Cardiovasc Intervent Radiol (2019) 42:1095–1101
https://doi.org/10.1007/s00270-019-02244-3

CLINICAL INVESTIGATION ARTERIAL INTERVENTIONS

Distal Edge Stenosis After Stent Placement for Isolated Superior Mesenteric Artery Dissection: Mechanisms and Risk Factor Analysis

Cheng Hang[1] · Wenhua Chen[2] · Haobo Su[3] · Zhongzhi Jia[4] · Chunjian Qi[5] · Jianping Gu[3]

Received: 13 March 2019 / Accepted: 9 May 2019 / Published online: 15 May 2019

Abstract

Purpose To analyze factors potentially associated with the occurrence of distal edge stenosis after stent placement for isolated superior mesenteric artery dissection (ISMAD).

Materials and Methods Cases of consecutive patients who were diagnosed with spontaneous ISMAD between February 2010 and July 2018 were retrospectively identified. Of the 123 cases identified, 45 patients (42 men; three women) underwent endovascular stent placement and were included in the study. Univariate and multivariate analyses were used to assess factors potentially associated with distal edge stenosis.

Results The technical success rate among study patients was 100%. During 26.7 ± 17.3 months of follow-up, CT angiography demonstrated good distal edge patency in 25 patients (55.6%) and evidence of distal edge stenosis in 20 patients (44.4%). In univariate analysis, stent length (odds radio [OR] 1.03; 95% confidence interval [CI] 1.01, 1.06; $P = .02$), stent-to-vessel (*S*/*V*) diameter ratio (OR 2.27; 95% CI 1.35, 3.82; $P < .01$), and angulation at the distal edge (OR 1.05; 95% CI 1.00, 1.10; $P = .03$) were significantly associated with distal edge stenosis; only *S*/*V* diameter ratio (OR 3.36; 95% CI 1.41, 7.99; $P < .01$) and angulation at the distal edge (OR 1.12; 95% CI 1.01, 1.23; $P = .03$) retained this significance in multivariate analysis.

Conclusions Distal edge stenosis after stent placement for ISMAD is common. *S*/*V* diameter ratio and angulation at the distal edge are independent risk factors for distal edge stenosis in patients with ISMAD who undergo stent placement.

Keywords Mesenteric artery · Dissection · Stent · Stenosis · Computed tomography

✉ Zhongzhi Jia
jiazhongzhi.1998@163.com

✉ Chunjian Qi
qichunjian@hotmail.com

✉ Jianping Gu
cjr.gujianping@vip.163.com

1 Department of Cardiothoracic Surgery, Changzhou No. 2 People's Hospital, Changzhou 213003, China

2 Department of Interventional Radiology, The Third Affiliated Hospital of Soochow University, Changzhou 213000, China

3 Department of Interventional Radiology, Nanjing First Hospital, Nanjing 210006, China

4 Department of Interventional and Vascular Surgery, Changzhou No. 2 People's Hospital, Changzhou 213003, China

5 Medical Research Center, Changzhou No. 2 People's Hospital, Changzhou 213003, China

Introduction

Spontaneous isolated superior mesenteric artery dissection (ISMAD) is an uncommon, but potentially catastrophic pathology; the etiology of spontaneous ISMAD remains unclear until now [1]. Although most cases of ISMAD can be managed successfully with conservative therapy according to the European Society for Vascular Surgery guidelines, approximately 20% of patients ultimately require an intervention [1]. Appropriate intervention is critical in preventing artery rupture, bowel necrosis, or even patient death [1]. More particularly, endovascular stent placement should be considered for cases of ISMAD that are not responding to medical treatment in patients with suspected bowel ischemia [1]. In such cases, endovascular stent placement can open the stenosed true lumen and promote thrombosis of the dissecting aneurysm [2, 3]. This procedure is not without its risks; neointimal hyperplasia can occur at the edges of a stent, leading to edge stenosis or occlusion [3].This stenosis or occlusion of the stent may result in the occurrence of intestinal ischemia, postprandial abdominal pain, and food aversion and weight loss in severe cases [1]. To date, the factors that may be associated with the occurrence of edge stenosis after stent placement for ISMAD are not completely understood.

