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Review

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Challenging situations in primary percutaneous coronary intervention: clinical scenarios and main approaches

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Abstract

Primary percutaneous coronary intervention (PCI) is one of the most effective treatment modalities for acute life-threatening diseases. Although successful PCI provides a direct positive effect on patient survival, failure may be associated with the disappearance of this benefit and, beyond that, worsening of the prognosis. Disparities in the coronary anatomy, the pathologic nature of the culprit lesion, and the underlying mechanisms of acute coronary syndrome can complicate PCI. An invasive cardiologist must be aware of these challenging situations and how best to manage them. This review aims to summarize troublesome scenarios such as no-reflow, large thrombotic lesions, ectasia-associated myocardial infarction, and spontaneous coronary artery dissection in primary PCI and to provide practical information on how to manage these situations.

Keywords: Acute myocardial infarction, thrombus, coronary artery ectasia, spontaneous coronary artery dissection

INTRODUCTION

ST-elevation myocardial infarction (STEMI) is one of the clinical spectrums of acute coronary syndromes. In general, acute atherothrombotic coronary occlusion is the cause of STEMI. Emergent and successful reperfusion is the most critical factor in reducing morbidity and mortality. Although reperfusion treatment with thrombolytic agents is an alternative, timely primary percutaneous coronary intervention (PCI) is the

preferred treatment modality. Successful reperfusion is defined as good coronary microvascular perfusion after PCI. However, successful reperfusion at the capillary level is not possible in all cases. Slow-flow/No-reflow, which indicates inadequate tissue reperfusion after PCI, is an essential poor prognostic predictor. Additionally, some anatomic, pathophysiologic, and mechanistic factors can complicate successful reperfusion in STEMI. Large thrombus burden, coronary artery ectasia/aneurysms, and spontaneous coronary artery dissection (SCAD) are challenging and can complicate primary PCI. This review provides an overview of the challenging clinical scenarios related to primary PCI and the management of particular situations to improve angiographic outcomes.

SLOW-FLOW/NO-REFLOW DEVELOPMENT

Overview

Coronary slow-flow is defined as inadequate coronary perfusion despite recanalization of the culprit lesion. Sometimes, opacification of the distal vessel completely interrupts, called no-reflow[1]. The term myocardial no-reflow was used for the first time by Kloner *et al.* in a description of a canine model of coronary ischemia[2]. Thrombolysis in myocardial infarction (TIMI) flow grade and myocardial blush grade (MBG) are used for the contemporary angiographic definition of slow-flow/no-reflow diagnosis[3]. The incidence of slow-flow/no-reflow depends on the detection method and interobserver variability. For example, angiographic studies have reported a no-reflow incidence of approximately 7%, whereas cardiac magnetic resonance imaging (MRI) has identified microvascular dysfunction in more than 50% of STEMI patients[4,5]. Furthermore, Rezkalla *et al.* found that the incidence of no-reflow was 32% when using the TIMI flow grade and 52% when using MBG in the same patient population[6]. According to TIMI flow classification, coronary perfusion is graded between TIMI flow 0 and TIMI flow 3[7]. TIMI flow 0 defines no distal perfusion beyond the culprit lesion, TIMI flow 1 defines contrast filling distal of the culprit lesion, but no filling of the entire vessel, TIMI flow 2 defines complete but slow opacification of the distal vessel, and TIMI flow 3 defines normal opacification of the distal vessel. According to the TIMI classification, distal circulation lower than TIMI 3 flow is considered slow-flow. However, microvascular perfusion may be low despite angiographic TIMI 3 flow. TIMI myocardial perfusion grade (TMPG) and MBG are used as markers of microvascular perfusion to evaluate tissue-level perfusion[8,9]. MBG compares infarcted myocardial contrast density with that of non-infarcted myocardial segments. If there is no contrast density, myocardial blush is defined as grade 0; if there is minimal contrast density, myocardial blush is defined as grade 1; if there is moderate contrast density, myocardial blush is defined as grade 2; and if there is similar contrast density compared with other territories, myocardial blush is defined as grade 3. ST segment resolution on electrocardiography (ECG) is another marker of myocardial perfusion status[10]. Contrast echocardiography and cardiac MRI are the other tools for evaluating microvascular myocardial perfusion[11,12]. Both imaging methods provide worthy information about the diagnosis and prognosis of slow-low/no-reflow; further discussion about these imaging methods is beyond the scope of this article as they could not be performed during primary PCI.

