Original Article

Value and Level of Galectin-3 in Acute Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention

Tzu-Hsien Tsai¹, Pei-Hsun Sung¹, Li-Teh Chang², Cheuk-Kwan Sun³, Kuo-Ho Yeh¹, Sheng-Ying Chung¹, Sarah Chua¹, Yung-Lung Chen¹, Chiung-Jen Wu¹, Hsuen-Wen Chang⁴, Sheung-Fat Ko⁵ and Hon-Kan Yip¹

Tzu-Hsien Tsai and Pei-Hsun Sung contributed equally to this work.

¹Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

²Basic Science, Nursing Department, Meiho Institute of Technology, Pingtung, Taiwan

³Department of Emergency Medicine, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan

⁴Department of Biological Sciences, National Sun Yat-Sen University, Kaohsiung, Taiwan

⁵Department of Radiology Kaohsiung Chang Gung Memorial Hospital, Chang Gung, University College of Medicine, Kaohsiung, Taiwan

Aim: This study investigated the impact of the circulating galectin-3 level on the 30-day prognostic outcome in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: From May 2009 to March 2011, blood samples for assessment of the circulating galectin-3 level were collected from 196 consecutive STEMI patients treated by primary PCI and from 30 healthy volunteers.

Results: The galectin-3 level was determined using ELISA. Our results demonstrated that the circulating level of galectin-3 was significantly higher in STEMI patients than in healthy control subjects ($p < 0.001$). As compared with patients with galectin-3 < 7.67 ng/mL, patients with galectin-3 ≥ 7.67 ng/mL were significantly older, had significantly lower left ventricular ejection fraction and significantly higher frequency of elevated white blood cell count, advanced Killip score (defined as $\geq$ score 3), congestive heart failure (defined as $\geq$ New York Heart Association Functional Class III), respiratory failure, unstable hemodynamics requiring a mechanical ventilator and intra-aortic balloon pump support, multiple vessel diseases and 30-day mortality (all $p < 0.04$). Furthermore, multivariate analysis showed that elevated circulating level of galectin-3 was the strongest independent predictor of the combined 30-day major adverse clinical outcome (MACO) (defined as advanced CHF or 30-day mortality) ($p < 0.0001$).

Conclusion: A high circulating galectin-3 level may serve as a useful biomarker for predicting 30-day MACO in patients with STEMI undergoing primary PCI.

J Atheroscler Thromb, 2012; 19:1073-1082.

Key words; Acute myocardial infarction, Galectin-3 level, Primary percutaneous coronary intervention, Major adverse clinical outcome

Address for correspondence: Hon-Kan Yip, Division of Cardiology, Department of Internal Medicine, Chang Gung Memorial Hospital, 123, Ta Pei Road, Niao Sung Hsiang, Kaohsiung city, 83301, Taiwan
E-mail: han.gung@msa.hinet.net
Received: December 20, 2011
Accepted for publication: June 7, 2012

Introduction

Despite state-of-the art treatment, acute myocardial infarction (AMI) is still a progressive disorder characterized by high morbidity and mortality¹⁻⁴, suggesting that important pathogenic mechanisms remain active and unmodified by current treatment^{5, 6}. Prior

clinical studies have reported that the occurrence of congestive heart failure (CHF) may denote a poor prognostic outcome in patients with decompensated cardiovascular diseases^{4, 7-9}. Many reports have also suggested a link between the biomarkers and CHF to short-term and long-term prognostic outcomes in AMI patients¹⁰⁻¹⁴. Of these biomarkers, the circulating level of galectin-3 has emerged as a novel informative biomarker on the prediction of fibrosis¹⁵, cardiac dysfunction⁶, cardiac remodeling¹⁶, and the development and progression of heart failure¹⁷. Furthermore, galectin-3 has been described as a useful indicator for identifying CHF patients with high risk of readmission or death¹⁷; however, the impact of the circulating level of galectin-3 on the prognostic outcome of STEMI patients undergoing primary PCI has not been well addressed.

Galectins has been identified to be a family of lectins that bind β -galactosides^{18, 19}. The expression of galectin-3 has been detected in leukocytes, mast cells^{20, 21} and various organ tissues²². Over-expression of galectin-3 has been observed in patients with decompensated CHF⁶. Involvement of galectin-3 in myofibroblast activation with resultant hepatic fibrosis¹⁵ and the promotion of renal fibrosis²³ has also been described. In addition, galectin-3 may play an important role in the inflammatory response, fibrosis and scar formation, cardiac remodeling and heart failure in the clinical setting of AMI^{16, 24-27}. The purpose of the present study was to verify the hypothesis that an elevated circulating galectin-3 level is a useful biomarker for predicting the major adverse clinical outcome (MACO) in patients with STEMI undergoing primary PCI.