In this retrospective study, we therefore sought to evaluate factors that may be associated with distal edge stenosis after the use of endovascular stent placement in patients with spontaneous ISMAD. We also used receiver operating characteristic curve analysis to determine the potential role of these factors in predicting the risk of distal edge stenosis.

Materials and Methods

Patient Selection

This retrospective study was approved by all participating Institutional Review Boards with a waiver of informed consent. The medical records were reviewed to identify cases of consecutive patients who were diagnosed with spontaneous ISMAD between February 2010 and July 2018. Of the 123 cases identified, 78 patients (63.4%) were treated successfully with conservative therapy and so were excluded from the study. The remaining 45 patients (36.6%; 42 men, three women, mean age, 51.8 ± 5.3 years, range 39–69 years) underwent endovascular stent placement and had clinical follow-up results available; these patients were included in the final study population.

Management Decisions Making

Management decisions were based on patient symptoms and the morphologic characteristics of ISMAD. Surgical repair was performed on patients with artery rupture and/or bowel necrosis. Endovascular stent placement was used as the first-line treatment (immediately after diagnosis of ISMAD) in ISMAD patients with a large dissecting aneurysm (defined as an aneurysm diameter ≥ 1.5 times larger than the normal mesenteric artery diameter) and without a re-entry tear. The remaining patients underwent conservative management. Patients in whom conservative management failed were considered candidates for endovascular stent placement as the second-line treatment. Failure of conservative management was defined as the persistence or aggravation of symptoms and signs, increasing size of aneurysmal dilation, or new appearance of a large dissecting aneurysm after conservative management.

Technique

Femoral access was gained via a 5 F sheath, and conventional mesenteric arteriography was performed. A weight-based bolus of heparin (120 units/kg) was immediately administered through the sheath, followed by 1000 units per hour continuously during the procedure, with control of activated clotting time to a target of approximately 150 s. The 5 F sheath was exchanged for an 8 F sheath, and an 8 F guiding catheter was used with the curved tip placed at the orifice of the mesenteric artery. A 0.035-inch stiff guidewire was inserted distally into the mesenteric artery. A stent introducer was then advanced over the stiff guidewire, and a self-expandable stent was deployed. Stent implantation was performed without a balloon before and after dilation [2]. Self-expandable bare metal stents, including Protégé EverFlex or Protégé RX Tapered stents (ev3, Plymouth, Minn) and RX Acculink stents (Abbott Vascular, Calif), were used. In general, a stent size approximately 10% larger than the proximal normal reference diameter was routinely selected. Finally, mesenteric angiography was repeated to confirm resolution of the dissecting aneurysm, stent patency, and improvement in blood flow through the dilated true lumen. Technical success was defined as successful deployment of stents to the target locations.

Post-procedural Care

All patients were treated with antiplatelet therapy after stent placement, including oral clopidogrel 75 mg/day for at least 3 months and aspirin 100 mg/day for at least 1 year. Patients with hypertension, diabetes mellitus, and/or hyperlipidemia were treated with the appropriate guidelines-based therapy. Patients with a history of smoking were advised to quit.

Clinical Follow-up

After discharge, outpatient clinic visits were scheduled at 1 and 6 months during the first year and annually thereafter to allow for follow-up regarding symptoms in all patients, blood pressure in patients with hypertension, fasting blood glucose and glycosylated hemoglobin levels in patients with diabetes mellitus, and blood fat in patients with hyperlipidemia. Besides, patients also underwent CT angiography (CTA) for evaluation of the ISMAD and stent patency during follow-up.

Imaging Analysis

Image interpretation focused on distal edge stenosis and the morphologic characteristics of ISMAD potentially associated with distal edge stenosis. Distal edge stenosis was defined as in-stent restenosis at the distal edge of the stent. The morphologic characteristics of ISMAD assessed in this study included stent-to-vessel (*S*/*V*) diameter ratio and angulation at the distal edge. The *S*/*V* ratio was determined by calculating the ratio between the stent diameter and the vessel diameter (Fig. 1A). The angulation at the distal edge was measured on CTA 6 months after stent placement and was defined as the angle between the tangent line of the distal stent edge and the tangent line of the distal main trunk of the mesenteric artery (Fig. 1B, C). All images were analyzed separately by two independent radiologists, and both of them had > 10 years of experience in vascular radiology.

