Journal of Geriatric Cardiology (2016) 13: 169–174

Research Article · Open Access ·

Intravascular ultrasound-based analysis of factors affecting minimum lumen area in coronary artery intermediate lesions

Jian LIU, Ying ZHANG, Wei-Min WANG, Zhao WANG, Qi LI, Chuan-Fen LIU, Yu-Liang MA, Ming-Yu LU, Hong ZHAO

Department of Cardiology, Peking University People's Hospital, Beijing, China

Abstract

Objective To identify clinical characteristics associated with the minimum lumen area (MLA) of proximal or middle intermediate lesions in the left anterior descending (LAD) artery, and to develop a model to predict MLA. **Methods** We retrospectively analyzed demographic data, medical history, and intravascular ultrasound findings for 90 patients with intermediate lesions in the LAD artery. Linear regression was used to identify factors affecting MLA, and multiple regression was used to develop a model for predicting MLA. **Results** Age, number of lesions, and diabetes mellitus correlated significantly with MLA of proximal or middle intermediate lesions. A regression model for predicting MLA (mm^2) was derived from the data: $7.00 - 0.05 \times (age) - 0.50 \times (number\ of\ lesions)$. A cut-off value of 3.1 mm^2 was proposed for deciding when to perform percutaneous coronary intervention. **Conclusion** This model for predicting MLA of proximal or middle intermediate lesions in the LAD artery showed high accuracy, sensitivity, and specificity, indicating good diagnostic potential.

J Geriatr Cardiol 2016; 13: 169–174. doi:10.11909/j.issn.1671-5411.2016.02.011

Keywords: Intermediate lesions; Intravascular ultrasound; Predictive model; Risk factors

1 Introduction

Intermediate coronary lesions, which involve stenosis of 40%–70% of vessel diameter, are often detected during coronary angiography.[1] Deciding whether such lesions require invasive percutaneous coronary intervention (PCI) is a challenge, since nearly 90% of lesions show < 60% stenosis, yet 6% of intermediate coronary lesions may develop into acute coronary events.[2,3] If physicians could gain detailed information about the severity of the intermediate lesion, mainly in terms of the minimum lumen area (MLA), they may be able to make a more informed decision about whether PCIs are appropriate.

Intravascular ultrasound is a novel technique that can provide quantitative data about individual blood vessels and lumen area. Using this technique, researchers have identified MLAs < 3.0 or < 2.4 mm^2 as associated with increased risk of myocardial ischemia.[4,5] However, the technique is expensive and difficult to perform correctly, and it can cause complications. We wanted to examine the possibility of developing a model to predict MLA that might work well enough to substitute for direct measurement using intravascular ultrasound. Therefore, we aimed to identify clinical characteristics of patients that may influence MLA and build a model to predict MLA. We examined patient characteristics, endovascular imaging data and vessel and plaque measurements.

2 Methods

2.1 Study population

This study included a consecutive sample of 90 coronary artery disease patients with proximal or middle intermediate lesions in the left anterior descending (LAD) artery (RVD ≥ 2.5 mm; diameter stenosis: 40%–70%) who underwent coronary angiography and intravascular ultrasound at our hospital between November 2008 and April 2014. The population comprised 58 men and 32 women, with ages ranging from 41 to 77 years. Among the included patients, 58 were males and 32 were females, with ages ranging from 41 to 77 years. Exclusion criteria were the presence of left main, bifurcation, small vessel, thrombus, and severe calcified lesions, as well as stent restenosis.

2.2 Coronary angiography

Coronary angiography was performed via the radial or

Correspondence to: Wei-Min WANG, MD, PhD, Department of Cardiology, Peking University People's Hospital, Beijing 100044, China.
E-mail: weiminwang@vip.sina.com
Received: August 15, 2015 **Revised:** November 19, 2015
Accepted: December 12, 2015 **Published online:** February 11, 2016

femoral artery using the standard Judkins technique and a Philips Allura Xper FD10 machine (Philips Healthcare, Best, the Netherlands). After catheter positioning, patients were given 200 μg of nitroglycerin intravenously. Typically, six images of the left coronary artery were captured for each patient, and the image showing the most severe stenosis was used in the analysis. The degree of stenosis was estimated independently by two experienced cardiologists.

