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Original Article

Predictors of Inappropriately Rapid Coronary Lesion Progression in Patients Undergoing Percutaneous Coronary Interventions

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ABSTRACT

Background: Patients undergoing percutaneous coronary intervention (PCI) may experience rapid atherosclerotic plaque progression in nontreated vessels that is unlikely to result from natural de novo atherosclerosis. We hypothesize that intra-lesion bleeding plays a central role in this process. The aim of this study is to investigate the factors that may contribute to accelerated narrowing in coronary diameter.

Methods: We reviewed 65 interventional procedures and their consequent staged PCIs and mapped the coronary tree into 16 segments (as divided by the American Heart Association), grading the percentage of stenosis in each segment and spotting the rapidly pro-

RÉSUMÉ

Contexte : Les patients qui subissent une intervention coronarienne percutanée (ICP) peuvent présenter une progression rapide de plaques d'athérosclérose dans des vaisseaux non traités, phénomène qui n'est probablement pas le résultat d'une athérosclérose *de novo* naturelle. Nous formulons l'hypothèse qu'un saignement intralésionnel jouerait un rôle central dans ce processus. Cette étude vise à explorer les facteurs qui pourraient contribuer à l'accélération de la réduction du diamètre coronarien.

Méthodologie : Nous avons étudié 65 interventions et les ICP en plusieurs étapes qui s'en étaient suivies, ainsi que divisé l'arbre coronarien en 16 segments (conformément à la segmentation de

Ischemic heart disease is currently one of the most studied pathologies. With millions of new cases per year, understanding the mechanisms involved in the evolution of ischemic heart disease has become crucial to the tailoring of a precise treatment strategy, which is one of the biggest therapeutic challenges at present.

Atherosclerosis begins to form during infancy and develops progressively through the entire lifespan.[1] From the buildup of fatty streaks by accumulation of lipoproteins in the vessel wall, and the formation of foam cells, to the resulting atherosclerotic plaque, numerous biological processes take place, and the cross-talk among these mechanisms determines the progression of the atherosclerotic lesion.[2,3] Additional mechanisms that may contribute to lesion progression include microcalcification, extracellular matrix breakdown, and intraplaque hemorrhage (IPH).

The process of IPH is intricate and potentially can impact plaque morphology in several ways. For example, bleeding into the plaque on its own expands the volume of the lesion.[4] In addition, the mechanism by which hemorrhage destabilizes the plaque likely results from the action of hemoglobin released from red blood cells at the hemorrhage site.[5] Hemoglobin is a potent proinflammatory agent by virtue of its ability to promote formation of radical oxygen species (ROS), which eventually accelerate atherosclerosis formation.[6]

During sequential coronary angiographies, we occasionally notice an exaggerated rapid progression of coronary lesions that cannot be explained by the natural development of the atherosclerotic plaque (Figs. 1 and 2). No universal definition of rapid progression of atherosclerosis has been established. However, most of the studies describing this phenomenon suggest that progression within a few months[7] constitutes an unusually fast atherosclerotic plaque progression. In this preliminary

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gressing lesions. Demographic, procedural, and laboratory data were recorded and analyzed.

Results: For the lesions that progressed rapidly in the time period between angiographies, the administration of eptifibatide intraprocedurally was associated with rapid progression of coronary lesions. Moreover, an increased white blood cell count prior to the index procedure was also associated with a trend toward rapid plaque progression.

Conclusions: In this hypothesis-generating study, treatment with a IIb/IIIa inhibitor in the index PCI was associated with an accelerated short-term progression of some of the nontreated lesions, suggesting that this mode of anti-aggregation therapy could facilitate plaque hemorrhage and consequent acceleration of coronary atherosclerosis in eroded plaques.

l'American Heart Association), afin d'évaluer le pourcentage de sténose dans chaque segment et de repérer les lésions qui progressaient rapidement. Les données démographiques et celles relatives aux interventions et aux résultats de laboratoire ont été consignées et analysées.

Résultats : En ce qui concerne les lésions qui avaient progressé rapidement durant l'intervalle entre les angiographies, l'administration d'éptifibatide lors de l'intervention semblait être un facteur contributif. De plus, un nombre accru de leucocytes avant l'intervention initiale a également été associé à une évolution rapide des plaques.

