Plasma levels of C-reactive protein and interleukin-10 predict late coronary in-stent restenosis 6 months after elective stenting

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Abstract

Background: In-stent restenosis (ISR) is one of the major limitations of percutaneous coronary intervention (PCI).

Aim: To evaluate the relationship between the levels of hs-CRP, IL-6, IL-10 and intimal hyperplasia six months after coronary bare metal stent (BMS) implantation.

Methods: The study population consisted of 73 consecutive patients who underwent bare metal stent implantation into narrowed coronary segments. A total of 74 stents were implanted. Angiographic study after six months, together with evaluation of serum level of IL-6 (pg/ml), IL-10 (pg/ml), hs-CRP (µg/ml), fasting insulin (µIU/ml) and glucose (mg%) was performed. Insulin sensitivity was calculated using the HOMA-IR formula. The QCA analysis of stented segments was performed at baseline, after intervention and at six-month follow-up.

Results: Restenosis at six months occurred in 10 patients (13.7%). The mean % diameter stenosis at follow-up was 27.8 ± 19% and late loss was 0.81 ± 0.6 mm. We found a correlation between late loss and serum hs-CRP, IL-6 and IL-10 concentration. There was no correlation between the lipid profiles, insulin levels and HOMA-IR and re-narrowing of the stented segments. Patients with restenosis were characterised by significantly higher serum concentration of CRP (2.04 ± 3.4 vs. 10.38 ± 6.7 µg/ml, p = 0.0036), IL-6 (14.98 ± 8.3 vs. 5.70 ± 5.5 pg/ml, p = 00062), and fasting glucose (184.0 ± 50.5 vs. 107.5 ± 40.4 mg%, p = 0.0051), as well as lower IL-10 levels (1.25 ± 0.6 vs. 4.85 ± 4.9 pg/ml, p = 0.0000). The ROC analysis indicated that CRP (> 2.86 µg/ml), IL-6 (> 6.24 pg/ml) and IL-10 (< 1.7 pg/ml) values predicted the restenosis with reasonable accuracy. A multiple logistic regression model identified CRP and IL-10 levels as independent predictors of restenosis.

Conclusion: We demonstrated that elevated inflammatory markers 6 months after PCI are associated with late angiographic in-stent restenosis.

Key words: restenosis, stent, interleukins, inflammation

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Introduction

In-stent restenosis (ISR) is one of the major limitations of percutaneous coronary interventions (PCI) procedures. The introduction of drug-eluting stents (DES) to clinical practice allowed this phenomenon to be significantly reduced. However, reports of late thrombosis of DES have drawn intense scrutiny of these stents and resulted in a resurgence in bare metal stent (BMS) use in contemporary practice.

Stent implantation is associated with a vessel wall injury resulting in activation of an inflammatory process. Secretion of interleukin-6 (IL-6) by activated macrophages is a powerful stimulus for smooth muscle proliferation, which additionally induces the production of acute phase proteins, including C-reactive protein (CRP) [1, 2].

Pre- and postprocedural high plasma levels of CRP and IL-6 have been found to predict the risk of restenosis [3, 4]. Insulin is another potentially important stimulator of vascular smooth cell proliferation, and diabetes is a well recognised risk factor of ISR [5, 6].

The impact of periprocedural high plasma levels of these markers following successful stent implantation

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on the risk of ISR has been well established, however the effects of persistent elevation of serum levels of CRP, IL-6, and IL-10 on ISR are still unknown.

Our goal was to determine the correlation between serum concentration of inflammatory markers and insulin resistance and the risk of ISR assessed 6 months after successful stent implantation.

Methods

Study group

The study population consisted of 73 consecutive patients enrolled in one centre meeting the following criteria: documented myocardial ischaemia, significant narrowing of coronary vessel (defined as a reduction > 50% of the luminal diameter – visual estimation) undergoing successful implantation of a stent. Exclusion criteria were: restenotic lesions, connective tissue disease, steroid therapy within the preceding 30 days, known contradictions to aspirin, ticlopidine or clopidogrel use, left main disease, chromium or nickel allergy.

The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all patients.

Study design

Two days before the procedure dual antiplatelet therapy with aspirin 150 mg once daily and ticlopidine 250 mg twice daily was started. A bolus of 100 U/kg of heparin was administered during the procedure, and supplemental doses were then given to maintain an activated clotting time > 300 s. The need for predilatation, choice of stent and final balloon size were left at the discretion of the operator. All patients received stainless steel tubular stent (Chopin® – Balton, Poland). Patients continued to receive aspirin 150 mg once daily indefinitely, and ticlopidine twice daily for four weeks.