2.3 Intravascular ultrasound

Patients were given 200 μg of nitroglycerin through the catheter, and intravascular ultrasound data were collected using a 40-MHz catheter (Atlantis SR Pro, Boston Scientific, Natick, MA). The catheter was positioned beyond the target lesion, and images were acquired using automatic pullback at 0.5 mm/s. Ultrasound data were stored on a hard disk and analyzed off-line.

Lesions were analyzed quantitatively using Qlvus (iMap Basic Viewer 2.1.32.0, Medis Medical Imaging Systems, Leiden, the Netherlands). The external elastic membrane (EEM) and lumen cross-sectional area (CSA) were measured using iMap software. Plaque CSA was calculated as the difference between EEM and lumen CSAs, while plaque burden was calculated by combining plaque area and media area, then dividing by the CSA of EEM. The MLA was defined as the minimum obtained after testing various sites.[6] The terms "proximal" and "distal" were defined to refer, respectively, to the normal lumen sites that were within 10 mm of the MLA and that were in front of any large side branches.

2.4 Statistical analysis

Demographic data, medical history, and ultrasound data were analyzed using SAS 9.1 (SAS, Cary, USA) and SPSS 13.0 (IBM, Chicago, USA); two-sided $P < 0.05$ was defined as the threshold of significance, unless otherwise noted. The entire dataset was randomly divided into a training set (80%), which was used to identify factors associated with MLA and to build a predictive model; and a validation set (20%), which was used to test the model. To identify factors associated with MLA, the training dataset was analyzed by linear regression in which MLA was the dependent variable and the other variables were independent variables. Factors potentially associated with MLA were then analyzed by multiple linear regression that combined global optimization and stepwise regression (inclusion level = 0.05, exclusion level = 0.10) in order to generate the final model. The regression equation predicted a positive value for MLAs < 3.0 mm^2 or a negative value otherwise.

The predictive power of the model was evaluated using a receiver operating characteristic (ROC) curve. Predictive power was considered significant if the area under the curve (AUC) was > 0.5; this cut-off value was based on the Youden index (sensitivity + specificity − 1).

3 Results

3.1 Patient characteristics and intravascular ultrasound results

Clinico-demographic data, medical history, and intravascular ultrasound findings for the patients in the study are shown in Tables 1–2.

3.2 Univariate analysis of factors affecting MLA

Linear regression in which numerous clinico-demographic variables were tested individually for their association with MLA identified the following covariates with $P < 0.15$: age, weight, sex, number of affected vessels, diabetes mellitus, highly sensitive C-reactive protein (hs-CRP), triglycerides (TG), and hematocrit (HCT) (Table 3).

3.3 Multivariate analysis of factors associated with MLA

Factors associated with $P < 0.15$ in the univariate analysis were considered in a multiple linear regression model, which was built using 80% of the total dataset (Table 4). The resulting model performed well against the data ($P = 0.0019$); the model took the form MLA (mm^2) = 7.07685 − 0.04216 × (age) − 0.46879 × (number of affected vessels). This model shows a decline in MLA of 0.04216 units with each 1-year increase in age, and a decline in MLA of 0.46879 units with each additional affected vessel. ROC curve analysis showed an AUC of 0.780 (95% CI: 0.661–0.899) (Figure 1A), suggesting high accuracy and good diagnostic performance.

To facilitate clinical application, we simplified the model to MLA (mm^2) = 7.00 − 0.05 × (age) − 0.5 × (number of affected vessels). This simplified form shows an AUC of 0.777 (95% CI: 0.658–0.896) under the ROC curve ($P = 0.001$, Figure 1B). This model indicates an optimal MLA cut-off of 3.10 mm^2 based on the Youden index (sensitivity + specificity − 1).

