Angiographic Geometric Predictors of Myocardial Infarction Are Not Associated with Ultrasonographic Markers of Plaque Vulnerability

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Objective

Some angiographic geometric features of coronary lesions have recently been described as independent predictors of myocardial infarction. The purpose of this study was to correlate these geometric markers with intravascular ultrasound findings known to be associated with greater vulnerability to plaque rupture.

Methods

A total of 30 patients with stable coronary syndromes and de novo lesions (31 lesions) underwent coronary angiography and intravascular ultrasound (IVUS). For each lesion, angiographic geometric features (degree of symmetry, degree of stenosis, lesion length, and outflow angle) were correlated with the following ultrasound variables: type of plaque (soft, fibrous, mixed, or calcified), plaque burden and remodeling index.

Results

Mean lesion length was 9.2 ± 4.4 mm, percent stenosis was 50.0% to 89.0% (mean 67.7 ± 12.1%), inflow angles ranged from 8.48º to 48.78º (mean 24.0 ± 11.4º), outflow angles ranged from 8.30º to 53.03º (mean 23.8 ± 11.7º), and the symmetry index ranged from 0 to 1 (mean 0.56 ± 0.32). On ultrasound evaluation, frequency of soft or calcified plaques, positive remodeling, and magnitude of plaque burden were not associated with any angiographic geometric feature ($p > 0.05$ for all analysis).

Conclusion

Angiographic geometric features that predispose to acute occlusion do not correlate with IVUS morphologic and quantitative findings associated with plaque vulnerability.

Key words

Coronary atherosclerosis; coronary angiography, intravascular ultrasonography.

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Acute coronary syndromes represented by unstable angina, acute myocardial infarction (AMI), and sudden death have been extensively associated with coronary atherothrombosis[1]. Plaque rupture or erosion with endothelial denudation seems to be a final common pathway, resulting in local thrombus formation and acute lumen obstruction[2]. However, the specific mechanisms involved in triggering this process are still unknown.

Postmortem studies have shown that "culprit" atherosclerotic plaques of patients with acute coronary syndromes have distinct characteristics when compared to "nonculprit" plaques or plaques of patients with stable chronic disease. These findings led to the concept that some plaque characteristics may render it more prone to disruption, such as large plaque burden, positive remodeling, and high lipid content, typical of the so-called vulnerable plaque[3]. Likewise, in clinical trials that studied the artery wall by intravascular ultrasound, increased frequency of plaques with those characteristics has been described in patients with unstable angina or myocardial infarction[4,5,6].

Identification of vulnerable plaques in patients with atherosclerotic disease has emerged as a field of growing interest in clinical research[7]. Although still considered a gold standard for diagnosing coronary disease, conventional angiography has not been commonly listed as a potential method for detecting vulnerable plaques. Nevertheless, previous studies have shown that certain geometric characteristics of the lesion derived from angiographic "lumenogram" have a high predictive value for future myocardial infarction[8,9]. In angiograms performed within 36 months preceding an acute myocardial infarction, culprit lesions were found to be longer, more symmetrical, more severely stenotic, and with steeper outflow angle than control lesions. Arterial wall and plaque characteristics related to these morphological risk factors are yet to be described. The present study was designed to evaluate IVUS characteristics associated with angiographic risk factors for acute myocardial infarction.

Methods

The study population consisted of 30 consecutive patients (31 lesions) with stable coronary syndromes referred for percutaneous treatment of *de novo* lesions in native vessels owing to symptoms or evidence of myocardial ischemia and who underwent intravascular ultrasound before any therapeutic intervention between December 1997 and January 1999.

Exclusion criteria were recent episode of acute coronary syndrome, angiographic evidence of thrombus or plaque rupture, and ostial or bifurcation lesion. The study protocol was approved by the institution's Ethics Committee and is in accordance with the Helsinki Declaration. All patients signed an informed consent before entering the trial.

