right ventricular systolic pressure; LA, left atrium; MR, mitral regurgitation; QOL, quality of life.

Table 4

Multivariable models for mitral regurgitation improvement

Variable	Univariate		Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
gal-3 (log-transformed)	0.16 (0.04-0.66)	0.01	---	---	0.14 (0.03-0.58)	0.007	0.15 (0.04-0.65)	0.01
hsTnI (log-transformed)	0.65 (0.45-0.95)	0.02	NS	NS	---	---	NS	NS
Aldosterone antagonists	0.41 (0.17-1.0)	0.05	0.35 (0.12-0.97)	0.04	0.25 (0.08-0.75)	0.01	0.24 (0.08-0.73)	0.01
Digoxin	0.32 (0.13-0.83)	0.02	0.30 (0.10-0.89)	0.03	NS	NS	NS	NS
QRS duration (log-transformed, then multiplied by 10)	1.4 (1.0-1.8)	0.02	1.4 (1.03-2.0)	0.03	NS	NS	NS	NS

Model 1: hsTnI, Aldosterone antagonists, digoxin and QRS duration

Model 2: galectin-3, Aldosterone antagonists, digoxin and QRS duration

Model 3: galectin-3, hsTnI, Aldosterone antagonists, digoxin and QRS duration

Stepwise selection considering the above described variables, requiring 0.10 significance for entry and 0.05 significance to remain.