The ability of the simplified model to predict MLA below 3.1 mm^2, which emerged here as the cut-off value for deciding whether to perform PCI, was assessed against the training dataset (80% of the total data; Table 5), as well as against the validation dataset (the remaining 20% of the total data; Table 6).

Table 1. Demographic and clinical data for 90 patients with proximal or middle intermediate lesions in the left anterior descending artery.

	Mean ± SD	Minimum	Maximum	Median	95% CI (25%, 75%)
Age, yrs	59.52 ± 9.70	41.00	77.00	57.00	(51.00, 69.00)
Weight, kg	72.18 ± 10.95	47.00	105.00	72.00	(65.00, 79.00)
Affected vessels, *n*	1.61 ± 0.77	1.00	3.00	1.00	(1.00, 2.00)
WBC, $\times 10^9$/L	6.38 ± 1.62	3.06	11.19	6.32	(5.35, 7.43)
PLT, $\times 10^9$/L	200.05 ± 56.21	53.60	351.00	193.00	(158.00, 238.00)
HGB, g/L	137.72 ± 16.79	92.60	225.00	136.00	(127.00, 148.00)
hs-CRP, mg/L	2.84 ± 3.96	0.08	19.93	1.40	(0.50, 2.78)
TG, mmol/L	1.69 ± 1.36	0.54	9.81	1.34	(0.93, 1.85)
CHO, mmol/L	4.47 ± 2.29	1.28	14.10	3.95	(3.28, 4.85)
LDL-C, mmol/L	2.29 ± 0.75	0.87	3.92	2.16	(1.69, 2.91)
HDL-C, mmol/L	1.03 ± 0.32	0.59	3.07	0.98	(0.85, 1.15)
GLU, mmol/L	5.31 ± 1.18	2.71	10.70	5.09	(4.59, 5.69)
CRE, μmol/L	70.86 ± 17.83	38.00	140.00	68.00	(59.00, 78.00)
eGFR, mL/min per 1.73 m^2	96.75 ± 23.75	40.00	169.00	96.00	(83.00, 109.00)
HCT, %	39.82 ± 4.15	26.33	49.48	39.66	(36.63, 43.21)
FIB, mg/L	304.75 ± 58.08	204.00	458.00	265.00	(265.00, 339.00)
MLA, mm^2	3.82 ± 1.38	1.60	9.08	2.98	(2.98, 4.36)
EEM, mm^2	11.56 ± 4.05	4.36	24.10	8.43	(8.43, 14.77)
Plaque burden, %	64.69 ± 11.38	34.00	92.00	57.00	(57.00, 73.00)

CHO: cholesterol; CRE: creatinine; EEM: external elastic membrane; eGFR: estimated glomerular filtration rate; FIB: fibrinogen; GLU: glucose; HCT: hematocrit; HDL-C: high-density lipoprotein-cholesterol; HGB: hemoglobin; hs-CRP: highly sensitive C-reactive protein; LDL-C: low-density lipoprotein-cholesterol; MLA: minimal lumen area; TG: triglycerides; PLT: platelets; WBC: white blood cells.

Table 2. Classification of patients based on coronary and vascular parameters.

Number of affected vessels	
One	51 (56.67)
Two	23 (25.56)
Three	16 (17.78)
Hypertension	
Yes	58 (64.44)
No	32 (35.56)
Diabetes mellitus	
Yes	25 (27.78)
No	65 (72.22)
Dyslipidemia	
Yes	33 (36.67)
No	57 (63.33)
Family history of coronary disease	
Yes	17 (18.89)
No	73 (81.11)
ST-segment depression, mV	
0	64 (71.11)
0.05	22 (24.44)
0.1	4 (4.44)
Minimal lumen area, mm^2	
≥ 4.0	32 (35.56)
< 4.0	58 (64.44)
Minimal lumen area, by category	
≥ 3.0 mm^2	67 (74.44)
< 3.0 mm^2	23 (25.56)

