RESEARCH CORRESPONDENCE

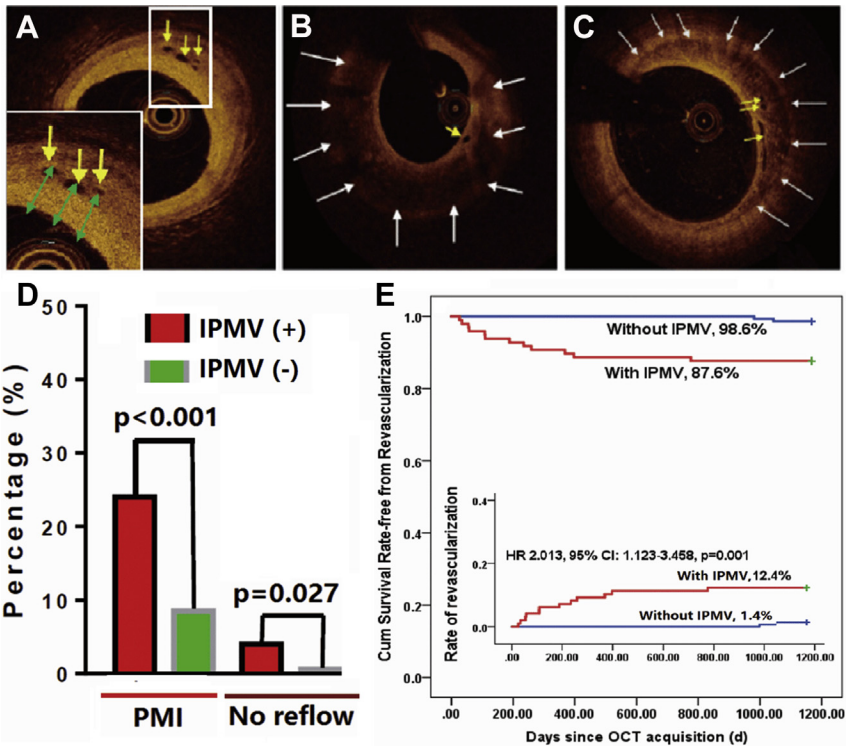
Coronary Artery Intraplaque Microvessels by Optical Coherence Tomography Correlate With Vulnerable Plaque and Predict Clinical Outcomes in Patients With Ischemic Angina

Atherosclerosis is a chronic inflammatory disease characterized by increased requirements of oxygen supply with cells in the plaque (1), which will promote the invasion of the vessel wall by the vasa vasorum and lead to the formation of newly restructured microvessels (MVs) in the plaque. MV formation is reported to be correlated with the vulnerability of plaques (2–4). We analyzed the prevalence and clinical relevance of MVs in patients with coronary artery disease.

This registry study was conducted at 2 centers between February 2012 and May 2015. Exclusion criteria were cardiogenic shock, lesions with diameter stenosis >70%, an estimated glomerular filtration rate <30 ml/min/kg, and left ventricular ejection fraction <30%. All patients provided written informed consent.

All plaque morphologies by optical coherence tomography were defined according to current consensus guidelines. A vulnerable plaque was defined as the presence of rupture, lipid-rich, thin-cap fibroatheroma, erosion, thrombus-containing, sporty calcification, or grade 3 or 4 inflammation. After the acquisition of optical coherence tomographic images, treatment approaches were left to the physician's discretion, and patients were prospectively followed up at 1 year. The primary endpoint was the rate of intraprocedural no reflow and periprocedural myocardial infarction (MI) for patients

FIGURE 1 Definition of Intraplaque Microvessels and Event Rate



(A to C) Distance **(green arrows)** between intraplaque microvessel (IPMV) **(yellow arrows)** and vessel lumen, lipid core, or suspected intraplaque hemorrhage **(white arrows)**; periprocedural myocardial infarction (PMI) and post-stenting no reflow **(D)**; rate of revascularization after medication alone **(E)**. CI = confidence interval; HR = hazard ratio; OCT = optical coherence tomographic.

undergoing implantation of a drug-eluting stent or need for revascularization for patients who were treated only with medication.

