ORIGINAL ARTICLE

Immune Biomarkers of Percutaneous Coronary Intervention Adverse Outcomes in Myocardial Infarction and Stable Angina Patients

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Abstract

Introduction: For the past 20 years, percutaneous coronary intervention (PCI) became a major method of treatment in myocardial infarction and stable angina patients. The study was aimed to assess the prognostic role of inflammation biomarkers to evaluate the risk for restenosis in myocardial infarction and stable angina patients undergoing PCI. **Materials and Methods:** A total of 73 patients with myocardial infarction and 109 patients with stable angina, aged 41–74 years were examined. The blood samples were tested immediately before and 7 days after PCI for interferon (IFN)-γ, Il-6, Il-8, IL-17/IL-17A, TNF-α, TNF-β, tumor necrosis factor (TGF)-β1, and TGF-β2, control coronary angiography was performed in all patients at 12 months follow-up. **Results:** The abnormally high rates of IFN-γ pre-PCI (odds ratio [OR] = 5.21) and 7 days after (OR = 3.84), IL-6 pre-PCI (OR = 1.59), IL-8 pre-PCI (OR = 1.73), IL-17 pre-PCI (OR = 3.07) and 7 days after (OR = 2.34), TNF-α pre-PCI (OR = 1.88), TNF-β pre-PCI (OR = 1.98) and growth factors – TGF-β1 7 days after PCI (OR = 1.82) and TGF-β2 7 days after PCI (OR =2.04) predict an event of restenosis during 1 year after PCI. **Conclusion:** Our results may help to explain the findings that inflammation-related endothelial cell and macrophage activation may predict restenosis event in acute myocardial infarction patients and stable angina patients with more significance in acute myocardial infarction patients.

Key words: Cytokines, growth factor, myocardial infarction, percutaneus coronary intervention, stable angina

INTRODUCTION

During the past decades, percutaneous coronary intervention (PCI) has become a major weapon against myocardial infarction and stable angina. This approach was compromised by the fact that restenosis was the main limitation. Great efforts have been made in resolving this vexing problem. Although the angiographic restenosis rate has been substantially reduced by stenting, especially with the drug-eluting stents, there still remains a problem particularly in a subset of patients and lesions. The predominant mechanism in the development of in-stent restenosis is intimal hyperplasia.[1]

The event of angiographic restenosis in the several months after initially successful PCI, although reduced in incidence with the development of stents, it still creates the great impact on clinical and socioeconomic outcome.[2]

Recent studies support the concept that inflammatory and proliferative foci arise from the adventitia. Neutrophils accumulate in adventitia in the first 3 days, followed by macrophages after angioplasty. Interestingly, the main inflammatory and proliferative foci were not limited to

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the adventitia but rather extended from the injured vessel throughout the surrounding tissues.[3]

At the same time, several studies in humans have been performed to investigate the role of inflammation in prognosis after PCI. There were identified that some pro-inflammatory biomarkers (interferon [IFN]-γ,[4] IL-6,[5] IL-8,[6] IL-17,[7] TNF-α,[8] and TNF-β[9]) and anti-inflammatory acting transforming growth factors (TGF-β1[5] and TGF-β2[10]) can be a potential link between inflammation and restenosis event after PCI. However, there is still not an endpoint of view on the prognostic value of these biomarkers in restenosis, and the problem is still discussible.

Consequently, the impact of pro- and anti-inflammatory biomarkers on the development of restenosis after PCI needs to be studied.

This study was objected to assess the prognostic role of inflammation biomarkers to evaluate the risk for restenosis in myocardial infarction and stable angina patients undergoing PCI.

SUBJECTS AND METHODS

This study was conducted in the period between January 2013 and January 2016. The study group includes 73 patients with myocardial infarction and 109 patients with stable angina admitted to the Pacific State Medical University and Primorye Regional Clinical Hospital №1, Vladivostok. All participants of the study had been angiographically diagnosed to have the adverse effect of PCI within 12 months after the procedure.

Inclusion criteria

Age 41–74 years, stable angina 1–3 functional grades, ST-segment elevation myocardial infarction (STEMI), primary PCI, and with no gender restrictions were included in the study.

