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Original article

Pregnancy-Associated Plasma Protein-A as an Inflammatory Biomarker in Patients Undergoing Coronary Artery Bypass Surgery

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Abstract. *Study Objectives:* Data is limited to show whether PAPA-A and/or VEGF are useful tests to predict the prognosis of coronary artery disease. We sought to investigate the potential roles of PAPP-A and VEGF in predicting the severity of coronary artery disease in patients undergoing coronary artery bypass grafting. *Methods:* A total of 212 male patients who were scheduled to undergo coronary angiography were included. Patients were divided into five groups. Group 0: Patients with normal coronary arteries, Group 1: Patients with <50% stenosis in only one coronary artery, Group 2: Patients with >50% stenosis in 1 or 2 coronary arteries, Group 3: Patients with >50% stenosis in 3 or 4 coronary arteries, Group 4: Patients with >50% stenosis in 5 or more coronary arteries. PAPP-A, TNF-α, IL-6, and VEGF, blood samples were centrifuged at a rate of 3500 rpm for 10 minutes. *Results:* In the preoperative measurements, all inflammatory biomarkers except VEGF were significantly associated with an increasing number of diseased coronary arteries where hsCRP and PAPP-A showed the highest level of association. In the 7th postoperative day measurements, only PAPP-A and IL-6 showed significant association with the dependent outcome. PAPP-A was found to be associated with an increased risk of a higher number of diseased coronary arteries. *Conclusion:* PAPP-A offers a useful tool in the diagnosis of the severity of coronary artery involvement in patients undergoing CABG. Its use alone or in combination with TNF- α and/or CRP may potentially distinguish patients with and without advanced disease.

Key words: coronary artery disease, coronary artery bypass grafting, cardiac biomarker

Introduction

There has been a growing body of knowledge regarding the association between inflammation, vascular endothelial dysfunction, and atherosclerotic coronary artery disease. Numerous inflammatory markers contributing to vascular inflammatory pathways have increasingly been used in the diagnosis of the presence and severity of coronary artery disease (CAD). C-reactive protein (CRP), fibrinogen, tumor necrosis factor-alpha (TNF-α), interleukins, and various adhesive molecules have recently gained popularity. More recently, pregnancy-associated plasma protein-A (PAPP-A) and vascular endothelial growth factors, which are known to be involved in numerous physiologic and pathologic processes, were also been suggested in diagnosing the presence and severity of CAD (1, 2).

TNF-α and IL-6 were proposed as early indicators of vascular dysfunction related to cardiovascular disease based on the fact that IL-6 stimulates the expression of endothelial cell adhesion molecules and inhibits activation of endothelial nitric oxide which directly stimulates endothelial cells (3). TNF-α is also responsible for vascular dysfunction by stimulating

cell proliferation and collagen accumulation within atherosclerotic plaques (4). CRP acts as an active mediator of atherogenesis and it reliably predicts the risk of cardiovascular mortality, which makes it one of the most useful biological markers in the assessment of coronary artery disease. In addition, fibrinogen was also suggested to be an independent predictor of acute coronary syndrome (5, 6).

PAPP-A is a zinc metalloprotease that has been used in the diagnosis of Down syndrome whilst its use in the diagnosis and assessment of acute coronary syndrome has also been proposed as it participates as an inflammatory cytokine in various pathogenetic processes (7). PAPP-A was thought to be responsible for the onset of cell damage since it increases the formation of insulin-like growth factor (IGF) which induces proliferation of vascular smooth muscle cells and formation of intimal lesions by stimulation of cell adhesion and migration. Thus, one of the main mechanisms of both acute and chronic vascular damage is to become activated (8). Increased levels of PAPP-A found in the presence of unstable coronary plaques support this hypothesis as well. It is also known that PAPP-A is well correlated with CRP (9).

Vascular endothelial growth factor (VEGF) exacerbates and accelerates the inflammatory response by increasing vascular permeability. Although similar to PAPP-A, high VEGF levels were suggested to be associated with a high risk of atherosclerosis, this issue is still controversial since increased VEGF levels were demonstrated to show a weak correlation with the severity of CAD (10). Data is limited to show whether PAPA-A and/or VEGF are useful tests to predict the severity and prognosis of coronary artery disease.

