EXPERIMENTAL & CLINICAL
Cardiology

EXPERIMENTAL & CLINICAL CARDIOLOGY

Volume 20, Issue 9, 2014

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How to reference: Association Between Mild Myocardial Injury Post Percutaneous Coronary Intervention and Improvement of Cardiac Function Through an Increase in Tissue Inhibitor of Metalloproteinase-1/Tomohiko Yamamoto, Shin-Ichiro Miura, Yuhei Shiga, Yuiko Miyase, Ayumi Nakamura, Amane Ike, Makoto Sugihara, Atsushi Iwata, Hiroaki Nishikawa and Keijiro Saku/Exp Clin Cardiol Vol 20 Issue9 pages 4849-4855 / 2014

Experimental and Clinical Cradiology

Association between mild myocardial injury post percutaneous coronary intervention and improvement of cardiac function through an increase in tissue inhibitor of metalloproteinase-1

Original Article

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Running Title: Myocardial injury post coronary intervention
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Abstract Peri-procedural myocardial injury (PMI) due to percutaneous coronary intervention (PCI) may decrease the beneficial effects of PCI. Anti-inflammation, angiogenesis and prevention of the destruction of extracellular matrix (ECM) may attenuate cardiac necrosis and/or apoptosis after PMI, and subsequently may reduce cardiac enzymes and improve cardiac function. We enrolled 47 consecutive patients who underwent elective PCI, and excluded those with acute coronary syndrome. We investigated the association between markers of anti-inflammation, angiogenesis or ECM and cardiac function after PCI. We measured blood levels of cardiac troponin-T (TnT), creatinine phosphokinase myocardial band (CK-MB), high sensitivity C-reactive protein, pentraxin-3 (PTX-3), matrix metallopeptidase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1) and vascular endothelial growth factor, and urinary liver-fatty acid-binding protein before and 1 day after PCI. Left ventricular ejection fraction (LVEF) was also analyzed before PCI and at follow-up coronary angiography. The levels of TnT, CK-MB and PTX-3 significantly increased after PCI. We divided the patients into tertiles according to ΔCK-MB [ΔCK-MB=CK-MB after PCI minus CK-MB before PCI; higher (but still only a mild increase), middle and lower ΔCK-MB groups]. The higher ΔCK-MB group showed a significant improvement of LVEF and an increase in TIMP-1 compared to the lower ΔCK-MB group. In conclusion, mild myocardial injury after PCI may be associated with the prevention of cardiac dysfunction through an increase in TIMP-1.

Key words: myocardial injury; percutaneous coronary intervention; cardiac function; creatinine phosphokinase myocardial band; tissue inhibitor of metalloproteinase-1.

1. Introduction

Percutaneous coronary intervention (PCI) has become one of the most important treatment strategies for coronary artery disease (CAD) and is the most frequently used means of myocardial revascularization for patients with both stable and unstable CAD (1). Due to advances in coronary stenting, there has been a decline in the rate of major adverse cardiac events (MACE) and cardiac death due to acute myocardial infarction (2-4). However, elevations of post-procedural cardiac enzyme markers, such as cardiac troponin T (TnT) and creatinine phosphokinase myocardial band (CK-MB), have been observed (5-7), and these increases are believed to represent peri-procedural myocardial injury (PMI). PMI due to PCI may decrease the beneficial effects of PCI. In clinical trials of PCI, PMI has been shown to be significantly associated with increased mortality (8, 9). The predictors of PMI can be categorized as patient-, lesion-, and procedure-related risk factors (10, 11). The risk factors of PMI are complex lesions (12), complex procedures (13), and complications (14). Cardiac biomarkers have been used over the past two decades to

establish the incidence and the prognostic implications of PMI (10). However, in recent reports, limited numbers of cardiac biomarkers were measured, such as CK-MB and TnT (13-16). Anti-inflammation, angiogenesis and prevention of the destruction of extracellular matrix (ECM) may attenuate cardiac necrosis and/or apoptosis after PMI, and subsequently may reduce cardiac enzymes and improve cardiac function (17). Therefore, as a working hypothesis, we assumed that markers of anti-inflammation, angiogenesis and ECM would be associated with the reduction of cardiac enzymes and the improvement of cardiac function. In this study, we investigated the association between markers of anti-inflammation, angiogenesis or ECM and cardiac function after PCI.