4 Discussion

Coronary angiography is widely regarded as the gold standard for diagnosing coronary atherosclerotic heart disease, but physicians typically use it as a qualitative tool when deciding whether to perform invasive PCI. This may not be the best way to triage intermediate lesions, some of which (6%) may develop into acute coronary syndrome and yet most of which (87%) involve < 60% stenosis.[2] Many physicians perform interventional therapy only when intermediate lesions present together with typical angina pectoris or objective evidence of myocardial ischemia. This remains an important treatment dilemma for cardiologists, highlighting the need for a more quantitative imaging-based approach to assessing stenosis severity.[7–11]

One such approach is intravascular ultrasound, which combines non-invasive ultrasound and invasive catheter technology to provide accurate measurements of EEM area, MLA, and plaque burden.[12–13] Several researchers have sought to correlate MLA values measured by ultrasound with flow fractional reserve (FFR). The prognostic importance of FFR was shown when patients in the FAME study were stratified by FFR: 20% of patients with lesion stenosis > 70% of vessel diameter based on coronary angiography nevertheless did not experience myocardial ischemia, while 35% of patients with lesion stenosis of 50%–70% experi-

Table 3. Simple linear regression to identify factors associated with MLA.

Variable	Regression coefficient	*P*
Age	–0.04476	0.0084
Weight	0.02578	0.1210
Sex (male)	0.52323	0.1269
Affected vessels	–0.47225	0.0183
Hypertension (yes)	–0.02877	0.9335
Diabetes mellitus (yes)	–0.83316	0.0171
Dyslipidemia (yes)	–0.08385	0.8048
Family history (yes)	–0.14774	0.7292
WBC	0.08124	0.4014
PLT	–0.00080	0.7789
HGB	0.01064	0.2528
hs-CRP	–0.08336	0.0951
TG	0.22573	0.1152
CHO	–0.07469	0.2599
LDL-C	–0.07732	0.7326
HDL-C	–0.52058	0.4577
GLU	–0.06956	0.6060
CRE	0.00056	0.9478
eGFR	0.00817	0.2059
HCT	0.06148	0.1034
FIB	–0.00390	0.1860
ST-segment depression	–0.31708	0.3073

CHO: cholesterol; CRE: creatinine; EEM: external elastic membrane; eGFR: estimated glomerular filtration rate; FIB: fibrinogen; GLU: glucose; HCT: hematocrit; HDL-C: high-density lipoprotein-cholesterol; HGB: hemoglobin; hs-CRP: highly sensitive C-reactive protein; LDL-C: low-density lipoprotein-cholesterol; MLA: minimal lumen area; TG: triglycerides; PLT: platelets; WBC: white blood cells.

Table 4. Multiple linear regression to identify variables that predict minimal lumen area.

Variable	Estimate	SE	*t*	*P*
Lumen area	7.07685	0.98767	7.17	< 0.0001
Age	–0.04216	0.01598	–2.64	0.0103
Number of affected vessels	–0.46879	0.19241	–2.44	0.0175

enced severe myocardial ischemia.[14] In fact, the FAME and DEFER studies have confirmed FFR as safe and reliable for designing strategies to treat single- and multiple-vessel lesions.[15,16] Although work from our research group suggested a cut-off of MLA ≤ 4.0 mm^2 as the standard when using intravascular ultrasound to decide whether to perform PCI, more recent work suggests that smaller MLA cut-offs may be more appropriate. Kang, *et al*.[4] reported that MLA < 2.4 mm^2 predicted FFR < 0.80 with a sensitivity of 90%, specificity of 60%, and Youden index of 0.38. Koo, *et al*.[5] showed that MLA < 3.0 mm^2 predicted RVD = 3.0 mm with a sensitivity of 76%, specificity of 62%, and Youden index of 0.38. A third study showed that MLA < 3.04 mm^2 predicted FFR < 0.80 with a Youden index > 0.7.[17]