Materials and Methods

Patient Population, Inclusion and Exclusion Criteria

All patients with acute STEMI are considered eligible for primary PCI at our institute. In order to circumvent other potential influences on the circulating level of galectin-3, patients with documented histories of recent surgery, intracranial hemorrhage, trauma or myocardial infarction within the preceding 2 months, malignancies, febrile disorders, acute or chronic inflammatory diseases, hematology disorders and autoimmune diseases with or without immunosuppressive therapy were excluded from the present study.

From May 2009 to March 2011, 196 patients presenting with STEMI of <12 hours' duration with primary PCI were recruited. Blood samples for assessment of the circulating galectin-3 level were collected

via the antecubital vein and stored in heparinized test-tubes 6 hours after the PCI procedure. The blood sample was collected during this time interval because the peak level of CK-MB and many inflammatory biomarkers will appear within 6 to 12 h after acute inflammatory stimulation. Additionally, the blood sample was collected 6 hours after PCI procedure based on the results of a previous experimental study²⁸, which showed that the accumulation of galectin-3 peaked 12 hours after acute inflammatory stimulation.

Blood samples were also obtained from 30 age- and gender-matched healthy volunteers during a health check in the Health-Promotion Center as normal controls. Informed consent was obtained from each study subject.

Procedure and Protocol

At our hospital, a transradial artery approach using a 6-French arterial sheath is routinely applied for the treatment of AMI unless both hands are positive for the Allen test. A 6-French Kimny Miniradi (Boston Scientific, Scimed Inc., Maple Grove, MN) was used for diagnostic studies and primary PCI. Intra-aortic balloon pump (IABP) support was performed with a right femoral arterial approach in patients with acute pulmonary edema associated with an unstable condition or hemodynamic instability. When necessary, the PercuSurge GuardWire device ((Medtronic AVE) was also utilized and the inclusion and exclusion criteria of the procedure have been described previously²⁹.

Clopidogrel (600 mg loading dose before stenting, then 75 mg/day) was given to patients who underwent primary stenting. Unless contraindicated, aspirin (100 mg orally, once a day) was routinely administered. Other commonly prescribed medications included angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, isornitrate and diuretic drugs.

Blood Sample Processing and Laboratory Investigations

After centrifugation, the samples were stored at -80°C before the assay of the galectin-3 level. White blood cell (WBC) counts, biochemical measurements and electrolyte levels were performed with standard laboratory methods.

Serum galectin-3 was measured in duplicate with a commercially available ELISA method (R & D). The intra-observer variability of the measurements of galectin-3 was also assessed and the mean intra-assay coefficients of variance were all <4.6%.

Table 1. Baseline Characteristics of Study Patients and Normal Control Subjects

Variables	Study patients (<i>n</i> = 196)	Normal control (<i>n</i> = 30)	<i>p</i> value
Age (yrs)	62.2 ± 12.1	62.1 ± 7.1	0.891
Male gender	82.7% (126)	76.7% (23)	0.591
WBC ($\times 10^3$ /dL)	10.9 ± 3.7	8.6 ± 1.8	<0.001
Creatinine level (mg/dL)	1.41 ± 1.83	0.86 ± 0.22	<0.001
LDL (mg/dL)	118.1 ± 39.5	121.3 ± 28.7	0.728
TC (mg/dL)	185.2 ± 43.8	198.8 ± 27.5	0.176
Galectin-3 (ng/mL)	7.59 ± 3.65	4.36 ± 1.89	<0.001
Diabetes mellitus	34.2% (67)	0 % (0)	–
Hypertension	55.6% (109)	0 % (0)	–
Current smoking	58.7% (115)	0 % (0)	–
Previous myocardial infarction	9.2% (18)	0 % (0)	–
Old stroke	6.1% (12)	0 % (0)	–
30-day mortality	3.6% (7)	0 % (0)	–

Data are expressed as the mean ± SD or % (No.) of patients.

LDL=low-density lipoprotein; TC=total cholesterol; WBC=white blood cell.

Definitions and Data Collection

Acute STEMI was defined as the presence of typical chest pain for more than 30 minutes with ST-segment elevation >1 mm in two consecutive precordial or inferior leads. Procedural success was defined as a reduction of residual stenosis by <20% by balloon angioplasty or successful stent deployment at the desired position with residual stenosis <10% followed by TIMI grade 3 flow in the infarct-related artery.

Advanced congestive heart failure (CHF) was defined as New York Heart Association functional class ≥ 3. Advanced Killip score was defined as ≥ Killip's classification 3 in patients upon presentation to the emergency room.

Detailed in-hospital and follow-up data, including age, sex, coronary risk factors, serial creatin kinase (CK-MB) levels, white blood cell counts, platelet counts, creatinine level, body temperature, Killip score on admission, severity of congestive heart failure (CHF), angiographic findings and the number of diseased vessels were recorded.

End Points and Statistical Analysis

The study endpoint was the 30-day composite occurrence of major adverse clinical outcomes (MACO), including advanced CHF or 30-day death.