2.Methods

2.1 Subjects

We enrolled 47 consecutive patients who underwent elective PCI at Fukuoka University Hospital, and excluded those with acute coronary syndrome (ACS). We performed blood and urine sampling on the morning of PCI and the next morning after PCI, and measured various markers. All coronary interventionalists performed their best to minimize an increase in CK after PCI. Follow-up coronary angiography (CAG) was performed at 6-9 months after PCI. We also performed ultrasound cardiography (UCG) before PCI and at the time of follow-up CAG. The protocol in this study was approved by the ethics committee of Fukuoka University Hospital, and all subjects gave their written informed consent to participate.

2.2 Measurement of various biomarkers and UCG parameters

Cardiac enzyme (TnT and CK-MB), high sensitivity C-reactive protein (hsCRP) and pentraxin-3 (PTX-3, Perseus Proteomics Inc., Tokyo, Japan) were measured. The concentrations of urinary liver-type fatty acid-binding protein (U-L-FABP, FUJIREBIO Inc, Tokyo, Japan), and angiogenic markers in plasma [matrix metalloproteinase-9 (MMP-9, eBioscience, San Diego, CA, USA), tissue inhibitor of metalloproteinase-1 (TIMP-1) and vascular endothelial growth factor (VEGF) (R&D Systems, Minneapolis, MN, USA)] were determined in duplicate by specific enzyme immunoassays according to the manufacturer's instructions.

Left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) were measured as UCG parameters.

2.3 Assessment of cardiovascular risk factors

Data on weight, height, smoking and medication use were collected. Medications included angiotensin II receptor blocker (ARB) / angiotensin converting enzyme inhibitor (ACE-I), calcium channel blocker (CCB), β-blocker, statin and oral hypoglycemic agent (OHA). The patient characteristics, including the history of hypertension (HTN), dyslipidemia (DL), diabetes mellitus (DM) and smoking, were obtained from the database of Fukuoka University Hospital. Patients who had a current SBP/DBP ≥ 140/90mmHg or who were receiving antihypertensive therapy were considered to have HTN. Patients with low-density lipoprotein cholesterol ≥ 140 mg/dl and/or triglycerides ≥ 150 mg/dl or high-density lipoprotein cholesterol ≤ 40mg/dl, or who were receiving lipid-lowering therapy were defined as DL. DM was defined using the Japanese Diabetes Society criteria. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

2.4 Evaluation of the clinical outcome

The cumulative incidence of major adverse cardiac events (MACE) was defined as death, AMI, or target lesion revascularization (TLR), either percutaneous or surgical. TLR was performed if the lesion had significant in-stent luminal stenosis (> 50 % stenosis) in the presence of anginal symptoms and/or proven myocardial ischemia in the target vessel.

2.5 Statistical analysis

Statistical analysis was performed using SAS 9.3 (SAS Institute Inc.). Data are shown as the mean ± standard deviation (SD). Categorical and continuous variables were compared between the groups by a chi-square analysis and unpaired or paired t-test, respectively. Comparison among 3 groups were assessed using analysis of variance followed by post hoc Bonferroni correction for multiple comparisons. The Spearman correlation was used to examine the correlation among continuous variables. A value of $p<0.05$ was considered significant.

3. Results

3.1 Patient characteristics in all patients

Table 1 shows the characteristics in all patients. The average age, percentage of (%)males and BMI were 68 years, 74 % and 24 kg/m^2, respectively. The % Smoking, HTN, DL, and DM were 62 %, 94 %, 91 %, and 53 %, respectively. MACE was not occurred in all patients.

