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Late Lumen Loss After Coronary Angioplasty Is Associated With the Activation Status of Circulating Phagocytes Before Treatment

Anneke Pietersma, Marcel Kofflard, L. Elly A. de Wit, Theo Stijnen, Johan F. Koster, Patrick W. Serruys, Wim Sluiter

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Abstract

Background The purpose of this pilot study was to identify biological risk factors for restenosis after percutaneous transluminal coronary angioplasty (PTCA) to predict the long-term outcome of PTCA before treatment.

Methods and Results To investigate whether blood granulocytes and monocytes could determine luminal renarrowing after PTCA, several characteristics of these phagocytes were assessed before angioplasty in 32 patients who underwent PTCA of one coronary artery and who had repeat angiograms at 6-month follow-up. The plasma levels of interleukin (IL)-1 β , tumor necrosis factor- α , IL-6, fibrinogen, C-reactive protein, and lipoprotein(a) before angioplasty were assessed as well. We found that the expression of the membrane antigens CD64, CD66, and CD67 by granulocytes was inversely associated with the luminal renarrowing normalized for vessel size (relative loss) at 6 months after PTCA, while the production of IL-1 β by stimulated monocytes was positively associated with the relative loss. Next, these univariate predictors were corrected for the established clinical risk factors of dilation of the left anterior descending coronary artery and current smoking, which were statistically significant classic predictors in our patient group. Only the expression of CD67 did not predict late lumen loss independent of these established clinical risk factors. Multiple linear regression analysis showed that luminal renarrowing could be predicted reliably ($R^2=.65$; $P<.0001$) in this patient group on the basis of the vessel dilated and only two biological risk factors that reflect the activation status of blood phagocytes, ie, the expression of CD66 by granulocytes and the production of IL-1 β by stimulated monocytes.

Conclusions The results of the present study indicate that activated blood granulocytes prevent luminal renarrowing after PTCA, while activated blood monocytes promote late lumen loss. To validate this new finding, further study in an independent patient group is required.

angioplasty leukocytes prognosis risk factors stenosis

Percutaneous transluminal coronary angioplasty (PTCA) is a nonsurgical treatment of obstructive coronary artery disease (CAD), which, despite its high initial success rate of 90%, is compromised by the occurrence of restenosis.¹ To improve the long-term outcome of PTCA, the identification of risk factors for restenosis seems crucial.

The pathophysiology of restenosis has not yet been elucidated.² It has been suggested that activated blood monocytes may contribute to this process by the production of cytokines and growth factors.^{1 3 4} The activation of granulocytes that occurs during PTCA, through the release of proteinases and oxygen-derived free radicals, may have a potential bearing on the development of restenosis as well.⁵

Circulating phagocytes are thought to reflect the in vivo state of the immune defense.⁶ The different phagocyte functions are mediated through specific membrane receptors. Members of the integrin class of adhesion receptors (CD11/CD18) function in the interaction of phagocytes with the endothelial lining,⁷ whereas receptors for the Fc moiety of IgG (CD16, CD32, and CD64) are involved in the pinocytosis of immune complexes and the phagocytosis of antibody-coated particles.⁶ The expression of these membrane receptors can be stimulated by inflammatory mediators. For example, interferon gamma induces de novo expression of the high-affinity Fc receptor CD64 on granulocytes.⁸ *N*-Formylated peptides increase the expression of the receptor for activated complement C3bi (CD11b/CD18) on both granulocytes and monocytes.⁶ Activated granulocytes also express increased levels of CD66 and CD67.⁹ In addition to the stimulated expression of membrane receptors, inflammatory mediators are capable of inducing a primed state in monocytes. In these primed cells, the stimulated production of cytokines is enhanced.¹⁰ Furthermore, stable, genetically determined interindividual differences in the secretion of interleukin (IL)-1 β and tumor necrosis factor (TNF)- α by lipopolysaccharide (LPS)-stimulated monocytes have been demonstrated.^{11 12}

To study whether circulating granulocytes and monocytes might contribute to the process of restenosis, we investigated whether luminal renarrowing after PTCA is associated with the activation status of circulating phagocytes.