Angiographic analysis - Quantitative coronary angiography: Angiograms were analyzed in the view that showed the coronary lesion with higher degree of stenosis and after intracoronary administration of isosorbide mononitrate 10 mg. Quantitative coronary angiography (QCA) was performed off-line using an automated edge-detection algorithm (CAAS II system, Pie Medical, Maastricht, The Netherlands), and the catheter tip was used for calibration. Minimal luminal diameter (MLD), interpolated reference diameter (IRD), percent stenosis, and lesion length were measured[10].

Angiographic geometric analysis - Inflow and outflow angles were measured from the luminal diameter function curve of quantitative coronary angiography measurement. Mean lesion inflow angle was defined as average slope of the luminal diameter function curve between the most stenotic point (i.e. MLD) and proximal boundary of the stenotic segment. Likewise, mean outflow angle was defined as average slope of the luminal diameter curve between the MLD and distal boundary of the lesion (Figure 1)[11]. Vessel wall contours estimated by angiographic lumenogram were used to evaluate the plaque symmetry index, calculated as percent ratio between plaque areas on both sides of stenosis. Lesions with symmetry index between 0 and 0.5 were classified as eccentric, and those greater than 0.5, as concentric.

IVUS imaging - All ultrasound examinations were performed before any therapeutic intervention. A commercially available IVUS system equipped with a 30 to 40 MHz transducer (Boston Scientific Corporation/ SciMed) was used, and images were acquired during automatic pullback at 0.5 mm/s. Qualitative analyses were performed according to previously established criteria12,13. Calcific plaques were brighter than the adventitia and resulted in acoustic shadowing. Fibrous plaques (hyperechoic) were as bright as or brighter than the adventitia, but with no acoustic shadowing. Soft plaques (hypoechoic) were less bright than the adventitia. When there was no dominance, the plaque was classified as mixed. Quantitative IVUS evaluations were performed at the most stenotic site and at the proximal and distal reference sites, selected as the cross-sections within 5 mm from the lesion, but before a major side branch.

The following measurements were obtained by planimetry: external elastic membrane (EEM) cross-sectional area and lumen cross-sectional area. Plaque area was calculated as the EEM area minus lumen area. Plaque burden was calculated as percent ratio between the plaque area and EEM area. The remodeling index was calculated as the ratio between EEM area at the proximal reference site and EEM area at the lesion site. Positive remodeling was defined as remodeling index greater than 1.05[14].

Statistical analysis - Categorical variables were presented as frequencies and compared by Fisher's exact test. Continuous variables were presented as

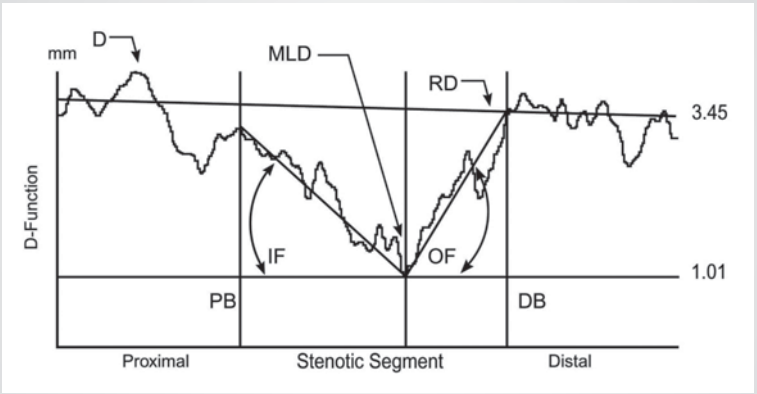

***Fig. 1** – Função do diâmetro luminal (Função-D) e ângulos médios de entrada (AE) e de saída (AS). O AE e AS são definidos pela inclinação média da função do diâmetro entre o DLM e o limite proximal (LP) e o limite distal (LD) do segmento estenótico, respectivamente.*

mean ± standard deviation and compared by ANOVA. Measurement distribution of lesion length, percent stenosis, symmetry index, plus inflow and outflow angles versus plaque burden and remodeling index were studied using linear regression analysis. Geometric angiographic variables with prognostic value for acute events (inflow and outflow angles, symmetry index, lesion length, and percent stenosis) were divided into three groups, according to terciles. IVUS findings in each group were analyzed and compared. All statistical tests were two-tailed, and p values < 0.05 were considered significant.

