What Is an Appropriate Reference Standard in the Quantitation of Plaque Surface Area by Intravascular Coronary Ultrasound?

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Abstract

We reevaluate the predictive accuracy of intravascular ultrasound (IVUS)-derived per cent plaque area stenosis (PAS) in significant coronary lesions (CLs) with or without proximal and distal reference vessel area adjustment. IVUS is valuable in defining moderate CL severity (30 to 70%) in left main (LM) or non-left main (NLM) coronaries using minimum luminal area (MLA) of ≤ 5.9 and ≤ 4 mm², respectively. Despite a strong correlation with severe CLs, PAS ($\geq 70\%$ for NLM and $\geq 67\%$ for LM) remains underutilized because of confusion about an appropriate reference standard. We studied 120 patients with symptomatic moderate CLs (74 NLM, 46 LM) who underwent IVUS. In-lesion and adjusted PAS were derived by subtracting MLA from in-lesion and proximal or distal reference's external elastic membrane (EEM) area, respectively, divided by corresponding EEM area multiplied by 100. In-lesion PAS was correlated with MLA cutoffs of ≤ 5.9 and ≤ 7.5 mm² for LM and ≤ 4 mm² for NLM. Adjusted PAS strongly correlated with in-lesion PAS irrespective of reference segment (proximal reference, $r = 0.879$, $p < 0.001$; distal reference, $r = 0.833$, $p < 0.001$; mean proximal and distal reference, $r = 0.896$, $p < 0.001$). Considering MLA of ≤ 4 mm² (for NLM) and ≤ 5.9 mm² (for LM), in-lesion PAS of ≥ 70 and $\geq 67\%$, respectively, explained the majority of severe CLs but the sensitive LM MLA cutoff of ≤ 7.5 mm² showed higher predictive accuracy. Based on results, both in-lesion PAS and adjusted PAS can be used interchangeably and correlate strongly with MLA.

Keywords

- ▶ intracoronary vascular ultrasound
- ▶ per cent plaque area stenosis
- ▶ coronary artery disease
- ▶ minimum luminal area

The importance of accurately evaluating angiographically moderate coronary lesions (CLs; 30 to 70%) continues to grow especially in an era of health care cost containment and increasing focus on quality interventional cardiology care.¹ Several tests may be applied to assess the functional significance of a moderate lesion including stress nuclear myocardial perfusion imaging, stress echocardiography, and fractional flow reserve (FFR). Furthermore, intraprocedural anatomic-based testing has been developed that correlates with functional significance of a moderate lesion. For in-

stance, minimum luminal area (MLA) measurement on intravascular ultrasound (IVUS) has been utilized when a functional correlate to the lesion is not available or questionable.^{2–4} Data confirm that MLA ≤ 5.9 and ≤ 4 mm² are predictors of significant functional obstructive coronary artery disease in the left main (LM) and non-left main (NLM) coronary arteries, respectively.^{5–11}

Per cent area stenosis (PAS) was also introduced as an IVUS measure with 70 and 67% cutoffs to predict functional significance of CLs in NLM and LM coronary arteries,

respectively.^{6,8,12} PAS, however, remains underutilized because of controversy about its accuracy when the reference external elastic membrane (EEM) area used is within the lesion rather than that of the EEM or luminal area of a proximal or distal reference segment.^{7,9,13} We comprehensively evaluate in lesion PAS by correlating it both with PAS adjusted to proximal or distal reference area and with established MLA cutoffs to confirm PAS's accuracy in predicting moderate CL significance.

Methods

The study was approved by the Institutional Review Board of our institution. All consecutive patients who had standard coronary angiography (for either medically refractory angina or angina with abnormal nuclear testing) and IVUS measurements of presumed culprit moderate CLs, were included if agreeable to research analysis. Angiographic severity of CLs was validated based on the average consensus of two interventional cardiologists. All IVUS evaluations were reviewed and quantitative plaque surface area, EEM area, and in-lesion MLA's measurements were performed.

