Growth-Differentiation Factor-15 and Major Cardiac Events

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Background: Growth-differentiation factor (GDF)-15 is a strong predictor of cardiovascular events in patients with ST-elevation myocardial infarction (STEMI). However, the effects of GDF-15 on left ventricular (LV) remodeling have not been clearly elucidated. The aim of this study is to investigate whether GDF-15 will be of benefit in predicting LV remodeling, heart failure and death in patients with STEMI. *Methods:* The authors enrolled 216 patients with STEMI who received measurement of GDF-15 level on day 2 of hospitalization. Echocardiographic studies were performed at baseline and were repeated 6 months later. Clinical events, including all-cause death and readmission for heart failure, were followed up for a maximum of 3 years. *Results:* Patients with GDF-15 levels above the median had lower LV ejection fraction at baseline (43.9% versus 48.0%, $P = 0.041$) and at 6 months (51.5% versus 56.9%, $P = 0.025$). In univariable regression model, log-transformed GDF-15 level was not a predictor of increase in LV end-diastolic volume index at 6 months ($P = 0.767$). Kaplan-Meier survival curves showed that the combination of high GDF-15 and high *N*-terminal pro-B-type natriuretic peptide was a strong predictor of death and heart failure ($P < 0.001$). In multivariable Cox regression model, the independent predictors of death and heart failure were age, GDF-15 level and diabetes mellitus. *Conclusions:* High GDF-15 level is a strong predictor of death and heart failure in patients with STEMI. Although patients with higher GDF-15 levels tend to have lower LV ejection fraction, they have similar degree of the increase in LV end-diastolic volume index at 6 months.

Key Indexing Terms: GDF-15; *N*-terminal pro-B-type natriuretic peptide; Acute myocardial infarction; Left ventricular remodeling. **[Am J Med Sci 2014;347(4):305–311.]**

Despite advances in primary percutaneous coronary intervention (PCI) and medical therapy, substantial myocardial necrosis occurs and leads to left ventricular (LV) remodeling in patients with ST-elevation myocardial infarction (STEMI).[1,2] LV remodeling is characterized by progressive LV dilatation and systolic dysfunction associated with an increased risk of congestive heart failure (HF) and mortality.[3–5] Therefore, the predictors and mechanisms of LV remodeling after STEMI need more investigation. Biomarkers, such as *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), seem to be useful in risk stratification and may be potential targets of therapy in patients with STEMI.[6–8]

Growth differentiation factor (GDF)-15 is a distant member of the transforming growth factor-β (TGF-β) cytokine superfamily. Endogenous GDF-15 is induced rapidly in cardiomyocytes and seems to be cardioprotective in mice with ischemia-reperfusion injury.[9] In contrast, data from Women's Health Study show that healthy women with higher serum GDF-15 concentrations are at increased risk of having cardiovascular events, including myocardial infarction (MI), stroke and cardiovascular death.[10] In patients with non-ST-elevation acute coronary syndrome, high GDF-15 level is a powerful predictor of mortality and may be useful for decision making in choosing an invasive treatment.[11,12] GDF-15 is also a strong predictor of decreased myocardial salvage and subsequent higher risks of death in patients with STEMI receiving primary PCI.[13] However, the effects of GDF-15 on LV remodeling in patients with MI have not been clearly elucidated.

The aim of this study is to investigate whether plasma GDF-15 will be of benefit in predicting the prognosis after STEMI, particularly for LV remodeling, HF and death.

METHODS

Study Population

The study population was prospectively enrolled at Buddhist Tzu-Chi Hospital, Taipei branch, in Taiwan between December 7, 2007, and February 22, 2012. With institutional ethics committee approval and written informed consent, we enrolled patients who presented to emergency department with STEMI and received primary PCI within 12 hours of symptom onset. Patients were excluded if there were cardiac disease states other than ischemic heart disease, scheduled coronary bypass graft, a history of active malignancy in past 3 years, significant renal or hepatic dysfunction (baseline serum creatinine >2.0 mg/dL; aspartate aminotransferase or alanine aminotransferase >80 mg/dL before MI), chronic bedridden status or concomitant inflammatory diseases such as infections or autoimmune disorders.