In the present study, we sought to investigate the potential roles of PAPP-A and VEGF in predicting the severity of CAD in patients undergoing coronary artery bypass grafting (CABG).

Material and Method

Participants

The study was approved by the local institutional review board. This cross-sectional study was performed between January 2014 and May 2015 in a tertiary care hospital and made up of a total of 212 male patients who were scheduled to undergo coronary angiography. Female patients were not included in order to overcome the potential confounding effect of gender. Patients receiving anti-TNF-α medications such as infliximab, etanercept, and adalimumab were not included since these drugs may affect blood TNF-α levels. Patients with congenital heart disease, any chronic inflammatory disorders (e.g. rheumatoid arthritis, Behçet's disease, sarcoidosis, systemic lupus erythematosus, juvenile idiopathic arthritis, scleroderma, Polyarteritis nodosa, and Sjögren syndrome) and tumoral disease were excluded. Patients with a history of a recent myocardial infarction (to avoid high PAPP-A secretion caused by an unstable plaque), excessive physical activity (to avoid a possible increase in blood IL-6 level) (11), surgical intervention, physical trauma, and renal failure within the last one month were also excluded.

An angiographic assessment was made by the same cardiologist. Any lesion that cause more than 50% narrowing within the coronary artery lumen was considered severe stenosis. Patients were divided into five groups based on the severity of coronary artery involvement. Group 0: Patients with normal coronary arteries, Group 1: Patients with <50% stenosis in only one coronary artery, Group 2: Patients with >50% stenosis in 1 or 2 coronary arteries, Group 3: Patients with >50% stenosis in 3 or 4 coronary arteries, Group 4: Patients with >50% stenosis in 5 or more coronary arteries. In groups 1 and 2, blood samples were taken only once on the day of angiography and the results were used for comparison with patients undergoing CABG. Patients in groups 2, 3, and 4 underwent coronary artery bypass grafting by the same surgical team using a standardized routine surgical technique. In these groups, blood samples were taken on the day before the operation and then on the 1st and 7th postoperative days.

Data Collection

Cardiac specific laboratory parameters included high-sensitive CRP (hsCRP), fibrinogen, CK-MB, troponin-I (TnI), N terminal proB-type Natriuretic

Peptide (NT-proBNP). For laboratory assessment of PAPP-A, TNF-α, IL-6, and VEGF, blood samples were centrifuged at a rate of 3500 rpm for 10 minutes. Samples were then preserved at -80 ^{0}C until the day of laboratory analysis.

Measurements

A specific type of human ELISA kit was used for each one of TNF-α (USCN Life Science Inc. USA), IL-6 (MyBioSource, San Diego, California, USA), VEGF (CUSABIO Biotech Co. Ltd, Wuhan, China), and PAPP-A (RayBiotech, Inc. Parkway Lane, Norcross, GA, USA) levels were measured using a specific type of human ELISA kits with the analytic levels being 0.54 pg/ml, 1 pg/ml, 25 pg/ml and 0.6, respectively.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 15,0 and InStat3 GraphPad softwares. Among the groups, normally distributed data were compared using one-way ANOVA whereas non-normally distributed data were compared using the Kruskal-Wallis test. Comparison of normally distributed data within the same group was made using repeated measures ANOVA whereas non-normally distributed data were compared using the Friedman test. The correlation was performed using Pearson's or Spearman's correlation analysis for normally or non-normally distributing variables, respectively. A multiple regression model was created to define the independent predictors of severity of the coronary artery involvement with the inflammatory markers being included in the regression model as potential predictors. In order to identify the relative risk that would be attributed to the positivity of each inflammatory biomarker, three distinct cut-off values were defined based on the values obtained from patients in groups 1 and 2 and also on the data from current literature (12). Fisher's exact test was used to identify the relative risk of coronary artery involvement that would be attributed to the positivity of anyone of the inflammatory biomarkers.

