Beyond the Coronary Lumen: Interaction Between the Plaque and the Obstruction

Más allá de la luz coronaria: entre la acción recíproca de la placa y la obstrucción

It is a very simple secret: It is only with the heart that one can see rightly.
What is essential is invisible to the eyes.
-What is essential is invisible to the eyes.
The little prince repeated,
so that he would be sure to remember
ANTOINE DE SAINT-EXUPÉRY, "The Little Prince"

INTRODUCTION

About four decades ago two paradigms emerged almost simultaneously that as a dogma continue permeating our way of thinking coronary disease.

In 1972, pathologists, led by William C. Roberts, found in autopsies that acute myocardial infarction (AMI) was the result of almost total luminal obstruction by the progressive growth of a coronary atheroma, and at the same time regarded thrombosis as the consequence and not the cause of myocardial infarction. Therefore, to quantify the disease, pathologists began to measure the coronary stenosis "cross sectional area". (1) Later, it became clear that quantification by CSA overestimated the disease compared with coronary angiography; for example, 50% of angiographic diameter stenosis represented 75% of anatomopathological cross-sectional area obstruction.

Since then, we assume that in order to consider chest pain, either an acute coronary syndrome (ACS) or a typical chest pain, as caused by ischemic heart disease the patient must have an obstructive lesion. In coronary angiography, we will classify this lesion as significant, due to our firm belief in animal experimentation performed by Gould and Lipscomb 2 years later, in 1974, (2) who tested the effect of progressive coronary stenosis on maximum and resting coronary flow, demonstrating that ≥ 50% reduction limited maximum vasodilator capacity and ≥ 85% reduction limited resting coronary flow.

These findings were directly transferred to clinical practice and we started talking about critical coronary subocclusions (≥ 85% coronary stenosis) in patients with ACS and of significant coronary lesion (≥ 50% coronary stenosis) in chronic stable angina (CSA). This basic science observation of the cross-sectional area, or else diameter effect turned these injuries into "ischemic stenoses" in the patient.

But about 15 years later, in 1989, Muller et al. described as "vulnerable" those coronary stenoses which do not limit flow (less than 50%) but are prone to rupture causing AMI. (3)

The skill needed to predict events that produce "plaque accident" still remains as a challenging task and even more so the understanding of the natural evolution and optimal medical therapy in the in vivo coronary atheroma.

IS ACUTE MYOCARDIAL INFARCTION DUE TO CORONARY PLAQUE ACCIDENT IN MILD DISEASE OR TO SIGNIFICANT OBSTRUCTIVE LESIONS?

Since the publication of Ambrose (4) and Little (5) in 1988 and other subsequent series of retrospective studies, we know that prior to the culprit lesion producing AMI, the baseline angiography showed a severity range of 30%-45%. Therefore, it could be assumed that the lesions producing AMI were not obstructive.

However, we should take into account that the time period between the baseline coronary angiography and the AMI event in all these studies was prolonged, with a range of 18 to 40 months. (6)

Therefore, what could happen during the period immediately prior to AMI, since when the event occurred, coronary angiography usually showed a critical lesion? Did it progress directly from a mild lesion to AMI by a single plaque accident with thrombotic obstruction, or did it develop an accelerated progression or perhaps silent plaque accidents, leading to a previous critical obstruction?

Ojio et al. (7) studied the unique situation of 20 patients with AMI who underwent an elective coronary angiography less than one week before the event (mean time 3 ± 3 days), (although in 10 subjects it was performed to analyze an effort angina and in 5 to study a previous angioplasty), who were compared with 20 control AMI patients with prior coronary angiography almost a year before the event. The mean diameter of stenosis severity in the group with angiography 3 days before AMI was 71 ± 12% compared with 30±18% in those with angiography performed almost a year before AMI. Although the research argues in favor of progressive obstruction or rupture and silent healing, it could be biased since the cases with angiography performed 3days before AMI had a history of chronic coronary disease.

Recently Zaman et al. (8) conducted a time-based analysis to assess the angiographic severity of coro-

nary stenosis leading to AMI. From 2003 to 2010, 84 patients with non ST-elevation AMI (NSTEMI) and 41 patients with ST-elevation AMI (STEMI) with ≥1 previous angiographic study in vessels without prior interventions were identified.

