Prognosis of stent implantation on variant angina with severe organic stenosis

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Research article

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Abstract

Objective: To explore the prognosis of stent implantation on variant angina (VA) with severe organic stenosis.

Background: Vasospasm is the pathogenesis of VA. Most VA patients are effective on calcium channel blockers (CCB) or nitrates, and the prognosis is generally good, but organic stenosis is a risk factor for VA.

Method: We collected 141 VA patients treated with CCB and (or) nitrates in the First Affiliated Hospital of Zhengzhou University from December 2010 to June 2019. VA patients with diameter stenosis ≥50% were enrolled .They were divided into two groups according to the presence of stent implantation. The main adverse cardiovascular events (MACE) were observed including cardiogenic death, non-fatal myocardial infarction, readmission due to angina attack, coronary revascularization and heart failure.

Results: 69 cases were included: 33 cases received stent implantation and 36 cases received medical treatment. The proportion of left anterior descending (LAD)(48% vs 44%,p=0.737)which was the culprit coronary artery was very high. Diameter stenosis (84.3%±6.5 %VS 59.9%±010.1%，P<0.001)in stenting group was higher than that in stent-free group. Following up for 24 ± 23 months, there was no significant difference in the incidence of MACE (9% VS 11%) including cardiac death (3% VS 2.8%), coronary revascularization (0% VS 3%) and readmission due to angina (6% VS 5.6%), and effectiveness (88% VS 89%) between the two groups.

CONCLUSION: Although the two groups showed similar clinical outcomes, with anti-spastic and antiplatelet medication, stent implantation was of benefit to the prognosis of VA with severe organic stenosis.

Background

Variant angina (VA), a concept first proposed by Prinzmetal in 1959, refers to angina at rest accompanied by transient elevation of ST segment on electrocardiogram (ECG). Angina caused by coronary artery spasm is currently called vasospastic angina (VSA)[1]. VA is characterized by complete occlusion of lumen, transmural ischemia and clinical chest pain. Coronary spasm may occur in normal coronary arteries, but often occurs in vessels with organic stenosis. Spasm may occur at the site of vascular stenosis in 90% of VA patients with severe organic stenosis [2]，Peter Ong et al. found that VA patients without organic stenosis had better prognosis than those with organic stenosis[3]. Japanese Coronary Spasm Association(JCSA) believed organic stenosis is a poor factor for VA [4]，therefore, stent implantation at the site of vascular stenosis can theoretically prevent future coronary artery spastic occlusion and improve symptoms. Many recent studies and case reports on stent implantation in VA refractory to medical treatment without organic stenosis showed higher incidence of stent deformity, stent-edge spasm and symptom recurrence [5–8], but there are few studies on stent implantation for VSA

with organic stenosis and there is no consensus on the prognosis of stent implantation on VSA with severe organic stenosis. In this study, we compared the clinical outcomes in stenting group with stent-free group to explore the prognosis of stent implantation on VA with severe organic stenosis.

Methods

2.1 patients

According to the diagnostic criteria: (1) chest pain at rest; (2) ST segment transiently elevates (>0.1mv) during angina attack and recovers to baseline level after symptom relief which was confirmed by 12 or 18 lead ECG and Holter monitoring;(3) no evidence of myocardial infarction, we collected all 141 consecutive patients admitted to the First Affiliated Hospital of Zhengzhou University from December 2010 to June 2019. We included all 69 consecutive VA patients with organic stenosis (Diameter stenosis ≥50%). We excluded VA patients who caused spasm by catheter and had the history of stent implantation. 69 cases were graded by JCSA risk score. Informed documents were acquired from all patients.

2.2 Coronary artery angiography (CAG) and stent implantation

CAG After the subcutaneous injection of lidocaine sufficiently, we inserted the sheath into a radial or femoral artery by using the Seldinger technique. After 6000–10000 IU heparin and 200 ug nitroglycerin were given, left and right coronary angiography was performed with 5-F multi-function catheter. At the end of the angiography, 100–200 ug nitroglycerin was injected and subsequent coronary angiography was performed again. The diagnosis was made independently by more than two cardiologists: Diameter stenosis ≥50% or ≥70% was defined as significant stenosis or severe organic stenosis in the left main artery (LM), left anterior descending artery(LAD), left circumflex artery(LCX), right coronary artery(RCA) or its main branches. If with significant coronary artery stenosis, stent implantation was performed with the standard technique by the attending physician’s decision and patients’ agreement, the optimal stent was placed in the stenotic coronary lesions.