Results

A comparison of baseline characteristics among groups was given in Table 1. There were no significant differences among groups in regard to age, presence of diabetes, tobacco use, and liver/kidney function tests.

Table 1. Baseline characteristic features of the patients.

	Group 0	Group 1	Group 2	Group 2	Group 4	p	p<0.05 in paired comparisons
Number of patients (%)	45 (21%)	40 (19%)	38 (18%)	46 (22%)	43 (20%)	-	
Age, years	66±7.1	68±8.0	68±8.0	67±7.9	69±7.3	[a] 0.4869	-
BMI, kg/m^2	26.5±2.6	27.1±2.0	28.8±3.3	29.4±2.8	29.1±2.4	[a] **<0.0001**	**0-2,0-3,0-4, 1-2, 1-3, 1-4,**
Waist circumference, cm	93.1±6.3	95.5±5.4	101.4±8.3	102.8±7.1	103.1±6.6	[a] **<0.0001**	**0-2,0-3,0-4, 1-2, 1-3, 1-4**
Diabetes, n (%)	5 (11)	7 (18)	9(24)	13(28)	11(26)	[b] 0.2824	
Hypertension, n (%)	11(24)	20(50)	25(67)	28(61)	31(72)	[b] **<0.001**	**0-2,0-3,0-4**
Tobacco use, n (%)	12(27)	16(40)	18(47)	26(57)	18(42)	[b] 0.068	-
AST, IU/L	32±14	34±15	35±15	36±13	37±12	[a] 0.4571	-
ALT, IU/L	37±18	38±18	42±30	41±25	38±17	[b] 0.9966	-
LDL, mg/dl	126±21	133±26	134±28	139±27	147±28	[a] **0.0046**	**0-4**
Trig, mg/dl	167±79	179±58	180±95	187±105	207±100	[a] 0.3287	-
HDL, mg/dl	42±10	38±8	37±9	36±9	36±7	[a] **0.0108**	**0-3,0-4,**
LDH, IU/L	285±58	264±64	287±84	288±81	311±93	[a] 0.0970	-

Table 1 (*Continued*)

	Group 0	Group 1	Group 2	Group 2	Group 4	p	p<0.05 in paired comparisons
Urea, mg/dl	36±7	37±6	37±7	36±8	39±9	[a] 0.2555	-
Creatinine, mg/dl	1.1±0.2	1.0±0.2	1.3±0.2	1.2±0.2	1.3±0.2	[a] 0.0738	-
Albumin, g/dl	4.3±0.4	4.4±0.3	4.3±0.4	4.2±0.4	4.2±0.4	[a]0.0636	-
Na, mmol/L	140±3.7	142±3.0	140±2.9	140±3.3	140±2.9	[a]0.1067	-
K, mmol/L	4.3±**0.4**	4.3±**0.4**	4.3±0.4	4.4±0.5	4.3±0.4	[a] 0.3769	-

[a]p-Value for one-way ANOVA (parametric) with post-hoc test,[b]p-Value for nonparametric ANOVA (Kruskal-Wallis test with post-hoc test). If the p-value obtained by ANOVA is <0.05, p- values of between groups (0, 1, 2, 3, and 4) are compared.BMI: Body mass index, WC: Waist circumference, HT/HL: Hipertansiyon/Hiperlipidemi, AST: Aspartate aminotransferase, ALT: Alanine transaminase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, LDH: Lactate dehydrogenase, Trig: triglyceride

Table 2. The Comparison of myocardial and inflammatory biomarker levels among groups before surgery.