When the interval of the initial angiography before AMI was> 3 months, mean baseline stenosis was 36 ± 21% in STEMI and 44 ± 16% in NSTEMI patients, similar to the initial studies with 71% and 63%, respectively, in patients with < 50% stenosis in the culprit artery. However, it was noteworthy that lesions leading to STEMI within 3 months after evaluation were more severe than those leading to STEMI in > 3 months; 59 ± 31% vs. 36 ± 21%, respectively (p = 0.02). However, initial lesions < 50% in the culprit artery were still found in 43% of patients compared with 71% of patients with > 3 months.

The currently prevalent interpretation is that plaque rupture (PR) of a minimal lesion causes an abrupt occlusion, leading to a clinical event in minutes. If this explanation were always true, lesions seen a few days before AMI should have a similar stenosis to that of a few months before. However, this study found that lesions closer to the event are more severe, thus claiming that some processes are lengthy and could span several days instead of several minutes.

The progression of coronary disease, which we had considered linear, could well progress in phases, where silent PR with subsequent healing in vivo would facilitate discontinued plaque progression, a hypothesis already raised by pathological studies. (9)

Yokoya et al. (10) studied the process of coronary lesion progression from mild to moderate stenosis to moderate to severe stenosis, based on four serial coronary angiographies with quantitative analysis performed during 1 year, selecting ≥ 1 major coronary artery (target vessel), without guide wire insertion, PCI or CABG before the final coronary angiography. Among the 486 patients who met these inclusion criteria, 36 target vessels of 36 patients had clinically significant progression (7% incidence of progression), with > 15% increase of diameter stenosis per year. This was evaluated as 20-74% stenosis from the initial coronary angiography of the target vessel. The degree of percent stenosis progression in each of the 3 intervals (≈ 4 months) of the four serial coronary angiographies was classified as marked (≥ 15%), mild (5% to 14%) or without (<5%) progression, respectively.

The pattern was classified into two types: type 1 with sudden marked progression in 14 of the 36 target vessels, with percent stenosis in the first, second, third and fourth or last angiography of 44 ± 14%, 46 ± 13% ± 46 ± 13% and 88 ± 10%, respectively (p <0.05 vs. the first angiography), and type 2 with continuous progression of 44 ± 11%, 50 ± 9%, 59 ± 9% and 67 ± 9% (p <0.05 for each angiography vs. the first).

What is distinctive in type 1 vessels is the sudden onset of severe stenosis due to marked progression with chest pain or myocardial infarction (71%) and Ambrose type II eccentric lesions indicating PR or thrombosis (57%). The distinctive feature in type 2 vessels is mild continuous progression with smooth vessel walls, and chest pain occurred when percent stenosis was severe.

UPDATING HYSTOPATHOLOGIC CHARACTERISTICS OF ATHEROSCLEROTIC CORONARY DISEASE TO CLASSIFY VULNERABLE PLAQUES

In a recent paper, Narula J et al. (11) evaluated 295 coronary atherosclerotic plaques dissected from the hearts of 181men and 32 women suffering from sudden death. The atherosclerotic plaques were classified as follows: stable plaque (fibroatheroma, FA) described as a well matured necrotic core covered by a thick fibrous cap (n = 105); vulnerable plaque [thin-cap fibroatheroma (TCFA)] defined as thin-cap lesions with infiltration of macrophages (n = 88) and PR characterized by the presence of an acute luminal thrombus with connection to a lipid-rich necrotic core through the disruption of the thin fibrous cap (n = 102).

They demonstrated that 70% PR had >75% cross-sectional area stenosis, 25% PR had 50% - 75% stenosis; and only 5% PR had < 50% cross-sectional area stenosis. Conversely, in TCFA, only 40% showed >75% cross-sectional area stenosis, 50% had 50% - 75% stenosis and 10% had < 50% cross-sectional area stenosis. This would suggest that the plaques that break are substantially narrowed at the time of the acute event.

Fibrous cap thickness emerged as the dominant plaque feature in its ability to discriminate between the three plaque types. Fibrous cap thickness was always ≥ 84 μm in stable FA, and the plaques that were < 84 μm at their thinnest region included almost all TCFA and PR. Moreover, the fibrous caps associated with PR measured < 54 μm at the rupture site. Therefore, plaques with fibrous cap ≥ 84 μm were stable, PR showed fibrous cap thinning < 54 μm and the majority of TCFA had fibrous cap between 54 to 84 μm, although some had < 54 μm. Furthermore, TCFA plaques with fibrous cap < 54 μm, and not yet broken, were more likely to show < 74% cross-sectional area stenosis. This finding allowed the authors to support the claim that vulnerable plaques need to encroach farther on the lumen and display a critically thinning fibrous cap before an acute clinical event.