2.3 Medical treatment and follow up

All VA patients were treated with CCB or (and) nitrates, patients after stent implantation were also treated with dual anti-platelet aggregation drugs and lipid-lowering drugs for 12 months. After discharge, drugs are adjusted according to the frequency of chest pain, despite increasing doses or the number of antispasmodic drugs, patients complain of chest discomfort, they can be treated by stent implantation by the physician. During the follow-up period, the information of chest pain, the use of antispasmodic drugs, repeated coronary angiography and MACE was collected. The follow-up methods were by telephone or questionnaire and the content was completed by professionals.

2.4 Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are expressed as frequencies (percentages). SAS 9.4(SAS Inc., Raleigh, N.C, USA) software is used for statistical analysis. A t-test was performed for continuous data between two independent samples and a chi-square test was performed for the categorical data. Statistical significance level was defined as a p-value <0.05.

Results

3.1 Baseline characteristics

We collected consecutive 69 VA patients with organic stenosis whose basic characteristics were summarized in Table 1. Diameter stenosis (84.3%±6.5 %VS 59.9%±10.1%，P<0.001) in stent -implanting group was higher than that in stent-free group. There was no significant difference in age, gender, cardiovascular risk factors, biochemical indicators, spastic vessels and hazard levels between the two groups.

3.2 Clinical follow up

All VA patients were treated with CCB or (and) nitrates, patients after stent implantation were also treated with dual anti-platelet aggregation drugs and lipid-lowering drugs for 12 months. After discharge, drugs are adjusted according to the frequency of chest pain, Following up for 24 ± 23 months, there was no significant difference in the incidence of effectiveness (88% VS 89%,p = 0.896) and MACE (9% VS 11%, p = 0.781) including cardiac death (3% VS 2.8%), coronary revascularization (0% VS 3%),and readmission due to angina (6% VS 5.6%) between the two groups (Table 2). 14 cases were reexamined by coronary angiography after one year. One case had 70% restenosis in stents, two cases had 30% restenosis in stents and the other stents had good adherence and no obvious restenosis.

Discussion

Vasospasm is the pathogenesis of VA. Most VA patients are effective on CCB or nitrates, and the prognosis is generally good, but organic stenosis is a risk factor for the prognosis of VA[9]. With the maturity of stent implantation technology and improvement of mechanism, stent implantation has become an important means of revascularization in patients with coronary heart disease. According to the guidelines, stent implantation can be performed in VA patients with severe organic stenosis[10]。In fact, as an unstable angina pectoris, VA is special in risk factors, diagnosis, medical treatment and instrument therapy. Our study found although the two groups showed similar clinical outcomes, with anti-spastic and dual antiplatelet medication, stent implantation was of benefit to the prognosis, improvement of symptoms and quality of life of VA with severe organic stenosis.

Abnormal contraction of coronary artery in VA patients contributes to complete occlusion of blood vessels and high shear stress. When high shear stress is higher than the threshold of damaging

endothelial cells (>70dyne·cm^{-2}) or acute denudation (about 400 dyne·cm^{-2}), von Willebrand factor is activated which makes platelets adhere and aggregate under high blood flow, which accelerates plaque formation [11]。In turn, plaque induces coronary vasospasm, which Peter Ong believes is a response to injured vascular endothelium. [3]。Macalpin et al. found among 69 VA patients with severe coronary stenosis, 62 (90%) cases had spasm at the stenotic site [2]. Stent implantation at the site of vascular stenosis can theoretically prevent future coronary artery spastic occlusion and improve symptoms, moreover, with the popularization and application of new generation drug-coated stents, there is no significant difference in the prognosis between VSA patients with severe organic stenosis and non-VSA patients with severe organic stenosis, which reduced the incidence of adverse cardiovascular events associated with endothelial dysfunction[12], therefore, we believe that stent implantation is a treatment for VA. However, Ge Junbo et al. found that the rate of restenosis and symptoms recurrence after stent implantation in VA patients with severe stenosis was high and the benefit was not satisfying [13]. They enrolled seven VA patients with severe stenosis, whose limitations were a relatively small number of patients and the lack of control group observation. Yasuhiko Tanabe et al. found that in 45 VA patients with severe stenosis, only one case experienced repeated chest pain during the follow-up period and the others inhibited symptoms completely, but during repeated provocation tests, spasm may occur at other sites different from the initial stenosis, so they thought the benefits of stent implantation for VA patients with severe stenosis are limited [14].Last study has shown that the long-term prognosis of VSA with organic stenosis is similar to that of medical therapy and stent implantation[15], whose vascular stenosis (66.3%+9% VS 60.5%+10%, P < 0.001) in VSA patients in stenting group is moderate stenosis, but vascular stenosis in stenting group in our study is sever stenosis. Vascular stenosis is an independent risk factor for MACE in patients with coronary heart disease, there is no significant difference in MACE between the two groups, so we believe that stent implantation reduces the incidence of MACE in VA patients with severe stenosis.