	Preoperative						
	G0	G1	G2	G3	G4	p	p<0.05 in paired comparisons
TNF-α, pg/ml	11.7±5.5	12.1±5.2	14.8±4.0	19.0±4.6	23.4±6.5	[a]**<0.0001**	0-3, 0-4, 1-3, 1-4, 2-3, 2-4, 3-4
PAPP-A, ng/ml	3.8±2.1	5.0±3.3	5.6±2.6	7.2±3.1	8.6±3.9	[a]**<0.0001**	0-3, 0-4, 1-3, 1-4, 2-4
hsCRP, mg/L	2.4±1.7	2.7±2.0	3.3±1.8	3.8±2.5	4.4±2.5	[b]**<0.0001**	0-3, 0-4, 1-4
Fibrinogen, mg/dl	265±72	290±65	312±68	336±68	346±78	[a]**<0.0001**	0-2, 0-3, 0-4, 1-3, 1-4
IL-6, ng/L	13.2±8.7	15.9±10.2	23.0±14.5	26.1±17.6	33.2±13.3	[b]**<0.0001**	0-2, 0-3, 0-4, 1-3, 1-4, 2-4
VEGF, pg/ml	69±31	82±30	87±32	92±34	95±36	[a]**0.0013**	0-3, 0-4
TnI, ng/ml	0.40±0.58	0.44±0.64	0.53±0.44	0.46±0.38	0.57±0.51	[a]0.5622	-
CK-MB, IU/L	12.0±7.2	13.5±5.9	13.4±5.2	13.7±4.3	15.4±6.3	[b]0.0872	-

TNF: Tumor necrosis factor, PAPP-A: Plasma associated pregnancy protein-A, IL: Interleukin, hsCRP: High sensitive C-reactive protein; TnI: Troponin I, CK-MB: Creatine Kinase-Myocardial Band; [a]p-value for one-way ANOVA (parametric) with Post-hoc test(Tukey-Kramer Multiple Comparisons Test); [b]p-value for Kruskal-Wallis test (nonparametric ANOVA) with Post-hoc test(Dunn's Multiple Comparisons Test); When the p-value obtained by ANOVA was <0.05, p-values of between groups (3, 3, and 4) were compared.

Mean body mass index and mean waist circumference were significantly lower in groups 0 and 1 compared to groups 2, 3, and 4. Hypertension was significantly less common in Group 0. Patients in groups 3 and 4 were significantly more tend to have dyslipidemia (Table 1).

Table 2 shows the comparison of myocardial and inflammatory biomarker levels among all groups before surgery. All inflammatory biomarkers showed a significant increase with an increasing number of diseased coronary arteries (p>0.001) whereas the slight increases observed in TnI (p=0.56) and CK-MB (p=0.08) levels were not of statistical significance. TNF-α and PAPP-A levels showed a significant increase in almost all pairwise comparisons whilst the significance in hsCRP, fibrinogen, IL-6, and VEGF levels were mainly due to the difference caused by Group 3 and Group 4 (Table 2).

Table 3 shows the comparison of myocardial and inflammatory biomarker levels among groups on 1st and 7th postoperative days. On 1st postoperative day, there were no significant differences among groups 2, 3, and 4 in regard to TNF-α (p=0.05), hsCRP (p=0.13), fibrinogen (p=0.10), IL-6 (p=0.08), VEGF (p=0.89), TnI (p=0.24), CK-MB (p=0.40). PAPP-A levels, however, showed a significant increase with an increasing number of diseased coronary arteries with the significance being mainly due to the difference between groups 2 and 4 (Table 3). On the 7th postoperative day, the high PAPP-A levels persisted. Both groups 3 and 4 had significantly higher PAPP-A levels compared to group 2. On that day, Group 4 had significantly higher hsCRP and IL-6 levels than Group 2 (Table 3).

In preoperative measurements, PAPP-A showed significant positive correlation with TNF-α (r=0.2958 p<0.0001); hsCRP (r=0.4580 p<0.0001); IL-6 (r=0.2006 p<0.0034); fibrinogen (r=0.3795 p<0.0001). In the 1st postoperative day, PAPP-A showed significant positive correlation with hsCRP ile (r=0.2876 p<0.0001) and fibrinogen (r=0.4860 p<0.0001). In the 7th postoperative day, PAPP-A showed significant positive correlation with TNF-α (r= 0.4860 p<0.0001); hsCRP (r= 0.3818 p<0.0001) and fibrinogen (r=0.1898 p=0.0326).