It is logical to assume that a thinner cap with a significant stenotic lesion would be more responsive to mechanical rupture and an acute event in response to hemodynamic disturbances. Conversely, the less stenotic TCFA may hypothetically be more amenable to rupture-healing cycles and substantially contribute to plaque growth.

Different degrees of coronary lumen stenosis from mild, moderate to severe can be observed in the 3 types of plaque; therefore, severe stenosis with a low-lipid calcified atheroma core and thick fibrous cap will

present CSA without an acute event, whereas a severe lesion with PR will present as an ACS.

CAN WE IDENTIFY THE CHARACTERISTICS OF CORONARY ATHEROSCLEROTIC PLAQUES IN VIVO?

Considering the above described histopathology characteristics of plaque, or high-risk or ruptured plaque progression: would it be possible to recognize them in vivo with the new imaging techniques, to identify human stable or unstable plaques and perhaps predict atherosclerotic events, to follow-up the response to therapy, for example with statins, and even to fantasize about directing specific therapy according to the developing stage of the coronary plaque?

In recent years, there has been a revival and proliferation of articles with new technologies with more refined imaging tools. Although we think that this field is in its infancy, we will briefly review the power of these new tools.

RadioFrequency-IntraVascular UltraSound and greyscale.

Although this technique allows a "virtual histology" (Figure 1 A and B) and TCFA assessment was an independent predictor of subsequent ischemic events in the cohort of the PROSPECT (Prospective Natural-History Study of Coronary Atherosclerosis) (13) and VIVA (Virtual histology-IVUS in Vulnerable Atherosclerosis) studies, (14) the limitations of the RF-IVUS to clearly identify fibrous cap thickness due to the low axial resolution, must be acknowledged. However, it may establish the presence of a plaque with necrotic core without evidence of fibrous tissue, over and next to the vessel lumen, often as an expansive remodeling to the outer wall (positive remodeling), first confirmed in vivo with the use of IVUS (15). This feature and plaque volume > 40% in at least three consecutive images, is associated with subsequent plaque rupture.

This method identified PR that was not the cause of the event as well as its evolution with or without statin therapy.

Ten years ago, in a landmark study performed in 14 patients presenting with ACS, Rioufol et al. (16) found 28 clear nonculprit PR (2 ± 1 per patient) without significant associated stenosis (minimal luminal cross-sectional area > 4 mm2). They were treated with 40 mg of statins, aspirin and clopidogrel and were followed-up clinically and with IVUS for almost 2 years (22 months). No clinical event related to the study lesion was found and in the final IVUS half of the ruptured plaques had healed with a decrease in the degree of stenosis (22% vs. 29% at baseline, p = 0.056).

Shortly after, Ohlmann et al. (17) confirmed these findings in 17 consecutive patients in whom IVUS identified secondary ruptures in plaques that did not limit the flow (minimal lumen area> 4 mm2) and which were not treated invasively. After a follow-up of 43 months there were no myocardial infarctions and only two revascularizations were performed (12%).