While substantial evidence suggests that intravascular ultrasound can provide a rigorous quantitative basis for deciding whether or not to perform PCIs on patients with intermediate lesions, the technique is not available or even feasible in many medical environments. The apparatus is expensive and requires expert training for proper operation and analysis. The technique can cause complications, which can increase the costs and duration of hospitalization. Therefore, we wanted to know whether we could use intravascular ultrasound to develop a predictive model that clinicians could rely upon in the absence of direct measurements to estimate likely MLA and therefore decide whether PCI is appropriate. Our model focused on the LAD artery since this is a major blood vessel, it is the most important coronary artery branch, and it strongly influences FFR.[17] Based on our data, we derived a simplified model MLA (mm^2) = 7.00 – 0.05 × (age) – 0.5 × (number of affected vessels), with a cut-off value of 3.10 mm^2. The high sensitivity and specificity of the model when applied against both the original training dataset and the validation dataset suggest satisfactory discrimination. Given the high negative

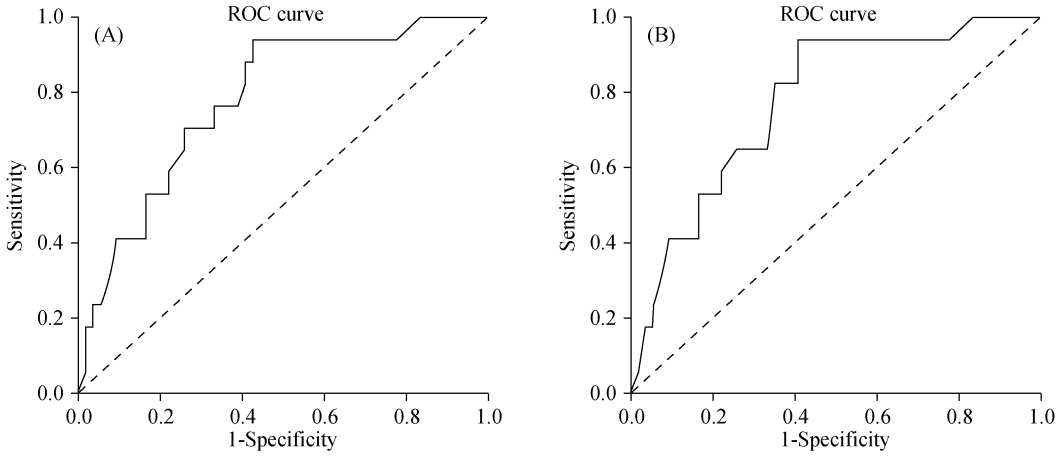

Figure 1. ROC curve describing the ability of the (A) original and (B) simplified multiple linear regression model to predict MLA.
MLA: minimal lumen area; ROC: receiver operating characteristic.

Table 5. Performance of simplified predictive model against the training dataset.

		MLA ≥ 3.0 mm^2 (negative)	MLA < 3.0 mm^2 (positive)	Total
Prediction	MLA ≥ 3.1 mm^2	35	3	38
	MLA < 3.1 mm^2	19	14	33
Total		54	17	71

Sensitivity, 82.35%; specificity, 64.81%; positive predictive value, 42.42%; negative predictive value, 92.11%. MLA: minimal lumen area.

Table 6. Performance of simplified predictive model against the validation dataset.

		MLA ≥ 3.0 mm^2 (negative)	MLA < 3.0 mm^2 (positive)	Total
Prediction	MLA ≥ 3.1 mm^2	9	1	10
	MLA < 3.1 mm^2	3	5	8
Total		12	6	18

Sensitivity, 83.33%; specificity, 75.00%; positive predictive value, 62.50%; negative predictive value, 90.0%. MLA: minimal lumen area.

prediction rate, we suggest that when MLA ≥ 3.10 mm^2, not performing PCI on an intermediate lesion is a reasonable treatment choice, and when no further imaging or functional examinations can be performed. We attribute the low positive prediction rate of the model to our small sample size, so larger studies are needed to verify our results. We caution that model-based MLA prediction should be used in conjunction with other diagnostic methods in order to determine the most appropriate therapy.

