

Prospective Use of an Intravascular Ultrasound-Derived Minimum Lumen Area Cut-Off Value in the Assessment of Intermediate Left Main Coronary Artery Lesions

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Background and objectives. Angiographic assessment of the severity of intermediate lesions in the left main coronary artery (LMCA) is subject to significant limitations. Intravascular ultrasound (IVUS) can provide accurate measurement, but there is no agreement on the minimum lumen cross-sectional area (MLA) that indicates significant disease. The aim of this study was to determine the long-term safety of applying a cut-off value of 6 mm² for the MLA in the LMCA.

Methods. The study included patients with intermediate lesions (ie, 25–50%) in unprotected LMCAs, with no previous evidence of associated ischemia. An IVUS examination was carried out and revascularization was indicated when the MLA was ≤6 mm².

Results. In total, 79 patients were recruited between 2000 and 2005. In 31 (39%), the MLA was ≤6 mm², and they underwent LMCA revascularization; in the remaining 48 (61%), the MLA was >6 mm², and patients either underwent angioplasty for other lesions (n=37) or continued medical treatment (n=11). In a follow-up period of 40 [17] months, 4 patients (8.3%) died from heart disease, all of whom had an MLA between 9 and 10 mm² in the baseline study. Revascularization of the LMCA was necessary in only 2 patients (4.2%), both of whom had elective surgery more than 2 years after the initial study.

Conclusions. Intravascular ultrasound assessment of intermediate LMCA lesions using an MLA cut-off value of 6 mm² appears safe over the long term provided the clinical and angiographic criteria applied to patient selection are similar to those used in this study.

Key words: Coronary angiography. Ultrasound. Ischemia.

Aplicación prospectiva de un valor de corte de área luminal mínima por ecografía intravascular en la evaluación de lesiones intermedias del tronco

Introducción y objetivos. La angiografía presenta limitaciones importantes para definir la severidad de las lesiones intermedias del tronco común. La ecografía endovascular (EEV) permite realizar una evaluación precisa, pero no hay consenso respecto a los valores de área luminal mínima (ALM) que indican significación. El objetivo de este estudio es evaluar la seguridad a largo plazo de la aplicación de un valor de corte de 6 mm² para el ALM en el tronco.

Métodos. Se ha incluido a pacientes con lesiones intermedias (25-50%) de tronco no protegido, sin datos previos indicativos de isquemia atribuible. Se realizó estudio con EEV y se indicó revascularización en los pacientes con ALM ≤ 6 mm².

Resultados. En el período 2000-2005 se ha incluido a 79 pacientes, en 31 (39%) el ALM fue ≤ 6 mm² y recibieron revascularización del tronco, en los restantes 48 (61%) el ALM fue > 6 mm² y sólo se actuó sobre otras lesiones (n = 37) o continuaron con tratamiento médico (n = 11). En un seguimiento de 40 ± 17 meses se han producido 4 muertes cardíacas (8,3%), que ocurrieron en casos con un ALM de 9-10 mm² en el estudio basal. Sólo en 2 casos (4,2%) fue preciso efectuar procedimientos de revascularización del tronco que consistieron en cirugías electivas tras más de 2 años del estudio inicial.

Conclusiones. La evaluación con EEV de las lesiones intermedias de tronco y la consideración de un valor de corte de 6 mm² para el ALM resulta segura a largo plazo, siempre que se consideren unos criterios clínicoangiográficos de aplicabilidad como los considerados en este estudio.

Palabras clave: Coronariografía. Ultrasonidos. Isquemia.

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INTRODUCTION

Precise angiographic assessment of the severity of left main coronary artery (LMCA) lesions is difficult and in some cases, impossible.¹ Angiographic measurements

ABBREVIATIONS

MLA: minimal lumen area
MLD: minimal lumen diameter
IVUS: intravascular ultrasound
PCI: percutaneous coronary intervention
LMCA: left main coronary artery
FFR: fractional flow reserve

of this anatomical structure are the least reproducible of the entire coronary tree² and post-mortem studies have shown considerable differences between angiography and the actual disease.³ Based on an imprecise evaluation of the severity of LMCA lesions, unnecessary revascularization (usually surgery or drug-eluting stents) might be performed with the associated risks and cost, or contrarily, an erroneously conservative approach might be adopted, also with associated risks. Hence, the limitations of angiography are relevant in these patients.