3.2 PCI procedures in all patients

Table 1 also shows PCI procedures (target vessels, methods of treatment, existence of side branch occlusion) in all patients. The average follow-up period was 265 days. The % target vessels was 43 % in the right coronary artery and 42 % in the left anterior descending artery. The % use of percutaneous old balloon angioplasty (POBA), bare-metal stent, and drug-eluting stent was 4 %, 15 %, and 81 %, respectively. Five cases underwent rotational atherectomy (11 %). Side branch occlusion at the end of PCI occurred in 1 patient (2 %).

Table 1. Patients characteristics and PCI procedures.

Patients characteristics		PCI procedures	
Age,y	69±9	Follow up period, day	265±62
Male,n (%)	35 (74)	Target vessel	
BMI, kg/m²	24±3	RCA/LAD/LCX,n (%)	20 (43)/20 (42)/7 (15)
Smoking, n (%)	29 (62)	POBA,n (%)	2 (4)
HTN, n (%)	44 (94)	Stent	
DL, n (%)	43 (91)	BMS/DES,n (%)	7 (15)/38 (81)
DM, n (%)	25 (53)	Stent diameter,mm	3.1±0.4
Medications		Stent Length,mm	22.8±5.5
ACE-I/ARB, n (%)	41 (87)	MAX inflation atm,atm	17.2±3.4
CCB, n (%)	31 (66)	MAX inflation time,sec	21.5±6.7
β-blocker, n (%)	6 (13)	Rota,n (%)	5 (11)
Statin, n (%)	41 (87)	SB occlusion,n (%)	1 (2)
OHA, n (%)	16 (34)		

PCI, percutaneous coronary intervention; BMI, body mass index; HTN, hypertension; DL, dyslipidemia; DM, diabetes mellitus; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; OHA, oral hypoglycemic agent; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; POBA, plain old balloon angioplasty ; BMS, bare metal stent; DES, durg eluting stent; Rota, rotational atherectomy; SB, side branch.

Table 2. Biomarkers before (in the morning of PCI) and after (the next morning of PCI) PCI.

	Before PCI	After PCI
TnT, ng/mL	0.017±0.019	0.14±0.23*
CK-MB, U/L	2.1±1.4	12.2±19.4*
hsCRP, mg/dL	0.20±0.33	0.41±0.92
PTX-3, ng/mL	2.2±1.0	2.9±1.6*
U-LFABP, μg/gCr	16±49	25±53
MMP-9, ng/mL	30±23	35±29
TIMP-1, ng/mL	104±33	105±30
VEGF, pg/mL	51±56	41±53

TnT, troponin T; CK-MB, creatinine phosphokinase myocardial band; hsCRP, high sensitivity C-reactive protein; PTX-3, pentraxin-3; U-LFABP, urinary liver-type fatty acid-binding protein; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor. *p<0.05 vs. before PCI.

3.3 Changes in biomarkers and UCG parameters

Table 2 shows changes in biomarkers between before and after PCI. The levels of TnT, CK-MB and PTX-3 significantly increased after PCI. Table 3 shows changes in UCG parameters between before PCI and at follow-up CAG. LVEDV significantly increased at follow-up CAG, whereas there was no change in LVEF.

Table 3. UCG parameters before PCI and at the time of follow-up CAG.

	Before PCI	Follow-up
LVEF, %	62±10	66±8
LVEDV, mL	72±27	77±26*
LVESV, mL	32±19	28±14

UCG, ultrasound cardiography; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume. *p<0.05 vs. before PCI.