Conclusions : Dans le cadre de cette étude servant à émettre une hypothèse, le traitement par un inhibiteur de la glycoprotéine IIb-IIIa lors de l'ICP initiale a été associé à une accélération de la progression à court terme de certaines lésions non traitées, ce qui laisse croire que ce mode de traitement antiagrégant pourrait favoriser les hémorragies intraplaques et l'accélération de l'athérosclérose coronarienne dans les plaques érodées.

study, our aim was to investigate demographic, clinical, and procedure-related predictors of rapid atherosclerotic progression in patients undergoing percutaneous coronary intervention (PCI).

Methods

We retrospectively collected data regarding patients who underwent staged PCI procedures in our institution. The time interval between the 2 procedures was 3 to 6 weeks. Two blinded certified interventional cardiologists who were not familiar with the study aims visually graded the percentage of stenosis in all 16 sections (using nomenclature specified by the American Heart Association[8]) of the coronary tree for each procedure. The delta in progressed lesions was calculated (delta = [percentage of stenosis in the second angiography] - [percentage of stenosis in the first angiography]). A delta of 20% or more in segmental stenosis between the 2 procedures was defined as an angiographic progression. A point worth noting is that most of the studies done in this field define a true/significant progression as a $\geq$ 10% decrease of lumen diameter in a preexisting lesion with $\geq$ 50% stenosis, or a $\geq$ 30% decrease of lumen diameter in a preexisting lesion with $<$ 50% stenosis.[9,10] Those definitions are considered to be expert opinion only, rather than official definitions. We used a 20% decrease in lumen diameter as a mean of the 2 definitions.

All the segments defined as having angiographic progression by both interventional cardiologists were regarded as having a true progression, and the patients were termed "progressors." Patients who did not have angiographic or true progression were designated as "non-progressors." Selected clinical and laboratory parameters, as well as chronic medications for each patient, were recorded. The laboratory parameters were mainly those that are associated with inflammatory response, and they were taken during the first hospitalization (first PCI).

The neutrophil-to-lymphocyte ratio (NLR) is a biomarker that indicates the balance between 2 types of white blood cells—neutrophils and lymphocytes. Neutrophils are part of the immune system's first line of defense and are typically associated with acute inflammation; lymphocytes play a crucial role in adaptive immunity and are involved in chronic inflammation and immune regulation.

The NLR has been recognized as an indicator of systemic inflammation and has gained attention for its usefulness in assessing various medical conditions, including atherosclerosis. Atherosclerosis is a chronic inflammatory disease characterized by the buildup of plaques in the arteries. In recent studies, a higher NLR has been associated with accelerated atherosclerosis formation and progression. Elevated NLR values suggest an imbalance between proinflammatory neutrophils and anti-inflammatory lymphocytes, indicating an enhanced inflammatory response. This imbalance can contribute to the development and progression of atherosclerosis through several mechanisms.

First, neutrophils play a role in the early stages of atherosclerosis by promoting endothelial dysfunction, which is a key event in plaque initiation. They adhere to the endothelial cells, release inflammatory mediators, and recruit other immune cells, leading to the recruitment of monocytes and the formation of foam cells—a hallmark of early atherosclerotic lesions.

Second, a high NLR has been associated with an increased release of proinflammatory cytokines and chemokines. These inflammatory molecules can promote the recruitment of immune cells, including monocytes, into the arterial wall, exacerbating the inflammatory response and contributing to plaque formation.

Third, lymphocytes, particularly T-cells, have an essential role in regulating the immune response and maintaining immune homeostasis. A decrease in the number of lymphocytes, as indicated by an elevated NLR, may result in impaired immune regulation and a diminished ability to counteract inflammation. This situation can lead to a chronic proinflammatory state, favoring the progression of atherosclerosis.