Table 4 shows multiple regression analyses for a higher number of diseased coronary arteries. In the preoperative measurements, all inflammatory biomarkers except VEGF were significantly associated with an increasing number of diseased coronary arteries where hsCRP and PAPP-A showed the highest level of association. In the 7th postoperative day measurements, only PAPP-A and IL-6 showed significant association with the dependent outcome. The level of association was relatively higher in favor of PAPP-A than that of IL-6 (Table 4).

Table 5 shows the relative risk values of each inflammatory biomarker for an increasing number of diseased coronary arteries. Relative risks were calculated based on three different cut-off values for each inflammatory biomarker (Table 5). A cut-off level of 7.24 for PAPP-A was found to be associated with a 5.56 times increased risk of a higher number of diseased coronary arteries.

Table 3. The Comparison of myocardial and inflammatory biomarker levels among groups on 1st and 7th postoperative days.

	Postoperative 1 day				p<0.05 in paired comparisons	Postoperative 7 day				p<0.05 in paired comparisons
	G2	G3	G4	p		G2	G3	G4	p	
TNF-α, pg/ml	23.0±7.3	24.9±8.9	27.5±8.3	[a]0.0540	-	16.8±4.6	19.2±5.6	19.7±6.0	[a]0.0509	-
PAPP-A, ng/ml	6.4±3.0	8.1±3.4	9.0±3.4	**[a]0.0016**	2-4	5.4±2.4	7.2±2.9	8.1±3.1	**[a]0.0001**	2-3, 2-4
hsCRP, mg/L	8.3±8.2	7.9±4.3	8.5±5.3	[b]0.1399	-	5.3±3.0	6.2±3.6	7.3±3.9	**[a]0.0369**	2-4
Fibrinogen, mg/dl	343±75	369±74	381±86	[a]0.1003	-	326±90	352±84	356±64	[a]0.2050	-
IL-6, ng/L	36.5±23.3	33.7±25.0	43.6±26.1	[b]0.0844	-	29.4±16.0	29.1±19.9	40.1±19.4	**[a]0.0068**	2-4, 3-4
VEGF, pg/ml	120±51	115±43	119±41	[a]0.8956		82±29	100±32	91±32	[a]0.0855	-
TnI, ng/ml	2.35±1.62	2.18±1.39	2.55±1.61	[b]0.2450	-	0.83±0.71	0.71±0.67	0.79±0.59	[a]0.6975	-
CK-MB, IU/L	57.8±24.0	59.8±33.0	51.9±26.0	[a]0.4000		27.9±13.0	26.2±14.9	28.8±12.7	[a]0.6478	-

[a]p-value for one-way ANOVA (parametric) with Post-hoc test(Tukey-Kramer Multiple Comparisons Test); [b]p-value for Kruskal-Wallis test (nonparametric ANOVA) with Post-hoc test (Dunn's Multiple Comparisons Test); When the p-value obtained by ANOVA was <0.05, p-values of between groups (2, 3, and 4) were compared.

Table 4. Multiple regression for an increasing number of diseased coronary arteries.

Preoperative measurements					
Variable	**Coefficient**	**SE**	**95% Confidence Interval**	**t ratio**	**p-value**
(constant)	-4.310	0.4519	-5.196 to -3.424	9.538	<0.0001
TNF-α	0.1151	0.0152	0.08530 to 0.1450	7.561	<0.0001
PAPP-A	0.1754	0.0304	0.1159 to 0.2350	5.776	<0.0001
hsCRP	0.2015	0.0453	0.1128 to 0.2902	4.454	<0.0001
IL-6	0.033	0.0066	0.0202 to 0.0459	5.027	<0.0001
Fibrinogen	0.0063	0.0013	0.0037 to 0.0090	4.701	<0.0001
VEGF	0.0041	0.0027	-0.0012 to 0.00945	1.504	0.1342
R squared: 0.6672, Adjusted R squared: 0.6575, Multiple R: 0.8168, F: 68.5051					

