Inflammatory Mediators and Clinical Outcome in Patients With Advanced Heart Failure Receiving Cardiac Resynchronization Therapy

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Expression of different cytokines and growth factors after myocardial injury has been associated with fibroplasia and dilatation versus reverse remodeling and myocardial repair. Specifically, the proinflammatory/fibrotic mediators: interleukin (IL)-6, epidermal growth factor, and fibroblast growth factor (FGF)-2 cause fibroplasia, whereas reparative cytokines including: IL-1α, IL-1β, IL-4, and IL-13 can limit fibrosis. In appropriate patients, cardiac resynchronization therapy (CRT) reverses cardiomyopathy and improves outcome. However, a significant proportion will not respond to this therapy. We conducted this study to assess the association of proinflammatory/fibrotic and/or reparative immune response mediators at baseline with outcome after CRT. In the multicenter RISK study, plasma samples were collected prospectively before CRT implantation. Plasma IL-6, epidermal growth factor, FGF-2, IL-1α, IL-1β, IL-4, and IL-13 were evaluated by Luminex technology. The primary outcome was predefined as freedom from heart failure hospitalization or death and a decrease in echocardiographic end-systolic volume of >15% at 12 months. To determine associations with the outcome, multivariate logistic regression models including baseline clinical characteristics and the specific cytokines and growth factors were constructed. On multivariate analysis of 257 patients, detectable reparative cytokine IL-13 was significantly associated with the primary outcome (odds ratio 3.79; 95% CI 2.10 to 6.82, p <0.0001). In contrast, detectable proinflammatory/fibrotic growth factor FGF-2 was negatively associated (odds ratio 0.31; 95% CI, 0.14 to 0.68; p = 0.004). In conclusion, in CRT recipients, baseline levels of inflammatory mediators affecting cardiac fibrosis versus repair were associated with subsequent clinical outcome. Published by Elsevier Inc. (Am J Cardiol 2016;117:617−625)

Plasma biomarkers may provide insight into future clinical response to cardiac resynchronization therapy (CRT).[1−4] Myocardial injury associated with inflammation results in fibroplasia and irreversible remodeling of the myocardium. Several cytokine and growth factor pathways act in a coordinated manner to drive a profibrotic cardiac environment. The cardiac inflammatory milieu may be detected in the peripheral blood plasma compartment.[5] We hypothesized that a proinflammatory immune response to cardiac injury by interleukin (IL)-6, epidermal growth factor (EGF), and fibroblast growth factor (FGF)-2 would counter the salutary effect of CRT. We also considered the reparative immune responses to cardiac injuries by IL-1α, IL-1β, IL-4, and IL-13 would allow CRT to effect reverse remodeling.[6−8] In this study, we evaluated the baseline plasma concentrations of specific previously identified mediators in CRT recipients and their association with subsequent remodeling and clinical outcome.

Methods

We conducted a multicenter study (RISK) to assess the potential role of biomarkers in risk stratifying patients receiving CRT. The method and primary results of the study have been previously reported.[4] Patients with standard clinical indications for a transvenous CRT system at the time were recruited. After giving written informed consent, patients were enrolled and followed for 12 months after implant. Patients with both ischemic and nonischemic cardiomyopathy were included. To qualify for CRT-D, patients met

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Biomarker assay was performed at the core lab University of California Los Angeles. Data collection, management, and analysis were conducted by St. Jude personnel with supervision and direct input from the authors. Authors had access to all the data and drafted the manuscript. The sponsor did not control approval of the manuscript.

See page 624 for disclosure information.

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standard indications during the timeframe of the study to include heart failure (HF), ejection fraction ≤35%, and QRS duration ≥120 msecs and stable, optimal medical therapy. For the purpose of the study, stable therapy for both β blockers and angiotensin converting enzyme inhibitor/angiotensin receptor blocker was considered to be: dose increases no more than 100% greater than initial dose at 30 days before study enrollment or decreases in dosing <50% of initial dose at 30 days before study enrollment with no changes in the 30 days preceding enrollment. Patients were excluded if they refused or withdrew consent, did not receive a transvenous CRT system, and had recent (<30 days) acute ischemic syndrome or acute decompensation of HF. At baseline visit, patients underwent a history and physical examination, responded to a standard HF quality of life questionnaire (Minnesota Living with Heart Failure Questionnaire) and a structured questionnaire for determination of New York Heart Association (NHYA) functional class, underwent a standard echocardiogram, had a blood sample drawn for proteomic analysis and underwent a 6-minute hall walk test. At 6 and 12 months, the same assessment including echocardiography was repeated. Echocardiogram acquisition at participating sites was standardized by protocol. All echocardiograms were analyzed in a blinded manner at the central core laboratory (University of Pittsburgh, Pennsylvania). Left ventricular end-diastolic and end-systolic volumes were quantified by biplane Simpson's rule. HF hospitalization (HFH) satisfied both following criteria: (1) admission to hospital for >24 hours with one of the following HF worsening symptoms: increased HF class, orthopnea, paroxysmal nocturnal dyspnea, edema, dyspnea on exertion, or gastrointestinal symptoms attributable to HF and (2) receipt of any of the following for HF within 24 hours of admission: intravenous diuresis or intravenous inotropic medications. All admissions were blindly adjudicated by 2 members of the steering committee. An a priori determination was made to assess the primary outcome as survival rate with freedom from HFH and end-systolic volume decrease by at least 15% at 12 months compared with baseline. Institutional review boards of participating centers and central core labs approved this study.