Exclusion criteria

Under 41 years of age and older than 74 years, non-ST-STEMI (NSTEMI), or unstable angina STEMI, cardiogenic shock, history of PCI or coronary artery bypass surgery, chronic heart failure of stage 3, fibrinolytic therapy prior emergency PCI, patients with oncology, autoimmune and psychiatric diseases were excluded from the study.

Healthy control group includes 90 healthy volunteers were enrolled in this study so as to compare the general level of the cytokines and growth factors involved in the study. Reference limits in the healthy population are listed in Table 1 and represented in pg/ml for cytokines and ng/ml for growth factors.

Table 1: Reference limits of cytokines and growth factors: Median, 25th and 75th quartiles

Markers	Reference limits in healthy population
Cytokine, pg/ml	
IFN-γ	10.54 (7.40;12.20)
IL-6	2.17 (1.07;2.64)
IL-8	19.47 (8.41;29.32)
IL-17	5.57 (1.89;9.45)
TNF-α	4.44 (3.62;5.13)
TNF-β	0.74 (0.02;3.40)
Growth factors, ng/ml	
TGF-β1	19.02 (17.50;23.54)
TGF-β2	150.82 (132.71;161.14)

IFN: Interferon

Blood sampling

Peripheral blood samples were taken immediately before and 7 days after PCI.

The Quantikine human IFN-γ, Il-6, Il-8, IL-17/IL-17A, TNF-α, TNF-β, TGF-β1, and TGF-β2 (R and D Systems, Inc., Minneapolis, MN, USA) immunoassay solid phase sandwich-type ELISA tests were used, for: Human IFN-γ, Il-6, Il-8, IL-17/IL-17A, TNF-α, TNF-β, TGF-β1, and TGF-β2.

Coronary procedures

Coronary angiography was performed with Judkin's left and right catheters (Jl 4.0; JR 4.0) through the left and right femoral artery using a digital angiographic system (Innova 3100, US, General Electrics). Angiography, coronary angioplasty, and stent implantation were performed by experienced doctors only. Target vessel angiographic stenosis >65% was the indication to PCI.

The event of restenosis was identified if luminal diameter loss of target vessel ≥50% of the acute minimal lumen diameter by angiography. Repeat coronary angiography was conducted in all patients (1 year after PCI).

Statistical analysis

Data are represented as the mean standard deviation for quantitative variables with distribution closed to a normal and were compared using Student's *t*-test. For quantitative variables with a nonnormal distribution are expressed as median and 25th–75th quartiles. The data were compared with the Mann–Whitney *U*-test. Categorical variables are represented as absolute and its percentage and compared with the Chi-square test. Logistic regression analysis was performed to determine predictors of restenosis event 1 year after PCI.

Before multiple logistic regression analysis, all patients with and without restenosis were divided into two groups according to the presence of abnormal rate of cytokines or growth factors, i.e., subjects who had abnormal rate of any cytokine or growth factor and developed restenosis during 12 months follow-up were assigned as the "risk" group and patients who had normal rate of any cytokine or growth factor and developed restenosis during 12 months follow-up were assigned as the "non-risk" group. Multiple logistic regression analysis was performed to assess the influences each factor cytokine and growth factor, and the odds ratio (OR), and 95% confidence interval (95% CI) were calculated. The predictors with OR and its 95% CI > 1.0 were considered as statistically significant in the prognosis of restenosis event.

Statistical analyses were processed using the Statistical Package for the Social Sciences software (SPSS 20.0). A critical limit of $P < 0.05$ was considered as significant.

Ethics

The study protocol was approved by the local ethics committee of the Pacific State Medical University according to the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects,[11] and the "Good Clinical Practice Principles in the Russian Federation" approved by the Russian Ministry of Health.[12] Written informed consent was obtained from all patients prior involving in the study (the protocol 3/13 from 09.12.2013).

RESULTS

General characteristics of the study groups related to vessel lesions are presented in Table 2. All patients had stenosis of target vessel more than 80%. Uni-vessel lesions were significantly predominant in group of stable angina patients (66.06% vs. 52.05%; $P = 0.04$). Restenosis rate was similar in patients with myocardial infarction or stable angina (9.59% vs. 9.17%; $P = 0.34$).