Atherothrombotic material embolization and reperfusion injury are the underlying pathophysiological mechanisms of no-reflow. These conditions result in microvascular obstruction, intramyocardial hemorrhage, and microvascular dysfunction[13]. Advanced age, diabetes, late intervention (> 6 h after symptoms), hypotension, worse Killip class, reduced ejection fraction, angiographic diffuse lesion, saphenous graft intervention, large vessel diameter, and heavy thrombus burden are the predictors of no-reflow development[14,15]. Angiography-based diagnostic tools are essential for diagnosis, as cardiac MRI and contrast echocardiography are inaccessible during primary PCI. The TIMI flow grade and myocardial blush grade can be used as ad hoc variables for diagnosis. Invasive intracoronary measurements, such as coronary flow reserve and microvascular resistance index, provide more objective information about coronary flow and microvascular resistance, but they are not recommended in routine clinical practice because of the lack

of scientific evidence. There are small proof-of-concept studies for their use in guiding Slow-flow/No-reflow management, and no prospective randomized study has addressed invasive coronary measurement-derived primary PCI to deal with Slow-flow/No-reflow[16].

Treatment

Prevention of slow-flow/no-reflow development is the best option; however, there is no evidence-based optimal strategy for this purpose. Intracoronary vasoactive agent administration, intensive antithrombotic treatment, pre- and postconditioning, thrombus aspiration, distal embolic protection device use, and direct stenting are all suggested methods for prevention[17,18]. When slow-flow/no-reflow develops, the operator must manage this situation. The initial approaches for slow-flow/no-reflow differ according to the distal TIMI flow. If there is TIMI 1-2 flow after intervention and the distal vessel is visible on angiography, intracoronary vasodilator and antithrombotic agents can be administered. However, if there is TIMI 0 flow, persistent stenosis, coronary artery dissection, flow limiting thrombus, or coronary artery spasm can be the cause of no-reflow. Therefore, the first thing that must be done is to exclude these mechanical factors. Distal contrast injection through a microcatheter or a perforated balloon enables visualization of the distal part of the vessel[19,20]. Intravascular imaging by optical coherence tomography (OCT) or intravascular ultrasound imaging (IVUS) is another option for such cases. The second thing is to increase blood pressure if there is profound hypotension. Vasoactive drug administration and antiplatelet/fibrinolytic therapies are first-line treatment options after excluding mechanical factors and profound hypotension. There is no optimal management strategy for slow-flow/no-reflow because none of the proposed therapies provide a mortality benefit. There is limited evidence regarding the effects of GpIIb/IIIa inhibitors on no-reflow treatment. Akpek *et al.* found that tirofiban improved TIMI flow after no-reflow development compared with placebo[21]. However, data on GpIIb/IIIa inhibitors are for the prevention of no-reflow rather than treatment. Current guidelines discourage their routine use, and only bailout administration is recommended[22].

Intracoronary vasoactive drug administration is the most frequently used management approach for resolving slow-flow/no-reflow. Epinephrine is one of the vasoactive agents used to manage no-reflow. Many case series and small-sized studies have demonstrated successful TIMI flow improvement with intracoronary epinephrine administration[23-25]. Adenosine, calcium channel blockers verapamil, diltiazem, and nicardipine, nitroprusside, nicorandil, and anisodamine are the other agents reported to combat no-reflow[26-31]. A network meta-analysis evaluated the efficacy of the seven drugs on no-reflow treatment[32]. Anisodamine was found to have more favorable effects on no-reflow than adenosine, diltiazem, nicorandil, nitroprusside, urapidil, and verapamil. Another study found that intracoronary epinephrine is as effective as adenosine in managing slow-flow/no-reflow, with a more favorable long-term prognosis than adenosine[33]. Given the paucity of data about the comparative effectiveness of particular agents and the need for more randomized trials of sufficient size, there are no firm recommendations regarding which agent should be selected in no-reflow. A critical factor in resolving slow-flow/no-reflow is the effective administration of vasoactive agents into the distal vasculature. In general, these agents are administered through a guiding catheter. However, vasoactive drugs cannot penetrate the capillary level in patients with TIMI 0/1 flow, and all administered drugs could pass to the non-infarcted perfused myocardium as there is no capillary perfusion during the no-reflow period in the infarcted area. Distal drug administration is an effective way to deal with this problem. Over-the-wire balloons, coronary microcatheters, and distal perfusion catheters can be used for distal drug administration[34-36]. Perforated monorail balloon catheters are also a cost-effective and simple method of distal drug administration[37]. Finally, therapeutic systemic or intra-coronary hypothermia and ischemic post-conditioning were tested to manage slow-flow/no-reflow. Both methods are suggested to decrease reperfusion injury and slow-flow/no-reflow[38-40]. However, further evidence is needed before their wider application. Figure 1 shows an example of coronary no-reflow dealing with distal