Our results should be interpreted conservatively since they are based on a small, single-center, retrospective study, raising the risk of several kinds of bias. In addition, since we identified age as a significant contributor to MLA, future studies should recruit large numbers of patients with diverse ages to allow robust subgroup analysis by age.

Despite these limitations, the model presented here may guide future work in defining evidence-based MLA cut-offs for deciding when to perform invasive procedure to treat intermediate lesions.

References

1 Stone GW, Ellis SG, Cox DA, *et al*. One-year clinical results withthe slow-release. polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004; 109: 1942–1947.

2 Glaser R, Selzer F, Faxon DP, *et al*. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. *Circulation*2005; 111: 143–149.

3 Tobis J, Azarbal B, Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. *J Am Coll Cardiol* 2007; 49: 839–848.

4 Kang SJ, Lee JY, Ahn JM, *et al*. Validation of intravascular ultrasound-derived parameters with fractional flow reserve for assessment of coronary stenosis severity. *Circ Cardiovasc Interv* 2011; 4: 65–71.

5 Koo BK, Yang HM, Doh JH, *et al*. Optimal intravascular ultrasound criteria and their accuracy for defining the functional significance of intermediate coronary stenoses of different locations. *JACC Cardiovasc Interv* 2011; 4: 803–811.

6 Liu CF, Wang WM, Liu J, *et al*. Application of intravascular ultrasound on diagnosis and treatment in patients with coronary artery intermediate lesions. *Chinese Circulation Journal* 2011; 26: 15–18.[Article in Chinese]

7 Schoenhagen P, McErlean ES, Nissen SE. The vulnerable coronary plaque. *J Cardiovasc Nurs*. 2000; 15: 1–12.

8 Badimon L, Badimon JJ, Vilahur G, *et al*. Pathogenesis of the acute coronary syndromes and therapeutic implications. *Pathophysiol Haemost Thromb* 2002; 32: 225–231.

9 Dickson BC, Gotlieb Al. Towards understanding acute destabilization of vulnerable atherosclerotic plaques. *Cardiovasc Pathol* 2003; 12: 237–248.

10 Farb A, Burke AP, Kolodgie FD, *et al*. Pathological mechanisms of fatal late coronary stent thrombosis in humans. *Circulation* 2003; 108:1701–1706.

11 Kawasaki M, Sano K, Okubo M, *et al*. Volumetric quantitative analysis of tissue characteristics of coronary plaques after statin therapy using three-dimensional integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 2005; 45: 1946–1953.

12 Takayama T, Hodgson JM. Prediction of the physiologic severity of coronary lesions using 3D IVUS: validation by direct coronary pressure measurements. *Catheter Cardiovasc Interv* 200l; 53:48–55.

13 Brugaletta S, Garcia-Garcia HM, Shen ZJ, *et al*. Morphology of coronary artery lesions assessed by virtual histology intravascular ultrasound tissue characterization and fractional flow reserve. *Int J Cardiovasc Imaging* 2012; 28: 221–228.

14 Tonino PA, Fearon WF, De Bruyne B, *et al*. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010; 55: 2816–2821.

15 Pijls NH, van Schaardenburgh P, Manoharan G, *et al*. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. *J Am Coll Cardiol* 2007; 49: 2105–2111.

16 Pijls NH, Fearon WF, Tonino PA, *et al*. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 2010; 56: 177–184.

17 Xu Tian, Ge Zhen, Zhang Jun-Jie, *et al*. Optimized quantitative angiographic and intravascular ultrasound parameters predicting the functional significance of single de novo lesions in patients with unstable angina. *Chin J Interv Cardiol* 2013: 284–289.