Data are expressed as the means ± SD or percentage of patients where appropriate. The clinical and laboratory data were analyzed and comparisons were made using the independent *t* test for continuous variables and Fisher's exact or chi-square test for categorical variables. Multiple stepwise logistic regression anal-

Fig. 1. Receiver operating characteristic (ROC) plot of serum level of galectin-3 predicting 30-day major advanced clinical outcomes (MACO), including advanced CHF or 30-day death. Area under the curve (AUC) was 0.783. When the cut-off value of galectin-3 was ≥7.67 (ng/mL), the sensitivity and specificity were 74.5% and 72.4%, respectively, for predicting 30-day MACO.

ysis was used for assessing independent predictors of the 30-day occurrence of MACO. Statistical analysis was performed using SPSS statistical software for Windows version 13 (SPSS for Windows, version 13; SPSS Inc., IL, USA). A *p* value of <0.05 was considered significant.

Results

Baseline Characteristics of the Patients with STEMI and Healthy Volunteers (Table 1)

Table 1 summarizes the baseline characteristics of

Table 2. Baseline Characteristics, Clinical Presentation, Laboratory Findings and 30-day Clinical Outcome of 196 Study Patients

Variables	Group 1 (n=78)*	Group 2 (n=118)*	p value [§]
Age (yrs)	66.6 ± 10.8	57.7 ± 11.7	< 0.001
Male gender	70.5% (55)	90.7% (107)	0.001
Diabetes mellitus	56.2% (41)	22% (26)	< 0.001
Hypertension	64.5% (51)	49.2% (58)	0.025
Current smoking	44.9% (35)	67.8% (80)	0.002
Previous myocardial infarction	5.1% (4)	11.9% (14)	0.178
Old stroke	11.5% (5)	5.9% (7)	0.256
Infarction location by ECG			0.543
Anterior wall	66.7% (52)	57.6% (68)	
Non-anterior wall	33.3% (26)	42.4% (50)	
WBC count (×10 ³ /dL)	11.8 ± 4.3	10.4 ± 3.2	0.008
Creatinine level (mg/dL)	1.81 ± 2.47	1.15 ± 1.17	0.013
TC (mg/dL)	176 ± 46	188 ± 43	0.142
LDL (mg/dL)	116 ± 42	120 ± 39	0.539
Peak CPK level (IU/L)	2192 ± 2318	1675 ± 1579	0.056
LVEF (%) [†]	54.3 ± 14.9	59.0 ± 11.8	0.014
Mechanical ventilator support	14.1% (11)	4.2% (5)	0.028
Intra-aortic balloon pump support	28.2% (22)	10.2% (10)	0.002
Advanced Killip score [‡]	48.7% (38)	10.2% (12)	< 0.001
Advanced CHF [¶]	35.9% (28)	8.5% (10)	< 0.001
30-day mortality	7.7% (6)	0.8% (1)	0.033

Data are expressed as the mean ± SD or % (No.) of patients.

CHF=congestive heart failure; CPK=creatinine phosphokinase; ECG=electrocardiogram; LVEF=left ventricular ejection fraction; WBC=white blood cell.

* Group 1=high galectin-3 (≥7.67 ng/mL); Group 2=low galectin-3 (<7.67 ng/mL)

[†] indicates data obtained by 2-D echocardiographic examination on day-2 following AMI.

[‡] defined as Killip score ≥ 3.

[¶] defined as New York Heart Association Functional classification ≥ 3.

[§] Indicated continuous variables were analyzed using the independent *t* test, and categorical variables with the Chi-square test.

the patients with STEMI and healthy volunteers. The patients with STEMI and normal controls showed no significant differences with respect to age, gender, and the levels of total cholesterol and low-density lipoprotein; however, the WBC count and the levels of creatinine and galectin-3 were significant higher in STEMI patients than in normal controls.

More than 55% STEMI patients had a history of current smoking and hypertension. On the other hand, less than 10% STEMI patients had a history of previous myocardial infarction and old stroke; however, none of the healthy volunteers had these histories.

Comparison of Baseline Variables, Laboratory Findings, Clinical Presentations, and 30-Day Outcomes in Patients with High and Low Circulating Galectin-3 Level (Fig. 1 and 2 and Table 2)

Receiver operating characteristics (ROC) curve analysis (Fig. 1) revealed that a circulating level of galectin-3 ≥ 7.67 ng/mL was the most powerful pre-

dictor of 30-day MACO with sensitivity of 74.5%, specificity of 72.4%, a positive predictive value of 61.3% and a predictive value of 89.1%. For further analysis (Table 2), patients with high circulating galectin-3 (≥ 7.67 ng/mL) were designated as group 1 and patients with low circulating galectin-3 (< 7.67 ng/mL) were designated as group 2.