Clinical and angiographic assessment

Patients were seen in the outpatient clinic 1 and 6 months after PCI. Follow-up coronary angiography was performed six months after the procedure or earlier if symptoms suggestive of coronary restenosis developed before that time.

The angiographic end-points were restenosis rate (defined as an in-stent stenosis ≥ 50% in the follow-up angiography) and late lumen loss [defined as the minimal luminal diameter (MLD) after the procedure minus the value at six-month follow-up]. Angiography was performed in two orthogonal views after intracoronary administration of 200 µg of nitroglycerine. Angiographic variables were assessed before, immediately after the procedure, and at the follow-up; the same two orthogonal views were always obtained. Quantitative angiographic analysis was done using the automated edge-detection system CMS (Medis Medical Imaging Systems). At baseline and at follow-up, the exertional angina was classified according to the Canadian Cardiovascular Society (CCS) classification.

Laboratory assessment

Venous blood samples were obtained on admission to the hospital at the 6-month follow-up visit. Plasma hs-CRP, IL-6, IL-10 and insulin concentrations were measured using the ELISA method (hs-CRP by DSL™, IL-6 and IL -10 by Biotek™, insulin by Tosoh™). Fasting glucose and cholesterol concentrations were determined according to the standard procedures. Homeostasis model assessment-estimated insulin resistance (HOMA), was calculated as fasting serum insulin [µIU/ml] multiplied by fasting serum glucose [mg%] and divided by 22.5.

Statistical analysis

Quantitative data are presented as the mean ± SD, and categorical data as the percentage. The Mann-Whitney test was used to compare the analysed variables between the groups and categorical variables were compared by the χ^2 or Fisher exact test where appropriate. Correlations were assessed by linear regression analysis. Receiver operating characteristic (ROC) curves were constructed for CRP, IL-6 and IL-10 values to determine their accuracy in predicting the restenosis risk (measured by the area under ROC curves, range 0.5-1.0).

Demographic, clinical, procedural, and biochemical variables were tested using univariate and multivariate analysis for their value in predicting binary restenosis. Statistical significance was indicated by a p value < 0.05.

Statistical analysis was performed with Medcalc® statistical software (release 8.0.0.1)

Results

Clinical and angiographic characteristics of patients

In a total of 73 consecutive patients, 74 coronary segments were covered with bare metal stents (Table I). None of the patients developed subacute thrombosis and/or non-Q-wave myocardial infarction (MI) after the stent implantation procedure.

The 6-month follow-up data were available for all patients. Five patients were admitted prior to the planned visit due to symptoms of recurrent ischaemia. In all these cases angiography revealed significant ISR. Restenosis at six months occurred in 10 (13.7%) patients. Five patients who had angiographic restenosis at six months were asymptomatic. None of the patients developed acute MI during the observation period. The mean % diameter stenosis at follow-up was 27.8 ± 19% and late loss was 0.81 ± 0.6 mm. At the 6-month follow-up visit all the patients received statins. Detailed data are shown in Table I.

Table I. Clinical, angiographic and coronary related stenting data

Age [years]	58.8 ± 10		
Gender-male n (%)	51 (68%)		
Smoking n (%)	31 (41%)		
Hypertension, n (%)	50 (67%)		
Hypercholesterolaemia, n (%)	53 (71%)		
Family CAD, n (%)	42 (56%)		
Previous MI, n (%)	14 (19%)		
Diabetes, n (%)	16 (22%)		
*NIDDM** n (%)	-13 (96%)		
*IDDM*** n (%)	-3 (4%)		
Exertional angina (CCS class)*, n (%)**	**baseline**	**follow-up**	
I	9 (12.3%)	25 (34.2%)	
II	20 (27.4%)	34 (46.6%)	
III	23 (31.5 %)	12 (16.4%)	
IV	21 (28.7%)	2 (2.7%)	
Location, n (%)			
LAD	36 (48.6)		
Cx	16 (21.6)		
RCA	22 (22.7)		
Type of lesion, n (%)			
A	34 (45.9)		
B1	21 (28.4)		
B2	9 (12.2)		
C	8 (10.8)		
QCA data	**pre-PCI**	**post-PCI**	**6-month follow-up**
RD [mm]	2.7 ± 0.6	3.0 ± 0.5	2.7 ± 0.5
MLD [mm]	1.01 ± 0.6	2.7 ± 0.5	2.08 ± 0.8
DS (%)	64.4 ± 25	10.6 ± 9	27.8 ± 19
Lesion length [mm]	15.4 ± 8		
Restenosis			10 (13.7%)
LL [mm]			0.81 ± 0.6