Factors Associated with Distal Edge Stenosis

Univariate and multivariate analyses were used to assess factors potentially associated with distal edge stenosis. Patient sex; age; history of hypertension, smoking, or diabetes mellitus; stent length (defined as length of the mesenteric artery segment covered with stents); *S*/*V* diameter ratio; angulation at the distal edge; and follow-up time were chosen as potential factors associated with distal edge stenosis.

Statistical Analysis

Interobserver reproducibility values for the evaluation of *S*/*V* diameter ratio, angulation at the distal edge, and distal edge stenosis were analyzed with Cohen's kappa (κ) coefficient in all cases. Factors associated with distal edge stenosis were assessed with a logistic regression model. Factors that demonstrated statistical significance ($P < .05$) as risk factors in the univariate analysis were included in the multivariate analysis, with results presented as odds ratios (ORs) and 95% confidence intervals (CIs). Receiver operating characteristic curve analysis was then used to assess the role of these potential risk factors in predicting distal edge stenosis. All statistical analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Treatments and Outcomes

The baseline clinical manifestations and imaging characteristics for all study patients are summarized in Table 1. All the included 45 patients were present with sudden onset of abdominal pain. The median interval between the onset

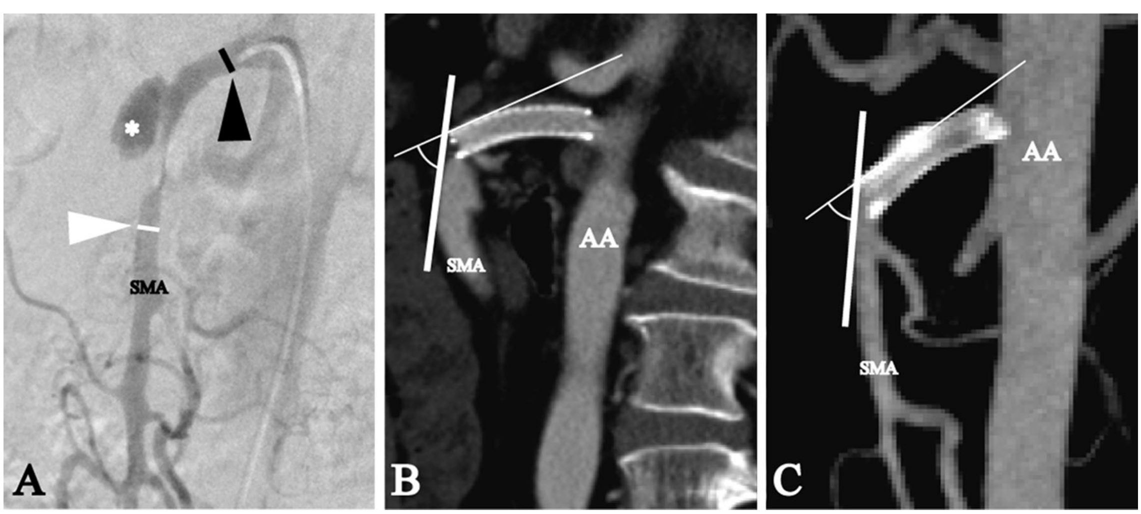

Fig. 1 Calculation of stent-to-vessel (*S*/*V*) diameter ratio and angulation at the distal edge. **A** The *S*/*V* diameter ratio was defined as the ratio of the stent diameter to the vessel diameter (white arrowhead). The vessel diameter was calculated as the axis diameter of the external elastic membrane area on the lateral projection of a mesenteric arteriographic image. The proximal reference diameter was also determined (black arrowhead). **B**, **C** Angulation at the distal edge was measured on CT angiography 6 months after stent placement. This angulation was defined as the angle between the tangent line of the distal stent edge (thin white line) and the tangent line of the distal main trunk of the mesenteric artery (thick white line). Star, dissecting aneurysm; AA, abdominal aorta; SMA, superior mesenteric artery