Methods

Patient Group

Thirty-four patients gave informed consent for the study and were included according to the following criteria: (1) stable or unstable angina pectoris (not refractory to medical treatment); (2) one culprit lesion responsible for the complaints; and (3) successful PTCA according to angiographic and clinical parameters.¹³ The mean age of the patients (26 men and 8 women) was 54.2 \pm 8.3 years. The severity of the anginal complaints was classified according to the New York Heart Association: 8 patients were in class II, 17 were in class III, and 9 were in class IV. Nine patients had unstable angina (pain at rest and refractory to medical treatment). The target vessel was the left anterior descending coronary artery (LAD) in 17 patients, the left circumflex coronary artery (LCx) in 7 patients, and the right coronary artery (RCA) in 10 patients. Fifteen patients had suffered from myocardial infarction in the past, 6 patients had previously undergone PTCA, and in 2 patients coronary artery bypass graft surgery was performed before entrance into the study. The study population included 2 patients with diabetes mellitus, 22 patients with hypercholesterolemia (excluding 3 not known), and 21 patients with a family history of CAD. Sixteen patients were smokers; the 18 nonsmokers included patients who had stopped smoking at least 6 months before PTCA.

Protocol

Sheaths were inserted into the arterial and venous femoral vessels. To exclude any effect of day-to-day variation in the biological risk factors under study, 30 mL of blood was collected from the venous sheath immediately before treatment, anticoagulated with 0.2% EDTA, and kept at 4°C. Coronary angioplasty was performed with a steerable, movable guide-wire system via the femoral route. Details regarding the procedure used in our catheterization laboratory have been reported.^{13 14} Angiograms were obtained before and directly after PTCA. Six months after the procedure, the patients were scheduled for follow-up angiography. The angiograms before and after PTCA and at 6-month follow-up were analyzed with the Coronary Angiographic Analysis System as described previously.^{13 14} When serious complaints of angina recurred before the 6-month follow-up, intercurrent coronary angiography was performed. If restenosis of the dilated segment was established, PTCA was repeated and the angiogram at that time (n=6 patients) was considered to be the end point for the study. Of the 34 patients who met the inclusion criteria, 32 repeat angiograms were obtained; 2 patients refused follow-up.

Luminal Loss

The continuous variable luminal loss is defined as the change in minimal lumen diameter (MLD) during follow-up normalized for vessel size according to the following equation: relative loss (RLOSS) = [(postintervention MLD–follow-up MLD)/vessel size] × 100%, and reflects the degree of luminal renarrowing. The vessel size is the value of the reference diameter function at the minimal position of the obstruction as previously described.¹⁴

Reagents

The monoclonal antibodies (mAb) used in the flow cytometric analysis of membrane antigen expression were mAb B-B15 directed against CD11a, mAb 44 against CD11b, mAb 3.9 against CD11c, mAb B-H8 against CD15, mAb YFC 120.5 against CD16, and mAb B-F1 against HLA-DR, all obtained from Serotec. mAb IV.3 directed against CD32 and mAb 32.2 directed against CD64 were obtained from Medarex Inc. mAb CLB gran10 against CD66 and mAb B13.9 against CD67 were obtained from the Central Laboratory for Blood Transfusion. mAb 5193, which recognizes HLA-DR₄, was from C-six Diagnostics Inc. The fluorescein conjugate of the hexapeptide *N*-formyl-Nle-Leu-Phe-Nle-Tyr-Lys, which is recognized by the receptor for *N*-formylated peptides on phagocytes, was obtained from Molecular Probes.

Flow Cytometric Analysis of Membrane Antigens

The binding of mAb to the cell surface was quantified by fluorescence-activated cell sorting (FACStar, Becton Dickinson). A buffy-coat fraction was obtained by centrifugation of the blood sample at 850g for 10 minutes. Contaminating erythrocytes were lysed in ammonium chloride solution consisting of 155 mmol/L NH₄Cl, 10 mmol/L NaHCO₃, and 0.1 mmol/L EDTA. Next, leukocytes were washed with PBS (pH 7.4) consisting of 140 mmol/L NaCl, 1.5 mmol/L KH₂PO₄, 8.1 mmol/L Na₂HPO₄·2H₂O, and 2.7 mmol/L KCl, centrifuged at 400g for 10 minutes, and resuspended in PBS with 2% fetal calf serum (FCS) and NaN₃ (1 mg/mL). Leukocytes (4×10⁵ cells) were incubated with mAb for 30 minutes. Leukocytes were washed four times and then incubated with fluorescein isothiocyanate (FITC)-conjugated anti-mouse or anti-rat antibodies for 30 minutes, after which the cells were washed four times and fixed with 1% paraformaldehyde in PBS with 2% FCS for 24 hours at 4°C. Monocyte and granulocyte populations were separated by gating on forward and perpendicular light scatter. Antigen expression is presented as specific linear fluorescence intensity (FI).