Abbreviations: CAD – coronary artery disease, MI – myocardial infarction, LAD – left anterior descending artery, Cx – circumflex artery, RCA – right coronary artery, RD – reference diameter, MLD – minimal lumen diameter, DS – diameter stenosis, LL – late loss

Laboratory data and their correlations with angiographic data

The mean values of plasma hs-CRP, IL-6, IL-10, fasting glucose and insulin concentration 6 months after PCI are shown in Table II.

We found a positive correlation between late loss and concentration of serum hs-CRP and IL-6, and a negative correlation with IL-10 concentration (Figure 1). In patients with restenosis, the levels of CRP and IL-6 were significantly higher and serum concentration of IL-10 significantly lower in comparison to patients without restenosis (Table II). The ROC analysis indicated that CRP, IL-6 and IL-10 values accurately predicted the risk of restenosis occurrence (Figure 2). Patients with values of CRP > 2.86 µg/ml (100% specifity, 84% sensitivity), IL-6 > 6.24 pg/ml (88% specifity, 69% sensitivity) and IL-10 < 1.7 pg/ml (80% specifity, 85% sensitivity) were at significantly higher risk of restenosis than the rest of the study population. Results of univariate logistic analysis are shown in Table III. Multivariate analysis identified IL-10 (OR 0.05; 95% CI, 0.004-0.0597; p = 0.015) and CRP (OR 1.38; 95% CI, 1.07-1.78; p = 0.01) levels as independent predictors of restenosis. There was no correlation between the lipid profiles, insulin levels, HOMA-IR and binary restenosis in stented segments.

Table II. Clinical and biochemical characteristics of subjects with and without restenosis

	Without restenosis	With restenosis	p
Hypertension, n (%)	43 (68%)	9 (90%)	0.2631
Diabetes, n (%)	14 (22%)	7 (70%)	0.006
Hypercholesterolaemia, n (%)	46 (73%)	9 (90%)	0.4336
Cigarette smoking, n (%)	29 (46%)	6 (60%)	0.5005
Family history of CAD, n (%)	32 (51%)	8 (80%)	0.1013
CRP [µg/ml]	2.04 ± 3.4	10.38 ± 6.7	**0.0036**
IL-6 [pg/ml]	5.70 ± 5.5	14.98 ± 8.3	**0.0062**
IL-10 [pg/ml]	4.85 ± 4.9737	1.25 ± 0.6	**0.00001**
Glucose [mg%]	107.5 ± 40.4	184.0 ± 50.5	0.0051
Insulin [uIU/ml]	18.81 ± 13.3	19.90 ± 15.5	0.8533
HOMA	5.15 ± 4.5	7.0 ± 4.0	0.3140
Cholesterol [mg/dl]	192.30 ± 36.9	201.62 ± 45.6	0.4908
Cholesterol-LDL [mg/dl]	117.56 ± 33.4	113.64 ± 45.7	0.7550
Cholesterol-HDL [mg/dl]	43.76 ± 9.8	44.30 ± 12.0	0.8808
Triglycerides [mg/dl]	154.94 ± 68.3	218.80 ± 83.4	**0.0133**

Discussion

Multiple factors can contribute to ISR, and the underlying mechanisms remain elusive. Vascular injury induced by angioplasty (PTCA) may upregulate local cytokine expression leading to release of proinflammatory factors. The cytokines released from activated macrophages, smooth muscle cells, lymphocytes and from cells forming the vascular wall may stimulate neointimal formation [7, 8].