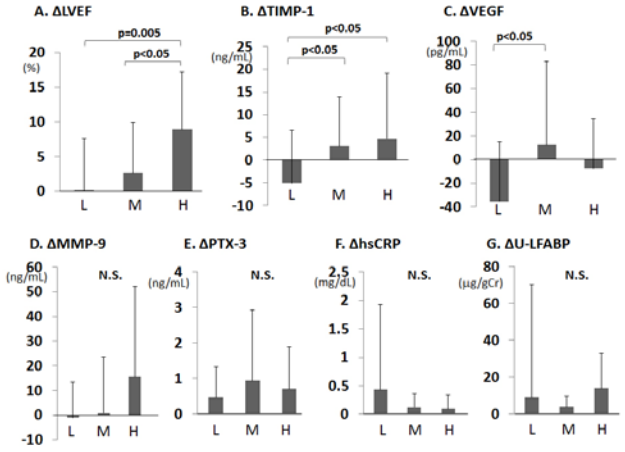

Figure 1. Various biomarkers in tertiles according to ΔCK-MB. Lower, middle and higher (but still only a mild increase) ΔCK-MB groups are indicated by the L, M and H, respectively. N.S., not significant.

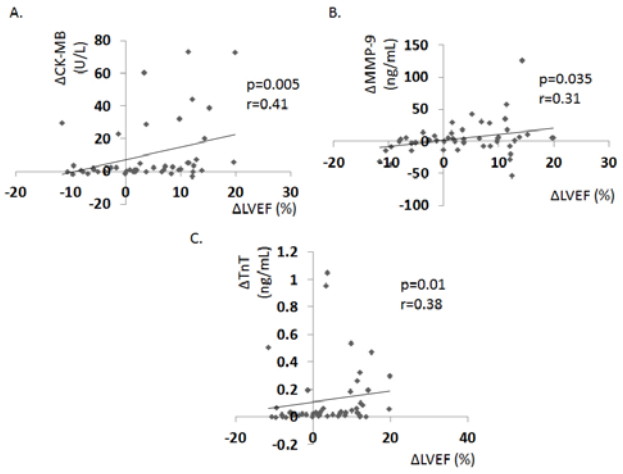

Figure 2. Associations between ΔLVEF and ΔCK-MB (A) or ΔMMP-9 (B) or ΔTnT (C).

Table 4. Patient characteristics, PCI procedures and UCG parameters before PCI in the lower, middle and higher ΔCK-MB groups.

Patient characteristics	Lower ΔCK-MB group	Middle ΔCK-MB group	Higher ΔCK-MB group	P value
Age, y	67±9	68±11	71±6	0.35
Male, n (%)	12 (80)	13 (76)	10 (67)	0.78
BMI, kg/m^2	23±4	25±3.0	24±2	0.59
Smoking, n (%)	8 (53)	11 (65)	10 (67)	0.69
HTN, n (%)	14 (93)	15 (88)	15 (100)	0.53
DL, n (%)	13 (87)	16 (94)	14 (93)	0.68
DM, n (%)	8 (53)	9 (53)	8 (53)	0.94
Medications				
ACE-I/ARB, n (%)	15 (100)	13 (76)	13 (87)	0.18
CCB, n (%)	8 (53)	11 (65)	12 (80)	0.26
β-blocker, n (%)	1 (7)	2 (12)	3 (20)	0.86
Statin, n (%)	13 (87)	15 (88)	13 (87)	0.99
OHA, n (%)	5 (33)	7 (41)	4 (27)	0.55
PCI procedures	**Lower ΔCK-MB group**	**Middle ΔCK-MB group**	**Higher ΔCK-MB group**	**P value**
Follow up period, day	273±68	260±70	262±49	0.42
Target vessel				
RCA/LAD/LCX,n (%)	6(40)/6(40)/3(20)	7(41)/8(47)/2(12)	7(47)/6(40)/2(13)	
POBA, n (%)	0 (0)	2 (12)	0 (0)	0.32
Stent				
BMS / DES, n (%)	0(0)/15(100)	4(23)/11(65)	3(20)/12(80)	
Stent diameter, mm	3.1±0.3	3.0±0.5	3.2±0.4	0.78
Stent Length, mm	22.2±6.8	23.9±5.0	22.2±4.4	0.81
MAX inflation atm, atm	17.3±2.6	16.8±4.6	17.5±2.8	0.83
MAX inflation time, sec	20.7±5.3	22.9±8.5	20.7±5.6	0.49
Rota, n (%)	1 (7)	1 (6)	3 (20)	0.38
SB occlusion, n (%)	0 (0)	0 (0)	1 (7)	0.38
UCG parameters	**Lower ΔCK-MB group**	**Middle ΔCK-MB group**	**Higher ΔCK-MB group**	
LVEF, %	63±11	62±11	61±6	0.72
LVEDV, mL	77±23	88±37	70±17	0.50
LVESV, mL	31±16	37±28	28±9	0.95