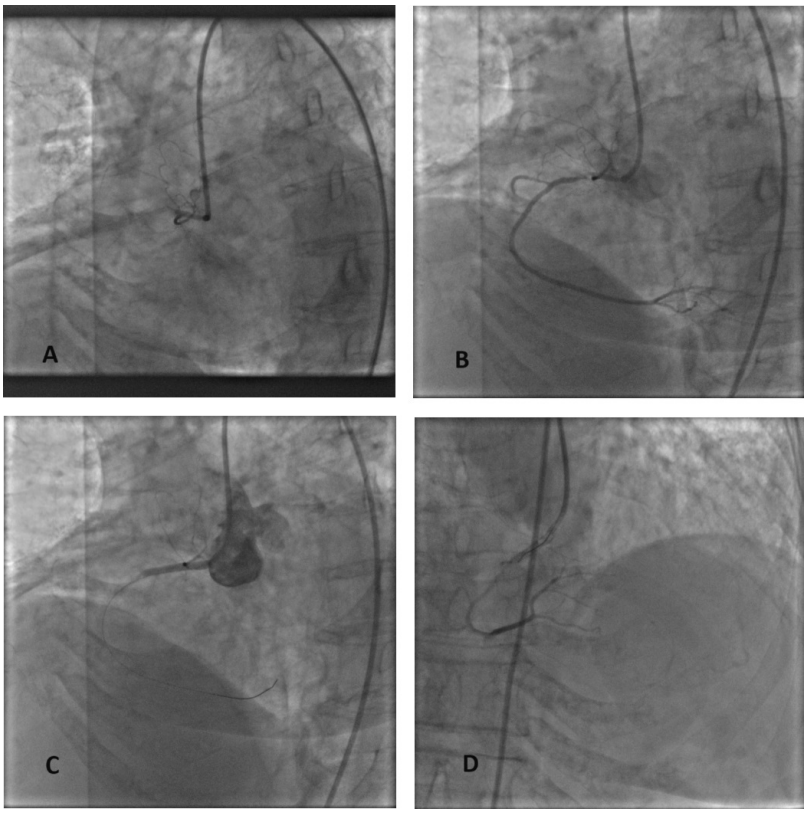

Figure 1. Diagnostic angiography of a patient with inferior myocardial infarction (A); After balloon dilatation, a satisfactory distal flow was provided (B); However, no-reflow developed after stent implantation (C); Predilatation balloon was perforated with a needle and 200 mcg of adenosine was administered through the balloon into the distal right coronary artery. TIMI 2-3 flow was achieved (D). TIMI: Thrombolysis in myocardial infarction.

adenosine administration through a perforated monorail balloon catheter.

LARGE THROMBUS BURDEN

Overview

Theoretically, there must be a thrombus in the culprit lesion in all Type 1 myocardial infarctions according to the universal definition of myocardial infarction document[41]. However, the thrombus burden is not the same in every case, and a large thrombus burden is significantly associated with angiographic success, long-term stent thrombosis, and mortality[42]. Angiographic success is better for small thrombotic lesions than for large thrombotic lesions. It is expected that a larger thrombus will be observed in saphenous graft infarctions and stent thrombosis compared to native coronary lesions. Additionally, coronary embolization from heart chambers or prosthetic heart valves can be the cause of large coronary thrombus[43]. Angiographic thrombus grading could be performed as described by Gibson *et al.* (TIMI Thrombus scale, Table 1). According to this classification, grade 4 and 5 thrombus are accepted as large coronary thrombus[44].