Laboratory Analysis

Approximately 10 mL of blood from a peripheral vein were collected into a tube containing potassium ethylenediamine tetra-acetic acid (1 mg/mL) at post-MI day 2. The samples were centrifuged within 20 minutes at 4°C. The plasma was separated and subsequently frozen at −80°C until further analysis without undergoing any additional freeze-thaw cycles. GDF-15 levels were determined by enzyme-linked immunosorbent assay, as previously described.[14]

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Echocardiographic Analysis

Comprehensive 2-dimensional Doppler echocardiography and pulse-wave tissue Doppler imaging were performed with the patients in the partial left lateral decubitus at baseline (mostly post-MI day 2) and were repeated 6 months later. The equipment used was a Philip SONOS 7500 (Agilent Technologies, Andover, MA) system. All measurements were performed and repeated by the same experienced echocardiologist.[15] The images were stored on magneto-optical discs for further analysis. The LV dimension was measured from an M-mode recording according to the recommendations of the American Society of Echocardiography.[16] With the use of apical 4- and 2-chamber views, LV volumes and LV ejection fraction (LVEF) were estimated by the modified Simpson's method. The degree of ventricular dilatation was evaluated by the change in LV end-diastolic volume index (LVEDVI) between baseline and 6 months, expressed as a percentage of baseline value.[17] The analysis remained unlinked to GDF-15 concentrations until completion of the study.

Clinical Endpoints

The composite endpoints of clinical events, including all-cause death and readmission to hospital for HF, were recorded by reviewing electric medical record or contacting patients by telephone. Patients were followed up for a maximum of 3 years.

Statistical Analysis

Patients were divided into 2 groups based on the median value of GDF-15 levels on day 2 of hospitalization. Categorical variables were expressed as number (percentage) and compared with χ^2 test. All continuous variables were tested for normal distribution by using the Kolmogorov-Smirnov test. Depending on normality, continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) and compared with Student's t test or Mann-Whitney's U test, respectively. Univariable linear regression was applied to identify the predictors of $\log_{10}$-transformed GDF-15 levels and the predictors of increase in LVEDVI. Stepwise multivariable linear regression was performed using variables with

TABLE 1. Clinical and demographic characteristics

	GDF < median (N = 108)	GDF > median (N = 108)	*P*
Age	58.5 (49.2–66.0)	61.0 (53.0–73.0)	0.044
Male gender	99 (91.7%)	92 (85.2%)	0.137
History			
Current smoker	73 (67.6%)	55 (50.9%)	0.013
Diabetes	28 (25.9%)	31 (28.7%)	0.647
Hypertension	60 (55.6%)	63 (58.3%)	0.680
Hypercholesterolemia	48 (44.4%)	46 (42.6%)	0.572
Coronary heart disease	17 (15.7%)	20 (18.5%)	0.588
Previous myocardial infarction	6 (5.6%)	8 (7.4%)	0.580
Stroke	6 (5.6%)	7 (6.5%)	0.775
Presentation			
Symptom-to-door time, min	70 (34–199)	105 (42–244)	0.188
Door-to-balloon time, min	75 (64–90)	95 (72–140)	0.002
Killip class > I	24 (22.2%)	24 (22.2%)	1.000
Heart rate	76.9 ± 20.0	76.9 ± 18.6	0.995
SBP, mm Hg	131.4 ± 25.6	130.0 ± 28.9	0.731
Multivessel disease	56 (51.9%)	45 (41.6%)	0.235
Anterior MI	48 (44.4%)	58 (53.7%)	0.310
Peak CK, IU/L	2080 (1151–3478)	2877 (1470–4387)	0.192
Hemoglobin, g/dL	15.2 (14.6–16.3)	14.5 (13.2–15.6)	0.002
Creatinine, mg/dL	1.00 (0.82–1.20)	1.00 (0.89–1.20)	0.623
Potassium, mmol/L	3.50 (3.20–3.85)	3.80 (3.50–4.10)	0.001
LDL cholesterol, mg/dL	123 (102–154)	123 (97–146)	0.399
Triglyceride, mg/dL	117 (70–166)	119 (65–157)	0.878
NT-proBNP, pg/mL	530 (279–988)	775 (386–1620)	0.044
LVEF, %	48.0 ± 12.4	43.9 ± 10.9	0.041
Mitral E/E′ ratio	11.4 ± 3.3	12.3 ± 4.2	0.235
LVMI, g/m^2	125.6 ± 30.6	126.3 ± 30.6	0.854
LVEDVI, mL/m^2	65 (55–79)	68 (57–79)	0.465
Follow-up			
PCI for IRA re-stenosis	14 (13.0%)	6 (5.6%)	0.060
PCI for non-IRA	29 (26.9%)	25 (23.1%)	0.530

Values are expressed as number of patients (%), mean ± SD, or median (25th–75th percentile).

SBP, systolic blood pressure; MI, myocardial infarction; CK, creatine kinase; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; Mitral E/E′ ratio, early transmitral flow velocity (E) to early diastolic mitral annular velocity (E′) ratio; LVMI, left ventricular mass index; LVEDVI, left ventricular end-diastolic volume index; PCI, percutaneous coronary intervention; IRA, infarct-related artery.