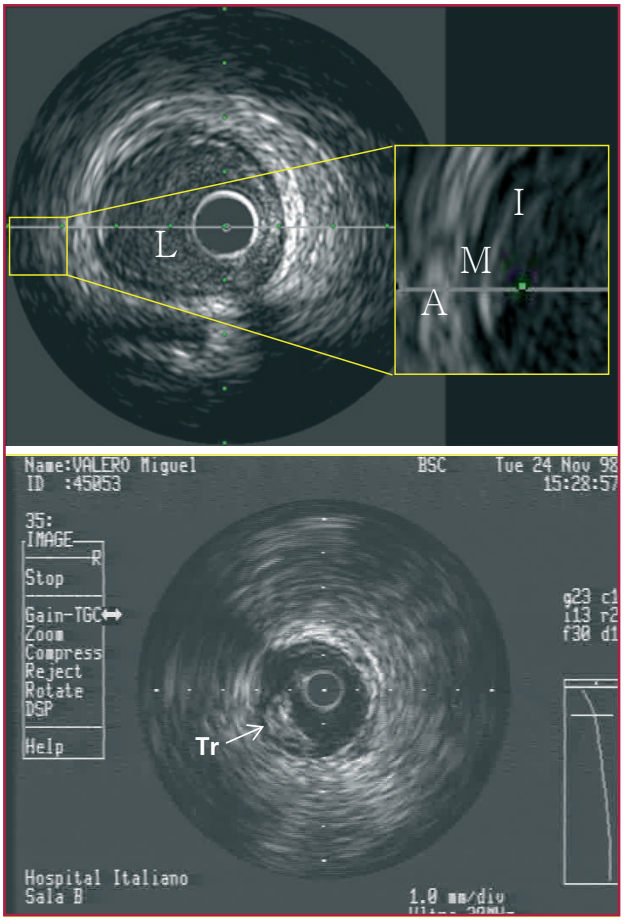

Fig. 1. A. Normal coronary artery with IVUS. Detail: amplification of the three layers: intima (I), external elastic membrane (M) and adventitia (A), and lumen (L). **B.** Thrombus (Th) without external-cap rupture , as seen in «erosion».

Finally, Hong et al. (18) evaluated the effect of statins on plaque stabilization and progression in 28 patients with non-stenotic ruptured plaques, half of them treated with statins, and with IVUS study at baseline and at 12-month follow-up. They observed complete healing in 29% of patients treated with statins and none in the untreated ones (p = 0.049). While patients treated with statins had an increased lumen cross-sectional area (0.4 mm2), untreated patients had a decrease in lumen area (- 0.8 mm2, p = 0.007) and the size of the plaque only increased in untreated patients (0.6 mm2, p = 0.05). During the one year follow-up, revascularizations were performed in 21% of untreated patients and in none of those treated with statins (p = 0.11). Therefore, it appears that nonculprit PR not treated with statins may be responsible for lesion progression and the need for revascularization.

In a recent secondary publication of the PROSPECT study, Xie et al. (19) presented the largest series of PR in nonculprit lesions. After successful stent implantation in 697 ACS patients, they performed virtual histology with greyscale IVUS in the proximal-mid

segments of all three coronary arteries. Of the 660 patients with complete IVUS data, 93 (14.1%) had 128 PR in nonculprit lesions. Although not differentiated by luminal area, ruptured plaques had ≥ 40% greater plaque burden compared with non-ruptured plaques (66.0% vs. 56.0%, p < 0.0001), and were more often classified as FA (77.1% vs. 51.4%, p < 0.0001). During the 3 year follow-up, the incidence of major adverse cardiac events did not differ significantly between patients with and without subclinical rupture of nonculprit plaques; although all patients were treated with statins and antiplatelet agents.

Optical coherence tomography

Optical coherence tomography (OCT), which measures tissue depth by the back reflection of infrared light, has a very good axial (5 to 20 μm) and transverse (30 μm) resolution, well above that of IVUS. (12)

With regards to the evaluation of a high-risk plaque, it allows a safe measurement of fibrous cap thinness, and lipid content and macrophage infiltration assessment; although the limitation is the similar optical properties of macrophage accumulation and lipid-rich plaques.

In an analysis by Kato et al. (20) of nonculprit plaques with ACS (45 in 17 patients) and without ACS (203 in 87 patients), patients with ACS had increased lipid volume, thinner fibrous cap (70.2 ± 20 μm vs. 103.3 ± 47 μm, p <0.001) and more frequent TCFA (64.7% vs. 14.9%, p <0.001), macrophage infiltration (82.4% vs. 37.9%, p = 0.001), and thrombi (29.4% vs. 1.1%, p <0.001); i.e., patients with ACS reveal more plaques in nonculprit arteries with characteristics that predict more acute ischemic events.

The OCT enables the identification of PR with a lipid core, as well as PR with underlying calcified nodule (CN), and erosion thrombosis (ET) with fibrous cap integrity in ACS patients.

In a study of 126 patients with ACS, Jia et al. (21) showed PR, ET and CN incidence of 43.7%, 30.1% and 7.9%, respectively. Erosion thrombosis patients compared with PR patients were 7 years younger (p = 0.005), had more ACS without ST-segment elevation (61.5% vs. 29.1%, p = 0.008), less frequent lipid-rich plaque (43.6% vs. 100%, p < 0.001), thicker fibrous cap (169.3 ± 99.1 μm vs. 60.4 ± 16.6 μm, p < 0.001) and also less severe stenotic diameter (55.4% ± 14.7 vs. 68.6% ± 12.9%, p < 0.001).