IVUS Measurements

After an intracoronary dose of nitroglycerin, IVUS was performed using either a 30-MHz Atlantis SR Pro or I-Cross transducer-tipped 3.2Fr monorail catheter system (Cardiovascular Imaging System, Boston Scientific Corp., Maple Grove, MN) or a 45-MHz transducer tipped 2.9 Fr monorail catheter system (Volcano Corp., Rancho Cordova, CA) using motorized imaging catheter pullback (0.5 or 1 mm/s).

The area selected for IVUS evaluation was the image slice with the smallest MLA (mm²). The area within the EEM

(mm²) was characterized by tracing the leading edge of the adventitial-media border.^{8,13} In defining atherosclerotic plaque burden, plaque media area (PMA) was calculated by subtracting EEM area by MLA area in lesion. PAS percentage (%) was measured using the formula (PMA/EEM area) × 100. Adjusted PAS for reference vessel area was obtained by using the EEM area of the proximal, distal, or mean of both proximal and distal reference segments (adjusted EEM area). Adjusted PAS was then calculated using (adjusted EEM area-in lesion MLA/adjusted EEM area × 100). Reference segments proximally and distally were defined as the most normal looking cross-sections within 10 mm of the lesion before the occurrence of any side branches. IVUS measurements were performed for each CL using the latest I-Review software version for windows (Boston Scientific Scimed, Maple Grove, MN).

Statistical Analysis

Discrete variables are presented as numbers (percentages) while continuous variables are presented as mean ± standard deviation. Correlation between in-lesion PAS and adjusted PAS (using proximal, distal, or mean of both) in all 120 patients were performed using the more specific ≥70% cutoff and were evaluated using Pearson statistical method. Similar Pearson correlation was performed in CL subsets between in-lesion PAS and MLA values. In the NLM and LM subsets, the PAS ≥70 and ≥67%, respectively, were compared with the established MLA cutoffs of ≤4 and ≤5.9 mm² (as well as the alternative LM cutoff of ≤7.5 mm²) for relative diagnostic accuracy of detecting significant obstructive disease. All statistical analyses were performed using SPSS 11.0.1 software package for windows (SPSS, Inc., 2001, Arlington, VA).

Table 1 Patient Demographic and Baseline Clinical Characteristics

Variable	n = 72
Patient age (years)	64.1 ± 10.4
Male (%)	72
Hypertension (%)	89
Hyperlipidemia (%)	86
History of smoking (%)	57
Family history of coronary artery disease (%)	60
Diabetes mellitus (%)	36
History of coronary artery disease (%)	76
Prior myocardial infarction (%)	29
Prior bypass surgery (%)	11
Previous percutaneous coronary intervention (%)	57
Multivessel coronary disease (%)	22
Abnormal nuclear stress test (%)	32
Chronic renal insufficiency (%)	22
Peripheral vascular disease (%)	19

Figure 1 Correlation between 120 moderate lesions plaque PAS and indexed values from IVUS: (A) In-lesion PAS versus lesion PAS indexed for proximal reference (prox. ref.) vessel's EEM area. (B) In-lesion PAS versus lesion PAS indexed for distal reference (dist. ref.) vessel's EEM area. (C) In-lesion PAS versus lesion PAS indexed for average reference (aver. ref.) vessel's EEM area. Lines at $\geq 70\%$ PAS delineate high grade (vs. nonhigh grade) lesions. aver., average; dist., distal; EEM, external elastic membrane; IVUS, intravascular ultrasound; PAS, per cent area stenosis; prox., proximal; ref., reference.

Results

In this study 72 patients (120 moderate lesions: 74 NLM, 46 LM) with symptomatic angina were included. All patients with CLs underwent IVUS. Descriptive demographic and clinical characteristics are shown in ►Table 1. In 115 lesions, all measurable IVUS values were present while in 5 CLs, severe calcification precluded accurate in-lesion EEM analysis. Overall MLA was $3.5 \pm 1.6 \text{ mm}^2$ and $4.3 \pm 1.9 \text{ mm}^2$ in LM CLs, respec-

tively. In-lesion PAS (%) was 81.8 ± 6.9 overall and slightly higher at 83.3 ± 8.0 in the LM subset, despite moderately severe CLs seen on angiography ($48.5 \pm 14.0\%$ stenosis overall with $51.1 \pm 16.1\%$ in LM CLs). Average in-lesion EEM diameters in the LM and NLM subsets of 6.4 ± 1.0 and $4.7 \pm 0.6 \text{ mm}$ were comparably sized to those in the respective original IVUS derivation studies for these vessel subsets.^{3,6,7,12}