Intravascular ultrasound (IVUS) can overcome these limitations and provide precise assessment of LMCA lesions.⁴⁻⁶ In 1 study, the minimal lumen diameter (MLD) measured with IVUS was the best predictor of events at 1 year in patients with deferred LMCA revascularization.⁷ Nevertheless, there is no agreement as to the minimal lumen cross-sectional area (MLA) or MLD values that should be used to consider a stable LMCA lesion significant,^{8,9} and MLA values of 6 to 9 mm² have been contemplated for this purpose. The 6-mm² cut-off was inferred from an equation establishing that the size of a vessel that gives rise to a bifurcation is 1.5 times the size of each of its 2 branches.^{10,11} Since the MLA value found for the left anterior descending artery and circumflex artery is 4 mm², the minimal value for the LMCA should be 6 mm². Moreover, in a recent study, a close association was observed between MLA <6 mm² and fractional flow reserve (FFR) <0.75.¹² Nevertheless, there are no prospective studies assessing the safety of using 6 mm² as the cut-off for deciding an intervention on intermediate LMCA lesions. Since 2000, we have used a specific ultrasound criterion (MLA <6 mm²) to determine the approach to take for treating intermediate LMCA lesions. We now present the results of that clinical experience.

METHODS

Since 2000, patients with confirmed or suspected ischemic heart disease referred to our unit for coronary angiography and found to have an intermediate LMCA lesion have been assessed with IVUS. In these cases we apply a cut-off value of 6 mm² for the MLA to indicate significant disease, associated with a plaque burden >50%. This latter factor was included to avoid considering lesions

with mild-to-moderate or absent plaque burden in small LMCAs as significant (eg, angiographic LMCA ostial stenosis in very small women).¹³ On this basis, the indication for LMCA revascularization was decided in all patients meeting the following characteristics:

1. Clinical

- Absence of cardiogenic shock
- Cases of stable angina or acute coronary syndrome with no clinical or angiographic suspicion that the LMCA was the culprit artery
- Absence of data indicating ischemia derived from an LMCA lesion on non-invasive testing in patients without significant left anterior descending artery or circumflex artery lesions

2. Angiographic

- Intermediate lesion (25%-50% stenosis visualized) with an uncomplicated appearance (no ulcer, dissection, or thrombus) in an unprotected LMCA
- No predominant involvement of the ostia of LMCA branches
- Absence of multivessel disease with an indication for surgery established on the other lesions, independently of the LMCA lesion
- Lesions in other vessels amenable to angioplasty could be present or not

Protocol for the Intravascular Ultrasound Study and Image Analysis

Following catheterization with a 6-Fr guide catheter and insertion of an intracoronary guidewire, 100 to 200 µg of intracoronary nitroglycerin were administered and IVUS was performed with an ultrasound catheter with automatic pullback (In-vision™ Imaging System, 20 MHz, 2.9 Fr, Volcano Inc., Rancho Cordova, California, U.S.A.). Pullback was started at a point distal to the LMCA bifurcation (in the left anterior descending or circumflex artery) and continued to the aortic outflow tract, maintaining the guide catheter outside the LMCA for proper assessment of the aorto-ostial junction.

Considering the lumen-intimal and media-adventitial interfaces, the following measurements were performed:

- At the lesion: *a*) MLA; *b*) maximal and minimal lumen diameters; *c*) external elastic membrane area or vessel area; *d*) plaque plus media area; *e*) plaque burden, defined as the ratio between plaque area and vessel area; and *f*) arc of calcification, when present.

The most normal point of the LMCA proximal or distal to the lesion was taken as the reference segment. In middle lesions, the average between the proximal and distal reference points was used.

– At the reference point, the following were measured: *a*) lumen area (RLA); *b*) maximal and minimal lumen diameters; *c*) external elastic membrane area or vessel area; *d*) plaque area; *e*) plaque burden; and *f*) arc of calcification.