Overall, an elevated NLR suggests an imbalance between proinflammatory and anti-inflammatory immune cells, indicating an enhanced systemic inflammatory response. This chronic inflammation contributes to accelerated atherosclerosis formation and progression by promoting

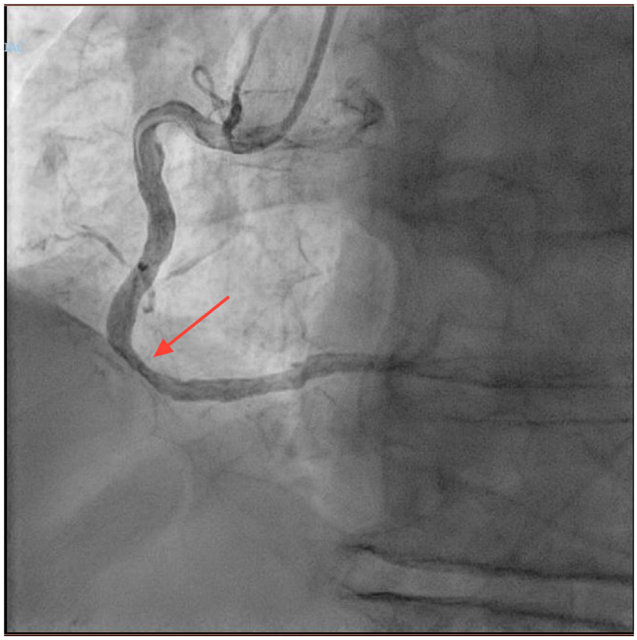

Figure 1. Left anterior oblique view of the right coronary artery showing 50% stenosis in the first angiography of a patient; eptifibatide was infused during this procedure.

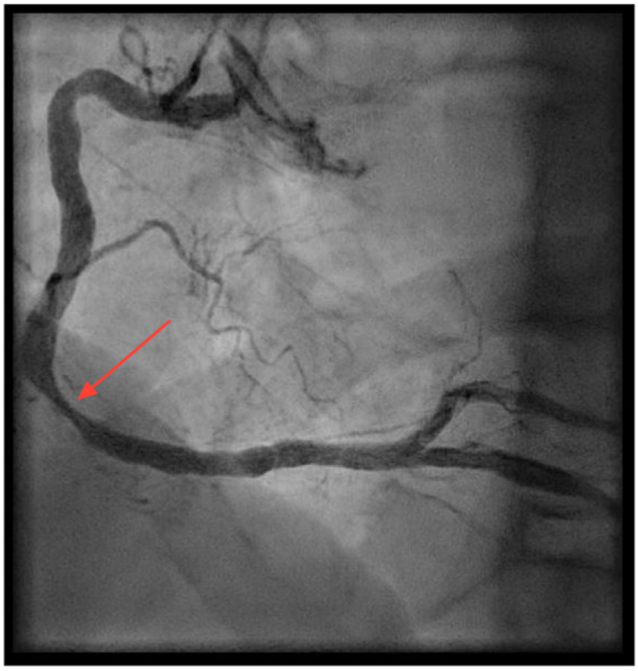

Figure 2. Left anterior oblique view of the right coronary artery showing 80% stenosis in the second angiography of the same patient as in Figure 1, 4 weeks later.

endothelial dysfunction, increasing the release of inflammatory molecules, and impairing immune regulation. Therefore, monitoring the NLR may serve to provide a useful biomarker in assessing the risk and progression of atherosclerosis.

The chronic medications retrieved were those that are associated with a higher bleeding tendency and were prescribed to be used chronically after the first PCI. The indication for eptifibatide infusion was "no-reflow," per the European Society of Cardiology Guidelines on Myocardial Revascularization, [11] with recommended dosages. Finally, all evaluated parameters were compared for the "progressor" vs "non-progressor" groups.

Patient population; inclusion and exclusion criteria

This study was conducted on all patients who underwent staged PCI in our institution. The inclusion criterion for this study was being a patient who underwent staged PCI as described above.

Inclusion criteria. All patients who underwent staged PCI initially were included in this study.

Exclusion criteria. The following patients were excluded in order to eliminate those who were not suitable for this study:

(i) patients who underwent coronary artery bypass grafting;
(ii) patients with a period of > 6 weeks or < 3 weeks between the 2 angiographies; and
(iii) patients who experienced serious adverse events, such as stroke, malignant arrhythmia, resuscitation, or dissection of an artery.