The preprocedural levels and follow-up on 7th day levels of plasma IFN-γ in both groups were significantly higher than those in the control group. Also was observed that plasma level of IFN-γ decreased from 36.89 (36.54; 37.92) pg/ml to 30.34 (29.76; 30.98) pg/ml on 7th day after PCI in acute myocardial infarction patients and from 28.89 (25.61; 32.17) pg/ml to 13.89 (7.89; 19.89) pg/ml in stable angina patients. Intergroup comparison showed that parameters of IFN-γ before and after 7 days were significantly higher in the group of acute myocardial infarction patients than in the stable angina group (36.89 [36.54; 37.92] pg/ml vs. 28.89 [25.61; 32.17] pg/ml; $P = 0.04$ before PCI and 30.34 [29.76; 30.98] pg/ml vs. 13.89 [7.89; 19.89] pg/ml; $P = 0.001$ in 7 days after procedure) [Table 3].

The concentration of IL-6 in the acute myocardial infarction and stable angina groups was significantly different relatively the healthy control group. Acute myocardial infarction intragroup dynamics the level of IL-6 decreased in 3 times from initial (12.02 (6.73; 12.76) pg/ml to 4.03 (3.72; 4.57) pg/ml) on 7th day after the procedure. Oppositely, the plasma concentration of IL-6 in stable angina patients tends to be increased from 4.14 (3.24; 5.05) pg/ml prior to 7.95 (5.53; 10.37) pg/ml after PCI. According to IL-6 measurements, the difference between acute myocardial infarction and stable angina patients was found in preprocedural levels only (12.02 [6.73; 12.76] pg/ml vs. 4.14 [3.24; 5.05] pg/ml; $P = 0.001$) [Table 3].

IL-8 pre-PCI level was also significantly exceeded in both patients groups than reference limits in healthy people. The concentration of IL-8 prior PCI and on 7th days after was stable in acute myocardial infarction patients. However, in the group of stable angina patients, the plasma concentration of IL-8 was prone to decreasing in 7 days after PCI procedure. It should be noted, that preprocedural and follow-up levels of IL-8 were significantly higher in the group of myocardial infarction compare to stable angina (pre-PCI: 221.81 [135.75; 229.81] pg/ml vs. 192.16 [173.22; 211.10] pg/ml; $P = 0.001$; 7 days: 226.57 [216.35; 258.87] pg/ml vs. 114.07 [106.14; 122.00] pg/ml; $P = 0.001$) [Table 3].

The concentrations of IL-17 in the myocardial infarction patients as well pre-procedure time as after 7 days were significantly lower than limit ranges in healthy. At the same time, the levels of IL-17 in stable angina patients were higher than control and myocardial infarction group [Table 3].

Pre-PCI and 7 days levels of TNF-α were closed to reference limits in acute myocardial infarction cases. Interestingly, but in stable angina patients, these parameters were significantly decreased compare opposite group (pre-PCI: 1.08 [0.78; 1.39] pg/ml vs. 5.96 [2.40; 6.10] pg/ml; $P = 0.01$ and 7 days: 1.91 [1.02; 2.81] pg/ml vs. 5.74 [2.32; 6.23] pg/ml; $P = 0.01$)

Table 2: General characteristics of the study groups: *n* (%)

Variable	Acute myocardial infarction (*n*=73)	Stable angina (*n*=109)	*P*-value
Stenosis of target vessel, %	89.94±10.58	81.77±12.45	0.42
Uni-vessel lesion	38 (52.05)	72 (66.06)	0.04
Multi-vessel lesion	35 (47.95)	37 (33.94)	0.04
Restenosis rate	7 (9.59)	10 (9.17)	0.34

Table 3: IFN-γ, IL-6, IL-8, IL-17, TNF-α, and TNF-β levels of pre-PCI, 7 days and follow-up at 12-month in patients with restenosis after PCI: Median, 25th and 75th quartiles