Because it is known that the necrotic core is 6 times more thrombogenic than any other plaque component, it is possible that thrombi produced by erosion rather than rupture, can better respond to fibrinolytic therapy.

To test this hypothesis Hu et al. (22) analyzed 23 patients with STEMI treated with tenecteplase, who after 24-48 hours of successful fibrinolysis underwent OCT in the culprit lesion vessel before any intervention.

Among 23 culprit lesions, PR, identified by the presence of fibrous cap discontinuity and a clear cavity formed within the plaque, was diagnosed in 47.8% of culprit lesions, plaque erosion, defined as the presence of an intracoronary thrombus attached to the lumen surface without any detectable sign of fibrous cap rupture, in 34.8%, whereas 17.4% did not meet any of the two criteria.

The study demonstrated that the size of the residual thrombus one day after fibrinolysis, was greater in the rupture than in the erosion site (14.2 ±9.4 vs. 6.5 ± 4.5, p = 0.049, semiquantitative analysis). In the rupture site, usually located proximal to the minimum cross-sectional area, the center of the thrombus consists mainly of platelets, and the erythrocyte-rich (red) thrombus (defined by high backscattering and high attenuation) is equally distributed to both sides of the culprit lesion, while in plaque erosion the platelet or white thrombus (defined by homogeneous backscattering and low-attenuation) was the predominant type at the minimum cross-sectional area, which was the culprit site. (Figure 2)

In a study by Fujii et al., TCFA frequency (≥ 1 quadrant with lipid content in the plaque and the thinnest part of the fibrous cap ≤ 65 μm) was analyzed with OCT in 35 patients with AMI and 20 patients with CSA. (23). In this setting, TCFA was more frequent in AMI than in CSA in both culprit lesions (77% vs. 25%, p < 0.001), and remote secondary lesions (77% vs. 30%, p < 0.001) and multiple TCFA were also more common (69% vs. 10%, p <0.001).

Tanaka et al (24) performed OCT in 43 consecutive patients with ACS, to visualize TCFA (defined as ≥ 2 quadrants with lipid content within the plaque and the thinner part of the fibrous cap ≤70 μm) along the culprit coronary artery. Forty two percent of patients had one TCFA and significantly higher C-reactive protein than in the rest of the patients (58%) without TCFA (median 3.3 mg/L vs. 1.7 mg/L, p = 0.03), as well as more multiple ruptures (28% vs. 0%, p = 0.01).

Kubo et al. used OCT to compare the instability of multiple lesions in 26 patients with AMI and 16 patients with CSA (25). Plaque rupture in the culprit lesion was more frequent in AMI compared with CSA (77% vs. 7%, p < 0.001) and also intracoronary thrombus (100% vs. 0%, p < 0.001). Fibrous cap thickness was significantly thinner in AMI (57 μm vs. 180 μm, p < 0.001) as well as TCFA frequency (< 65 μm) (85% vs. 13%, p < 0.001). In nonculprit lesions there were also significant differences between AMI and CSA, both in fibrous cap thickness (111 μm vs. 181 μm, p < 0.002) as in the frequency of TCFA (< 65 μm) (38 % vs. 6%, p < 0.03) and multiple TCFA (38% vs. 0%, p = 0.007). Therefore, OCT, as well as IVUS before, demonstrates multiple unstable lesions in AMI compared to CSA

Multislice computed tomography

In recent years, different publications have evaluated the usefulness of multislice computed tomography

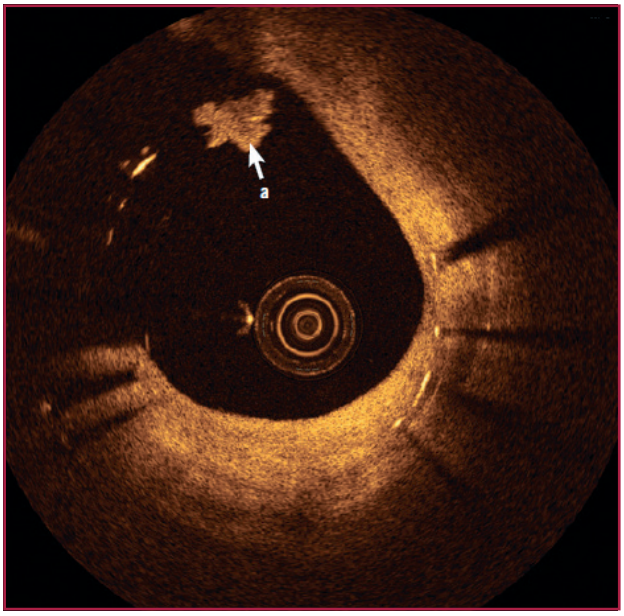

Fig. 2. OCT image showing white or platelet thrombus (a).