CK-MB, creatinine phosphokinase myocardial band. Other abbrevaitions as in Tables 1 and 3.
There were no significant differences in all parameters among 3 groups.

3.4 Various biomarkers in tertiles according to ΔCK-MB

We divided the patients into tertiles according to ΔCK-MB [ΔCK-MB = CK-MB on the next morning after PCI minus CK-MB on the morning of PCI; higher (4.7~73.4 U/L) (n=16, but still only a mild increase), middle (0.5~3.6 U/L) (n=16) and lower (-2.9~0.1 U/L) (n=15) ΔCK-MB groups]. Table 4 shows the patient characteristics, PCI procedures and UCG parameters before PCI into tertiles according to ΔCK-MB. There were no significant differences in all parameters among

3 groups. Interestingly, the higher ΔCK-MB group showed a significant improvement of LVEF and an increase in TIMP-1 compared to the lower ΔCK-MB group (Figure 1). In addition, the middle ΔCK-MB group showed significant increases in TIMP-1 and VEGF compared to the lower ΔCK-MB group. On the other hand, there were no significant differences in MMP-9, PTX-3, hs-CRP or U-LFABP among the tertiles according to ΔCK-MB.

3.5 Associations between ΔLVEF and Δ various markers

Figure 2 shows the associations between ΔLVEF [ΔLVEF = LVEF at follow-up CAG minus LVEF before PCI] and Δ various markers [Δvarious markers = various markers on the next morning after PCI minus various markers on the morning of PCI]. As a result, ΔLVEF was significantly associated with ΔCK-MB (p=0.005, r=0.41), ΔTnT (p=0.01, r=0.38) and ΔMMP-9 (p=0.035, r=0.31). On the other hand, ΔLVEF was not correlated with other markers [ΔPTX-3 (p=0.45, r=0.11), ΔU-LFABP (p=0.33, r= -0.16) and ΔVEGF (p=0.24, r=0.18)]. ΔLVEDV and ΔLVESV were not significantly associated with ΔCK-MB, ΔTnT, ΔMMP-9, ΔPTX-3, ΔU-LFABP and ΔVEGF (data not shown).

4. Discussion

In this study, we hypothesized that the decreased levels of biomarkers of anti-inflammation, angiogenesis and prevention of the destruction of ECM after PMI would be associated with the reduction of cardiac enzymes and the improvement of cardiac function. If the elevation of inflammatory responses was inhibited and biomarkers that were associated with angiogenesis and prevention of the destruction of ECM were increased, we considered that cardiac function with prevention of the elevation of cardiac enzymes would be improved after PCI. As a result, TIMP-1 as an endogenous MMP inhibitor was increased in the higher ΔCK-MB group, and LVEF at follow-up was improved in this group (Figure 1). Although this result regarding TIMP-1 was consistent with our hypothesis, other biomarkers were not associated with ΔCK-MB. Generally, severe PMI is associated with the reduction of cardiac function. In a contradictory statement, there was a positive correlation between ΔCK-MB and ΔLVEF. Moreover, ΔLVEF was not associated with other biomarkers except for MMP-9. Thus, we found that a larger PMI, albeit still mild, showed a mild improvement in LVEF, and it is possible that mild PMI improves LVEF probably due to prevention of the destruction of ECM by an increase in TIMP-1. Biomarkers other than MMP-9 and TIMP-1 may not be associated with the improvement in cardiac function.