In order to determine whether a circulating level of galectin-3 ≥ 7.67 ng/mL was also a powerful predictor of severe left ventricular dysfunction [defined as left ventricular ejection fraction [(LVEF) < 40%], ROC curve analysis was performed and the results showed that it was a significantly powerful predictor with a sensitivity of 62.8% and specificity of 81.7%, respectively (Fig. 2-A).

Similarly, to elucidate whether a circulating level of galectin-3 ≥ 7.67 ng/mL was also a powerful predictor of higher circulating level of CPK (defined as > 3000 IU/L), ROC curve analysis was performed. As expected, the results showed that a circulating level of

Fig. 2. A) ROC plot of serum level of galectin-3 predicting lower left ventricular ejection fraction [(LVEF) < 40%]. AUC was 0.723. When the cut-off value of galectin-3 was ≥ 7.67 (ng/mL), the sensitivity and specificity were 62.8% and 81.7%, respectively for predicting LVEF < 40%. B) ROC plot of serum level of galectin-3 predicting a higher circulating level of creatine phosphokinase [CPK] > 3000 IU/L. AUC=0.723. When the cut-off value of galectin-3 was ≥ 7.67 (ng/mL), the sensitivity and specificity were 61.1% and 75.3%, respectively, for predicting CPK > 3000 IU/L.

galectin-3 ≥ 7.67 ng/mL was significantly predictive of a higher circulating level of CPK with sensitivity of 61.1% and specificity of 75.3%, respectively.

The patients in group 1 were significantly older and had a higher frequency of male gender, hypertension, diabetes mellitus, acute respiratory failure requiring mechanical ventilation, unstable hemodynamics requiring IABP support, an advanced Killip score on presentation, advanced CHF recorded during hospitalization, a higher WBC count and serum creatinine level, and a significantly lower frequency of current smoking and lower left ventricular ejection fraction than the patients in group 2. However, group 1 and group 2 showed no significant differences with respect to the frequency of old stroke, previous myocardial infarction, the infarction location identified on electrocardiograms, serum levels of total cholesterol and low-density lipoprotein, and peak level of creatinine phosphokinase. Moreover, the 30-day mortality rate was significantly higher in group 1 than in group 2.

Angiographic Findings in Patients with High and Low Circulating Galectin-3 Level (Table 3)

Table 3 shows the comparisons of angiographic features between the patients in group 1 and group 2. Group 1 and group 2 showed no significant differences with respect to the frequency of infarct-related artery, pre-PCI TIMI flow grade, lesion length, severity of obstruction of the infarct-related artery, pre- or post-PCI minimal lumen diameter or reference lumen diameter and post-PCI residual stenosis, utilization of a PercuSurge device, stent implantation, and final

TIMI-3 flow; however, the patients in group 1 had a significantly higher frequency of multiple vessel disease than the patients in group 2.

Linear Regression Analysis of the Correlation of the Galectin-3 Level to Killip Score, WBC Count, Creatinine Level, Multiple Vessel Disease, and LVEF (Fig. 3)

Linear regression analysis revealed significant positive correlations of the circulating galectin-3 level to the Killip score on presentation ($r=0.427$, $p<0.001$), WBC count ($r=0.260$, $p<0.001$) and creatinine level ($r=0.225$, $p=0.002$) but a significant negative correlation to LVEF ($r=-0.253$, $p<0.001$). Additionally, analysis also revealed significant positive correlations of the number of vessel diseases to circulating galectin-3 [$r=0.203$, $p=0.004$] and WBC count [$r=0.183$, $p=0.017$].

Spearman Rank Correlation (R) Analysis between Circulating Galectin-3 Level and Advanced CHF, Unstable Hemodynamics Requiring IABP Support and CADILLAC Risk Score (Table 4)

Spearman rank correlation analysis revealed significant correlations between the circulating level of galectin-3 and advanced CHF, unstable hemodynamic requiring IABP support and the CADILLAC risk score³⁰.

Correlation (R) between Level of Circulating Galectin-3 and CADILLAC Risk Score

The correlation between the circulating galectin-

Table 3. Comparisons of Angiographic Features between the Patients in Group 1 and Group 2

Variables	Group 1 (n=78)*	Group 2 (n=118)*	p value
Multiple vessel disease [†]	69.2% (54)	45.8% (54)	0.001
Infarct-related artery			
Left main trunk	3.8% (3)	3.4% (4)	0.234
Left anterior descending artery	43.4% (49)	56.6% (64)	0.637
Left circumflex artery	5.1% (4)	6.8% (8)	0.886
Right coronary artery	28.2% (22)	35.6% (42)	0.355
Pre-PCI TIMI flow grade			0.833
≤ 1	78.2% (61)	80.5% (95)	
≥ 2	27.5% (17)	27.6% (23)	
Duration of PCI (minutes)	36.4 ± 18.5	34.7 ± 20.3	0.603
Lesion length (mm)	23.5 ± 10.2	23.6 ± 9.8	0.879
Pre-PCI stenosis (%)	92.3 ± 7.5	93.8 ± 8.5	0.475
Pre-PCI MLD	0.26 ± 0.51	0.19 ± 0.29	0.274
Pre-PCI RLD	2.99 ± 0.55	3.02 ± 0.57	0.831
Post-PCI stenosis (%)	18.5 ± 5.2	15.4 ± 4.2	0.482
Post-PCI MLD	2.65 ± 0.64	2.81 ± 0.59	0.201
Post-PCI RLD	3.21 ± 0.57	3.32 ± 0.48	0.311
Stent implantation	93.6% (73)	97.5% (115)	0.332
Utilization of PercuSurge device	35.9% (28)	50% (59)	0.072
Final TIMI-3 flow	94.9% (74)	94.9% (112)	1.0