Results

Clinical characteristics of the thirty patients included in the study (31 lesions) are shown in table 1. Most patients were male (70%), with a relatively high prevalence of diabetes mellitus (30%). Half of the cases had multivessel disease, and 23% had a history of myocardial infarction (in all these patients, infarct location was not related to the coronary lesion under study). The left anterior descending artery was the most frequently treated vessel, and approximately one-third of the patients had type B2 or C lesions. All procedures achieved angiographic success and were followed by good in-hospital clinical outcomes.

Quantitative coronary angiography and morphologic angiographic findings of the 31 lesions studied are shown in Table 2. On average, lesions were relatively short (9.2 ± 4.4 mm in length), located in large vessels (reference diameter 2.90 ± 0.45 mm), and with percent stenosis ranging from 50.0% to 89.0% (mean 67.7 ± 12.1%). Inflow angles ranged from 8.48º to 48.78º (mean 24.0 ± 11.4º), and outflow angles, from 8.30º to 53.03º (mean 23.8 ± 11.7º). Symmetry evaluation showed extremely eccentric (symmetry index 0) and maximal concentric lesions (symmetry index 1), with mean symmetry index of 0.56 ± 0.32.

Geometric variables (lesion length, percent stenosis,

Table 1 – Clinical characteristics

Number of patients/lesions	30 / 31
Age, years ± SD	59 ± 9
Masculine gender, n (%)	21 (70)
Systemic arterial hypertension, n (%)	18 (60)
Diabetes mellitus, n (%)	9 (30)
Smoking, n (%),	10 (33)
Previous myocardial infarction, n (%)	7 (23)
Previous CABG n (%)	1 (3)
Extent of coronary artery disease	
Single-vessel disease, n (%)	15 (50)
Two-vessel disease, n (%)	11 (37)
Three-vessel disease, n (%)	4 (13)
Clinical presentation	
Silent ischemia, n (%)	7 (23)
Stable angina, n (%)	23 (77)
Lipid profile	
Total cholesterol, mg/dL± SD	210 ± 34
HDL-C, mg/dL ± SD	39 ± 12
LDL-C, mg/dL ± SD	139 ± 30,4
Triglycerides, mg/dL ± SD	149 ± 65
Target vessel	
Right coronary artery, n (%)	7 (23)
Left anterior descending artery, n (%)	18 (58)
Left circumflex artery, n (%)	6 (19)
Type B2/C lesion, n (%)	9 (29)

SD- standard deviation.

Table 2 – Quantitative coronary angiography and geometric angiographic variables (n = 31 lesions)

Minimal luminal diameter, mm ± SD	0.93 ± 0.38
Reference diameter, mm ± SD	2.90 ± 0.45
Percent stenosis, % ± SD	67.7 ± 12.1
Lesion length, mm ± SD	9.2 ± 4.4
Inflow angle, degree ± SD	24.0 ± 11.4
Outflow angle, degree ± SD	23.8 ± 11.7
Symmetry index, mean ± SD	0.56 ± 0.32

ST- standard deviation.