Treatment

Diagnostic angiography can provide clues for the presence of a large thrombus. For example, in case of a cut-off pattern of occlusion, persistent dye stasis at the distal part of the occlusion, a floating thrombus in the proximal portion of the occlusion, and a large infarct-related artery (reference diameter > 4 mm), the probability of a large thrombus increases. After wire crossing and balloon dilation with a small balloon, the

Table 1. The thrombolysis in myocardial infarction thrombus grading

Grade	Description
0	No angiographic thrombus
1	Angiographic features suggestive of thrombus like decreased contrast density on the culprit lesion, haziness of contrast, irregular appearance of the lesion, smooth convex meniscus at the site of total occlusion suggestive but not firmly diagnostic of thrombus
2	There is a small-sized definite thrombus. The greatest diameter of the thrombus is smaller than the half of the vessel diameter
3	There is a moderate-sized definite thrombus. The greatest diameter of the thrombus is between ½ and 2 times of the vessel diameter
4	There is a large-sized definite thrombus. The greatest diameter of the thrombus is greater than 2 times of the vessel diameter
5	There is a definite thrombus appearance, and the vessel is totally occluded

thrombus burden must be classified according to the TIMI thrombus scale. Dual antiplatelet treatment with aspirin, a potent P2Y12 inhibitor, and parenteral anticoagulation administration are the standard of care measures. If the thrombus burden is small after wire crossing and small-sized balloon dilation, direct stenting or lesion preparation and stenting can be performed. There is no additional intervention or medication if TIMI flow and myocardial blush are satisfactory. Glycoprotein IIbIIIa inhibitors are recommended in slow-flow/no-reflow and thrombotic complicated cases. If the thrombus burden is large and there is no improvement after balloon dilation, mechanical thrombus removal or dissolution is required. Manuel thrombus aspiration catheters are the most widely used devices for this purpose. Although the TOTAL trial[45] demonstrated no reduction in cardiovascular death, recurrent myocardial infarction (MI), cardiogenic shock, or heart failure within 180 days by routine application in patients with STEMI, thrombus aspiration has an essential role in successful angiographic results in selected cases. Thromboembolic stroke risk increases by thrombus aspiration, and care must be taken during aspiration. First, the guiding catheter must be well engaged in the coronary artery. Negative pressure must be applied continuously until the aspiration catheter is removed from the guiding catheter. After this, retrograde bleeding through the guiding catheter should be checked. Remnant large thrombus particles can obstruct the guiding catheter. Repeat aspirations can be performed according to the residual thrombus burden and success of the thrombectomy. Mechanical thrombectomy using some dedicated devices is an alternative to manual thrombus aspiration. AngioJet (Bayer Healthcare) and the Penumbra system are commercial devices for mechanical thrombectomy[46,47]. A distal embolic protection device is another option to prevent distal embolization. Their use is encouraged for saphenous vein graft interventions. Combined thrombus aspiration and low-dose intracoronary thrombolytic administration can be used in resistant cases. Finally, deferring stent implantation may have a beneficial impact on TIMI flow and MBG in patients with residual large thrombus after initial balloon dilation and thrombus aspiration. Stent implantation in large thrombotic lesions, especially in large coronary arteries, can result in slow-flow/no-reflow. Adjunctive antithrombotic treatment and deferred stenting improve microvascular flow in these selected cases. Additionally, optimal stent sizes could be selected in a deferred stenting strategy instead of immediate stenting in this particular patient group[48,49]. Figure 2 shows an example of an inferior myocardial infarction with a large thrombus which was managed by thrombus aspiration.