Variable, pg/ml	Acute myocardial infarction (*n*=73)	Stable angina (*n*=109)	*P*-value
IFN-γ pre-PCI	36.89 (36.54; 37.92)***	28.89 (25.61; 32.17)***	0.04
IFN-γ 7 days	30.34 (29.76; 30.98)***	13.89 (7.89; 19.89)	0.001
IL-6 pre-PCI	12.02 (6.73; 12.76)***	4.14 (3.24; 5.05)*	0.001
IL-6 7 days	4.03 (3.72; 4.57)**	7.95 (5.53; 10.37)**	0.06
IL-8 pre-PCI	221.81 (135.75; 229.81)***	192.16 (173.22; 211.10)***	0.001
IL-8 7 days	226.57 (216.35; 258.87) ***	114.07 (106.14; 122.00)***	0.001
IL-17 pre-PCI	3.03 (2.31; 3.64)*	18.98 (16.42; 21.55)*	0.001
IL-17 7 days	2.41 (1.59; 2.85)*	14.14 (10.69; 17.59)*	0.001
TNF-α pre-PCI	5.96 (2.40; 6.10)	1.08 (0.78; 1.39)*	0.01
TNF-α 7 days	5.74 (2.32; 6.23)	1.91 (1.02; 2.81)*	0.01
TNF-β pre-PCI	10.14 (5.77; 10.14)***	5.25 (4.24; 6.26)*	0.01
TNF-β 7 days	21.74 (16.55; 21.74)***	3.57 (2.63; 4.51)	0.001

*P<0.05 in comparison with the control group; **P<0.01 in comparison with the control group; ***P<0.001 in comparison with the control group

Table 4: TGF-β1 and TGF-β2 levels of pre-PCI, 7 days, and follow-up at 12-month in patients with restenosis after PCI: Median, 25th and 75th quartiles

Variable, ng/ml	Acute myocardial infarction (*n*=73)	Stable angina (*n*=109)	*P*-value
TGF-β1 pre-PCI	33.39 (27.15; 42.76)*	22.76 (20.38; 25.140)	0.04
TGF-β1 7 days	34.62 (30.29; 37.71)*	20.02 (17.90; 22.15)	0.04
TGF-β2 pre-PCI	84 (72.56; 87.51)***	66.89 (53.81; 79.97)***	0.01
TGF-β2 7 days	62.18 (45.10; 67.94)***	62.11 (56.33; 67.90)***	0.27

*P<0.05 in comparison with the control group; **P<0.01 in comparison with the control group; *P<0.001 in comparison with the control group

and concentrations in healthy volunteers group [Table 3].

The plasma concentration of TNF-β increased on 7th day after PCI in acute myocardial infarction patients which was significantly different from the results of stable angina group. There was tendency to normalization 7 days past. In general picture, we observed significantly higher levels in the group of myocardial infarction than in the stable angina group (pre-PCI: 10.14 [5.77; 10.14] pg/ml vs. 5.25 [4.24; 6.26] pg/ml; $P = 0.01$ and 7 days: 21.74 [16.55; 21.74] pg/ml vs. 3.57 [2.63; 4.51] pg/ml; $P = 0.001$) [Table 3].

The concentrations of TGF-β1 in time before PCI and in 7 days after were very near in acute myocardial infarction. The similar trend we found in stable angina patients. Wherein TGF-β1 pre-PCI and TGF-β1 7 days concentration in the group of myocardial infarction were significantly higher than in the stable angina group (pre-PCI: 33.39 [27.15; 42.76] ng/ml vs 22.76 [20.38; 25.140] ng/ml; $P = 0.04$ and 7 days: 34.62 [30.29; 37.71] ng/ml vs. 20.02 [17.90; 22.15] ng/ml; $P = 0.04$). The plasma level of TGF-β2 was higher prior RCI in myocardial infarction patients than in stable angina patients (84 [72.56; 87.51] ng/ml vs. 66.89 [53.81; 79.97] ng/ml; $P = 0.01$). But, and before procedure, and in 7 days after TGF-β2 concentrations were significantly lower than in reference ranges of the control group (P<0.001) [Table 4].

The pre- and post-procedural levels of cytokines: IFN-γ, IL-6, IL-8, IL-17, TNF-α, TNF-β, and growth factors: TGF-β1 and TGF-β2 were associated with restenosis event in myocardial infarction and stable angina patients. However, the role of statistically significant predictors of PCI's adverse outcome during 12-months follow-up in the study played IFN-γ pre-PCI (OR = 5.21) and 7 days after (OR = 3.84), IL-6 pre- PCI (OR = 1.59), IL-8 pre-PCI (OR = 1.73), IL-17 pre-PCI (OR = 3.07) and 7 days after (OR = 2.34), TNF-α pre-PCI (OR = 1.88), TNF-β pre-PCI (OR = 1.98) and growth factors – TGF-β1 7 days after PCI (OR = 1.82) and TGF-β2 7 days after PCI (OR = 2.04) [Figures 1 and 2].