Cytokine Release

To assess the capacity of monocytes to produce cytokines in vitro, monocytes were isolated from the buffy-coat fraction, which was reconstituted with PBS to 20 mL, layered on top of a Lymphoprep gradient (Nycomed), and centrifuged at 800g for 10 minutes at room temperature. The fraction containing the mononuclear leukocytes was washed with PBS. Next, the erythrocytes were lysed in ammonium chloride solution, and the remaining mononuclear leukocytes were washed once with ammonium chloride solution and once with PBS and resuspended in RPMI (Flow Laboratories) with 2% FCS. The percentage of monocytes in this fraction was determined from cytopspin preparations and in general amounted to 25%. Cells (6.3×10⁵) were transferred into 96-well culture plates (Costar) and incubated at 37°C in a humidified environment of 5% CO₂/95% air in the presence or absence of 5 ng/mL LPS according to the method described by Endres et al.¹⁵ After 24 hours, supernatants were collected and stored at –70°C until analysis of IL-1β, IL-6, and TNF-α by an enzyme immunoassay (EIA, Medgenix). During this incubation period, cell viability as determined by trypan blue dye exclusion did not decrease significantly and was >95%. Cytokine release was expressed in picograms per 10⁴ monocytes.

Fibrinogen

High- and low-molecular-weight fibrinogen levels were determined with an EIA as previously described¹⁶ and expressed in grams per liter.

C-Reactive Protein

C-Reactive protein (CRP) was measured with an EIA (Dakopatts) and expressed in milligrams per liter.

Lipoprotein(a)

The lipoprotein(a) [LP(a)] concentration in plasma was determined with a radioimmunoassay (Pharmacia) and expressed in milligrams per liter.