Adjusted PAS strongly correlated with PAS irrespective of the reference segment used (proximal reference, $r = 0.879$,

Table 2 Pearson r Correlation of PAS: In-lesion versus Adjusted by Reference EEM Area(s)

PAS Adjusted by Ref.	Lesion Features	In-lesion PAS Correlation	PAS Adjusted by Prox EEM Reference	PAS Adjusted by DistEEM Reference
Prox EEM reference	# Lesions Pearson r P value	$n = 115$ $r = 0.879$ $p < 0.001$	NA	NA
Dist EEM reference	# Lesions Pearson r P value	$n = 115$ $r = 0.833$ $p < 0.001$	$n = 120$ $r = 0.844$ $p < 0.001$	NA
Aver EEM reference	# Lesions Pearson r P value	$n = 115$ $r = 0.896$ $p < 0.001$	$n = 120$ $r = 0.979$ $p < 0.001$	$n = 120$ $r = 0.933$ $p < 0.001$

PAS, per cent area stenosis; EEM, external elastic membrane; ref, reference vessel; prox, proximal; dist, distal; aver, average; NA, not applicable.

Figure 2 Correlation of in-lesion PAS to lesion MLA in 74 non-left main coronary arteries measured by IVUS (ref. vessels 4.7 ± 0.6 mm) using cutoffs of $\geq 70\%$ and ≤ 4 mm² to delineate severe lesions. IVUS, intravascular ultrasound; MLA, minimum luminal area; PAS, per cent area stenosis; ref., reference.

Figure 3 Correlation of in-lesion PAS to lesion MLA in 46 left main coronary arteries measured by IVUS (ref. vessels 6.4 ± 1.0 mm) using cutoffs of $\geq 67\%$ and ≤ 5.9 mm² to delineate severe lesions. IVUS, intravascular ultrasound; MLA, minimum luminal area; PAS, per cent area stenosis; ref., reference

$p < 0.001$; distal reference, $r = 0.833$, $p < 0.001$; mean proximal and distal reference, $r = 0.896$, $p < 0.001$) (►Fig. 1 and ►Table 2). The strongest PAS correlation was seen with the mean of the proximal and distal reference EEM area although the clinical significance is unclear.

When established MLA cutoffs of ≤ 4.0 mm² (for NLM) and ≤ 5.9 mm² (for LM) were used as predictors of significant obstructive disease, both in-lesion PAS of ≥ 70 and $> 67\%$, respectively, explained the majority of significant lesions with high sensitivity, positive predictive value, and overall diagnostic accuracies (►Figs. 2 and 3, and ►Table 3). Notably, when PAS correlations using $\geq 67\%$ were made in the LM subset, the less utilized MLA cutoff of ≤ 7.5 mm² compared with that of ≤ 5.9 mm², had much higher specificity, positive predictive values, and accuracy in predicting severe CLs (►Figs. 3 and 4, ►Table 3) based on PAS.

Discussion

This article demonstrates that in-lesion PAS is reliable as a marker for significant obstructive coronary artery disease when the cutoff of 67 and 70% are used for LM and NLM disease, respectively. The proposition that adjusted PAS^{5,7,9}

corrected for reference area might offer better predictability of disease severity than in-lesion PAS could not be demonstrated in this study. Therefore the use of the easier to derive in-lesion PAS is sufficient to determine significantly severe plaque burden. Furthermore, given that in-lesion PAS correlates strongly with MLA, both MLA and in-lesion PAS can be used independently to predict which lesions are likely to be obstructive. Some studies even suggested that in-lesion PAS offers similar if not more accurate predictability of CL severity than MLA.^{3,6–8} Furthermore, Briguori et al⁸ found that combined use of PAS greatly enhanced the specificity and diagnostic accuracy of CL severity assessment in NLMs when used with other markers versus use of MLA criterion of ≤ 4 mm² alone. Whether MLA and in-lesion PAS in combination are better than either measurement alone cannot be determined from this study and correlation with FFR or other functional testing will be needed.