DISCUSSION

The biology of restenosis is different from that seen after balloon angioplasty. After balloon angioplasty, there are thrombus formation, intimal hyperplasia development, elastic coil, and negative remodeling. Negative remodeling is a condition in which the vessel area decreases in size, often as a result of

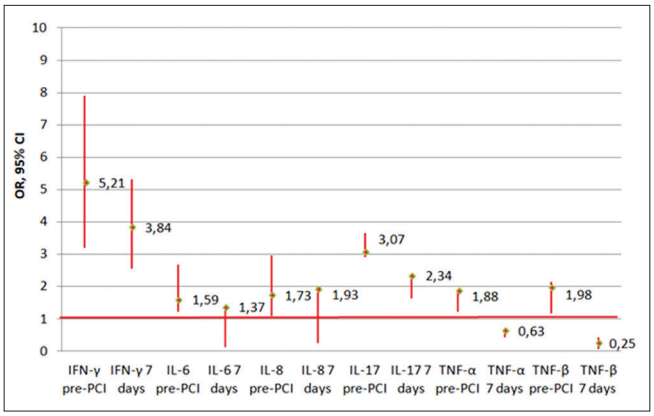

Figure 1: Interferon-γ, interleukin (IL)-6, IL-8, IL-17, tumor necrosis factor (TNF)-α, and TNF-β abnormal rate odds ratio of pre-percutaneous coronary intervention (PCI), 7 days and follow-up at 12-month in patients with restenosis after PCI

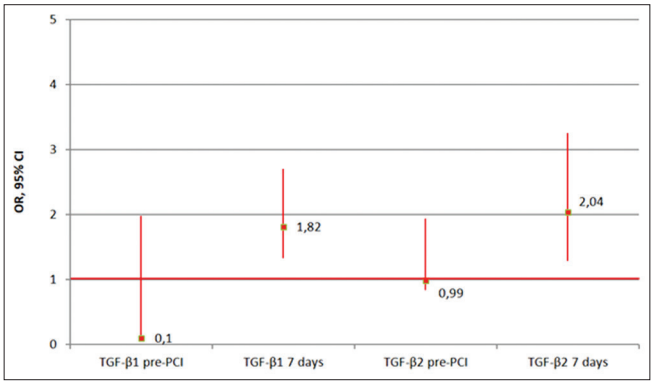

Figure 2: TGF-β1 and TGF-β2 abnormal rate odds ratio of pre-percutaneous coronary intervention (PCI), 7 days and follow-up at 12-month in patients with restenosis after PCI

a structural change in the vessel wall. It is a major factor in restenosis following balloon angioplasty. In contrast, after stent placement, elastic coil and negative remodeling are eliminated, and thrombus formation followed by intimal hyperplasia development are the main contributors to restenosis.[13]

The present study showed that elevated circulating levels of IFN-γ, IL-6, IL-8, IL-17, TNF-α, TNF-β, and growth factors: TGF-β1 and TGF-β2 were associated with rapid angiographic coronary artery stenosis progression in patients with acute myocardial infarction and stable angina. Our study confirms previous observations from others regarding restenosis after PCI and indicates that restenosis development is associated with inflammatory mechanisms and endothelial activation.

Some studies have shown that the predictor ability of IFN-γ is significant only at the stage before stenting, and in follow-up, it has no predictive significance.[5]

We found that acute myocardial infarction patients tend to have the highest level of preprocedural and follow-up at 7 days IFN-γ. Despite the common ways of pathomorphological changes in vessels are injured by stent placement there were significant differences IFN-γ. Probably, these findings are explained by the earlier and faster inflammatory initiation of IFN-γ in patients with acute myocardial infarction than in stable angina group.