Lastly, lumen area stenosis was calculated as $RLA - MLA \times 100 / RLA$, and the remodeling index as the ratio between the vessel area in the region of the lesion and in the reference region.

Quantitative Angiography

The analysis was done with validated software for automatic border detection (CMS-MEDIS). The MLD was measured in the view showing most severe stenosis. The reference diameter was obtained in the healthiest segment of the LMCA on angiography.

Clinical Follow-Up

The clinical records were reviewed and all patients were contacted directly. The primary cardiac events defined for the study were cardiac death (including all sudden deaths), infarction, coronary surgery, and LMCA angioplasty. The decision to carry out additional coronary angiography or revascularization procedures was left to the discretion of the attending physician.

Statistical Analysis

Continuous variables are expressed as the mean (standard deviation) and are compared with the Student *t* test for unpaired data. Categorical variables are expressed as percentages and compared with the χ^2 test. A *P*-value less than .05 was considered significant. Analyses were performed with SPSS 11.0.

RESULTS

The study included 79 patients. In 31, the MLA of the LMCA was $\leq 6 \text{ mm}^2$ (39%) and revascularization was performed, consisting of surgery in 28 patients and angioplasty with stent placement in 3 who were at high surgical risk. The MLA was $>6 \text{ mm}^2$ in the remaining 48 patients (61%) and they comprised the group without LMCA revascularization; 37 of these patients (77%) underwent angioplasty for lesions in other locations.

The clinical characteristics of the groups with and without significant LMCA lesions on IVUS are shown in Table 1. The angiographic characteristics and ultrasound results of both groups are presented in Table 2. The groups were characterized on the basis of lumen area alone and not plaque burden, since there were no cases of $MLA < 6 \text{ mm}^2$ and plaque burden $< 50\%$.

TABLE 1. Clinical Characteristics of Patients With and Without Significant LMCA Lesions

	MLA $> 6 \text{ mm}^2$ (n=48)	MLA $\leq 6 \text{ mm}^2$ (n=31)	P
Age, mean (SD), years	62.5 (10)	64 (11)	.5
Women, %	7 (15)	2 (6.5)	.4
Diabetes, %	11 (23)	8 (26)	.9
Hypertension, %	20 (42)	16 (51.6)	.5
Prior infarction, %	14 (29)	8 (26)	.9
Ejection fraction, mean (SD), %	53 (9)	54 (9)	.6
Treatment with statins, %	21 (44)	17 (55)	.5
Prior angioplasty, %	1 (23)	9 (29)	.7
Prior surgery	0	0	1
Indication of the procedure			
Infarct, %	18 (37.5)	10 (32)	.8
Unstable angina, %	13 (27.1)	9 (29)	.9
Stable angina, %	17 (35.4)	12 (39)	.8
Extent of disease			
LMCA lesion only, %	11 (23)	4 (13)	.4
Lesion $> 50\%$ in 1 vessel, %	7 (14.6)	6 (19.3)	.8
Lesion $> 50\%$ in 2 vessels, %	30 (62.5)	21 (67.7)	.8

TABLE 2. Comparison of Angiographic and Sonographic Characteristics of Patients With and Without Significant LMCA Lesions*

	MLA $> 6 \text{ mm}^2$ (n=48)	MLA $\leq 6 \text{ mm}^2$ (n=31)	P
Angiography			
Stenosis, mean (SD), %	38 (9)	45 (6)	.03
MLD, mean (SD), mm	2.35 (0.9)	1.9 (0.8)	.02
Diffuse, n (%)	6 (12.5)	13 (42)	.007
Ostial, n (%)	21 (43.7)	4 (13)	.008
Calcification, n (%)	7 (14.6)	7 (22.5)	.6
IVUS			
Minimal lumen area, mean (SD), mm^2	8.4 (1.8)	4.9 (0.8)	$< .01$
Minimal lumen diameter, mean (SD), mm	3 (0.5)	2.2 (0.2)	$< .01$
Lesion plaque burden, mean (SD), %	60 (13)	72 (7)	$< .01$
Vessel area at lesion, mean (SD), mm^2	21 (6)	17.6 (5.2)	.01
Reference lumen area, mean (SD), mm^2 †	15 (3)	9.7 (2)	$< .01$
Reference plaque burden, mean (SD), %†	39 (8)	44 (17)	.2
Vessel area at reference, mean (SD), mm^2 †	24.5 (6.2)	17.3 (5.5)	$< .01$
Lumen area stenosis, mean (SD), %†	43 (14)	47 (9)	.4
Remodeling index, mean (SD)	0.9 (0.1)	1.04 (0.1)	$< .01$
Calcification $> 180^\circ$, n (%)	7 (14.6)	6 (19)	.8
Calcification $< 180^\circ$, n (%)	12 (25)	6 (19)	.7