Peripheral venous blood samples from participating patients were collected at baseline before CRT implantation. Plasma sample collection and initial processing techniques for all centers were standardized by training of site personnel and providing them written instructions for sample preparation, handling, and shipping to the central laboratory at University of California Los Angeles. Blood samples (10 ml) were drawn by venipuncture into vacutainer tubes containing EDTA and immediately placed on ice. Samples were then centrifuged at 3,400 rpm (1383 g) for 30 minutes at 4°C using a table top centrifuge. Plasma samples were centrifuged as soon as possible after drawing and no later than 30 minutes after blood drawing. Plasma was then drawn off using a disposable pipette without disturbing the buffy coat. Plasma was then immediately frozen to −20°C until shipped on ice to the core laboratory. At the core laboratory, the plasma was kept frozen at −80°C until thawed for cytokine analysis.

Table 1
Baseline demographic and clinical variables for the cohort as a whole and in both groups

Baseline Variable	All Enrolled Patients (N=257)	Group I (N=123)	Group II (N=134)	p-value
Age (years)	66 ± 11	66 ± 11	66 ± 11	0.7113
Female	54 (21.0%)	36 (29.3%)	18 (13.4%)	
Male	203 (79.0%)	87 (70.7%)	116 (86.6%)	
Ejection Fraction	25 ± 8	26 ± 8	25 ± 8	0.2940
LV End Systolic Volume	132 ± 63	130 ± 59	134 ± 67	0.6701
QRS (msec)	154 ± 27	160 ± 27	149 ± 27	0.0022
NYHA Class				0.5374
I	6 (2.3%)	3 (2.5%)	3 (2.2%)	
II	36 (14.0%)	19 (15.6%)	17 (12.7%)	
III	193 (75.1%)	90 (73.8%)	103 (76.9%)	
IV	8 (3.1%)	2 (1.6%)	6 (4.5%)	
Ischemic Cardiomyopathy	137 (53.3%)	59 (48.0%)	78 (58.2%)	0.1002
Myocardial Infarction	108 (42.0%)	41 (33.3%)	67 (50.0%)	0.0068
Coronary Artery Bypass Surgery	96 (37.4%)	42 (34.1%)	54 (40.3%)	0.3085
Paroxysmal Atrial Fibrillation	55 (21.4%)	20 (16.3%)	35 (26.1%)	0.0542
Diabetes	41 (16.0%)	13 (10.6%)	28 (20.9%)	0.0239
Hypertension	180 (70.0%)	87 (70.7%)	93 (69.4%)	0.8163
Minnesota Living With Heart Failure Questionnaire	51 ± 26	51 ± 26	50 ± 26	0.7657
6-Minute Hall Walk Test (Feet)	938 ± 348	931 ± 352	944 ± 344	0.7591
Pharmacologic Therapy				
Beta Blockers	224 (87.2%)	106 (86.2%)	118 (88.1%)	0.6525
ACE-I/ARB	209 (81.3%)	104 (84.6%)	105 (78.4%)	0.2031
Aldosterone Inhibitors	22 (8.6%)	13 (10.6%)	9 (6.7%)	0.2701
Diuretics	104 (40.5%)	45 (36.6%)	59 (44.0%)	0.2245
Detectable Reparative Cytokines				
Inter-Leukin_1α (≥9.4 pg/ml)	83 (32.3%)	47 (38.2%)	36 (26.9%)	0.0520
Inter-Leukin_1β (≥ 0.06 pg/ml)	229 (89.1%)	117 (95.1%)	112 (83.6%)	0.0030
Inter-Leukin_4 (≥ 0.42 pg/ml)	164 (63.8%)	88 (71.5%)	76 (56.7%)	0.0135
Inter-Leukin_13 (≥ 0.18 pg/ml)	119 (46.3%)	75 (61.0%)	44 (32.8%)	<.0001
Detectable Pro-inflammatory Cytokines				
Inter-Leukin_6 (≥ 0.2 pg/ml)	253 (98.4%)	121 (98.4%)	132 (98.5%)	0.9312
Epidermal Growth Factor (≥ 2.8 pg/ml)	167 (65.0%)	81 (65.9%)	86 (64.2%)	0.7786
Fibroblast Growth Factor_2 (≥7.6 pg/ml)	214 (83.3%)	98 (79.7%)	116 (86.6%)	0.1392

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; NHYA = New York Heart Association; LV = left ventricular.

Group I: Met the primary outcome of survival free from HF hospitalization and end systolic volume decrease by at least 15%. Group II: Did not meet the primary outcome.