The present study revealed a significant association between extent of neointimal proliferation and plasma levels of cytokines. The plasma concentrations of hs-CRP

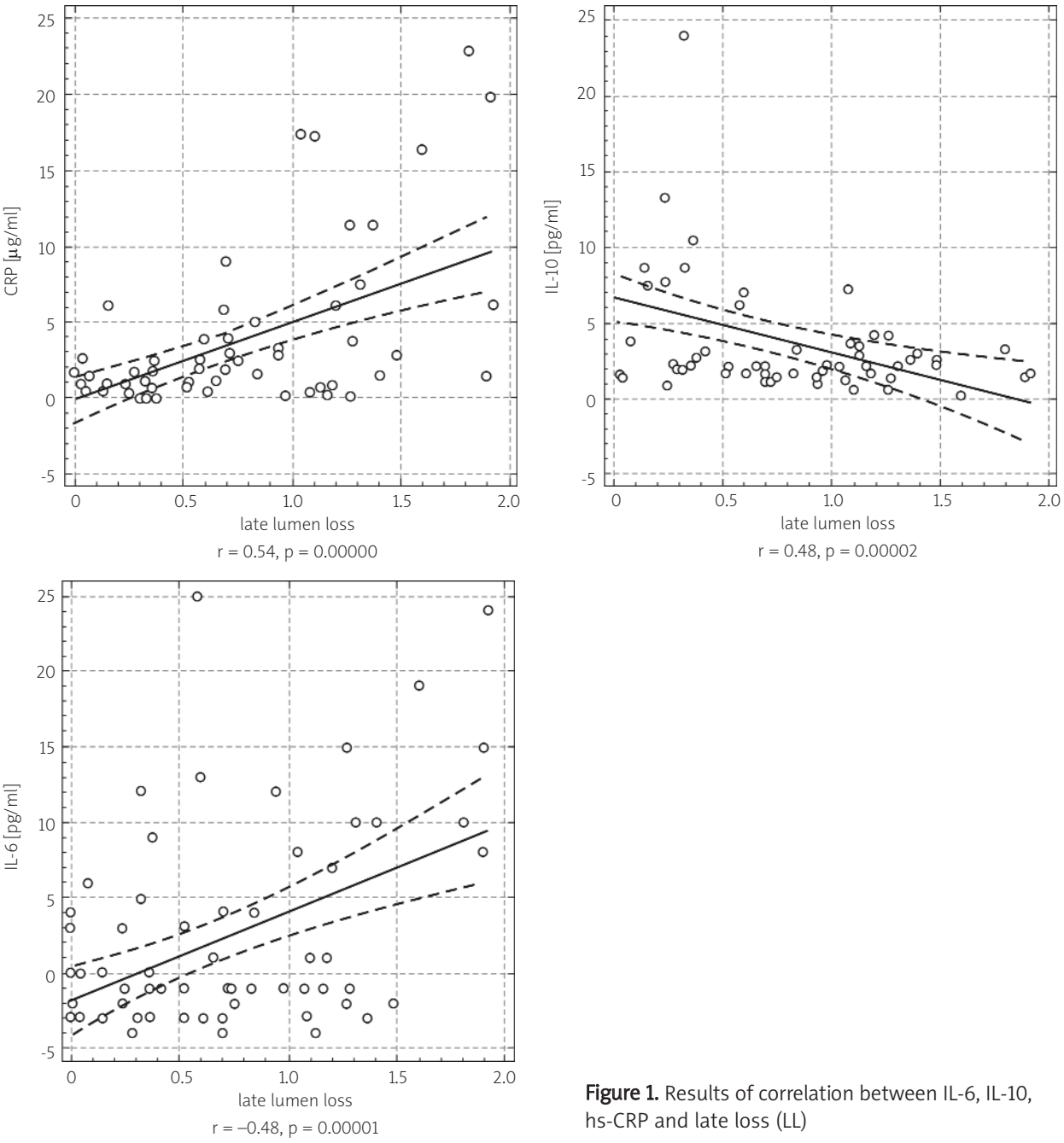

Figure 1. Results of correlation between IL-6, IL-10, hs-CRP and late loss (LL)

and IL-6 were markedly higher in patients with in-stent restenosis than in the non-restenotic population. Patients with restenosis have significantly lower plasma concentration of IL-10 than patients without restenosis. Moreover, there was no association between the serum concentration of insulin and insulin resistance (expressed by HOMA) and late restenosis, although higher fasting glucose concentration was present in patients with ISR.

Previous studies have shown that elevated periprocedural serum levels of inflammatory markers are predictive for occurrence of ISR. For example, Hoyo et al. [9] found a close correlation between changes in IL-6 concentration after PCI in blood samples collected from the coronary sinus directly after PCI and late loss index six months after stent implantation. On the other hand, in another recent study, Dibra et al. [10] showed that baseline CRP did not predict restenosis in 1152 patients undergoing PCI with stenting. Therefore, it seems that the post-intervention rise of inflammatory markers reflects the inflammation response and is more predictive for ISR than absolute levels measured prior to PCI. This theory is supported by a recently published study which showed a close correlation between raised post-intervention CRP levels and angiographic restenosis [11].