Data are expressed as the mean ± SD or % (No.) of patients.

MLD=minimal lumen diameter; RLD=reference lumen diameter; PCI=percutaneous coronary intervention; TIMI=thrombolysis in myocardial infarction.

[†] defined as obstruction of ≥ 50% of epicardial vessel.

* Group 1 = high galectin-3 (≥ 7.67 ng/mL); Group 2 = low galectin-3 (< 7.67 ng/mL)

tin-3 level and unfavorable prognostic variables, i.e. three strata of risk (low risk, score 0 to 2; intermediate risk, score 3 to 5; and high risk, score ≥ 6) was assessed based on the CADILLAC risk score³⁰). The results of the present study revealed a strong and good significant correlation between elevated galectin-3 and an increase in the CADILLAC risk score [lower-risk score (2.69 ± 3.06) vs. intermediate-risk score (4.83 ± 3.19) vs. high-risk score (5.69 ± 2.49), $p < 0.001$].

Univariate Analysis of Baseline Variables, Clinical Features and Angiographic Findings for Predicting 30-Day Major Adverse Clinical Outcomes (Table 5)

After univariate analysis of the variables in Tables 2 and 3 for the prediction of 30-day MACO, the data of the significant variables are summarized in Table 5. Significant predictors of 30-day MACO included high galectin-3 (≥ 7.67 ng/mL), old age, diabetes mellitus, multiple vessel disease, low LVEF, high WBC count, creatinine level, and peak level of CPK.

Independent Predictors of 30-Day MACO (Table 6)

A wide variety of baseline clinical and laborato-

ries variables were evaluated and multiple stepwise logistic regression analysis revealed that high galectin-3 (≥ 7.67 ng/mL), multiple vessel disease, low LVEF, and a high creatinine level were significant independent predictors of 30-day MACO among patients with STEMI undergoing primary PCI.

Discussion

The creatinine level^{30, 32}, LVEF^{7, 12} and multiple vessel disease³³ are three traditional risk factors for predicting an unfavorable clinical outcome after AMI and the present study confirmed that these three traditional risk factors were also significant independent predictors of 30-day MACO in patients with STEMI undergoing primary PCI. In addition to traditional risk factors, many biomarkers have been linked to unfavorable clinical outcomes¹⁰⁻¹⁴ of AMI-induced CHF. Recently, galectin-3 has been reported to be a novel mediator which may participate in the development and progression of CHF^{16, 17}; however, the role of the circulating galectin-3 level in the clinical outcome prediction of patients with STEMI undergoing

Fig. 3. Highly significant correlation between the circulating galectin-3 level and Killip scores on presentation (A). Relatively weak but still significant correlation between the circulating galectin-3 level and white blood cell count (B). Also, relatively weak but still significant correlation between the circulating galectin-3 level and creatinine level (C). Conversely, a significant negative correlation between the circulating galectin-3 level and left ventricular ejection fraction (LVEF) (D). Additionally, the analysis also revealed a relatively weak but still significant correlation of the number of vessel disease to WBC count (E) and circulating galectin-3 (F).

Table 4. Spearman Rank Correlation (R) between Serum Galectin-3 and Advanced CHF, Unstable Hemodynamics Required IABP Support and CADILLAC Risk Score

Variables	R*	p value
Advanced CHF and serum galectin-3	0.457	<0.001
Unstable hemodynamics and serum galectin-3 [†]	0.361	<0.001
CADILLAC risk score and serum galectin-3	0.512	<0.001

CHF = congestive heart failure; TIMI = thrombolysis in myocardial infarction;

*Spearman rank correlation.

[†]indicates patients receiving intra-aortic balloon pump support.**Table 5.** Univariate Analysis of Baseline Variables in Prediction of 30-Day Major Adverse Clinical Outcome (MACO)*

Variables	OR	95% CI	p value
Age (yrs)	1.057	1.027-1.088	<0.001
Diabetes mellitus	2.109	1.095-4.060	0.026
WBC ($\times 10^3$ /dL)	1.115	1.025-1.213	0.011
Creatinine (mg/dL)	1.448	1.098-1.909	0.009
Peak CPK level (IU/L)	1.024	1.007-1.041	0.005
High galectin-3 level (≥ 7.67 vs. < 7.67 ng/mL)	11.364	7.673-15.882	<0.001
Multiple vessel disease [†]	4.773	2.222-10.252	<0.001
LVEF (%)	0.910	0.876-0.945	<0.001

LVEF = left ventricular ejection fraction; CPK = creatine phosphokinase; WBC = white blood cell.