(MSCT) to describe the characteristics of high-risk plaques and delineate the individual plaque components. Although MSCT identifies plaque components with accuracy similar to that of RF IVUS, an important limitation of MSCT is its spatial resolution which does not allow measuring fibrous cap thickness, precluding its use to identify TCFA. (26)

The presence of coronary vessel positive remodeling (POSR) and low attenuation plaques (LAP) forming a lipid necrotic core (Figure 3 A and B) were analyzed by Motoyama et al. (27) in 1059 patients undergoing MSCT angiography, to evaluate the possibility of ACS during a 27-month follow-up period.

When the plaques had both features, POSR and LAP, 22.2% of cases had ACS, compared with 3.7% when they had a single feature and 0.5% with none of these features ($p < 0.001$). None of the patients with normal MSCT angiography had an acute coronary event. Comparison among patients who developed or not ACS showed significant hypertension, dyslipidemia, previous infarction and plaques with one or two positive features; but in the Cox regression analysis of these four selected variables, presence of plaques with one or two of the positive characteristics was the only significant independent predictor of ACS (HR 22.8 95% CI 6.9-75.2, $p < 0.001$)

This study shows that large and even extremely large plaques shortly precede the acute event, even though these plaques may compromise only part of the vessel lumen due to their positive or external remodeling, since all the patients who subsequently presented with ACS in this study had culprit lesions that were < 75% at the time of MSCT angiography. Conversely, stable plaques or ACS associated with plaque erosion do not show expansive remodeling. Larger plaques also lodge large necrotic cores with LAP areas and are associated with ACS. The MSCT information from this study is similar to the descriptions available on RF-IVUS studies, where plaques leading to late acute coronary events showed eccentric, large plaques containing IVUS echolucent zones.

"VISUALIZING" PLAQUE RESPONSE TO STATIN THERAPY

It is known that HMG-CoA reductase inhibitors (statins) reduce vascular events, among them coronary events, as shown by primary and secondary prevention randomized clinical trials. During the last years, imaging studies have been the key to illustrate changes in plaque composition with statin therapy.

Hattori et al. (28) integrated two complementary imaging techniques, OCT and IVUS, to assess the effects of statin treatment on the composition and morphology of the coronary plaque in 42 patients with CSA. Twenty-six of these patients received 4 mg pitavastatin after the baseline study, and the remaining 16 patients refused statin therapy. Follow-up imaging studies were performed after a median of 9 months.

IVUS images showed that during this period, pitavastatin significantly decreased plaque percent volume (48.7% to 42.0%; $p = 0.03$) as well as plaque lipid volume (34.9% to 28.2%; $p = 0.02$), while there was no change in the diet-only group. OCT also showed a significant increase in fibrous cap thickness (140 μm to 189 μm; $p < 0.001$), with no changes in the group treated only with diet. Over time, highly significant differences were found in percent lipid volume (-6.8% vs. 2.8%; $p = 0.03$ and fibrous cap thickness (52 μm vs. 2 μm; $p < 0.001$) changes between pitavastatin and diet groups.

In a more recent randomized clinical trial performed by Kini et al. (29), known as the YELLOW study (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy), 87 patients with CSA and multivessel disease, and at least one residual severely obstructed vessel (> 70%) [coronary fractional flow

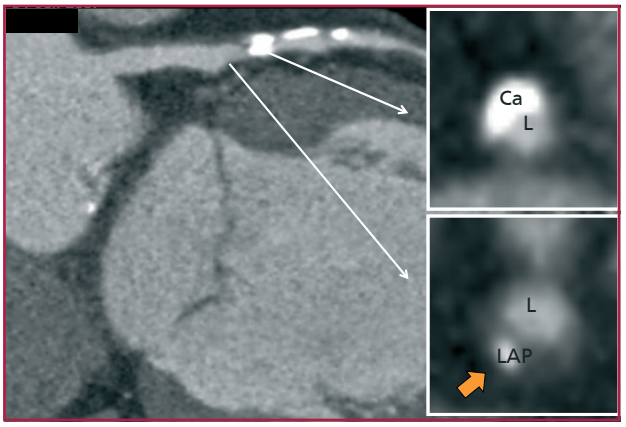

Fig. 3. Coronary angiotomography showing in **A:** calcified plaque (Ca) without lumen (L) involvement and in **B:** large lipid-rich plaque (LAP) with positive remodeling without L involvement.