Table 1 Baseline characteristics of study patients

Characteristic	Study patients (n = 45)
Age (year)[a]	51.8 ± 5.3
Sex	
Female	3 (6.7)
Male	42 (93.3)
History of hypertension	16 (35.6)
History of smoking	12 (26.7)
History of diabetes mellitus	5 (11.1)
Symptoms at time of diagnosis	
New abdominal pain	45 (100.0)
Nausea/vomiting	4 (8.9)
Bloody stools	1 (2.2)
Interval (day)[b]	2 (4 h–2 months)
Radiologic features of ISMAD	
Dissection aneurysm	40 (88.9)
Thrombosed false lumen	5 (11.1)
Located at the anterior wall of the SMA	45 (100.0)
Entry sites	40 (88.9)
Re-entry sites	0
True lumen stenosis (≥ 50%)	41 (91.1)

Unless otherwise specified, data are the number of patients, with percentages in parentheses

[a]Data are means ± standard deviations

[b]The median interval between the onset of symptoms and diagnosis of ISMAD

of symptoms and diagnosis of ISMAD was 2 days (4 h–2 months). In the 45 study patients, endovascular stent placement was performed as the first-line treatment in 11 patients (24.4%) and as the second-line treatment in 34 patients (75.6%). Of the 34 patients who underwent stent placement as the second-line treatment, the intervals between the diagnosis of ISMAD and stent placement and the reasons for conservative treatment failure were 5.5 ± 2.0 days (range 3–10 days) for 15 patients without relief of abdominal pain and 42.4 ± 9.4 days (range 35–70 days) for 19 patients with progression of the dissecting aneurysm (n = 14) or with new appearance of a dissecting aneurysm (n = 5).

Of the 45 study patients, the Protégé stent was used in 34 patients (75.6%) and the RX Acculink stent was used in 11 patients (24.4%). A total of 52 self-expandable metal stents were used in study patients; one stent was used in 38 patients, and two stents were used in seven patients. The median stent diameter was 6 mm (range 6–8 mm), and the mean stent length was 65.7 mm ± 26.2 (range 30–140 mm). The mean *S*/*V* diameter ratio was 1.47 ± 0.3 (range 1.1-2.2). Technical success was achieved in 100% of patients (45/45). Of the 45 patients, 26 patients (57.8%) had symptoms before stent placement, and all of the symptoms were resolved within 2.8 ± 0.6 days following stent placement. No procedure-related major complications occurred.

Interobserver Variability

Near-perfect agreement was shown for the *S*/*V* diameter ratio (κ = 0.89, concordance 93%), angulation at the distal edge (κ = 0.92, concordance 91%), and distal edge stenosis (κ = 0.84, concordance 90%).

CTA Findings

The mean angulation at the distal edge was 11.9° ± 20.8° (range 0°–90°). During 26.7 ± 17.3 months (range 6–84 months) of follow-up, CTA demonstrated good distal edge patency in 25 cases (55.6%) and evidence of distal edge stenosis in 20 cases (44.4%). No cases of occlusion of stented arteries, delayed complications, or symptomatic relapse occurred during the follow-up period.

Risk Factors for Distal Edge Stenosis

Of the nine factors assessed, univariate analysis identified three factors significantly associated with distal edge stenosis: stent length (OR 1.03; 95% CI 1.01, 1.06; P = .02), S/V diameter ratio (OR 2.27; 95% CI 1.35, 3.82; P < .01), and angulation at the distal edge (OR 1.05; 95% CI 1.00, 1.10; P = .03) (Table 2). However, only *S*/*V* diameter ratio (OR 3.36; 95% CI 1.41, 7.99; P < .01) and angulation at the distal edge (OR 1.12; 95% CI 1.01, 1.23; P = .03) were found to be significantly associated with distal edge stenosis on multivariate analysis. On receiver operating characteristic curve analysis, the areas under the curve for *S*/*V* diameter ratio, angulation at the distal edge, and a combination of both factors were 0.87, 0.70, and 0.95, respectively (Fig. 2).

Discussion

In this study, we found that distal edge stenosis occurred in nearly half of patients who underwent stent placement for the treatment of ISMAD. The distal edge stenosis had tendency to occur more commonly with greater oversizing of the stent and a steeper angle. *S*/*V* diameter ratio and angulation at the distal edge were determined to be independent risk factors for the occurrence of distal edge stenosis in these patients.