In our study, 7 cases of whom 5 cases take one kind of anti-spastic drugs, 1 case takes two kinds of anti-spastic drugs and 1 case takes three kinds of anti-spastic drugs have MACE including 2 cases for cardiac death,1 case for coronary revascularization and 4 cases for readmission due to angina during the follow-up period, we hypothesize that one of reasons to MACE is incomplete medical treatment. In stenting group, 14 cases were reexamined by coronary angiography after one year. One case had 70% restenosis in stents, two cases had 30% restenosis in stents and the other stents had good adherence and no obvious restenosis. The effective rate of CCB in VA patients in Japan was 92.5%[16]。which is similar to our stenting group (88%)and stent-free group(89%)。Other literatures reported that aspirin, statins and ACEi could prevent spasm and improve the prognosis of patients[17–19]. In addition, we included VA patients,whose diagnostic criteria included resting angina and transient elevation of ST segment one ECG without spasm provocation test, but could be diagnosed as VA with high specificity [10, 20, 21], it has been reported that provocation test is safe and effective for VA patients with no significant stenosis[22],but provocation test has more advantages than disadvantages for VA patients with severe stenosis[23], We believe that provocation test may lead to unstable plaque shedding, which increases the incidence of

MACE and affects the results of the trial. Most of the studies mentioned in this paper are diagnosed as VSA by provocation test, but ST-segment depression is more common than elevation during coronary spasm [24], so we don't think the two situations should be studied together. JCSA believes that chest pain at rest and ST-segment elevation may be indicative of severe MACE, so they listed angina at rest and transient elevation of ST segment as two predictors in JCSA risk score system. According to the score system, VA patients scored at least 3 points and were assessed as moderate-risk group or high-risk group whose incidence of MACE was 7.0% or 13.0% [4, 25]. In our study, there was no significant difference in the distribution of moderate-risk groups (73% VS 75%, P = 0.830) and high-risk groups (27% VS 25%, P = 0.830), so we study the effect of stent implantation on the prognosis of VA patients with severe organic stenosis.

Conclusions

In conclusion, although the two groups showed similar clinical outcomes, with anti-spastic and antiplatelet medication, stent implantation was of benefit to the prognosis, improvement of symptoms and quality of life of VA with severe organic stenosis, which reduced the incidence of MACE.

Limitations(1) This study is a retrospective observation study with a relatively small number of patients, moreover we cannot decide whether medical treatment or stent implantation at that time.(2) None of the patients underwent coronary spasm provocation test, therefore, the selection of target vessels for stent implantation was based on the severity of stenosis, the diagnose of spastic vessels was based on the monitoring of 12 or 18 lead ECG and Holter.(3) Intravascular ultrasound and optical coherence tomography are not used to evaluate the changes of vascular wall structure.

In conclusion, although the two groups showed similar clinical outcomes, with anti-spastic and antiplatelet medication, stent implantation was of benefit to the prognosis, improvement of symptoms and quality of life of VA with severe organic stenosis, which reduced the incidence of MACE.

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Declarations

Availability of data and material

All data generated or analyzed during this study are included in this article.

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Ethics Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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The authors declare that they have no founding

Authors' contributions

WANG Zhe and ZHENG Rujie analyzed and interpreted the patient data regarding variant angina. JIANG Yaohui performed the collection of the cases and was a major contributor in writing the manuscript. SANG Haiqian was the leader of the study.gAll authors read and approved the final manuscript.