reserve (FFR) ≤ 0.8], who underwent culprit vessel percutaneous coronary intervention, and were randomized to receive rosuvastatin 40 mg/daily or standard care, were evaluated with IVUS and near-infrared spectroscopy. (29) At 7-week follow up, intensive therapy with statins was associated with significantly higher median reduction of the lipid-core burden index at the 4 mm maximal segment (-149.1 vs. 2.1; p = 0.001).

Interestingly, in patients with some FFR improvement, median lipid-core burden reduction was significantly higher than in those without FFR improvement (-109. 6 vs. 122.3; p = 0.03). Also, FFR increased in a stepwise fashion with the magnitude of plaque lipid-core reduction.

The YELLOW study is important in showing that even in a short period of time, evident changes consistent with plaque regression are possible, by lowering initial LDL-cholesterol from 79.1 mg/dL to 58.4 mg/dL.

In addition to assessing the arterial lumen, computed tomography angiography (CTA) can also characterize the vessel wall noninvasively and hence coronary plaque morphology.

Inoue et al. (30) performed CTA in 32 patients with suspected coronary disease. Twenty-four of these patients received fluvastatin after the baseline study and the remaining 8 who refused statin treatment were followed-up as control subjects. The imaging study was repeated after a median of 12 months. All vessels were examined in each patient, excluding segments severely calcified and with < 75% stenosis. A 10-mm long segment was identified for comparison before and after the intervention.

In patients treated with statins, total plaque volume was significantly reduced over time (92.2 mm3 vs. 76.4 mm3; p < 0.01), as well as LAP volume which measures the necrotic core (4.9 mm3 vs. 1.3 mm3; p = 0.01). On the other hand, no change was observed in the plaque characteristics of control subjects. Changes in total plaque volume (-15.9 mm3 vs. 4.0 mm3; p < 0.01) and in the LAP volume (-3.7 mm3 vs. 0.2 mm3; p < 0.01) were significantly different between both groups.

The study showed that the reduction in plaque volume was due to reduced LAP volume (R = 0.83; p < 0.01) and was not related to any change in vessel lumen volume. Therefore, statin therapy resulted in decreased plaque and necrotic core volume, features known to be associated with plaque instability.

LESSONS LEARNT FROM PATIENTS WITH CHRONIC STABLE ANGINA. IS ISCHEMIA THE SAME AS CLINICAL RISK?

Ever since the COURAGE study showed no difference between optimal medical treatment (OMT) and OMT + PCI in patients with CSA, a powerful concept emerged, postulating that not every angiographic obstructive lesion needs to be revascularized.

Flow fraction reserve measured during catheterization was used to improve the stratification of vessels that produce real ischemia. This new technique was tested in the FAME study, (31) where patients with multivessel coronary artery disease were randomized to angiography-guided PCI or FFR-guided PCI. In the latter group, 37% of angiographic stenotic lesions but with negative FFR did not undergo PCI. Avoiding PCI in non-ischemic lesions resulted in a significant 5% reduction of absolute risk in the composite endpoint of death, nonfatal AMI and revascularization at one year.

Therefore, if the conclusion of this first study is that avoiding PCI in FFR-guided ischemic negative lesions allowed the selection of patients that really benefited from PCI, the logical consequence was to select a group of patients with CSA and ischemia-positive FFR who might benefit from PCI, randomizing them into two groups to compare OMT with OMT + PCI. This study was called FAME II. (32)

The study was prematurely discontinued, as the final endpoint (death, or AMI or urgent revascularization) was lower in the OMT + PCI group compared with the only OMT group (4.3% vs. 12.7%, respectively; p < 0.001). However, the difference in the number of events was primarily due to urgent revascularization (1.6% vs. 11.1%; p < 0.001), with no difference between the scarce number of deaths and infarctions. It should be noted that the definition of urgent revascularization was mainly clinical, not requiring evidence of ischemia or positive biomarkers in all patients, which in an open-label study might lead researchers to recommend revascularization at a lower threshold in patients receiving only medical treatment. In conclusion, the necessary-to-treat number would lead to the absurd conclusion that 10 patients with positive FFR should undergo PCI to prevent… 1 episode of PCI in the group with OMT alone, without any other clinical coronary event.