*MLD indicates minimal lumen diameter; IVUS, intravascular ultrasound.

†Excluding patients with diffuse lesions affecting the entire LMCA.

TABLE 3. Major Clinical Events in Patients With and Without LMCA Revascularization Over a Follow-Up of 40 (17) Months*

	MLA > 6 mm ² (n=48)	MLA ≤ 6mm ² (n=31)
Death, %	7 (14.6)	4 (13)
Cardiac, %	4 (8.3)	2 (6.4)
Noncardiac, %	3 (6.25)	2 (6.4)
Nonfatal infarction, %	1 (2)	2 (6.4)
PCI for LMCA, %	0	0
PCI for other lesion, %	4 (8.3)	1 (3.2)
Coronary surgery, %	2 (4.2)	0
Nonfatal stroke, %	1 (2)	2 (6.4)

*PCI indicates percutaneous coronary intervention.

Although there were significant differences between the groups with respect to angiographic stenosis and MLD values, considerable overlapping between the groups was observed. Minimal lumen diameters between 2 and 2.5 mm were found in 58% of patients with MLA >6 mm² and in 41% of those with MLA <6 mm², and angiographic stenosis was >40% and <50% in 29% of patients with MLA >6 mm² and in 59% with MLA <6 mm².

No clinical complications occurred in the IVUS diagnostic procedures. Clinical follow-up was performed in all patients. The events occurring in both groups over a mean follow-up of 40 (17) months (range, 16-72 months) are shown in Table 3.

In the group without LMCA revascularization, there were 4 cases of cardiac death, 3 due to infarction and 1 sudden death. The first was an 80-year-old man with an MLA value of 9 mm² in the LMCA and angioplasty with stent implantation in the circumflex artery, which presented restenosis at 9 months and required a repeat procedure. At 3 years he died of an anterior infarction. The second was an 81-year-old man with an MLA value of 10 mm², several moderate lesions in the left anterior descending artery and right coronary artery, and a severe lesion in the circumflex artery that was stented. At 7 months he died of an inferior infarction. The third case was a 68-year-old man with an MLA value of 10 mm² and angioplasty with stent placement in the circumflex artery. At 2 weeks following the intervention he presented stent thrombosis and an inferior infarction with several complications (renal failure, acute peripheral ischemia, and pneumonia) that led to his death. Lastly, sudden death occurred in a 64-year-old man with an LMCA MLA of 10.5 mm² and lesions in the proximal left anterior descending artery and distal circumflex artery treated with rapamycin-eluting stents; the ejection fraction was normal. He died suddenly at 20 months. The noncardiac deaths included neoplastic disease (3 years), grade IV sarcoidosis and pneumonia (1 year), and massive pulmonary fibrosis (2 years).

Coronary surgery was needed in 2 patients, at 2 and 3 years after the initial study. In both cases, the indication

for the procedure was based on the findings of noninvasive testing in patients with stable angina. Progression of the LMCA lesion was observed in both patients on angiographic study (from 47% to 60% and from 48% to 65%) and IVUS (MLA decreased from 7 to 5.2 mm² and from 7.5 to 5.5 mm²). Four other patients required new angioplasty procedures for lesions in vessels other than the LMCA, including 1 case of infarction. Angiographic progression of the LMCA lesion was not observed in any of these cases.

The clinical status at the end of follow-up in the 39 survivors was asymptomatic in 33 (84.6%) patients, very sporadic chest pain in 3 (7.6%), and evident class II stable angina in 3 others (7.6%).