The interesting observation was that mild PMI induced an improvement in LVEF. PMI has been considered to play an important role in cardiac function for 20 years (8-16). Many reports have indicated that PMI causes the reduction of cardiac function and a worse prognosis. PMI is related to dysfunctional microcirculation due to side-branch occlusion or iatrogenic plaque rupture by balloons and stents. Since cardiac TnT and CK-MB are considered to reflect the severity of cardiac injury, higher levels of these markers indicate severe cardiac injury and cardiac dysfunction. However, since PMI in the present study was mild in the higher ΔCK-MB group, we consider that this level does not lead to severe cardiac dysfunction.

The mechanism by which mild PMI improved LVEF in this study may involve the inhibition of ECM destruction by TIMP-1. ECMs are involved in cardiovascular diseases, such as myocardial infarction, heart failure and vascular diseases such as arteriosclerosis and aneurysm. MMPs are important regulators of ECM decomposition (18). According to the Framingham Heart Study, high levels of plasma MMP-9 are associated with left ventricular wall thickness and left ventricular end-diastolic diameter (19), as well as left ventricular remodeling (20, 21), which is considered to affect cardiac function. MMP-9 activity is high in acute myocardial infarction (22) and heart failure (23). Administration of an MMP-9 inhibitor (24) and MMP-9 deficiency (25) can prevent left ventricular dysfunction. Thus, MMP-9 activity plays an important role in ventricular remodeling. TIMP-1, which can inhibit MMP-9 activity, is considered to regulate myocardial healing after myocardial infarction (26). In addition, a mouse model of myocardial infarction with a reduction of TIMP-1 shows worsening of left ventricular remodeling (27). We considered that the improvement of cardiac function by the prevention of left ventricular remodeling may be due to the suppression of MMP-9 activity by TIMP-1 under mild PMI. Another possibility is that ischemic pre-conditioning by repeated balloon dilatation in PCI may affect myocardium and may improve cardiac function. Remote ischemic preconditioning (RIP) affects the reduction in cardiovascular events or smaller PMI by pressurizing the upper arm before PCI (28, 29). It is possible that RIP with mild PMI by repeated balloon dilatation may improve cardiac function.

Another important issue in this study was that PTX-3 was not associated with the improvement of cardiac function. PTX-3 is produced from vascular endothelial cells, vascular smooth muscle cells, and monocytes/macrophages (30), and its elevation is associated with ACS (31, 32). PTX-3 levels increased after coronary stenting, and it has been correlated with stent intimal thickening (33). PTX-3 may have a cardioprotective effect against MI. We predicted that changes in PTX-3 may be associated with the improvement of LVEF in this study. However, there

was no association between ΔPTX-3 and ΔLVEF. This may be because this study included patients with stable angina, although PTX-3 is considered to be abundantly expressed in migrated macrophages in vulnerable plaque in patients with ACS (31, 32).

Study limitation

This study has several important limitations. First, the sample size was relatively small, which limited our ability to determine significance. Therefore, a larger-scale study will be needed in the future. Second, PCI was performed under various treatments (anti-hypertensive, anti-dyslipidemic and/or anti-diabetic medications etc.) that may have influenced PMI.

Conclusion

Mild myocardial injury after PCI is a possibility to prevent the deterioration of cardiac function through an increase in TIMP-1.

5. Acknowledgements

We thank A. Nakayama and S. Tomita for their excellent technical assistance.

6. Disclosure

K.S. is a Chief Director and S.M. is a Director of NPO Clinical and Applied Science, Fukuoka, Japan. K.S. is the Chairman of an Endowed Department, the "Department of Molecular Cardiovascular Therapeutics", supported by MSD, Co. LTD. S.M. belongs to the Department of Molecular Cardiovascular Therapeutics, supported by MSD, Co. LTD.

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