Approaches such as conservative treatment, stent placement, and surgical repair have been previously reported, given the paucity of ISMAD, the optimal

Table 2 Risk factors for distal edge stenosis

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex (male)	–	–	–	–
Age (years)	1.01 (0.93, 1.10)	.82	–	–
History of hypertension	2.10 (0.61, 7.27)	.24	–	–
History of smoking	1.36 (0.36, 5.11)	.65	–	–
History of diabetes mellitus	–	–	–	–
Stent length[a]	1.03 (1.01, 1.06)	.02	–	–
S/V diameter ratio	2.27 (1.35, 3.82)	< .01	3.36 (1.41, 7.99)	< .01
Angulation at the distal edge	1.05 (1.00, 1.10)	.03	1.12 (1.01, 1.23)	.03
Follow-up time	1.00 (0.97, 1.04)	1.00	–	–

CI, confidence interval; *OR*, odds ratio; S/V, stent-to-vessel

[a]Stent length was defined as the length of the mesenteric artery segment covered with stents

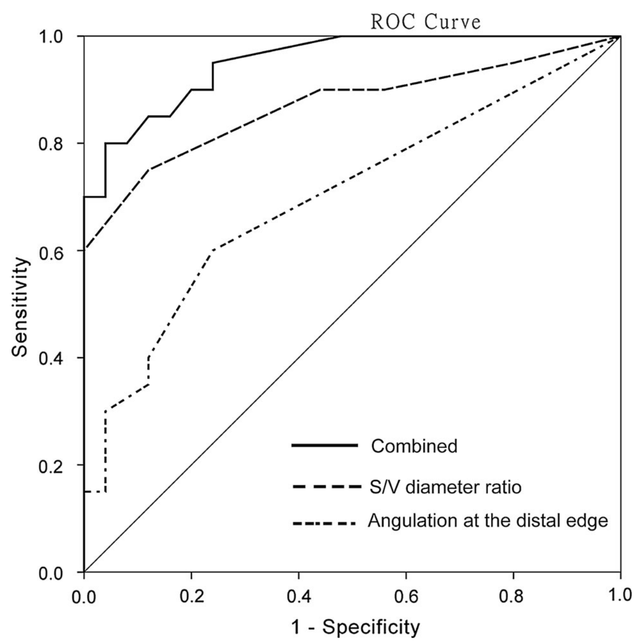

Fig. 2 Receiver operating characteristic (ROC) curve analysis demonstrated areas under the curve of 0.87, 0.70, and 0.95 for stent-to-vessel (*S/V*) diameter ratio, angulation at the distal edge, and a combination of these factors

treatment for ISMAD remains a matter of some controversy [1]. With the development of endovascular techniques, endovascular stent placement has become an accepted and widely used alternative to the surgical repair in the recent years [1]. Although endovascular stent placement has been used widely in the management of ISMAD, with several recent studies demonstrating good stent patency after 1–2 years of follow-up [2, 4, 5], the incidence of edge stenosis after stent placement in this patient population had not previously been determined. In our analysis, distal edge stenosis was common, occurring in 44.4% of patients over 26.7 ± 17.3 months of follow-up. To the best of our knowledge, this is the first study to assess the incidence of distal edge stenosis after stent placement for ISMAD. Although no symptomatic relapse occurred in this study, potential problems, such as intestinal ischemia, postprandial abdominal pain, food aversion, and weight loss, may occur during the longer follow-up. Therefore, to identify the risk factors that may be associated with the occurrence of edge stenosis after stent placement for ISMAD is helpful in making management decision, and also, it is critical in making follow-up strategies.

A number of factors have previously been shown to increase the incidence of edge stenosis in patients undergoing peripheral or coronary artery stent placement, including a history of diabetes mellitus, poor distal runoff, malapposition at the stent edge, a larger reference percentage of plaque area, and hinge motion [6–10]. In the current study, *S/V* diameter ratio and angulation at the distal edge were found to be independent risk factors for the occurrence of distal edge stenosis in patients undergoing stent placement for the treatment of ISMAD, suggesting that these factors could be used to predict the occurrence of distal edge stenosis in this patient population.