Applying appropriate MLA criteria in vessel sizes similar to those in validated studies are crucial in any IVUS study especially those proposing alternative MLA cutoffs. This is emphasized by the fact that different criteria are needed for LM and NLM subsets based on large- versus medium-sized vessels but highlighted even more directly in a recent study

Table 3 Comparison of Diagnostic Accuracy of PAS Criteria Using Established MLA Cutoffs

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
PAS $\geq 70\%$ vs. MLA ≤ 4.0 mm ² in NLM	97%	67%	97%	67%	97%
PAS $\geq 67\%$ vs. MLA ≤ 5.9 mm ² in LM	98%	29%	89%	67%	87%
PAS $\geq 67\%$ vs. MLA ≤ 7.5 mm ² in LM	98%	100%	100%	67%	98%

PAS, per cent area stenosis; MLA, minimum luminal area; PPV, positive predictive value; NPV, negative predictive value; vs., versus; NLM, non-left main [coronary artery]; LM, left main [coronary artery].

Figure 4 Correlation of in-lesion PAS to lesion MLA in 46 left main coronary arteries measured by IVUS (ref. vessels 6.4 ± 1.0 mm) using cutoffs of $\geq 67\%$ and ≤ 7.5 mm² to delineate severe lesions. IVUS, intravascular ultrasound; MLA, minimum luminal area; PAS, per cent area stenosis; ref., reference.

by Ben-Dor et al¹⁴ in which different thresholds of ischemic MLA of < 2.5 , < 2.8 , and < 3.7 were correlated to FFR < 0.8 in varying vessel sizes of < 3 , 3 to 3.5 , and > 3.5 mm, respectively. In fact the original derivation study for the 4 mm² cutoff included a highly accurate formula for correcting MLA severity values for varying vessel sizes but its use was ultimately surpassed in favor of a single value that could be “universally applied.”⁷ These studies suggest that different MLA cutoffs are needed based on reference vessel diameter and/or additional supportive markers, such as PAS, are needed to enhance the accuracy and clinical relevancy of abnormal MLA measurements. In fact, the one unifying marker that seems to be applicable to reliably assess CL severity across all vessels sizes is PAS between > 60 and 73% rather than a specific MLA cutoff.^{5–9,12} We therefore argue that in-lesion or adjusted PSA can be universally used with little concerns about reference vessel size, making it likely to be more reliable and easier to use in the cath laboratory than a fixed MLA value.

In this study we have also evaluated PAS with MLA cutoff for LM of ≤ 7.5 mm² in addition to the traditional cutoff of < 5.9 mm². The ≤ 7.5 mm² cutoff was previously validated in a large outcome study¹² but the 5.9 mm² cutoff for LM disease, despite a much smaller study,⁶ has gained wider acceptance based on its comparison with FFR of < 0.75 . Given recent consideration of the value < 0.8 as a more reliable FFR ischemic standard (i.e., than prior < 0.75),^{15,16} reevaluation of whether a 5.9 or 7.5 mm² has higher clinical accuracy in LM CLs may be warranted. Our study did show higher overall specificity, positive predictive value, and overall diagnostic accuracy compared with PAS using the ≤ 7.5 versus ≤ 5.9 mm² cutoff. Future studies correlating PAS values of $> 67\%$, MLA < 7.5 mm², and FFR will be of interest.

We conclude that in-lesion PAS is reliable in predicting severe obstructive disease at the ≥ 67 and $\geq 70\%$ cutoffs when compared with MLA of ≤ 5.9 or ≤ 7.5 mm² for LM disease and

≤ 4 mm² for NLM disease. This marker appears to be an alternative marker for MLA.

Conclusions

This study is retrospective and patient and lesion selection bias cannot be excluded. However, given that all patients were symptomatic with moderate CLs and that IVUS measurements were quantitative, this potential source of error is reduced. Finally, we cannot conclude from this study whether PAS added to MLA improves the identification of functionally significant obstructive lesions. This will need to be validated in future prospective studies. However, the purpose of the study was to determine the best measure of PAS (in-lesion vs. adjusted to proximal or distal reference diameter) when compared with MLA and not to compare the additive value of PAS to MLA.

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