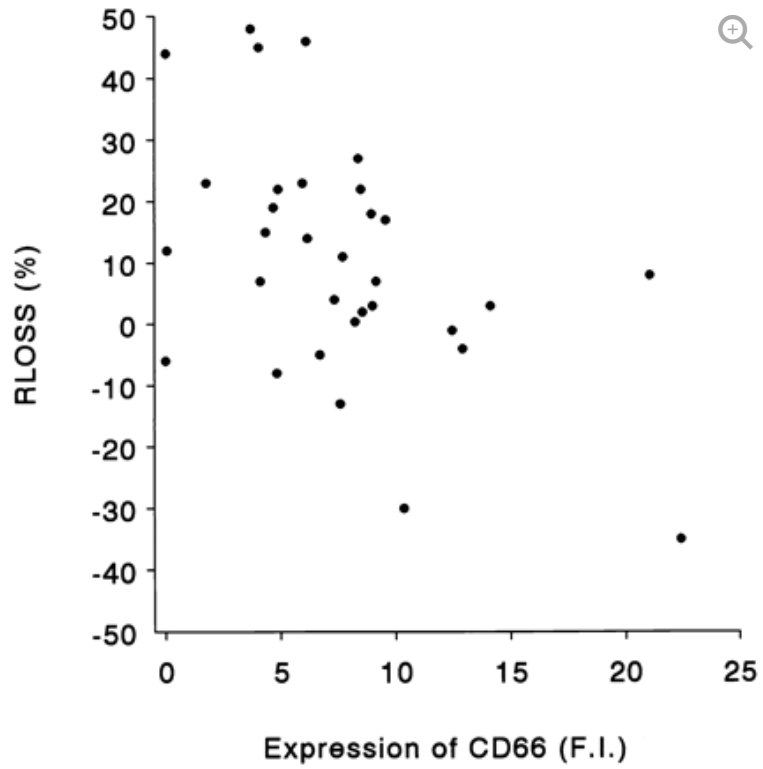
Statistical Analysis

The variation in duplicate measurements (intra-assay variation) did not exceed 10%. The strength of the association of late lumen loss with each of the potential biological risk factors described in the previous sections was assessed by linear regression analysis. Each new finding should be considered suggestive and needs validation in an independent patient group. No attempt was made to correct for multicomparisons, since it is not clear whether such a procedure is an improvement here.^{17 18} Since the expression of HLA-DR₄ is a characteristic cells may or may not have, this variable is treated as a categorical one (no expression=0, expression=1). Each variable that proved to be statistically significant ($P<.05$) in the univariate regression analysis was assessed by multiple linear regression analysis to establish whether it was a risk factor independent of established clinical risk factors. The established risk factors included the vessel dilated ($P=.001$; $\beta=.5495$) (LAD=1, other=0) and current smoking ($P=.024$; $\beta=.3988$) (yes=1, no=0). Other risk factors reported in the literature were not statistically significant in the present study, ie, family history of CAD ($P=.072$; $\beta=.3275$), diabetes mellitus ($P=.120$; $\beta=.2807$), hypercholesterolemia ($P=.332$; $\beta=.1867$), unstable angina ($P=.363$; $\beta=.1665$), hypertension ($P=.569$; $\beta=.1046$), angina class ($P=.674$; $\beta=.0772$) (class I/II=0, class III/IV=1), patient age ($P=.826$; $\beta=.0405$) (age <65 years=0; ≥ 65 years=1), and sex ($P=.882$; $\beta=.0274$). The new independent risk factors, together with the established clinical risk factors, were used in a stepwise multiple linear regression analysis with P values for inclusion and elimination set at .05 and .10, respectively, to build a model that predicts the luminal renarrowing.

Results

Variables Predictive for Late Lumen Loss

To investigate whether circulating phagocytes could contribute to luminal renarrowing after PTCA, we determined the activation status of circulating phagocytes before treatment and assessed its association with the degree of luminal renarrowing (RLOSS) at 6 months after PTCA. We identified several new univariate predictors of late lumen loss, the expression of CD64, CD66, and CD67 by granulocytes, and the stimulated production of IL-1 β by monocytes (Table↓; Figs 1↓ and 2↓). Next, the relative importance of these new univariate predictors with respect to established clinical risk factors was assessed. Multivariate regression analysis showed that three of the new univariate predictors were statistically significant independent predictors for luminal renarrowing after PTCA (Table↓). CD66, an antigen expressed by granulocytes only, showed an inverse association with the relative luminal renarrowing at 6-month follow-up. This also was the case for the expression of CD64, the high-affinity receptor for immunoglobulin G (IgG). Furthermore, the RLOSS was positively associated with the amount of IL-1 β produced by monocytes in response to LPS. No other variables under study, including the plasma levels of LP(a), IL-1 β , TNF- α , and fibrinogen, showed a significant relation with late lumen loss (Table↓).



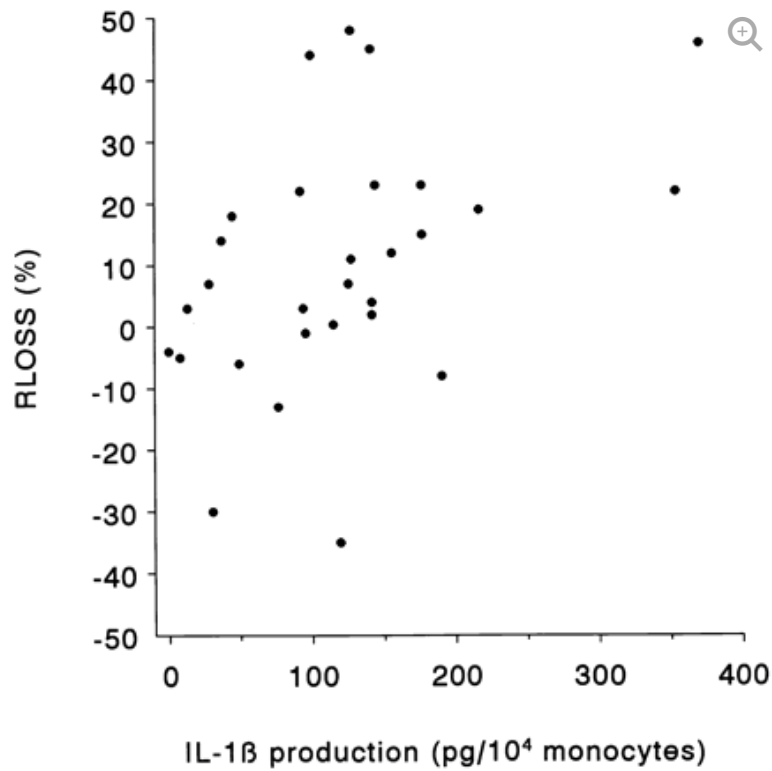
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Figure 1.