Table 4 (*Continued*)

Measurements in the 7th postoperative day					
Variable	**Coefficient**	**SE**	**95% Confidence Interval**	**t ratio**	**p-value**
(constant)	-0.6527	0.7645	-2.167 to 0.8610	0.8538	0.3949
TNF-α	0.03281	0.02303	-0.01279 to 0.07841	1.425	0.1569
PAPP-A	0.2923	0.04640	0.2004 to 0.3841	6.299	<0.0001
hsCRP	0.06987	0.03786	-0.005097 to 0.1448	1.845	0.0674
IL-6	0.01954	0.007016	0.005647 to 0.03343	2.785	0.0062
Fibrinogen	0.001047	0.001615	-0.002150 to 0.004245	0.6485	0.5179
VEGF	0.003616	0.004078	-0.004458 to 0.01169	0.8867	0.3770
R squared: 0.3976, Adjusted R squared: 0.3675, Multiple R: 0.6305, F: 13.1998					

Table 5. The relative risk of atherosclerotic coronary artery disease after adjusting for risk factors

Risk Factors	CutoffValues	RR	95% Confidence Interval	p-value
hsCRP level, mg/L	>2.70	1.648	1.113 to 2.443	0.0039
	>3.30	1.832	1.029 to 3.261	0.0241
	>3.83	2.002	0.977 to 4.101	0.0405
PAPP-A level, ng/ml	>5.04	1.796	1.167 to 2.766	0.0022
	>5.62	2.344	1.331 to 4.128	0.0004
	>7.24	5.569	1.833 to 16.918	<0.0001
TNF-α level, pg/ml	>12.14	1.819	1.301 to 2.543	<0.0001
	>14.8	2.175	1.390 to 3.402	<0.0001
	>19.0	2.560	1.180 to 5.553	0.0059
IL-6 level, pg/ml	>15.9	1.751	1.208 to 2.539	0.0004
	>23.0	2.425	1.324 to 4.441	0.0006
	>26.1	4.311	1.659 to 11.206	0.0001
Fib level, mg/dl	>290	1.677	1.154 to 2.436	0.0017
	>312	1.886	1.168 to 3.045	0.0025
	>336	2.810	1.392 to 5.672	0.0005
VEGF level, pg/ml	>82.0	1.506	1.012 to 2.241	0.0285
	>86.5	1.865	1.155 to 3.013	0.0040
	>92.5	2.048	1.157 to 3.626	0.0059

RR: Relative Risk,
Relative risk was estimated by using Fisher's Exact Test.
Cutoff values were obtained from means of group 1, group 2, and group 3.

Discussion and Conclusion

Several investigators tried to explain the association between obesity and cardiovascular disease based on chronic low-degree inflammation. It was reported that adipose tissue produces a considerable amount of hormone, peptides, and molecules participating in the cytokine-mediated inflammation which triggers atherosclerosis (13, 14). The significant association we found between the number of diseased coronary vessels and obesity markers including BMI and WC supports the above suggestions. However, the relationship between WC and atherosclerosis was stronger than that between BMI and atherosclerosis. While this may

partly be due to the fact that BMI does not adequately represent the amount of body fat, the close relationship between WC and the metabolically active visceral fat tissue which acts as an endocrine organ should also be considered (15, 16).

We found that patients with a higher number of diseased coronary arteries tend to have an increase in inflammatory biomarker levels in the postoperative period. This finding supports the view inflammatory process is the major mechanism that is responsible for coronary atherosclerosis (17, 18). We observed an increasing trend in multiple inflammatory markers indicating that all these markers contribute to a common process by triggering the functions of each other. This hypothesis may also be supported by one study on coronary artery cell cultures where endothelial PAPP-A and mRNA release increased as a response to activation with TNF- α. It was also reported that IL-6 strongly stimulates PAPP-A in coronary artery smooth muscle cells whereas such an effect was not found in endothelial cells. Moreover, PAPP-A increase in patients with acute coronary syndrome was found well-correlated with CRP levels (19, 20).