Table 3 – Ultrasound findings in each tercile subgroup of geometric angiographic variables (n = 31 lesions)*

	Percent stenosis			Lesion length			Symmetry index			Inflow angle			Outflow angle		
	Lower tercile	Middle tercile	Upper tercile	Lower tercile	Middle tercile	Upper tercile	Lower tercile	Middle tercile	Upper tercile	Lower tercile	Middle tercile	Upper tercile	Lower tercile	Middle tercile	Upper tercile
Soft plaque, n	6	8	7	7	5	7	6	6	7	6	8	5	5	7	7
Calcific plaque, n	2	2	2	2	0	1	2	0	2	1	1	2	2	2	0
Plaque burden, % ± SD	84±10	86±8	91±7	84±10	88±10	89±9	87±11	87±11	88±7	87±10	89±10	86±10	86±10	87±10	89±9
Positive remodeling, n	3	2	3	1	2	5	4	0	4	4	1	3	4	2	2

*ST- standard deviation. * p > 0.05 for all comparisons between geometric angiographic characteristics and ultrasound variables.*

symmetry index, inflow and outflow angles) were divided into terciles. Table 3 shows IVUS findings analyzed separately for each tercile. Frequency of soft or calcific plaques, positive remodeling, and magnitude of plaque burden were not associated with any geometric feature, and no significant difference was found between tercile subgroups (P > 0.05 for all analysis). As a matter of illustration, scatterplots of individual measurements of lesion length, percent stenosis, symmetry index, inflow and outflow angles *versus* plaque burden and remodeling index are shown in Figures 2 and 3, respectively (P > 0.05 for all analysis).

Discussion

In this study, angiographic factors shown to be predictive of future myocardial infarction were not associated with IVUS markers of plaque instability. Specifically, angiographic features such as percent stenosis, symmetry index, lesion length, and inflow and outflow angles were not associated with IVUS detection of soft plaque, positive remodeling or greater plaque burden.

There are many possible explanations for the lack of correlation between angiographic predictors of future events and IVUS markers of vulnerability: 1) most properties currently associated with increased plaque vulnerability, such as plaque inflammation[15], thin fibrous cap[16], plaque deformability[17] and shear stress[18], are not identifiable by conventional intravascular ultrasound; 2) the correlation between soft plaque and lipid content is weak and, in addition, IVUS image of the "soft plaque" may correspond to thrombus, lipid, necrotic tissue, or none of these; 3) in our series, mean percent stenosis was 67%, unlike those of 46% and 47% reported in previous studies that have shown the prognostic value of angiographic variables[8,9]. It seems reasonable to assume that, in theory, our patients might have been in a more advanced stage of coronary artery disease, which may invalidate a direct extrapolation of previous results from patients with milder coronary lesions.

Hypothetically, angiographic morphology may be affected by plaque structure and composition[8]. However, our findings do not support this hypothesis. Even though conventional IVUS imaging allows only a relatively rough estimate of vessel wall structure, no association was noted between geometric angiographic variables and plaque characteristics on IVUS. Despite the relatively small number of lesions included in this study, it is unlikely that a greater number of lesions would have changed these findings, because no trend towards significant correlations was found when different variables were analyzed.

Study limitations lie in the small number of patients and lesions studied. However, both patients and lesions had well-defined characteristics (*de novo* lesions in native vessels in patients with stable coronary syndromes and no history of infarction related to the artery studied); and were judiciously studied using two methods (coronary angiography and IVUS). Any extrapolation of our findings to other lesion and patient groups should be done cautiously.

We conclude that geometric features of coronary lesions favoring acute occlusion and myocardial infarction are not correlated with ultrasound markers of plaque vulnerability. Whether angiographic predictors of future coronary events - which are independent of IVUS markers of plaque vulnerability - are associated with other local parameters, such as flow pattern and shear stress, remains unknown and warrant further study.