Scatterplot showing association of the expression of the membrane antigen CD66 (specific linear fluorescence intensity [F.I.]) by blood granulocytes obtained from patients before percutaneous transluminal coronary angioplasty with the degree of luminal renarrowing expressed as relative loss (RLOSS) at 6 months after treatment, which can be described by the equation $y=25.25-1.92x$ ($R^2=.25$; $P=.004$).



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Figure 2.

Scatterplot showing association of the production of interleukin-1 β (IL-1 β) (pg/10⁴ monocytes) by blood monocytes obtained from patients before percutaneous transluminal coronary angioplasty with the degree of luminal renarrowing expressed as relative loss (RLOSS) at 6 months after treatment, which can be described by the equation $y = -2.34 + 0.10x$ ($R^2 = .19$; $P = .017$). The monocytes were stimulated by lipopolysaccharide (5 ng/mL) in vitro for 24 hours.

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Table 1.

Correlates of Late Lumen Loss

Variable	Univariate		Multivariate		n		
	P	Regression Coefficient	P	Regression Coefficient			
		b		β		b	β
Membrane antigens expressed by							
Granulocytes							
CD66 ¹	.004	-1.92	-.4984	.016	-1.44	-.3760	32

Variable	Univariate			Multivariate			n
	P	Regression Coefficient		P	Regression Coefficient		
		b	β		b	β	
CD67	.014	-1.65	-.4363	NS			31
CD64	.029	-3.91	-.3926	.044	-3.11	-.3125	31
CD11c	.054	-2.50	-.3434				32
fMLP ²	.075	-4.39	-.3247				32
HLA-DR ₄ ³	.128	-11.69	-.2795				30
CD16	.133	0.11	.3309				22
CD15	.385	0.12	.1589				32
CD11b	.499	-0.22	-.1240				32
CD32	.539	0.18	.1126				32
HLA-DR ³	.598	-0.32	-.0985				30
CD11a	.679	-0.17	-.0761				32
Monocytes							
CD15	.077	-1.14	-.3174				32
fMLP ²	.117	-5.89	-.2874				31
CD64	.318	-0.22	-.1824				32
HLA-DR ₄ ³	.361	-6.54	-.1670				32
CD11a	.417	0.12	.1486				32
CD11b	.561	-0.14	-.1067				32
CD16	.749	-0.15	-.0722				22
CD11c	.825	-0.08	-.0406				32
CD32	.948	-0.02	-.0119				32
HLA-DR ³	.996	-0.00	-.0010				32

Variable	Univariate			Multivariate			n
	P	Regression Coefficient		P	Regression Coefficient		
		b	β		b	β	
Inflammatory mediators							
Produced by monocytes							
IL-1 β ⁴	.017	0.10	.4415	.025	0.08	.3329	29
TNF- α ⁴	.080	0.14	.3303				29
IL-6 ⁴	.126	0.01	.2908				29
IL-1 β ⁵	.165	0.07	.2558				31
IL-6 ⁵	.355	0.01	.1721				31
TNF- α ⁵	.443	0.04	.1430				31
Plasma levels of							
CRP	.280	-0.74	-.1969				32
TNF- α	.501	0.25	.1234				32
Fibrinogen	.554	2.62	.1086				32
IL-6	.642	-0.17	-.0854				32
IL-1 β	.803	0.07	.0458				32
LP(a)	.965	<0.01	.0080				32

IL indicates interleukin; TNF, tumor necrosis factor; and CRP, C-reactive protein.

1 CD indicates cluster of differentiation. From Knapp W, Dörke B, Gilks WR, Rieber EP, Schmidt RE, Stein H, von dem Borne AEGKr, eds. *Leucocyte Typing IV. White Cell Differentiation Antigens*. Oxford, UK: Oxford University Press; 1989.