Despite the significant difference among groups in regard to preoperative measurements, TNF- α, *fibrinogen and VEGF levels did not show any significant difference* between 1th and 7th days after the operation (i.e in groups 2, 3, and 4 who received CABG). Also, there was no significant correlation between the number of diseased coronary arteries and the level of inflammatory markers. These findings indicate that inflammatory markers are quite affected by surgical trauma. Because of the increase in acute phase reactants, surgical trauma might have masked the correlation between the inflammatory markers and coronary disease severity. In other words, the proposed relationship between the number of diseased coronary arteries and blood levels of TNF-α, fibrinogen, and VEGF will be unavailable for a while in the postoperative period. This is also true for CRP levels. However, we observed that CRP levels were significantly different among groups on the 7th postoperative day and also there was a weak but significant correlation between the number of diseased coronary arteries and CRP levels. This finding may indicate that the effect of surgery on CRP disappears earlier than that on other biomarkers. Supporting this was the study by Aono et al. (21) where CRP levels were demonstrated to decrease gradually between the 4th and 14th days after the operation. Also, in another study on patients undergoing spinal surgery, it was shown that CRP levels peaked at the 3rd postoperative day and resume within the normal ranges by the end of the 5th postoperative day (22). Although all but one (i.e VEGF) of the inflammatory biomarkers showed a significant relationship with the number of diseased coronary arteries in the preoperative measurements, multiple regression analyses revealed that only PAPP-A was achieved to predict the higher number of diseased vessels on the 7th day. PAPP-A values also showed a moderate and significant correlation with the number of diseased vessels. This may be indicative that PAPP-A is less affected by other forms of inflammation such as surgical trauma, underscoring the potential value of PAPP-A in the diagnosis of the severity of coronary artery disease.

In contrast to us, Liu et al. reported that they found no association between PAPP-A levels and an increasing number of diseased coronary vessels (23). This controversy may be about the difference in patient selection since we did not include female patients. Moreover, we did not include the patients with a recent acute coronary syndrome since unstable plaques may release more amount of PAPP-A compared to stable plaques (24).

We observed that PAPP-A showed a significant positive correlation with CRP and TNF- α in preoperative measurements whilst this correlation was lost at 1st postoperative day and resumed at 7th postoperative day. This may partly be explained by the effect of acute trauma that emerged as a result of CABG. When compared to the sharp rise in CRP and other inflammatory biomarkers, the response of blood PAPP-A levels to acute trauma may be slower. This finding may be interpreted as; i) PAPP-A is more dependent on chronic inflammatory processes rather than acute traumatic events, ii) PAPP-A may potentially be more specific than other inflammatory biomarkers diagnosing the inflammatory process underlying the chronic atherosclerotic coronary artery disease.

Li et al. reported that PAPP-A was a strong predictor of long-term restenosis in patients undergoing

coronary angioplasty (25). When results of that study are taken together with our finding that PAPP-A was more predictive of coronary artery severity by the 7th day of CABG, it may be postulated that PAPP-A may be a well surrogate for coronary artery disease severity both early and late after CABG.

Although both CRP and IL-6 levels were found to be significantly correlated with the number of diseased coronary arteries in the preoperative period, such a relationship was no longer present after the operation, indicating that levels of these biomarkers are quite susceptible to the presence of extensive trauma. This highlights the need for new biomarkers specific to the inflammation that emerged from chronic atherosclerotic coronary artery disease. PAPP-A may be regarded as valuable since we found that its increasing levels were predictive of disease severity both before and early after the operation. Moreover, we think that the combined use of PAPP-A and CRP would provide more useful information in the preoperative period.

Our study demonstrated that PAPP-A offers a useful tool in the diagnosis of the severity of coronary artery involvement in patients undergoing CABG. Its use alone or in combination with TNF-α and/or CRP may potentially distinguish patients with and without advanced disease. Moreover, its prognostic value in the postoperative period is more valuable than any other inflammatory or cardiac biomarkers.

Conflict of interest: The authors declare that there is no conflict of interest in this manuscript.

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