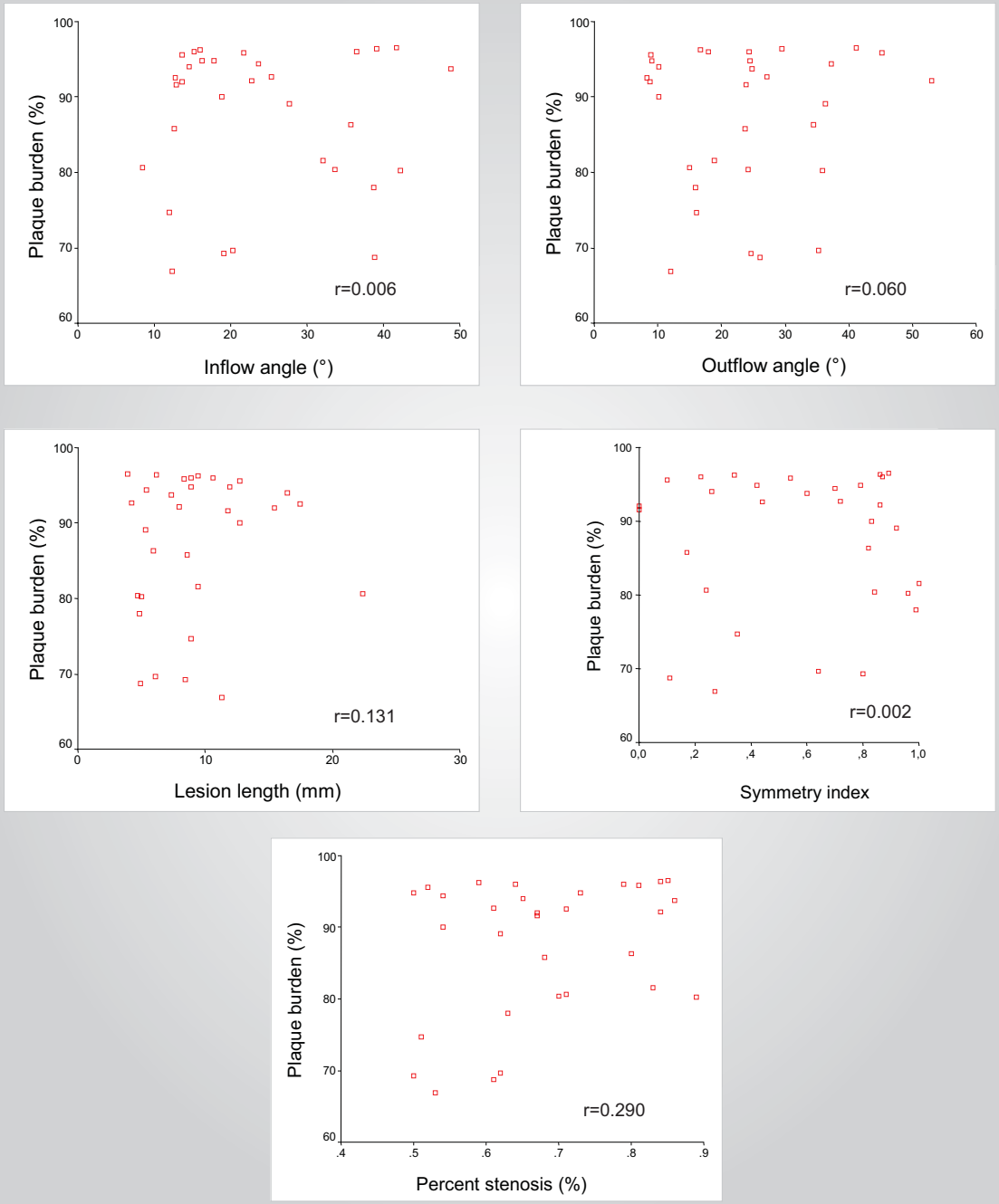

Fig. 2 *– Distribution of geometric angiographic variables (inflow angle, outflow angle, lesion length, symmetry index, and percent stenosis) and plaque burden on intravascular ultrasound (p > 0.05 for all correlations).*