2 The receptor for N-formylated peptides.

3 HLA-DR indicates human leukocyte-associated antigens, class II, type DR.

4 Cytokine production of monocytes stimulated with 5 ng/mL lipopolysaccharide for 24 hours.

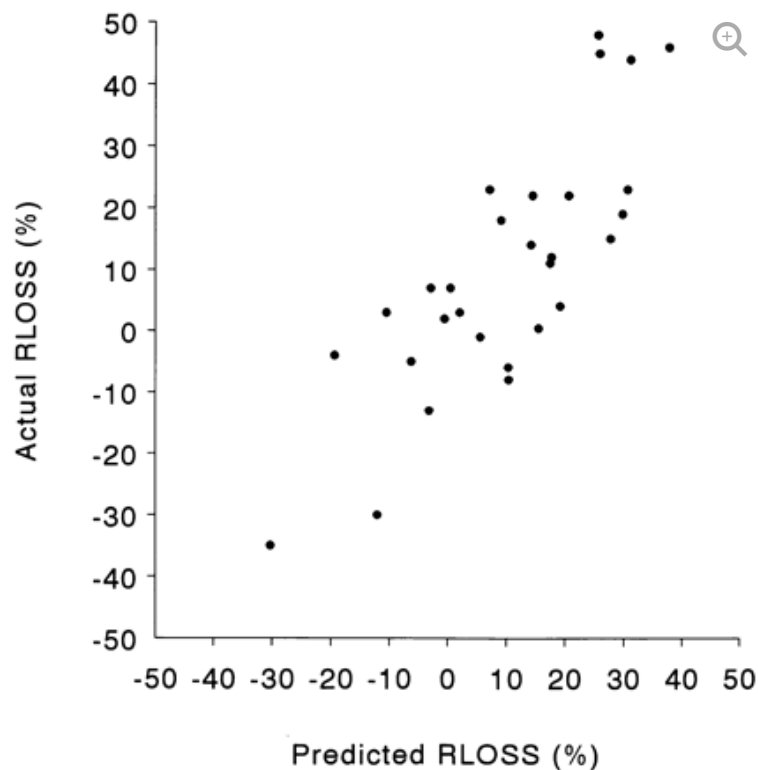
5 Cytokine production of unstimulated monocytes.

Multiple Regression Model to Predict Late Lumen Loss Before PTCA

To obtain a model that predicts the RLOSS before treatment, the relative contributions of the three new independent predictors of late lumen loss and the two established risk factors were analyzed by multiple regression using the stepwise procedure. This analysis showed that the RLOSS can be predicted from the expression of the activation marker CD66 (median, 7.8 FI; range, 0.0 to 22.4 FI) by granulocytes, the production of IL-1 β (median, 119.4 pg/10⁴ monocytes; range, 0.0 to 368.9 pg/10⁴ monocytes) by stimulated monocytes, and the vessel dilated (LAD versus RCA or LCx) according to the following equation:

($R^2=.65$; $P<.0001$), with standard errors of 6.3, 0.5, 0.03, and 4.8 for the constant and the regression coefficients, respectively. The standardized regression coefficients (β) of CD66, IL-1 β , and LAD amounted to -0.4671 , 0.3055 , and 0.4328 , respectively.

Although it is fundamentally not correct but merely an attempt to show what could be expected of the model in an independent patient group, in Fig 3↓ the relation between the predicted luminal diameter loss, calculated on the basis of this equation, and the observed relative loss is presented for each of our present patients. It is clear, however, that definitive conclusions about the predictive value of the model can be obtained only in an independent patient group.



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Figure 3.

Scatterplot showing relation between the predicted degree of luminal renarrowing expressed as relative loss (RLOSS) at 6 months after treatment, calculated according to the equation (see also under "Results") $RLOSS=6.8-2.0(CD66)+0.07(IL-1\beta)+17.3(LAD)$, and the observed RLOSS for each patient in our study group. Although this figure is fundamentally not correct, it is offered merely to illustrate the equation.

Discussion

The major finding of the present study is that the activation status of phagocytes is associated with luminal renarrowing after PTCA. Predictors for the degree of late lumen loss include characteristics of monocytes (IL-1 β production) and granulocytes (expression of CD64 and CD66). These new predictors and two established clinical risk factors (vessel dilated and current smoking) were used to build a model by multiple linear regression analysis that predicts the RLOSS before treatment from (1) the production of IL-1 β by stimulated monocytes, (2) the expression of the activation marker CD66 by granulocytes, and (3) the vessel dilated (LAD versus LCx and RCA).