In the group with LMCA revascularization and a comparable follow-up, mortality was similar and there was a lower need for percutaneous coronary interventions (PCI) on lesions in vessels other than the LMCA.

DISCUSSION

Several studies have incorporated IVUS evaluation of intermediate LMCA lesions. Nevertheless, this is the first that has prospectively assessed application of a cut-off value of 6 mm² for the MLA over the long-term. To our knowledge there is only 1 study in which a cut-off value for the MLA was prospectively evaluated. The authors inferred the cut-off with the values obtained in a cohort of patients with angiographically normal LMCAs (mean MLA minus 2 SD=7.5 mm²).⁹ In the clinical follow-up of a group of 114 patients with MLA ≥7.5 mm² and no revascularization, the rate of major cardiac events (death, infarction, and LMCA revascularization) was 8% in the first year, which was comparable to the rate in patients with LMCA lesions that had been revascularized.

We used the 6-mm² cut-off associated with a plaque burden >50% to avoid considering lesions in small LMCAs with only mild or moderate disease as significant (particularly ostial lesions occurring in very small women). This value was based on Murray's law, which is derived from the physiological principle of minimum work and establishes that when a parent vessel branches, the cube of the radius of the parent vessel is equal to the sum of the cubes of the radii of the branches¹⁴:

$$(r \text{ of parent vessel})^3 = \sum (r \text{ of branches})^3$$

If the LMCA has 2 branches (left anterior descending and circumflex arteries) and the MLA threshold for ischemia in these branches is 4 mm²,^{10,11} then, according to the equation, the MLA threshold for ischemia of the LMCA would be around 6 mm² (exactly 6.3 mm²). In a recent study, the findings obtained with a pressure guidewire were compared with those of IVUS and a good correlation was obtained between MLA <6 mm² and FFR <0.75 with the use of relatively small doses of intracoronary adenosin.¹² In this study, the 1-year event

rate (death, infarction, and LMCA revascularization) in the 37 patients with FFR >0.75 and no revascularization was 6%.

In the present study we report the clinical results of applying a cut-off value of <6 mm² for the MLA in combination with a plaque burden >50%. We did not include parameters of lumen area stenosis because of the frequently diffuse character of LMCA disease, which impedes establishment of a normal reference value for the vessel. Among 79 patients with an intermediate LMCA lesion as assessed by IVUS, there were 48 with MLA >6 mm², who, therefore, did not undergo LMCA revascularization, whereas the remaining 31 patients were treated with surgery or angioplasty and stent placement. After a 1- to 6-year follow-up of the group of 48 patients, cardiac death occurred in only 4 cases: 2 octogenarian patients with a baseline LMCA MLA of 9 to 10 mm² who died due to an infarction at 7 months and 3 years, 1 patient with subacute thrombosis of a circumflex artery stent and multiple posterior complications, and 1 sudden death at 20 months. This last case might raise the suspicion of LMCA involvement, but the baseline MLA was 10.5 mm², with only 35% lumen area stenosis and 54% plaque burden. The cause of death in this patient might also have been late thrombosis (2 rapamycin-eluting stents, 1 in the left anterior descending artery, and 1 in the circumflex artery) or infarct in another location.

As to surgery, only 2 patients required revascularization at 2 and 3 years and the procedure was elective. The 1-year rate of primary events was 4.2%.

Cardiac mortality in the nonrevascularized group (8%) after a mean follow-up of more than 3 years is comparable to that observed in large secondary prevention trials, such as the Heart Outcomes Prevention Evaluation (HOPE) or the Scandinavian Simvastatin Survival Study (4S), in which cardiovascular mortality was reported at 1.5% to 2% per year.^{15,16} With regard to the cited studies in which IVUS was used to determine the severity of the LMCA lesion, cardiac mortality was 3% at 1 year,⁷ and total mortality was 11% in 3.6 years⁹; hence, the results were comparable to those of the present study. In a report by Jasti et al,¹² there were no deaths over a follow-up of 3 years, although the series assessed had a much lower associated risk, since patients with an infarct <6 weeks or unstable angina were excluded. In fact, angioplasty was only performed in 13 patients (24%) in that series and all except 4 patients presented additional single-vessel disease.