CORONARY ARTERY ECTASIA

Overview

Coronary artery ectasia refers to a coronary artery segment > 1.5 times dilated compared to the adjacent normal artery. “Coronary artery aneurysm” is used if the dilatation is focal, and “coronary artery ectasia” is used if the dilatation is diffuse in the terminology. The prevalence of coronary artery ectasia is reported to be between 0.5% and 10% in angiography series, with significant regional disparities[50]. Atherosclerosis is the most frequent underlying factor; however, inflammatory diseases, such as Kawasaki, uncontrolled hypertension, and some genetic disorders affecting vessel walls may be the cause of coronary artery

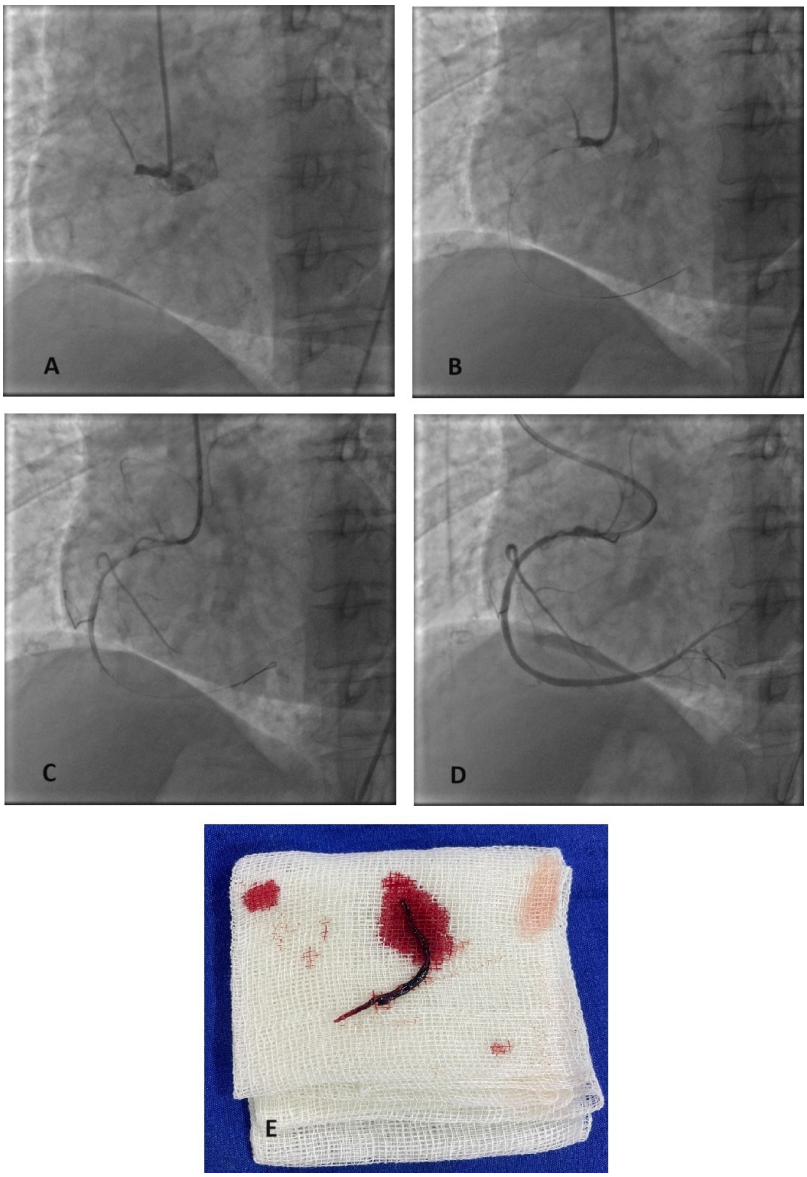

Figure 2. Inferior myocardial infarction with a large thrombus treated with thrombus aspiration. Diagnostic initial angiography(A); Angiography after wire crossing (B); The thrombus shifted to the mid-portion of the RCA after balloon dilatation (C); TIMI III flow was achieved after thrombus aspiration (D); Aspirated thrombus material (E). TIMI: Thrombolysis in myocardial infarction; RCA: Right coronary artery.

ectasia[51]. Disruption of normal laminar flow and spontaneous thrombus formation, acute plaque rupture, or distal embolization from a proximally occurred thrombus may be the underlying mechanism of STEMI in patients with coronary artery ectasia[51].