*major adverse clinical outcome (MACO) defined as composite endpoint of advanced congestive heart failure or 30-day mortality.

[†]defined as obstruction of $\geq 50\%$ of epicardial vessel.

primary PCI is currently unclear. The present study suggests several important clinical implications of the circulating galectin-3 level in such clinical conditions.

First, our study verifies that circulating galectin-3 was significantly higher in AMI patients than in normal controls. Inflammation and oxidative stress³⁴⁻³⁶ play a key role in all stages of atherosclerosis and vascular remodeling, from initiation, progression of athermanous plaques and luminal narrowing, finally leading to acute coronary syndromes^{11, 31}) as a consequence of plaque rupture. Interestingly, galectin-3 has been shown to be an important contributor to inflammation^{6, 16}). In the present study, compared with the healthy controls, the circulating galectin-3 level and WBC count, an index of inflammation, were significantly higher in STEMI patients. Furthermore, multiple vessel disease, an indirect index of a higher degree of inflammation, was significantly more frequently seen in patients with high galectin-3 than in those with low galectin-3. In addition, linear regression analysis revealed significant positive correlations of multiple vessel disease to the circulating level of galectin-3 and WBC count. These findings could partially explain the impact of inflammation on multiple vessel disease, progression of athermanous plaques (i.e., mul-

tiplique plaque in coronary artery tree), and plaque rupture/STEMI in our patients. Of importance was that these findings imply that galectin-3 may, at least in part, participate in inflammatory reactions and atherosclerosis in patients presenting with STEMI.

Second, there were significant positive correlations of high circulating galectin-3 to an advanced Killip score, unstable hemodynamics requiring IABP support, advanced CHF and a high CADILLAC risk score. Conversely, a significant negative correlation between the galectin-3 level and LVEF was also noted. Such correlations imply that elevated circulating galectin-3 may be an indirect indicator of left ventricular dysfunction and pump failure following AMI.

Third, the present study demonstrated that there were strong correlations between elevated galectin-3 and the WBC count and creatinine level, two important indices of an unfavorable clinical outcome, in STEMI patients after primary PCI. Most importantly, elevated circulating galectin-3 was proven to be a strong independent predictor of 30-day MACO among patients with STEMI undergoing primary PCI and thus can be utilized as a useful biomarker for stratifying high and low risk subgroups in daily clinical practice.

Table 6. Multiple Stepwise Logistic Regression Analysis of Predictors for 30-Day Major Adverse Clinical Outcome*

Variables	OR	95% CI	p value
Creatinine (mg/dL)	1.403	1.112-1.771	0.004
LVEF (%)	0.925	0.839-0.958	<0.001
Multiple vessel disease [†]	4.497	1.756-11.518	0.002
Higher galectin-3 level (≥ 7.67 vs. < 7.67 ng/mL)	5.484	2.385-12.606	<0.001

CI=confidence interval; LVEF=left ventricular ejection fraction; OR=odds ratio.

*major adverse clinical outcome (MACO) defined as composite endpoint of advanced congestive heart failure or 30-day mortality.

[†]defined as obstruction of $\geq 50\%$ of epicardial vessel.

Limitations

The current study has several limitations. First, this study did not assess serial changes in the circulating level of galectin-3 after STEMI; therefore, the best timing for measuring the peak level of galectin-3 in patients after STEMI could not be identified. Second, this study did not measure the time interval of galectin-3 levels prior to and just after the PCI procedure. Thus, the impact of balloon dilation during PCI on stimulating the release of galectin-3 from the vessel wall remains uncertain. Third, the role of the circulating galectin-3 level for predicting the long-term clinical outcome of patients with STEMI undergoing primary PCI remains unclear; therefore, further large series studies and more experiments for evaluating the time course of serum galectin-3 level with respect to long-term follow-up is needed. Finally, we did not measure the circulating levels of high-sensitivity C-reactive protein and brain natriuretic peptide, which are two well-known biomarkers predicting the prognostic outcome of STEMI and CHF. Thus, we remain uncertain whether these two biomarkers, which are similar to the circulating galectin-3 level, could influence the morbidity/mortality of our patients.

Conclusion

The present study demonstrated that elevated circulating galectin-3 was a strong independent predictor of 30-day MACO among patients with STEMI undergoing primary PCI and thus can be utilized as a useful biomarker for stratifying high and low risk subgroups in daily clinical practice.

Conflict of Interest

None.