In the present study, the group without LMCA vascularization included 37.5% with an indication for coronary angiography for infarction and 27% for unstable angina; in addition angioplasty was performed in 77% of the cases with considerable multivessel disease. We believe that our group more closely reflects daily clinical practice than the series in the above-mentioned study.¹²

Comparison of the angiographic findings, and particularly the IVUS findings between the groups with

and without significant lesions, provided several interesting observations. First, although significant differences were found in the mean values for the angiographic parameters, there was considerable overlapping that notably limited the predictive value of angiography. Moreover, angiographic interpretation of LMCA findings is known to be subject to higher interobserver variability.¹⁷ Lesions with MLA >6 mm² were more often at the ostium and much less often diffuse.

As to the IVUS findings, nonsignificant lesions showed a significantly lower remodeling index, which is consistent with previous studies reporting that, for a comparable grade of angiographic stenosis, ostial lesions present greater lumen areas, lower plaque burden, and less remodeling than lesions in other locations.¹⁸ The lesion load at the MLA point was different between the groups, but overlapping was frequent. There was a high degree of plaque burden in the reference segments, approximately 40% in both groups of lesions, a fact indicating that LMCA disease only becomes evident on angiography when the disease is already quite diffuse. The fact that the reference lumen area was smaller and remodeling was greater in the group with MLA <6 mm² (higher overall plaque burden in the entire LMCA) explains why the lumen stenosis area (ratio of lesion lumen to reference lumen) was not significantly different between the groups. This situation illustrates the substantial limitation of angiography as a luminogram (planar silhouette) to determine the severity of arteriosclerotic disease in this location.

Lastly, with regard to the use of IVUS or a pressure guidewire for assessing these lesions, both techniques are valid, although their effectiveness depends on the operator's experience with each of them. Guidewires provide a more physiological assessment with an evident cutoff, which, however, may be dependent on the intracoronary dose of adenosine administered.¹⁹ It would be advisable to use intravenous adenosine in all cases, particularly in ostial LMCA lesions in order to guarantee maximum hyperemia. As to IVUS, the cut-off value for the parameters measured is less certain, although more studies are available than with the pressure guidewire (the present study attempts to contribute to establishing the cut-off). Intravascular ultrasound provides anatomic information, the exact location and extension of the lesion, and characteristics of the plaque. The values obtained are less dependent on the technique.

Limitations

The main limitation of this study is the small number of patients included, which limits its applicability and the subgroup analyses. Nevertheless, the related studies cited do not include extensive series either, despite the fact that they were conducted in high-volume centers. The precise inclusion criteria limit the enrollment of a large number of cases at a single site, and for this reason multicenter studies involving large case series are required.

Although the clinical follow-up is comparable to that reported in previous studies, it may still be insufficient. Another important limitation is the absence of a comparison group resulting from randomization, but this factor is difficult to resolve. The validity of a specific MLA cut-off value for the LMCA, in our case 6 mm², is based on the outcome of a nonvascularized group with an MLA value of >6 mm² and the only fully valid comparison sample would be with a nonvascularized group with MLA <6 mm², circumstances that we doubt would be feasible.

In addition, comparison with the revascularized group depends on many specific factors (type of revascularization applied and surgical morbidity, and mortality), which would require local validation for each center. Once again, true assessment of the results in this group would require comparison with an equivalent non-vascularized group.

Patients were consecutive, but it is likely that not all those meeting the criteria were included, mainly for logistic reasons, but also because of disagreement on the indication for an IVUS study (patients in whom the main operator visualized a mild stenosis and later analysis showed that the value was intermediate).

CONCLUSIONS

Intravascular ultrasound assessment of intermediate LMCA lesions using an MLA cut-off value of >6 mm² as the basis for not indicating interventions on the LMCA seems safe at long-term. Nevertheless, application of this strategy should be limited to the type of patients selected for this study. This approach can reduce the cost and risk derived from unnecessary revascularization procedures and avoids withholding treatment for truly significant lesions.

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