Treatment

The vast majority of patients with STEMI associated with coronary artery ectasia have large intracoronary thrombus, which complicates percutaneous coronary intervention. GpIIbIIIa inhibitors and thrombus aspiration are commonly used in STEMI cases with coronary artery ectasia. The residual thrombus burden could be high despite thrombus aspiration. Continuing intense antithrombotic treatment with parenteral heparin + GpIIbIIIa inhibitors and deferred stenting is commonly used in such cases. Although routinely

deferred stenting has no beneficial effect on cardiovascular outcomes compared with standard primary PCI, ectatic coronaries with large thrombus are beyond this perspective and should be applied in selected cases[52,53]. Long-term management should be individualized and the patient's underlying condition is important. Aggressive risk factor modification is required as atherosclerosis is implicated in the pathogenesis[54]. Longer dual antiplatelet treatment and the combination of oral anticoagulant and antiplatelet agents should be selected according to patient-specific conditions regarding ischemic and bleeding risk[55]. Figure 3 illustrates a case of posterior myocardial infarction associated with coronary artery ectasia. This condition was managed with thrombus aspiration without the need for stent implantation.

SPONTANEOUS CORONARY ARTERY DISSECTION

Overview

SCAD is observed in young women (90%); however, males with SCAD have been reported[56]. The prevalence of this condition increases in women < 50 years, pregnant, and postpartum[57]. Concomitant fibromuscular dysplasia is reported up to 70%[58]. Lifting a heavy weight or emotional triggers could be a typical feature of the patient's history. The underlying mechanism of myocardial infarction in SCAD is the development of a non-traumatic, non-iatrogenic separation of coronary intima-media layers and compressing intramural hematoma. There are two hypotheses for explaining intramural hematoma development: outside-in and inside-out theories[59]. With the widespread use of intravascular imaging, different angiographic appearance patterns of SCAD have been defined well[60]. There are four different types according to the current classification. In type 1, there is a visible angiographic dissection flap, and the contrast persists in the dissected segment. There is long diffuse narrowing in type 2. The dissected segment continues with the normal distal vessel segment in type 2A. The dissection expands to the distal tip of the coronary in type 2B. Type 3 has a focal angiographic lesion appearance (less than 20 mm), which is hard to differentiate from an atherosclerotic lesion. In type 4, the coronary is totally occluded. Intracoronary imaging plays a pivotal role in the definitive diagnosis of SCAD. OCT is preferred over IVUS. It could be hard to differentiate intramural hematoma from homogenous atherosclerotic plaque on IVUS. OCT shows intimal tear and intramural hematoma with good resolution[61].

Treatment

Interventionists should always keep in mind that the culprit lesion could be a SCAD. Angiographic diagnosis of SCAD depends on high suspicion, and care must be taken, especially in young women. Although intravascular imaging by OCT and IVUS diagnoses an underlying SCAD, it should be noted that these facilities are not available in every catheterization laboratory, and it could not be possible to perform intravascular imaging in the middle of the night during primary PCI[62]. The primary factors influencing interventional treatment decisions in SCAD-associated MI are ongoing ischemic symptoms and findings. Conservative treatment is recommended for patients whose symptoms and ischemic findings are resolved. Percutaneous intervention must not be performed in this patient group despite the presence of severe stenotic angiographic lesions. Beta-blockers are the mainstay of medical treatment. There is no firm recommendation about antiplatelet therapy. Single or dual antiplatelet therapy (DAPT) and the recommended duration of DAPT are based on expert opinions. A recent registry showed that single antiplatelet treatment had significantly more favorable outcomes compared with 12-month DAPT[63]. Anticoagulant agents, glycoprotein IIbIIIa inhibitors, and fibrinolytic agents are not recommended for SCAD. Statins do not play an additional role, as the underlying mechanism is not atherosclerosis; therefore, statins could be used if there is another indication.