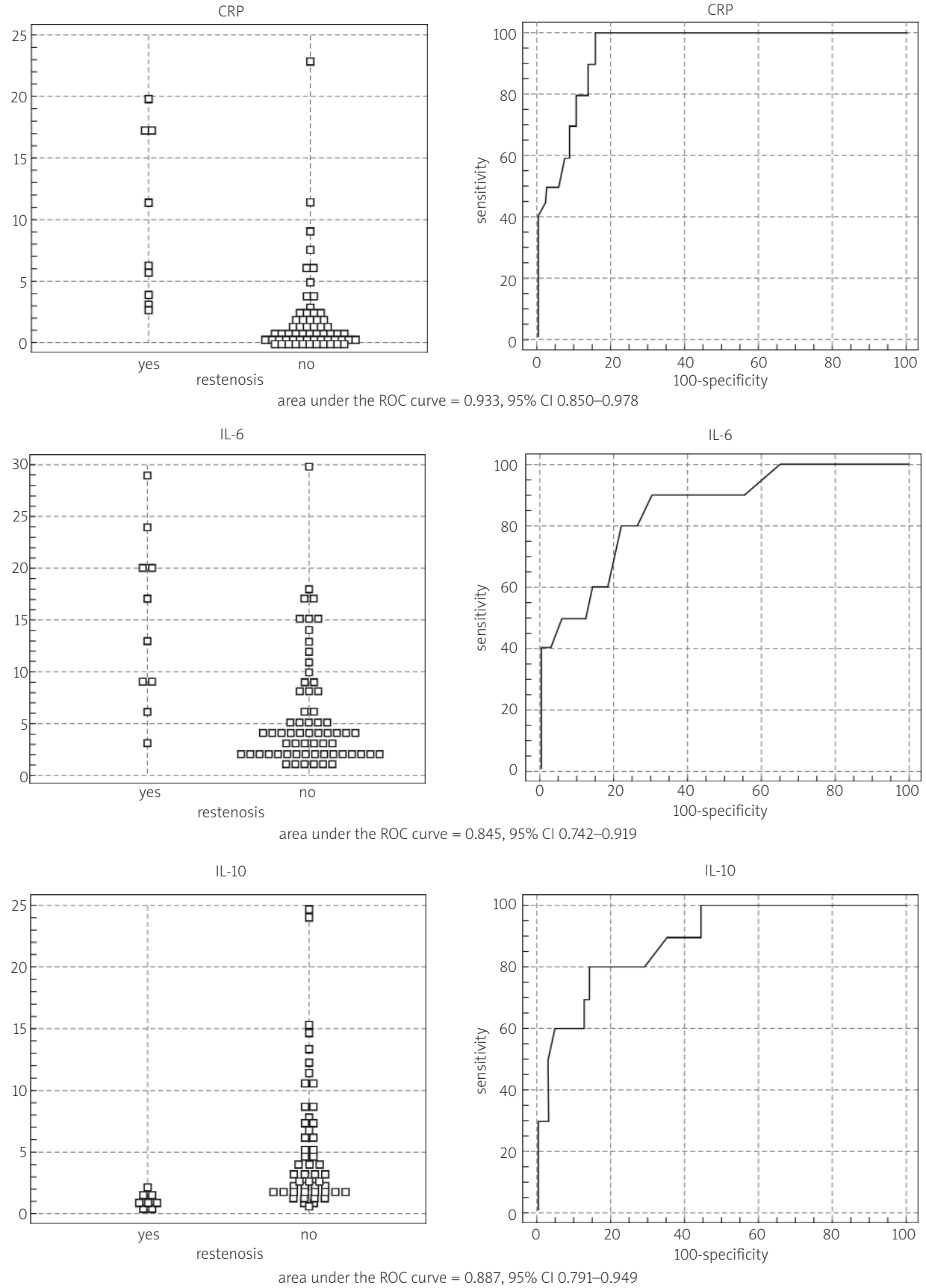

Figure 2. Individual values and ROC curve analysis for CRP, IL-6 and IL-10

Table III. Clinical, angiographic and biochemical univariate predictors of in-stent restenosis