References

- 1) Murray CJ, Lopez AD: Global mortality, disability, and

the contribution of risk factors: Global burden of disease study. *Lancet*, 1997; 349: 1436-1442

- 2) Chen JS, Ko WJ, Yu HY, Lai LP, Huang SC, Chi NH, Tsai CH, Wang SS, Lin FY, Chen YS: Analysis of the outcome for patients experiencing myocardial infarction and cardiopulmonary resuscitation refractory to conventional therapies necessitating extracorporeal life support rescue. *Crit Care Med*, 2006; 34: 950-957
- 3) Sheu JJ, Tsai TH, Lee FY, Fang HY, Sun CK, Leu S, Yang CH, Chen SM, Hang CL, Hsieh YK, Chen CJ, Wu CJ, Yip HK: Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with st-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med*, 2010; 38: 1810-1817
- 4) Tsai TH, Chua S, Hussein H, Leu S, Wu CJ, Hang CL, Fang HY, Chung SY, Fu M, Chen HC, Chang LT, Yeh KH, Yip HK: Outcomes of patients with killip class III acute myocardial infarction after primary percutaneous coronary intervention. *Crit Care Med*, 2011; 39: 436-442
- 5) Yndestad A, Ueland T, Oie E, Florholmen G, Halvorsen B, Attramadal H, Simonsen S, Froland SS, Gullestad L, Christensen G, Damas JK, Aukrust P: Elevated levels of activin A in heart failure: Potential role in myocardial remodeling. *Circulation*, 2004; 109: 1379-1385
- 6) Sharma UC, Pokharel S, van Brakel TJ, van Berlo JH, Cleutjens JP, Schroen B, Andre S, Crijns HJ, Gabius HJ, Maessen J, Pinto YM: Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. *Circulation*, 2004; 110: 3121-3128
- 7) Wu CJ, Chang HW, Hung WC, Yang CH, Chen YH, Su CY, Yip HK: N-terminal pro-brain natriuretic peptide is a biomarker of congestive heart failure and predictive of 30-day untoward clinical outcomes in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ J*, 2006; 70: 163-168
- 8) Karlstrom P, Alehagen U, Boman K, Dahlstrom U: Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure: Responders to treatment have a significantly better outcome. *Eur J Heart Fail*, 2011; 13: 1096-1103
- 9) Noveanu M, Breidhardt T, Potocki M, Reichlin T, Twerenbold R, Uthoff H, Socrates T, Arenja N, Reiter M, Meissner J, Heinisch C, Stalder S, Mueller C: Direct comparison of serial b-type natriuretic peptide and nt-probnp levels for prediction of short- and long-term out-