Interventional therapy is indicated in patients with ongoing ischemic symptoms, extensive jeopardized myocardium, and recurrent/incessant symptoms. Although some patients may present with ST elevation MI, proximal left anterior descending artery (LAD), or left main involvement, most SCAD patients could be

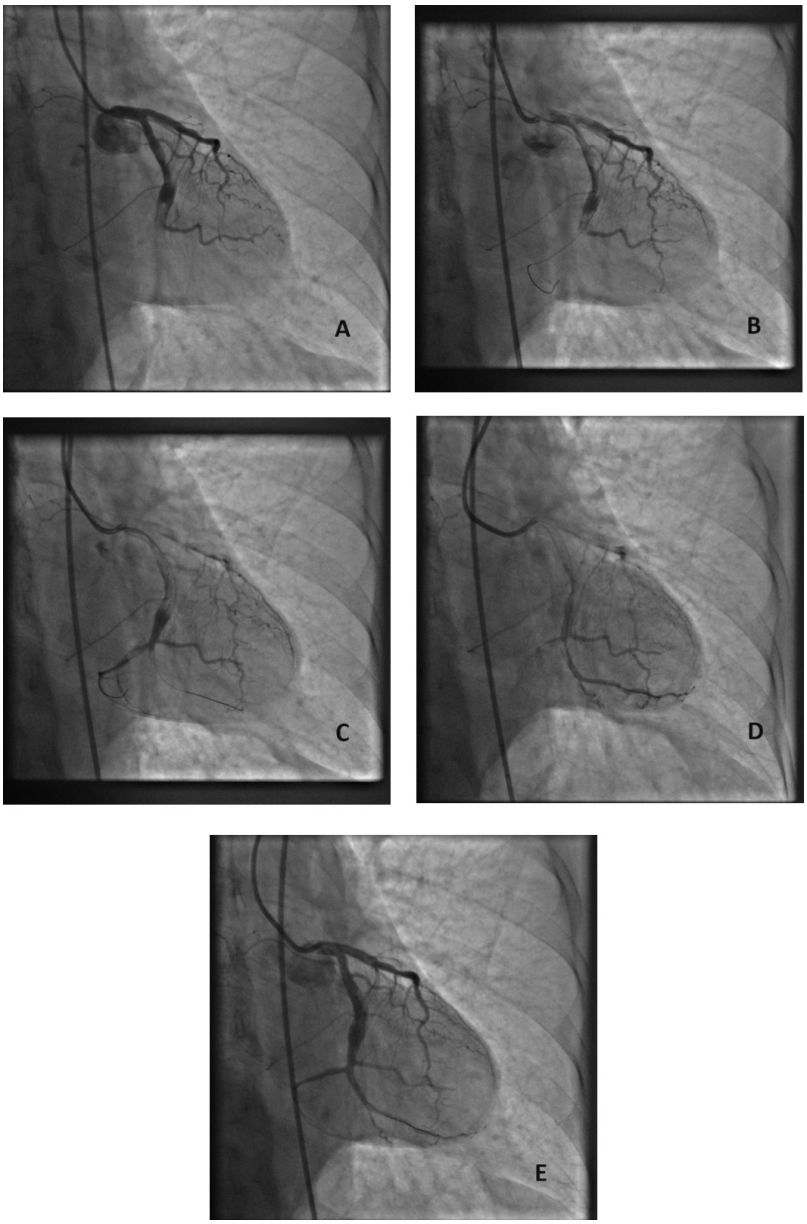

Figure 3. Coronary artery ectasia-associated posterior MI, managed with thrombus aspiration without stent implantation. Diagnostic angiography demonstrating a large thrombus in the ectatic Cx lesion (A); Thrombus appearance persisted after wire crossing (B). Thrombus shifted different branches after balloon dilation (C and D); Successful thrombus aspiration provided TIMI III flow without stenting (E). Cx: Circumflex artery; MI: Myocardial infarction.

managed conservatively[64]. In the Canadian SCAD cohort study, only 14.7% of the patients were treated by PCI or coronary artery bypass grafting (CABG); patients who underwent PCI at the index hospitalization had similar post-discharge major adverse cardiovascular events compared with those who did not undergo PCI[65]. The success rate of PCI in SCAD is considerably low. Overall, PCI was successful in 29.1% of the patients, partially successful in 40.8%, and unsuccessful in 30.1% of the patients in the study above[62]. The causes of PCI failure in SCAD are intramural hematoma propagation to the proximal or distal segments after stent implantation, stent malapposition due to late hematoma resorption, long dissected segments extending to the distal vessel, and difficulty in distal true lumen wiring[66]. Care must be taken at all steps of SCAD PCI. First, these patients have fragile intima; therefore, catheter manipulations and engagements