	p	OR (95% CI)
IL-10	0.0058	0.1151 (0.0231–0.5487)
CRP	0.0005	1.2913 (1.1152–1.4455))
IL-6	0.0012	1.1815 (1.0665–1.3089)
HOMA	0.34	1.2014 (0.8242–1.7513)
Insulin	0.5346	0.9659 (0.8236–1.099)
Glucose	0.0072	1.0221 (1.0062–1.0382)
Cholesterol	0.1730	1.0138 (0.9935–1.0344)
Cholesterol LDL	0.7499	0.9968 (0.9775–1.0165)
Cholesterol HDL	0.7628	1.0103 (0.9438–1.0815)
Triglycerides	0.0175	1.1126 (1.0179–1.2369)
Diabetes	0.0053	8.16671 (8642–35.7756)
Current cigarette smoking	0.4154	1.7586 (0.4519–6.8432)
Stent diameter	0.4857	0.2265 (0.0032–15.925)
Stent length	0.0603	1.4033 (0.9794–2.0108)
MLD (post stent implantation)	0.0173	0.0961 (0.0135–0.6841)

In contrast to the results of the study published by Yip et al. [12] we found that elevated serum levels of inflammatory markers (CRP, IL-6) six months after PCI were associated with risk of in-stent restenosis. This high concentration of IL-6 and CRP may be an indicator of the extent of inflammation in atheromatous lesions, and such plaques could be prone to development of ISR. Another explanation of these phenomena is postulated by the results published by Danenberg et al. [13]. They found that non-specific systemic inflammation caused by injected bacterial lipopolysaccharide in an animal model of restenosis significantly increased neointimal formation after stent implantation. It is possible that in our study population, elevated levels of proinflammatory markers were caused not only by a local reaction in the vessel wall, but also by a systemic inflammatory process. However, based on our results it is impossible now to distinguish these two processes. We have no data concerning baseline values (before and after the procedure) and we do not know if this elevation was associated with the PCI procedure.

Interleukin-10 (IL-10) is another cytokine playing a possible role in excessive proliferation of neointima after stent implantation. IL-10 is an anti-inflammatory cytokine endogenously expressed in the human atherosclerotic plaque, with potent inhibitory effects on proinflammatory cytokine synthesis by activated mononuclear cells. In addition to being an inhibitor of monocyte activation, IL-10 may be protective against restenosis by inhibition of cell adhesion molecules, fibrinogen, metalloproteinase-9 and smooth muscle cell proliferation.

We found that high plasma concentration of IL-10 diminishes the risk of ISR. These data are consistent with study results reported by other investigators. For example, Laurent et al. [14] showed that administration of recombinant human IL-10 (rhuIL-10) attenuated in-stent intimal growth by around 50% in an animal restenosis model. 30 days' administration of rhuIL-10 caused major inhibition of IL-1β release by circulating leukocytes and reduced infiltration of the arterial wall by activated macrophages. These results show a very important role of inflammatory processes not only shortly after stent implantation but also in longer follow-up. The ROC analysis of hs-CRP, IL-6 and IL-10 levels showed that in our population we could predict with high probability the risk of ISR by assessing their serum concentration six months after stent implantation.

Impaired glucose tolerance and diabetes mellitus are well known risk factors of exaggerated neointimal proliferation after coronary stent implantation. Some studies indicate that there is a relationship between glycaemic control after stent implantation and subsequent risk of in-stent restenosis [15]. Hyperglycaemia was reported by several authors as an important risk factor of restenosis. It promotes enhanced platelet aggregation, reflected by raised thromboxane A2 levels, and greater endothelial dysfunction, mediated by endothelin-1, a potent smooth muscle cell mitogen.

Hyperglycaemia can also lead to the modification of macromolecules, for example, by forming advance glycation end products (AGEs). They accumulate in the vascular tissue with aging and at an accelerated rate in diabetes. The AGEs are particularly abundant at sites of atherosclerotic lesions. By binding with its receptors (RAGE) these AGE-modified proteins may stimulate the expansion of neointima in response to acute arterial injury, such as that induced by angioplasty.

Our study showed that subjects with ISR had significantly higher fasting glucose levels than patients without restenosis, which may be associated with increased levels of AGE due to chronic elevated concentration of serum glucose. Animal studies have shown that inhibition of RAGE may be very effective in diminishing the vascular response to injury caused by

angioplasty. It may explain the elevated risk of restenosis in the patient subset with chronic hyperglycaemia after coronary stent implantation.