S/V diameter ratio has previously been assessed as a potential risk factor for complications after stent placement; in one study, this ratio was shown to be an independent risk factor for restenosis factor after superficial femoral artery stent placement [11]. In the treatment of ISMAD, the size of stent used is often determined in reference to the ostium of the mesenteric artery. However, the vessel diameter at the ostium of the mesenteric artery is often larger than the diameter at the distal site, which can lead to a higher-than-expected *S/V* diameter ratio at the distal site. The mean *S/V* diameter ratio in this study was 1.47 ± 0.3, which was much more than expected. This high *S/V* diameter ratio may induce stress on the vessels and cause intimal proliferation, increasing the risk of distal edge stenosis. Artery stretch and vascular injury attributable to stent over sizing may also be associated with deep penetration of the artery wall, leading to proliferation of neointimal hyperplasia [12]. In addition, self-expanding stents produce a continuous outward force on the vessel that may increase over time [13, 14]. To reduce the incidence of distal edge stenosis, a lower *S*/*V* diameter ratio should be in mind. Therefore, a stent with a tapering configuration is more suitable for placement in the mesenteric artery. Also, a stent size approximately equal to the proximal normal reference diameter may be a better choice than the 10% oversizing.

In this study, angulation at the distal edge was common, as most cases of ISMAD occurred in the curved portion of the mesenteric artery. This type of angulation has previously been reported to induce endothelial shear stress, which is a potential mechanism for the proliferation of neointimal hyperplasia and distal edge stenosis [15]. Research has also shown that physical stress determined by angulation at the stent edge segment and the biomechanical properties of the stent may represent a potential mechanism for edge stent restenosis [16]. In our study, the mean angulation at the distal edge was 11.9° ± 20.8°, and this angulation was shown to be a risk factor for the occurrence of distal edge stenosis. To prevent or reduce this angulation, stents with more flexibility and weaker radial force should be chosen.

This study had several limitations. First, this was a retrospective analysis. Second, the calculations of S/V diameter ratio and angulation at the distal edge were performed manually, not automatically, and the reference vessel diameter was difficult to determine precisely because of the rather small diameter of the mesenteric artery; these factors may have biased the results. Third, because of the rarity of ISMAD, this study is limited by its small sample size; nevertheless, it remains one of the largest patient cohorts to be reported in the literature to date and is the first study to analyze factors associated with distal edge stenosis after endovascular stent placement in patients with ISMAD. Fourth, some residual and unmeasured confounding factors such as arterial stretch and deep injury due to continuous movement of the mesenteric artery were not assessed. Fifth, the effect of platelet aggregation inhibition was not checked. Sixth, we did not analyze factors associated with proximal edge stenosis because this type of stenosis is less common and occurred in few of our study patients. Further investigation regarding the potential risk factors for proximal edge stenosis is needed. Finally, although no symptomatic relapse occurred during the follow-up period, potential problems, such as intestinal ischemia, postprandial abdominal pain, and food aversion and weight loss, may occur during the longer follow-up.

In conclusion, our results demonstrated that distal edge stenosis is common after patients are treated with self-expanding nitinol stents for ISMAD, the distal edge stenosis had tendency to occur more commonly with greater oversizing of the stent and a steeper angle, and S/V diameter ratio and angulation at the distal edge are independent risk factors for distal edge stenosis in these patients. In light of these findings, caution should be taken in stent placement for ISMAD; also, we suggest that when a stent is placed in the curved area of the mesenteric artery, the stent-landing zone for the angle of the edge should be minimal. Additionally, a stent with a tapering configuration or a newer-generation stent with better flexibility and weaker radial force may be appropriate options in this patient population.

Acknowledgements We thank Jian Wang, Qiao Chen and Weixing Zhuang, for their help with data analysis; and Megan Griffiths, scientific writer, Cleveland, Ohio, USA, for her help with revising the manuscript.

Funding This study was supported by the China Postdoctoral Science Foundation (2018M630582), the Natural Science Foundation of China (81401498), and the Jiangsu Provincial Medical Youth Talent (QNRC2016270). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors indicated no potential conflicts of interest.

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