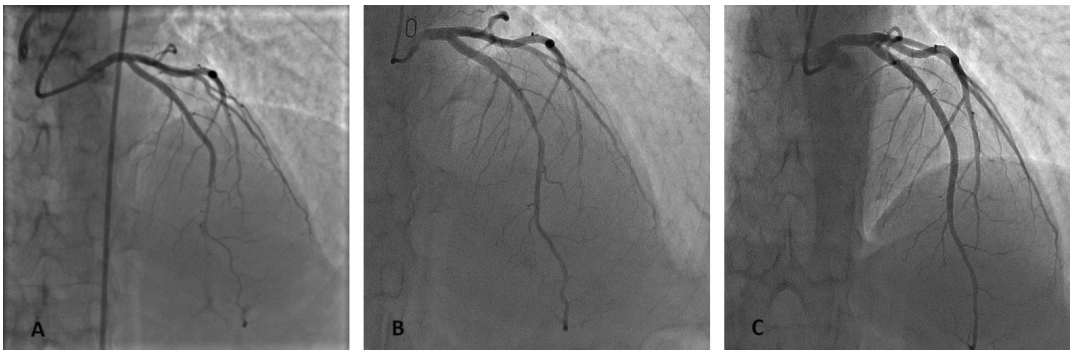

Figure 4. Type 2 spontaneous coronary dissection involving LAD mid and distal segments (A); A young woman patient presented with non-ST elevation myocardial infarction, followed by conservative management using aspirin 100 mg and metoprolol 50 mg. After two years, she suffered from another acute coronary syndrome. Diagnostic angiography showed that previous type 2 dissection healed, but a new type 3 spontaneous coronary dissection developed (B); The patient was treated with a long zotarolimus-eluting stent without complications (C). LAD: Left anterior descending artery.

must be carefully performed. Contrast injection at high pressure could propagate dissection. Correct distal lumen wiring (true lumen wiring) is vital for successful balloon dilatation and stenting. Balloon dilatation or stenting could result in hematoma extension to the proximal or distal part. Small-sized balloon dilatation and following conservatively is a good option in patients whose TIMI flow is satisfactory and whose symptoms are resolved after balloon angioplasty. Cutting balloon is another option for balloon angioplasty as it can unload subintimal hematoma into the true lumen. If stenting is decided, different strategies can be used. Focal stent implantation could be a good option to close the proximal entry if the proximal flap is apparent. Implantation of a single long stent is another option. Focal stenting to the proximal and distal segments and overlapping a third stent between them can also be performed. None of these strategies have been tested in clinical studies. Therefore, firm recommendations for SCAD PCI could not be made. A recently published observational DISCO trial showed that patients with TIMI flow 0 and 1 tended to undergo intervention more frequently than those with TIMI 2-3 flow. Although adverse event ratios were similar between the conservative and intervention groups in patients with TIMI 2-3 flow, adverse events were significantly higher in the intervention group than in the conservative group in patients with TIMI 0-1 flow. This difference was because of the high number of repeated revascularisations in the intervention group in patients with TIMI 0-1 flow[67]. Figure 4 shows an example of SCAD from our archive.

CONCLUSION

Slow-flow/No-reflow, myocardial infarction associated with coronary artery ectasia, large thrombotic lesions, and SCAD are potential troublesome conditions that might complicate primary PCI. Vasoactive agent administration can be used to restore distal flow in Slow-flow/No-reflow cases. Distal drug administration could be the only problem-solving option if the flow grade is TIMI 0. Thrombus aspiration could give a very effective result in large thrombotic lesions and thrombotic ectasia-associated myocardial infarctions. Percutaneous intervention for SCAD-associated MI is still a matter of debate. Symptomatic status and the incessant nature of the clinical presentation are the most critical factors for interventional treatment decisions.

DECLARATIONS

Authors' contributions

Conceptualization: Kızıltunç E, Candemir M, Topal S

Methodology: Kızıltunç E, Candemir M, Topal S
Literature review: Kızıltunç E, Candemir M, Topal S
Writing - original draft: Kızıltunç E
Writing - review and editing: Kızıltunç E, Candemir M, Topal S
Visualization: Kızıltunç E, Candemir M, Topal S

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The data are available from the corresponding author upon reasonable request.

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Not applicable.

Consent for publication
Not applicable.

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