On the other hand, plaque reduction in the OMT group may also reduce the extent of ischemia and improve the prognosis, and thus, positive FFR lesions would lead to less cardiovascular events. This was recently demonstrated in the YELLOW study described above where a dose of 40 mg rosuvastatin during 7 weeks has the potential clinical value of producing evident plaque regression, and regressed plaques show improved FFR.

CONCLUSIONS

Although the real history of coronary artery disease has become clearer over time, technological developments during the last years constitute a pivotal period for its understanding.

We have learnt that non-obstructive plaques cannot be classified as “non-significant” from the innocent point of view of angiography, as in a shorter rather than longer period of time some of them will progress to thrombotic plaques. Therefore, the non-

stenotic lumen is no longer a passive spectator but becomes a quick actor in the critical obstructive lesion.

It is now evident that the progression of plaque burden with the simultaneous presence of a lipid core, fibrous TCFA and minimal lumen area (≤ 4 mm2), as seen in the PROSPECT study, (13) is associated with 18% major coronary events at 3.4-year follow-up, representing an increase of more than 11 times (HR 11.5). But as the simultaneous occurrence of these three high risk parameters was rare, since they were present in only 4.2% of all plaques studied, it is very difficult to predict which plaque will develop events, because the positive predictive value is less than 10%.

The thrombosis that follows an ACS is mainly due to PR, to a lesser degree to plaque erosion with intact fibrous cap and sometimes to calcified nodules. Plaque rupture is observed in ST-segment elevation ACS in younger patients, with larger plaque volume and thinner fibrous cap than plaque erosions. Also, the thrombus presents a white or platelet-rich core and two erythrocyte-rich tails, instead of a predominantly platelet-rich thrombus in the erosion zone with the highest stenosis. Due to these characteristics, the residual thrombus volume after successful thrombolysis is smaller in plaque erosions.

Patients with ACS compared with those with CSA present systematically severe plaques in the rest of vessel segments that are not the culprit segment, as they have a greater number of future accident-prone plaques due to larger plaque volume with remodelling and greater number of thin fibrous cap plaques, in addition to more ruptured plaques in non-culprit coronary segments. Plaque composition also plays a vital role, with only 0.7% major coronary events at 3 years in fibrotic lesions (common in CSA) compared with 2.7% for lipid-rich FA (common in ACS) ($p< 0.0001$). (33)

As demonstrated by the different imaging techniques (IVUS, OCT, MSCT) and also shown in the PROSPECT study, we now know that the average percent diameter stenosis in the nonculprit lesions responsible for future events at 3.4 years is 32%. Almost all lesions involved in future coronary events have a diameter stenosis < 70%; however at the moment of the event the lumen diameter stenosis had increased to 65%. Therefore, although high-risk plaques can produce PR and thrombosis in a wide range of coronary stenosis, they need to achieve a critical level of stenosis to produce sufficient luminal occlusion to develop an ACS.

Besides continuous and sustained plaque growth which was our old paradigm, we now have in vivo evidence of silent PR that possibly evolve discontinuously, in waves, until they become critically stenotic plaques.

The different in vivo imaging methods enabled the visualization of fast coronary plaque regression, in less than 2 months, by decreasing LDL-cholesterol from levels considered to be therapeutic (79.1 mg/dL) to levels near 50 mg/dL (58.4 g%) in the YELLOW study. (29)

These findings turn OMT with statins at maximum doses and antiplatelet agents into the fundamental therapy for coronary artery wall disease and questions, in stable patients, the indication for revascularization based only on the presence of ischemia, as we now know that plaque regression is associated with decreased FFR, the best current method to assess the physiology of reduced coronary flow.

We could finish stating that thinking "beyond the coronary lumen", as expressed in the title, leads us to acknowledge the reciprocal action established between coronary plaque progression, external to the vessel lumen, and the different degrees of coronary occlusion.

In the next years, we will see an explosion of studies that will allow us to delineate the real history of coronary atherosclerotic disease… and what is more important for medical practice, how to reduce it.

Dr. Hernán C. Doval[MTSAC]
Director of the Argentine Journal of Cardiology

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