- come in acute decompensated heart failure. *Crit Care*, 2011; 15: R1
- 10) Yip HK, Wu CJ, Chang HW, Yip HK, Wu CJ, Chang HW, Yang CH, Yu TH, Chen YH, Hang CL: Prognostic value of circulating levels of endothelin-1 in patients after acute myocardial infarction undergoing primary coronary angioplasty. *Chest*, 2005; 127: 1491-1497
 - 11) Yip HK, Wu CJ, Chang HW, Yang CH, Yu TH, Chen YH, Hang CL: Level of high-sensitivity c-reactive protein is predictive of 30-day outcomes in patients with acute myocardial infarction undergoing primary coronary intervention. *Chest*, 2005; 127: 803-808
 - 12) Yip HK, Youssef AA, Chang LT, Yang CH, Sheu JJ, Chua S, Yeh KH, Lee FY, Wu CJ, Hang CL: Association of interleukin-10 level with increased 30-day mortality in patients with st-segment elevation acute myocardial infarction undergoing primary coronary intervention. *Circ J*, 2007; 71: 1086-1091
 - 13) Klip IT, Voors AA, Anker SD, Hillege HL, Struck J, Squire I, van Veldhuisen DJ, Dickstein K: Prognostic value of mid-regional pro-adrenomedullin in patients with heart failure after an acute myocardial infarction. *Heart*, 2011; 97: 892-898
 - 14) Mayr A, Mair J, Schocke M, Klug G, Pedarnig K, Haubner BJ, Nowosielski M, Grubinger T, Pachinger O, Metzler B: Predictive value of nt-pro bnp after acute myocardial infarction: Relation with acute and chronic infarct size and myocardial function. *Int J Cardiol*, 2011; 147: 118-123
 - 15) Henderson NC, Mackinnon AC, Farnworth SL, Poirier F, Russo FP, Iredale JP, Haslett C, Simpson KJ, Sethi T: Galectin-3 regulates myofibroblast activation and hepatic fibrosis. *Proc Natl Acad Sci U S A*, 2006; 103: 5060-5065
 - 16) de Boer RA, Yu L, van Veldhuisen DJ: Galectin-3 in cardiac remodeling and heart failure. *Curr Heart Fail Rep*, 2010; 7: 1-8
 - 17) de Boer RA, Voors AA, Muntendam P, van Gilst WH, van Veldhuisen DJ: Galectin-3: A novel mediator of heart failure development and progression. *Eur J Heart Fail*, 2009; 11: 811-817
 - 18) Barondes SH, Cooper DN, Gitt MA, Leffler H: Galectins. Structure and function of a large family of animal lectins. *J Biol Chem*, 1994; 269: 20807-20810
 - 19) Cooper DN: Galectinomics: Finding themes in complexity. *Biochim Biophys Acta*, 2002; 1572: 209-231
 - 20) Hughes RC: The galectin family of mammalian carbohydrate-binding molecules. *Biochem Soc Trans*, 1997; 25: 1194-1198
 - 21) Hughes RC: Secretion of the galectin family of mammalian carbohydrate-binding proteins. *Biochim Biophys Acta*, 1999; 1473: 172-175
 - 22) Kim H, Lee J, Hyun JW, Park JW, Joo HG, Shin T: Expression and immunohistochemical localization of galectin-3 in various mouse tissues. *Cell Biol Int*, 2007; 31: 655-662
 - 23) Henderson NC, Mackinnon AC, Farnworth SL, Kipari T, Haslett C, Iredale JP, Liu FT, Hughes J, Sethi T: Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. *Am J Pathol*, 2008; 172: 288-298
 - 24) Friedman SL: Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. *J Biol Chem*, 2000; 275: 2247-2250
 - 25) Brown RD, Ambler SK, Mitchell MD, Long CS: The cardiac fibroblast: Therapeutic target in myocardial remodeling and failure. *Annu Rev Pharmacol Toxicol*, 2005; 45: 657-687
 - 26) Frangogiannis NG: The immune system and cardiac repair. *Pharmacol Res*, 2008; 58: 88-111
 - 27) Sheu JJ, Chua S, Sun CK, Chang LT, Yen CH, Wu CJ, Fu M, Yip HK: Intra-coronary administration of cyclosporine limits infarct size, attenuates remodeling and preserves left ventricular function in porcine acute anterior infarction. *Int J Cardiol*, 2011; 147: 79-87
 - 28) Sato S, Ouellet N, Pelletier I, Simard M, Rancourt A, Bergeron MG: Role of galectin-3 as an adhesion molecule for neutrophil extravasation during streptococcal pneumonia. *J Immunol*, 2002; 168: 1813-1822
 - 29) Yip HK, Wu CJ, Chang HW, Fang CY, Yang CH, Chen SM, Hung WC, Chen CJ, Cheng CI, Hsieh YK: Effect of the percutaneous guardwire device on the integrity of microvasculature and clinical outcomes during primary transradial coronary intervention in acute myocardial infarction. *Am J Cardiol*, 2003; 92: 1331-1335
 - 30) Halkin A, Singh M, Nikolsky E, Grines CL, Tcheng JE, Garcia E, Cox DA, Turco M, Stuckey TD, Na Y, Lansky AJ, Gersh BJ, O'Neill WW, Mehran R, Stone GW: Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: The cadillac risk score. *J Am Coll Cardiol*, 2005; 45: 1397-1405
 - 31) Ross R: The pathogenesis of atherosclerosis: A perspective for the 1990s. *Nature*, 1993; 362: 801-809
 - 32) Sadeghi HM, Stone GW, Grines CL, Mehran R, Dixon SR, Lansky AJ, Fahy M, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Stuckey TD, Turco M, Carroll JD: Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. *Circulation*, 2003; 108: 2769-2775
 - 33) Chen HC, Tsai TH, Fang HY, Sun CK, Lin YC, Leu S, Chung SY, Chai HT, Yang CH, Hsien YK, Wu CJ, Yip HK: Benefit of revascularization in non-infarct-related artery in multi-vessel disease patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Int Heart J*, 2010; 51: 319-340
 - 34) Takeshima H, Kobayashi N, Koguchi W, Ishikawa M, Sugiyama F, Ishimitsu T: Cardioprotective effect of a combination of rho-kinase inhibitor and p38 mapk inhibitor on cardiovascular remodeling and oxidative stress in dahl rats. *J Atheroscler Thromb*, 2012; 19: 326-336
 - 35) Ishigami N, Isoda K, Adachi T, Niida T, Kujiraoka T, Hakuno D, Kondo H, Kusuhashi M, Ohsuzu F: Deficiency of cuzn superoxide dismutase promotes inflammation and alters medial structure following vascular injury. *J Atheroscler Thromb*, 2011; 18: 1009-1017
 - 36) Hashizume S, Akaike M, Azuma H, Ishikawa K, Yoshida S, Sumitomo-Ueda Y, Yagi S, Ikeda Y, Iwase T, Aihara K, Abe M, Sata M, Matsumoto T: Activation of peroxisome proliferator-activated receptor alpha in megakaryocytes reduces platelet-derived growth factor-bb in platelets. *J Atheroscler Thromb*, 2011; 18: 138-147