The exclusion criteria were implemented to ensure that the results of this study would be as accurate as possible, and to eliminate patients who might have a negative impact on the results of this study.

Statistical analysis

Categorical and nominal variables were reported as number and percentage, and continuous variables were reported as mean and standard deviation, or as median and range. Continuous variables between the various study groups were tested for normality by the Shapiro-Wilk test, and when a non-normal distribution was found, nonparametric tests were performed. The Mann-Whitney test was performed to compare 2 groups, When the distribution was normal, a *t*-test was used. Categorical and nominal variables were analyzed using Pearson's χ^2 test or the Fisher exact test.

Univariate and multiple logistic regression analyses were done to identify predictors of lesion progression. Calibration was tested with the Hosmer and Lemeshow test; a significance value of the Hosmer-Lemeshow statistic of $<$ 0.05 represents poor fit. The model discrimination was evaluated with C-statistics, as calculated from the receiver operating characteristic curve of the predicted probabilities of lesion progression from 3 different models. High discrimination represents high sensitivity and specificity of the test.

The results were considered to be significant when the *P*-value was < 0.05. Analyses were performed with SPSS27 (IBM, Armonk, NY) and R Core Team (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

After patients were excluded who either underwent coronary artery bypass grafting or experienced peri-procedural complications, a total of 55 patients were included in the study. Among them, 19 patients were classified as progressors, and 36 patients were classified as non-progressors. However, among the 36 patients in the non-progressor group, 5 were deemed to be "non-true" progressors based on the differentiation of their deltas.

Initially, a total of 297 non-culprit lesions with at least 20% stenosis were observed. During the follow-up period, 29 of these lesions showed progression, accounting for a progression rate of 9.76%. The average age in the non-progressor group was 69 years, slightly higher than the average age of 67.5 years in the progressor group, but this difference was not statistically significant. Although the non-progressor group had more female patients, this difference did not reach statistical significance. All background diseases show no significant differences between the 2 groups, except for diabetes mellitus, which had a higher prevalence in the non-progressor group (P-value of 0.072, approaching significance). The incidence of chronic diseases was twice as high in the non-progressor group, but this difference also did not reach statistical significance (see Table 1).

Most of the laboratory parameters assessed in the study were within the normal reference range, with 2 exceptions. In the progressor group, the NLR had a median value of 4.22, which is generally considered higher than the normal range and indicates a proinflammatory state. Additionally, the erythrocyte sedimentation rate in the non-progressor group was elevated beyond the normal range.

Although statistically significant differences were found in the white blood cell count ($P = 0.031$) and the absolute neutrophil count ($P = 0.039$), a point worth noting is that both median values were still within the normal reference range (see Table 2).

The level of use of anticoagulant medication was found to be relatively low, with no significant difference observed between the 2 groups. Similarly, no significant difference occurred in the level of use of oral antiplatelet drugs. However, the prevalence of administration of eptifibatide was significantly different between the 2 groups ($P = 0.023$; see Table 3).

In certain instances, the antiplatelet medication was switched between the 2 angiographies, such as transitioning from prasugrel to clopidogrel, based on the patient's clinical condition or due to adverse reactions. In such cases, both medications were recorded in our database.

Clinical outcomes

Progression of coronary lesions was observed in 34.5% of the patients (n = 19); of these, 10 patients showed progression in only 1 site, 8 patients showed progression in 2 sites, and only 1 patient showed progression in 3 distinct sites (Table 4).

We used univariate logistic regression in order to isolate the variable that has the most impact on the final outcome of lesion progression. The analysis revealed that only eptifibatide was associated with rapid lesion progression (odds ratio, 6.41; $P = 0.016$). To find confounding variables, we used a few models of multivariate logistic regression; we found that when combining eptifibatide with white blood cell count, the odds ratio decreased to 5.6; moreover, eptifibatide was combined with the NLR or the absolute neutrophil count, the odds ratio decreased to 4.9 (Table 5).