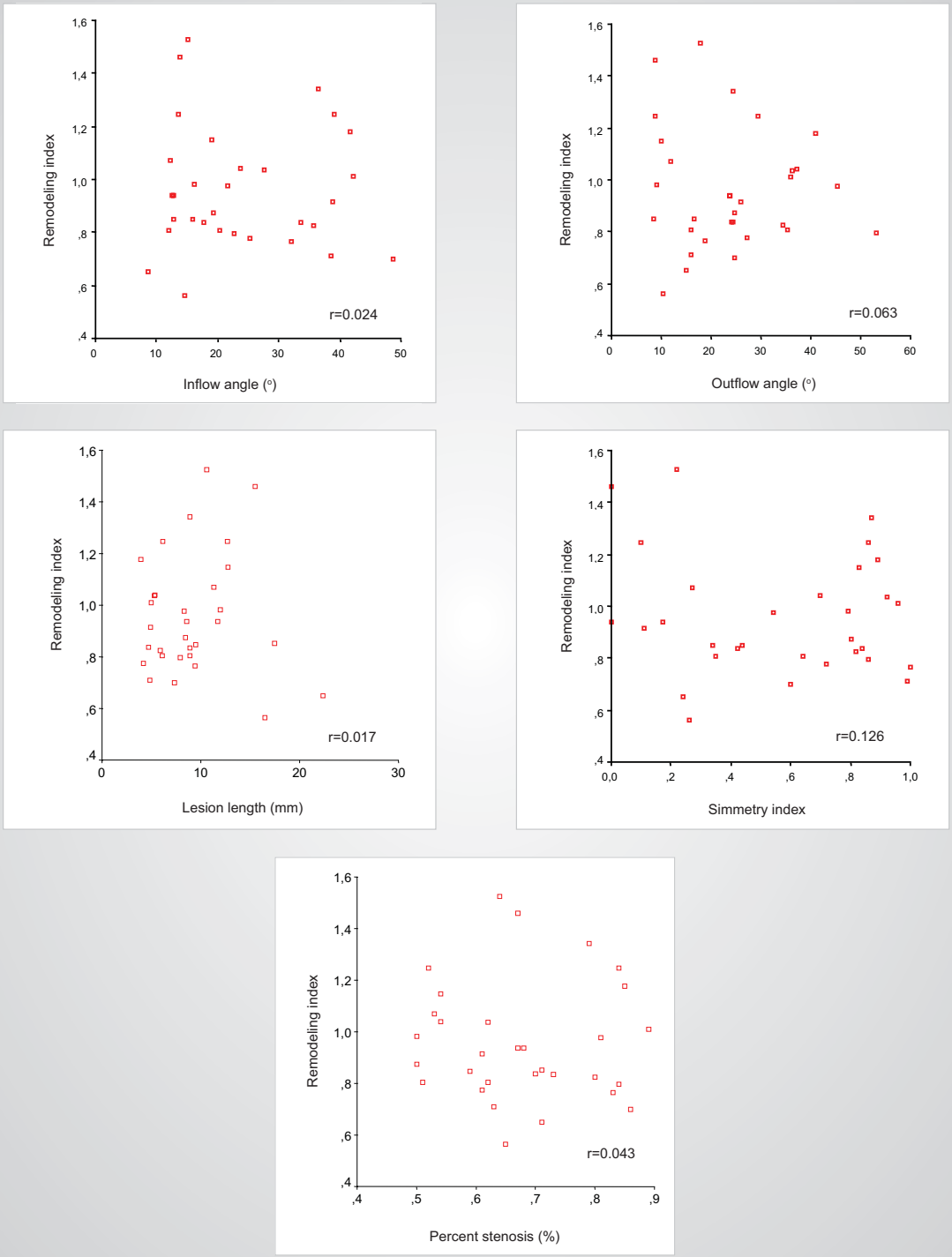

Fig. 3 *– Distribution of geometric angiographic variables (inflow angle, outflow angle, lesion length, symmetry index, and percent stenosis) and remodeling index on intravascular ultrasound (p > 0.05 for all correlations).*

Potencial Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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