Abbreviations

VA: variant angina calcium channel blockers

CCB: calcium channel blockers

MACE: main adverse cardiovascular events

VSA: vasospastic angina

ECG: electrocardiogram

JCSA: Japanese Coronary Spasm Association

CAG: Coronary artery angiography

LAD: left anterior descending

LM: the left main artery

LCX: left circumflex artery

RCA: right coronary artery

SD: standard deviation

TG: triglyceride

HDL-C: high-density lipoprotein-cholesterol,

LDL-C: low-density lipoprotein-cholesterol,

References

[1]E.K. Yoshiki Kusama, Akihiro Nakagomi, Toshiaki Otsuka,et al. Variant Angina and Coronary Artery Spasm: The Clinical Spectrum,Pathophysiology, and Management. J Nippon Med Sch, 2011, 78(1):4-12.

[2]R.N. Macalpin. Relation of coronary arterial spasm to sites of organic stenosis. J. Am. Coll. Cardiol., 1980, 46(1):143–153.

[3] P. Ong, A. Athanasiadis, G. Borgulya, et al. 3-year follow-up of patients with coronary artery spasm as cause of acute coronary syndrome: the CASPAR (coronary artery spasm in patients with acute coronary syndrome) study follow-up. J Am Coll Cardiol, 2011, 57(2):147-152.

[4]Y. Takagi, J. Takahashi, S. Yasuda, et al. Prognostic stratification of patients with vasospastic angina: a comprehensive clinical risk score developed by the Japanese Coronary Spasm Association. J Am Coll Cardiol, 2013, 62(13):1144-1153.

[5]Toshihiko Yoshida, Yoshio Kobayashi, Takashi Nakayama, et al. Stent Deformity Caused by Coronary Artery Spasm. Circ J, 2006, 70(6):800-801.

[6]M. Achille Gaspardone, Fabrizio Tomai, Francesco Versaci, et al. Coronary Artery Stent Placement in Patients With Variant Angina Refractory to Medical Treatment. J. Am. Coll. Cardiol., 1999, 84(1):96-98.

[7]Bunji Kaku, Kanaya Honin, Yhuki Horita, et al. The Incidence of Stent-edge Spasm After Stent Implantation in Patients With or Without Vasospastic Angina Pectoris. Int Heart J 2005, 46(1):23-33.

[8]Vicens Mart´ı, Carmen Ligero, Joan Garc´ıa, et al. Stent Implantation in Variant Angina Refractory to Medical Treatment. Clin. Cardiol, 2006, 29(12):530-533.

[9]F. Takatsu and M. Watarai. Mild stenosis makes prognosis of vasospastic angina worse. Coron. Artery Dis., 2011, 22(1):1-5.

[10]J.C.S.J.W. Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J, 2014, 78(11):2779-2801.

[11]E.S. Shin, A.Y. Her, S.H. Ann, et al. Thrombus and Plaque Erosion Characterized by Optical Coherence Tomography in Patients With Vasospastic Angina. Rev Esp Cardiol (Engl Ed), 2017, 70(6):459-466.

[12]R. Hata, N. Oka, S. Kubo, et al. Impact of Stent Type and Presence of Vasospastic Angina on Long-Term Prognosis. Circ J, 2018, 82(2):469-476.

[13]H. Zy, Q. Jy, Y. Hb, et al. [Clinical and angiographic outcomes of coronary drug-eluting stenting in treating vasospastic angina patients with severe organic stenosis]. Zhonghua Xin Xue Guan Bing Za Zhi, 2012, 40(7):560-564.

[14]Y. Tanabe, E. Itoh, K. Suzuki, et al. Limited role of coronary angioplasty and stentingin coronary spastic angina with organic stenosis. J. Am. Coll. Cardiol., 2002, 39(7):1120-1126.

[15]M. Kim, J.H. Park, J.H. Lee, et al. Comparison of long-term clinical outcomes of percutaneous coronary intervention in vasospastic angina patients associated with significant coronary artery stenosis. Int J Cardiol, 2016, 218:75-78.

[16]Eiichi Kimura and Hiroshi Kishida. Treatment of Variant Angina with Drugs: A Survey of 11 Cardiology Institutes in Japan. Circ J, 1981, 63:844-8448.

[17]B.G. Choi, S.Y. Jeon, S.W. Rha, et al. Impact of Renin-Angiotensin System Inhibitors on Long-Term Clinical Outcomes of Patients With Coronary Artery Spasm. J Am Heart Assoc, 2016, 5(7): e003217.

[18]M. Ishii, K. Kaikita, K. Sato, et al. Impact of Statin Therapy on Clinical Outcome in Patients With Coronary Spasm. J Am Heart Assoc, 2016, 5(5): e003426.