Discussion

Chronic inflammation, usually in the context of chronic inflammatory diseases such as chronic kidney disease, or any type of rheumatic disease predispose patients to accelerated atherosclerosis.[12,13] The speed of progression usually is discussed in terms of years, but in comparison with healthy subjects, this progression can occur over a period as short as a couple of years.[14] In the setting of a very rapid progression (several weeks), as was tested herein, a more dramatic and vigorous process such as intra-plaque bleeding must be taken into consideration. The mechanism of the bleeding into atherosclerotic coronary lesions contributing to vessel occlusion was suggested back in the 1930s by Wartman,[15] with case series describing intra-mural bleeding combined with thrombosis of the coronary artery as a cause of death in 6 patients. More recent studies have described the relationship between IPH, resulting in presence of erythrocytes within atherosclerotic lesions, and promotion of lipid accumulation, stimulating excessive influx of macrophages and further buildup of atherosclerotic plaque.[16,17] As an acute event, IPH by its nature either directly causes a rapid plaque expansion or createa a hostile environment that triggers accelerated inflammation in situ.[18,19]

The proposed mechanism of bleeding into the vascular wall and the sequela leading to aggravation in plaque burden was the primal assumption in our study, but what is the index facilitator of this process? As mentioned earlier, while building the methodology for this study, we focused on medications that usually are related to excessive bleeding, such as anticoagulants and antiplatelet medications that are routinely used,

Table 1. Baseline characteristics

Characteristic	Non-progressors 36	Progressors 19	p
Age, y, mean (SD)	69.08 (10.07)	67.47 (11.70)	0.596
Female	8 (22.2)	1 (5.3)	0.141
Previous PCI	12 (33.3)	3 (15.8)	0.213
Valvular disease	6 (16.7)	4 (21.1)	0.723
PVD	7 (19.4)	3 (15.8)	1.000
CRF	8 (22.2)	1 (5.3)	0.141
Smoker	13 (36.1)	4 (21.1)	0.360
Diabetes	22 (61.1)	6 (31.6)	0.072
HTN	25 (69.4)	10 (52.6)	0.348
HF	8 (22.2)	7 (36.8)	0.401
Obesity	9 (25.0)	5 (26.3)	1.000
COPD	5 (13.9)	1 (5.3)	0.653
Chronic disease	7 (19.4)	2 (10.5)	0.473

Values are n (%), unless otherwise indicated. Items on list indicate presence of characteristic.

COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; HF, heart failure; HTN, hypertension; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation.

Table 2. Laboratory parameters

Lab parameter	Non-progressors	Progressors	
n	36	19	*p*
HB (g/dl)	13.61 (1.80)	14.49 (1.67)	0.116
WBC (K/ul)	7.73 [6.30, 8.90]	8.85 [8.19, 11.70]	**0.031**
RBC (M/ul)	4.53 (0.69)	4.81 (0.40)	0.144
PLT (K/ul)	200.00 (62.54)	222.12 (55.08)	0.246
Neut.abs (K/ul)	5.05 [3.68, 6.01]	6.11 [4.82, 9.67]	**0.039**
Lymp.abs (K/ul)	2.10 (1.11)	1.91 (0.88)	0.548
NL.ratio	2.68 [1.44, 4.28]	4.22 [2.03, 5.76]	0.102
ESR (mm/h)	36.80 (33.35)	9.40 (8.21)	0.223
CRP (mg/dL)	0.66 [0.33, 1.56]	0.30 [0.17, 1.21]	0.200

Values are mean (standard deviation) or median [interquartile range], unless otherwise indicated. Bold indicates significance.

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HB, Lymp.abs, absolute lymphocyte; Neut.abs, absolute neutrophil; NL.ratio, neutrophil-to-lymphocyte ratio; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

which, in our opinion, could trigger bleeding or erosion in potentially vulnerable coronary plaques.