Data are reported as counts and percentages or as mean ± SD for continuous variables. The chi-square test or Fisher exact test was used to compare categorical variables. The Student's *t*-test or Wilcoxon rank sum scores for continuous variables were used to compare continuous variables as appropriate. A p value of < 0.05 was considered to indicate statistical significance.

Of a total of 535 patients with 666 vessels, 260 patients (48.6%) with 294 vessels (44.1%) had intraplaque MVs (IPMVs). Sixty-five percent of lesions were localized in the left anterior descending coronary artery, with 78% of IPMVs at the proximal segment of the lesions. However, 17.8% of patients with unstable angina and recent MI had IPMVs at the body lesion ($p = 0.019$) but less often at the distal shoulder (4.2%, $p = 0.011$) and had more frequent vulnerable plaques compared with patients with stable angina. Importantly, the minimal distance from IPMV to intimal surface was 122 ± 13 μm in patients with unstable angina and 108 ± 11 μm in those with recent MI, compared with 407 ± 49 μm ($p < 0.001$) in those with stable angina (**Figures 1A to 1C**). Patients without IPMVs had a larger mean minimal luminal area (2.74 mm^2 vs. 2.45 mm^2; $p = 0.036$) and less vulnerable plaque (56.8% vs. 47.6%; $p = 0.019$) by optical coherence tomography and smaller plaque burden (50.7% vs. 68.2%; $p = 0.035$) compared with patients with IPMVs.

A total of 340 patients with 422 vessels underwent implantation of drug-eluting stents. Rates of intraprocedural no reflow and periprocedural MI were 4.0% and 24.0% in patients with IPMVs, significantly different from 0.6% and 1.6% in patients without IPMVs, respectively ($p < 0.005$ for all) (**Figure 1D**).

Of the remaining 195 patients with 244 vessels who were treated with medication alone, during a median of 3.2 years of follow-up, clinically driven target vessel revascularization was required in 12.4% vessels from 85 patients with IPMVs, compared with 1.4% of vessels in 110 patients without IPMVs ($p < 0.001$) (**Figure 1E**).

The prevalence of IPMVs varies from 38% to 44.6%, depending on patient selection (2–4). We found that IPMVs were more commonly seen at the proximal shoulder and that the plaque burden was the main trigger of IPMV development, supported by previous studies that also showed that vessels containing IPMV had a smaller minimal luminal area (2–4), a surrogate for severe ischemic condition.

In the coronary artery plaque, the narrowest place has extremely high shear stress (2–4), which triggers the plaque to be prone to rupture. This was supported by our result that the minimal distance from the IPMV to the intimal surface was significantly shortened in patients with unstable angina and recent MI. Notably, the presence of IPMVs was more often associated with no reflow and periprocedural MI after implantation of a drug-eluting stent. This finding might suggest the leakage of substances from the plaque into the distal blood flow and, furthermore, strengthens the relationship of IPMVs with plaque vulnerability and intraprocedural safety.

ACKNOWLEDGMENT The authors thank Hai-Mei Xu, Lingling Liu, Wen Teng, and Yingying Zhao for remote monitoring and data collection. We also appreciate the support through the whole study period of the Cooperative Innovational Center of Nanjing Medical University.

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https://doi.org/10.1016/j.jcin.2018.02.011

Please note: This study was funded by a grant from the National Science Foundation of China (NSFC 91639303 and NSFC 81770441). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Tarkin JM, Joshi FR, Evans NR, et al. Detection of atherosclerotic inflammation by ^{68}Ga-DOTATATE PET compared to [18F] FDG PET imaging. J Am Coll Cardiol 2017;69:1774–91.

2. Virmani R, Kolodgie FD, Burke AP, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. Arterioscler Thromb Vasc Biol 2005;25:2045–61.

3. Taruya A, Tanaka A, Nishiguchi T, et al. Vasa vasorum restructuring in human atherosclerotic plaque vulnerability: a clinical optical coherence tomography study. J Am Coll Cardiol 2015;65:2469–77.

4. Amano H, Koizumi M, Okubo R, et al. Comparison of coronary intimal plaques by optical coherence tomography in arteries with versus without internal running vasa vasorum. Am J Cardiol 2017;119:1512–7.