The lack of a significant difference in insulin sensitivity expressed by the HOMA-IR index between investigated groups may be explained by the relatively small number of patients with restenosis or the insufficient ability of the HOMA-IR index to characterise the metabolic status of the study population. For example, Piatti et al. [15] demonstrated that patients with restenosis when compared to non-restenotic showed a small reduction in insulin sensitivity but a large compensatory elevation in insulin response during the oral glucose tolerance test (OGTT), probably reflecting their inability to use insulin more efficiently. In that study, multiple regression analysis confirmed that only the incremental (above basal) insulin excursion during OGTT expressed by the insulin sensitivity index (SI oral), and not the HOMA-IR index, was independently correlated with MLD at follow-up.

Study limitations

The sample size is relatively small, which may have distorted some important variables that only showed a trend towards statistical significance. The sensitivity of intravascular ultrasound may reinforce the claimed association between serum concentration of insulin, glucose and restenosis.

The lack of basal values of investigated biochemical parameters does not allow us to distinguish whether elevated pro-inflammatory markers were related to the index procedure or to a chronic systemic inflammatory process. Therefore it was impossible to determine whether excessive neointimal proliferation is related to vascular wall injury or to systemic inflammation.

Conclusion

Chronic inflammation after stent implantation may be a significant risk factor of ISR. Assessment of hs-CRP, IL-6, and IL-10 levels in subjects followed up after PCI may help to identify those of higher risk. It has to be proved that lowering the non-specific inflammatory process will reduce the risk of ISR.

References

1. Pietersma A, Kofflard M, de Wit LE. Late lumen loss after coronary angioplasty is associated with the activation status of circulating phagocytes before treatment. *Circulation* 1995; 91: 1320-5.
2. Kornowski R, Hong MK, Tio FO, et al. In stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. *J Am Coll Cardiol* 1998; 31: 224-30.
3. Walter DH, Fichtlscherer S, Sellwig M, et al. Preprocedural C-reactive protein levels and cardiovascular events after coronary stent implantation. *J Am Coll Cardiol* 2001; 37: 839-46.
4. Gaspardone A, Crea F, Versaci F, et al. Predictive value of C-reactive protein after successful coronary artery stenting in patient with stable angina. *Am J Cardiol* 1998; 82: 515-8.
5. Piatti P, Di Mario C, Monti LD, et al. Association of insulin resistance, hyperleptinemia, and impaired nitric oxide release with in-stent restenosis in patients undergoing coronary stenting. *Circulation* 2003; 108: 2074-7.
6. Babalik E, Gürmen T, Orhan L, et al. Increased secretion of insulin during oral glucose tests can be a predictor of in stent restenosis in nondiabetic patients. *Catheter Cardiovasc Interv* 2003; 58: 306-12.
7. Kowalski J, Kośmider M, Pawlicki L. Complement activates neutrophils during PTCA procedure in patients with unstable angina pectoris. *Int J Cardiol* 1997; 58: 229-40.
8. Serrano CV Jr, Ramires JA, Venturinelli M, et al. Coronary angioplasty results in leukocyte and platelet activation with adhesion molecule expression. *J Am Coll Cardiol* 1997; 29: 1276-83.
9. Hojo Y, Ikeda U, Katsuki T, et al. Interleukin 6 expression in coronary circulation after coronary angioplasty as a risk factor for restenosis. *Heart* 2000; 84: 83-8.
10. Dibra A, Mehilli J, Braun S, et al. Association between C-reactive protein levels and subsequent cardiac events among patients with stable angina treated with coronary artery stenting. *Am J Med* 2003; 114: 715-22.
11. Dibra A, J Mehilli SB, Hadamitzky H, et al. Inflammatory response after intervention assessed by serial C-reactive protein measurements correlates with restenosis in patients treated with coronary stenting. *Am Heart J* 2005; 150: 344-50.
12. Yip HK, Wu CJ, Yang CH, et al. Serial changes in circulating concentrations of soluble CD40 and C-reactive protein in patients with unstable angina undergoing coronary stenting. *Circulation* 2004; 69: 890-5.
13. Danenberg HD, Welt FG, Walker M, et al. Systemic inflammation induced by lipopolysaccharide increases neointimal formation after balloon and stent injury in rabbits. *Circulation* 2002; 105: 2917.
14. Laurent J, Feldman LJ, Aguirre L, et al. Interleukin-10 inhibits intimal hyperplasia after angioplasty or stent implantation in hypercholesterolemic rabbits. *Circulation* 2000; 101: 908-16.
15. Piatti PM, Di Mario C, Monti LD, et al. Association of insulin resistance, hyperleptinemia, and impaired nitric oxide release with in-stent restenosis in patients undergoing coronary stenting. *Circulation* 2003; 108: 2074-81.