[19] M. Ishii, K. Kaikita, K. Sato, et al. Impact of aspirin on the prognosis in patients with coronary spasm without significant atherosclerotic stenosis. Int J Cardiol, 2016, 220:328-332.
[20]S. Stern and A. Bayes De Luna. Coronary artery spasm: a 2009 update. Circ J, 2009, 119(18):2531-2534.
[21]Antti Saraste , Davide Capodanno , Emanuele Barbato , et al. 2019 ESC Guidelines on the diagnosis and management of chronic coronary syndromes. Eur. Heart J., 2019, 12: ehz425.
[22]Tateishi K, Saito Y, Kitahara H, et al. Safety and usefulness of acetylcholine provocation test in patients with no culprit lesions on emergency coronary angiography. Int J Cardiol, 2018, 269:27-30.
[23]M. Ishii, K. Kaikita, K. Sato, et al. Acetylcholine-Provoked Coronary Spasm at Site of Significant Organic Stenosis Predicts Poor Prognosis in Patients With Coronary Vasospastic Angina. J Am Coll Cardiol, 2015, 66(10):1105-1115.
[24]H. Nakagawa, Y. Morikawa, Y. Mizuno, et al. Coronary spasm preferentially occurs at branch points: an angiographic comparison with atherosclerotic plaque. Circ. Cardiovasc. Interv., 2009, 2(2):97-104.
[25]X. Wang, L. Zhang, C. Gao, et al. ST-segment elevation and the Tpeak-Tend/QT ratio predict the occurrence of malignant arrhythmia events in patients with vasospastic angina. J. Electrocardiol., 2019, 53:52-56.

Tables

Table 1.

Comparison of basic characteristics between the two groups.

	VA with coronary artery stenosis (n = 69)		p-Value
	PCI (+) (n = 33)	PCI (−) (n = 36)	
Age	53.6± 11.4	53.0±11.7	0.813
Male	31(94%)	30(83%)	0.534
Blood chemistry			
Total cholesterol(mmol/L)	3.37±0.91	3.75±0.86	0.078
TG(mmol/L)	1.29±0.55	1.48±0.78	0.239
HDL-C(mmol/L)	1.08±0.19	1.13±0.3	0.458
LDL-C(mmol/L)	2.12±0.72	2.17±0.67	0.792
Cardiovascular risk factors			
Hypertension	14(42%)	13(36%)	0.591
Diabetes mellitus	2(6.0%)	2(5.6%)	0.929
Current smoker	16(48%)	16(44%)	0.737
Dyslipidemia	4(12%)	4(11%)	0.896
Current drinker	13(39.3%)	14(38.9%)	0.966
liver disease	0(0%)	1(3%)	0.335
Nephropathy	4(12%)	6(17%)	0.592
Stroke	2(6%)	1(3%)	0.504
Heart failure(HF)	0(0%)	0(0%)	0.764
Arrhythmia	4(12%)	5(14%)	0.828
Type of spasm			
Single-vessel spasm	26(79%)	27(75%)	0.710
Multi-vessel spasm	7(21%)	9(25%)	0.710
Single vessel spasm			
LM	0(0%)	0(0%)	0.895
LAD	16(48%)	16(44%)	0.737
LCX	1(3%)	0(0%)	0.292
RCA	9(28%)	11(31%)	0.764
Preoperative stenosis	0.843±0.065	0.599±0.101	<0.001
Hazard Level			
High level	24(73%)	27(75%)	0.830
Middle level	9(27%)	9(25%)	0.830

TG: triglyceride, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, LM: left main coronary artery, LAD: left anterior descending coronary artery, LCX: left circumflex coronary artery, RCA: right coronary artery.

Table 2

Comparison of the clinical outcomes between stenting group and stent-free group

	VA with stenosis (n = 69)		p-Value
	PCI (+) (n = 33)	PCI (−) (n = 36)	
MACE	3(9%)	4(11%)	0.781
Readmission due to angina	2(6.0%)	2(5.6%)	0.929
Cardiogenic death	1(3%)	1(2.8%)	0.950
Coronary revascularization	0(0%)	1(3%)	0.335
Outcome			
Effectiveness	29(88%)	32(89%)	0.896
Ineffectiveness	4(12%)	4(11%)	0.896

MACE: main adverse cardiovascular events