Our results are consistent with those of Li et al.'s study from 2014, which demonstrated that patients have an increased tendency toward bleeding into existing plaque while using coumarin-type anticoagulants, but not while using aspirin or clopidogrel.[20] Similarly, eptifibatide, which has never been assessed in the clinical setting of intra-plaque bleeding, is known to be more potent than other antiplatelet agents and thus has a higher potential to promote intraplaque bleeding.[21-23] Moreover, the increased tendency of patients to bleed post-eptifibatide infusion eventually led to the downgraded IIb guideline recommendation that it be used only as a bailout treatment.[11]

Indeed, our study showed that the use of eptifibatide increased the odds of promoting rapid plaque progression by 6.3, and thus, its infusion during coronary intervention can serve as the initiating event for the process of IPH in this particular clinical setting.

In another study, Virmani et al. attributed the tendency to bleed into atherosclerotic plaque to the leakiness of the vasa vasorum and plaque fissuring.[4] The disruption of the normal activity of platelets by eptifibatide may impact the body's ability to properly repair the endothelium and regulate the leakiness of the vasa vasorum, thereby causing accumulation of erythrocytes inside existing plaque. Additionally, eptifibatide may promote exaggerated entry of erythrocytes through fissured or eroded non-culprit plaques. The finding that "vulnerable" patients have multiple inflamed plaques that explain recurrent events suggests that this particular population is likely to experience rapid acceleration of eptifibatide-inducible plaque hemorrhage and rapid plaque progression.

The notion that certain processes or medications can lead to IPH may change the way we approach certain patients; Michel et al. found that IPH enhances plaque vulnerability and independently can increase the tendency for plaque rupture,[24] and if these combined results are to be verified in a dedicated event-driven clinical trial, they may have an impact on the decision to initiate IIB3A inhibitors in the event of a thrombus-rich plaque during PCI.

Table 3. Medication

Medication	Non-progressors	Progressors	
n	36	19	*P*
Eptifibatide	3 (8.3)	7 (36.8)	**0.023**
Aspirin	26 (72.2)	15 (78.9)	0.749
Clopidogrel	29 (80.6)	11 (57.9)	0.140
Ticagrelor	1 (2.8)	1 (5.3)	1.000
Prasugrel	9 (25.0)	8 (42.1)	0.318
Dabigatran	0 (0)	0 (0)	NA
Rivaroxaban	2 (5.6)	0 (0.0)	0.539
Apixaban	2 (5.6)	2 (10.5)	0.602

Values are n (%), unless otherwise indicated. Bold indicates significance. Medications on list indicate patients were taking this medication.

NA, not applicable.

Table 4. Number of progressed lesions per patient

Progressed lesions, #	n	%
0	36	65.5
1	10	18.2
2	8	14.5
3	1	1.8

Limitations

This study was conducted at a single centre with a relatively small number of patients. Our original theory led us to investigate only medications that can potentially lead to an increased tendency toward bleeding; other medication groups should be studied also. We did not use intravascular imaging techniques to demonstrate IPH. Optical coherence tomography potentially can help to identify this process,[25,26] but its use is controversial.[18]

Conclusion

In this hypothesis-generated study, we were able to identify an association between use of eptifibatide during PCI and accelerated advancement of coronary lesions. The suggested explanation for this progression is the activation of IPH triggered by the IIBIIIA inhibitor. These findings highlight the importance of taking a cautious approach in selecting medications administered during coronary interventions. Further research, especially studies focused on clinical factors,

Table 5. Univariate analysis for notable parameters

	Univariate models			
			95% CI for OR	
Variable	Sig.	OR	Lower	Upper
Eptifibatide	**0.016**	**6.417**	1.42	28.91
WBC	0.163	1.166	0.94	1.45
Neut.abs	0.083	1.240	0.97	1.58
NL.ratio	0.089	1.220	0.97	1.53
PLT	0.238	1.006	1.00	1.02
Lymp.abs	0.534	0.815	0.43	1.55

Bold indicates significance.

CI, confidence interval; Lymph.abs, absolute lymphocyte; Neut.abs, absolute neutrophil; NL.ratio, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLT, platelet; Sig., significance; WBC, white blood cell.

is necessary to fully support these findings so they can be implemented into practical guidelines.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Kaplan Medical Center (KMC-008-22, 7 March 2022).

Patient Consent

Informed consent was waived as this study was a deidentified retrospective review.

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Disclosures

The authors have no conflicts of interest to disclose.

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