Czy stężenie interleukiny 10 i białka C-reaktywnego 6 miesięcy po zabiegu przezskórnej angioplastyki wieńcowej pozwala przewidzieć wystąpienie restenozy w stencie?

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Streszczenie

Wstęp: Restenoza w stencie jest jednym z głównych ograniczeń zabiegów przezskórnej śródnaczyniowej angioplastyki wieńcowej (ang. *percutaneous transluminal coronary angioplasty*, PTCA).

Cel: Ocena związku osoczowego stężenia białka C-reaktywnego oznaczanego metodą o wysokiej czułości (hs-CRP), interleukin 6 i 10 (Il-6, IL-10) z nasileniem przerostu neointimy w stencie metalowym (BMS) w okresie 6 miesięcy od zabiegu PTCA.

Metody: Badana populacja składała się z 73 kolejnych osób z objawową chorobą niedokrwienną serca, u których wykonano zabieg implantacji stentu w miejsce istotnego zwężenia naczynia wieńcowego. Średni wiek badanych osób wynosił 58,8 ± 10 lat, cukrzycę stwierdzono u 22% chorych, nikotynizm – u 41%, hipercholesterolemię – u 71%, obciążenie rodzinne – u 56%. Protokół badania zakładał implantację stentu do zmian *de novo* w naczyniach natywnych, 6-miesięczną obserwację kliniczną oraz kontrolną koronarografię po 6 miesiącach. U każdego chorego wykonywano 3 angiogramy docelowej zmiany – jeden bezpośrednio przed interwencją, drugi bezpośrednio po zakończeniu zabiegu i trzeci podczas 6-miesięcznej kontroli. Wszystkie angiogramy były analizowane przez niezależnego badacza metodą cyfrowej automatycznej analizy ilościowej przy użyciu programu Medis. Podczas 6-miesięcznej kontroli oznaczono u wszystkich chorych osoczowe stężenie IL-6 (pg/ml), IL-10 (pg/ml), hs-CRP (µg/ml), insuliny (µIU/ml) i glukozy (mg%). Insulinowrażliwość kalkulowano na podstawie formuły HOMA-IR.

Wyniki: Łącznie implantowano 74 stenty. Restenoza w stencie w okresie 6-miesięcznej obserwacji wystąpiła u 10 (13,7%) chorych. Średnie zwężenie ocenianych segmentów naczyniowych wynosiło 27,8 ± 19%, późna utrata światła 0,81 ± 0,6 mm. Analiza statystyczna ujawniła istotną korelację pomiędzy późną utrata światła w obrębie stentu a osoczowym stężeniem hs-CRP, Il-6 i IL-10. Podobnych zależności nie znaleziono dla stężenia insuliny, lipidów oraz wskaźnika HOMA-IR. Chorzy z istotnym nawrotem zwężenia w stencie charakteryzowali się podwyższony stężeniem hs-CRP (10,38 ± 6,7 *vs* 2,04 ± 3,4 µg/ml, p = 0,0036), IL-6 (14,98 ± 8,3 *vs* 5,70 ± 5,5 pg/ml, p = 00062) glukozy na czczo (184,0 ± 50,5 *vs* 107,5 ± 40,4 mg%, p = 0,0051) oraz niższym stężeniem IL-10 (1,25 ± 0,6 *vs* 4,85 ± 4,9 pg/ml, p = 0,0000). Analiza krzywych ROC ujawniła, iż stężenie CRP > 2,86 µg/ml, IL-6 > 6,24 pg/ml i IL-10 < 1,7 pg/ml pozwala przewidzieć wystąpienie restenozy. Wieloczynnikowa logistyczna analiza regresji wskazała stężenie CRP i IL-10 jako niezależne predyktory restenozy.

Wnioski: Podwyższone stężenie osoczowych markerów zapalnych 6 miesięcy po zabiegu PTCA zwiększa ryzyko wystąpienia angiograficznej restenozy, podczas gdy stężenie IL-10 koreluje z zahamowaniem proliferacji neointimy.

Słowa kluczowe: restenoza, stent, interleukiny, zapalenie

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