The amount of IL-1 β a monocyte can secrete upon stimulation is genetically determined^{11 12} and depends on the primed state of this type of phagocyte.^{10 19} It is assumed that IL-1 is an important determinant of intimal hyperplasia.²⁰ In vitro studies have shown that IL-1 stimulates the thrombogenicity of endothelial cells and elevates levels of platelet-derived growth factor (PDGF)-A and PDGF-B chain transcripts in endothelial cells.^{21 22} Since PDGF has been shown to stimulate the migration of smooth muscle cells into the intima,²³ this mechanism might be relevant. We found no relation between the degree of luminal renarrowing after PTCA and the spontaneous release of IL-1 β by blood monocytes in vitro or the IL-1 β level in the plasma before treatment. However, the capacity of blood monocytes to synthesize IL-1 β upon stimulation in vitro was associated with the late outcome after PTCA. This led us to hypothesize that the patients' blood monocytes, in a response to vascular injury, may infiltrate the lesion, become stimulated, and depending on their capacity, secrete IL-1 β that promotes intimal hyperplasia. Why only the stimulated production of IL-1 β and not of IL-6 and of TNF- α by monocytes is associated with relative lumen loss is a matter of speculation. In the cascade model for restenosis, Libby et al²⁰ proposed that macrophages, which are a major source of IL-1, by the early acute cytokine generation evoke a secondary cytokine and growth factor response from other types of cells in the lesion, including smooth muscle cells and endothelial cells that might establish a positive, self-stimulatory autocrine and paracrine feedback loop, amplifying and sustaining the proliferative response.

We found an inverse association of relative luminal renarrowing with the expression of the high-affinity receptor for IgG (CD64) by granulocytes. Granulocytes express this antigen only after activation.⁸ However, CD64 did not significantly predict late lumen loss independent of the other multivariate predictors in our patient group. CD66, an antigen expressed exclusively by granulocytes, is considered to be an activation marker as well.⁹ Recent evidence suggests that the CD66 antigens function as presenter molecules of the sialylated Lewis(x) antigen that binds to endothelial leukocyte adhesion molecule-1 expressed by activated endothelial cells.²⁴ The important finding of the present study was that the degree of late lumen loss was low if the expression of CD66 by granulocytes was high. This suggests that activated granulocytes in fact could serve a protective role in the process of luminal renarrowing after PTCA. In a way, this was an unexpected finding, since activated granulocytes are supposed to aggravate tissue damage by their potentially destructive armamentarium.⁵ However, the invasion of granulocytes at sites of injury is a normal response to injury that facilitates tissue repair. Could this be a likely initial response to PTCA as well? A number of independent findings indeed point in that direction. First, in the cuffed rabbit carotid artery model of restenosis, one of the earliest events is the infiltration of granulocytes into the lesion.²⁵ The first 2 to 3 days of the inflammatory phase after PTCA may be crucial for the ultimate outcome.³ Second, granulocytes relax human (internal mammary) artery.²⁶ And finally, some years ago it was found that granulocytes could have a significant biological role in preventing thrombosis, rather than augmenting thrombosis, by the generation of 6-keto-prostaglandin-E₁ to inhibit platelet aggregation and by providing 13-hydroxy-octadecadienoic acid in the absence of endothelial cells to inhibit platelet adhesion.²⁷ Since local thrombosis after PTCA might be a key event in the cascades of cytokine/growth factor production by macrophages and smooth muscle cells,²⁰ a protective role of granulocytes could therefore be anticipated.

Recently it has been shown that granulocyte activation occurs directly after angioplasty.⁵ Our data indicate that the activation status of granulocytes before treatment may be crucial in limiting luminal renarrowing at 6 months after PTCA.

Taken together, we conclude that the degree of late lumen loss might be predicted before treatment from the amount of IL-1 β produced by stimulated monocytes, the expression of CD66 by granulocytes, and the vessel treated by PTCA. If our model reflects some major aspects of the process of lumen loss after PTCA, interventional therapy could be directed to the function of granulocytes and monocytes. The failure of a multicenter trial conducted to determine whether corticosteroids infused before

PTCA could reduce the rate of restenosis²⁸ indicates that broad-spectrum drugs are not a first choice and that timing to allow granulocytes to perform their beneficial role could be important. However, the model presented here first needs to be validated in an independent and larger patient group to establish its prognostic value.

Acknowledgments

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