Kubica *et al*. indicated the effect of TNF-α on the complications prognosis after PCI. They found that combined analysis of C-reactive protein and TNF-α can be an effective approach to predicting clinical restenosis, and the long-term result is significantly dependent on the activation of inflammation during the PCI.[14] Navarro-López *et al*. found that plasma concentrations of TNF-α and IL-6 increase significantly after PCI and remain high for 6 months.[15] However, the study Hoole *et al*., no associations with TNF-α prognosis after myocardial infarction PCI was not found.[16] TNF-β is a part of the family of tumor necrosis factor cytokines that mediate the inflammatory and immune response, can also affect cell death or differentiation and provides an important link between lymphocytes. Several genetic and clinical studies demonstrated the role of TNF-β as a risk factor in the pathogenesis of cardiovascular diseases, including myocardial infarction, aortic aneurysm, and cerebral infarction.[17] IL-6 is a pro-inflammatory cytokine, whose production of cardiomyocytes and mononuclear cells is sharply activated in the post-infarction period. Some authors suppose that IL-6 influences on the acute myocardial infarction prognosis. A number researchers noted that serum IL-6 in myocardial infarction patients occurs more frequently than leukocytosis, elevating of the erythrocyte sedimentation rate, a rise in temperature and suggested using it as a biomarker of myocardial infarction prognosis.[8,19] However, other authors, in particular, Klitkou *et al.* did not find the association between IL-6 and adverse outcomes prognosis for the 6-month follow-up period after PCI.[20] The study Qi *et al*. showed that changes in IL-8 plasma levels are highly predictive in the risk assessing of early complications in patients are underwent PCI.[21,22]

The similar to IFN-γ analysis trend was observed in preprocedural plasma concentrations of IL-6, IL-8, TNF-α, and TNF-β. That may be connected with faster amplification of pro-inflammatory cytokines levels, and their more rapid increasing in the blood of acute myocardial infarction patients than in stable angina patients.

Earlier, in experimental studies were shown that in animals lacking the gene responsible for the production of IL-17 were not chronic hypertensive reaction and endothelium-dependent vasodilation disorders, in contrast to animals with induced hypertension. It was found that IL-17 stimulates the chemotaxis of inflammatory cells, especially neutrophils.[23]

The opposite of previous pro-inflammatory cytokines dynamics was explored in the analysis of IL-17 levels. In stable angina patients directly before PCI and 7 days after the procedure were revealed stably higher concentrations of IL-17. Possibly, this can be explained by the later response of IL-17 in acute myocardial infarction patients to the signal of pathological

vascular remodeling than in stable angina patients in which IL-17 elevating process probably started earlier and faster.

Other cytokines are studied TGF-β1 and TGF-β2. TGF-β1 plays a significant role in the pathogenesis of restenosis and is determined at high levels in the hyperplastic lesions of the intima. In the review, Khan *et al.* were highlighted the impact TGF-β1 and TGF-β2 restenosis prognosis after PCI.[24]

There were identified significantly increased pre- and 7 days TGF-β1 in acute myocardial infarction patients that were not typical to the stable angina group. However, we found markedly elevated levels of TGF-β2 prior PCI and 7 days after in both groups of patients.

We performed multiple logistic analysis on confounding factors, which indicated that subjects who had abnormally higher rate of IFN-γ pre-PCI (OR = 5.21) and 7 days after (OR = 3.84), IL-6 pre-PCI (OR = 1.59), IL-8 pre-PCI (OR = 1.73), IL-17 pre-PCI (OR = 3.07) and 7 days after (OR = 2.34), TNF-α pre-PCI (OR = 1.88), TNF-β pre-PCI (OR = 1.98), as well as to growth factors: TGF-β1 7 days after PCI (OR = 1.82) and TGF-β2 7 days after PCI (OR =2.04) were much more likely to be in "risk" group of restenosis.

Study limitations

We measured inflammatory markers at 2-time points only in the study, hence, were unable to ascertain whether dynamic changes in inflammatory marker levels took place during follow-up and whether it was of relevance in this setting. Our results may be more important as descriptors of a pathophysiological mechanism rather than of practical clinical relevance.

CONCLUSION

Our observations may help to explain findings that inflammation-related endothelial cell and macrophage activation may predict restenosis event in acute myocardial infarction patients and stable angina patients with more intensity in acute myocardial infarction patients. Further study with a bigger sample size is needed to confirm the association of these factors with restenosis after PCI.

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