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Carbon dioxide-angiography for patients with peripheral arterial disease at risk of contrast-induced nephropathy

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Abstract

Patients with peripheral arterial disease (PAD) and critical limb ischemia are at risk for limb amputation and require urgent management to restore blood flow. Patients with PAD often have several comorbidities, including chronic kidney disease, diabetes mellitus, and hypertension. Diagnostic and interventional angiography using iodinated contrast agents provides excellent image resolution but can be associated with contrast-induced nephropathy (CIN). The use of carbon dioxide (CO₂) as a contrast agent reduces the volume of iodine contrast required for angiography and reduces the incidence of CIN. However, CO₂ angiography has been underutilized due to concerns regarding safety and image quality. Modern CO₂ delivery systems with advanced digital subtraction angiography techniques and hybrid angiography have improved imaging accuracy and reduced the incidence of CIN. Awareness of the need for optimal imaging conditions, contraindications, and potential complications have improved the safety of CO₂ angiography. This review aims to highlight current technological advances in the delivery of CO₂ in vascular angiography for patients with PAD and critical limb ischemia, which result in limb preservation while preventing kidney damage.

Key words: Endovascular procedures; Angiography; Digital subtraction; Chronic kidney disease; Peripheral artery disease; Carbon dioxide

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Core tip: Patients with peripheral arterial disease and critical limb ischemia require diagnostic and interventional angiography; however, iodinated contrast agents can be associated with contrast-induced nephropathy. Carbon dioxide angiography represents a safe and effective alternative to the use of iodinated contrast medium. This updated review provides readers with a comprehensive analysis of the current technological

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advances in the delivery and imaging of carbon dioxide for vascular angiography and its diagnostic value, with limitations and challenges being addressed.

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INTRODUCTION

Approximately 8.5 million Americans have peripheral arterial disease (PAD)^[1], and these patients can have several associated comorbidities, including diabetes mellitus, chronic kidney disease (CKD), and hypertension. Patients with diabetes mellitus are reported to account for the majority of lower limb amputation with a rate of 1.5-5.0 events per 1000 persons per year^[2,3]. When medication and exercise do not reduce the symptoms of claudication, and in cases of critical limb ischemia (CLI) when the patient is at risk of lower limb amputation, endovascular revascularization is the standard of care^[4].

Diagnostic and therapeutic angiography procedures used to salvage the limb have traditionally used contrast agents to identify regions of stenosis in the target artery. Diagnostic angiography routinely uses iodinated contrast material, but for patients with impaired renal function or contrast allergy, alternatives include the use of gadolinium and dilute iodinated contrast material^[5]. Iodinated contrast agents provide excellent resolution but carry the risk of kidney damage due to immediate effects that damage the nephron, including vasoconstriction, induction of cell apoptosis, and oxidative stress associated with the generation of reactive oxygen species^[6-9]. Contrast-induced nephropathy (CIN) typically presents within 24-72 h following injection of contrast and can be harmful to patients with pre-existing renal impairment^[10]. A recently published review has highlighted the associations between PAD and CKD that lead to increased morbidity associated with interventional vascular procedures^[11]. Therefore, to avoid further kidney damage, there may be a reluctance to perform interventional angiography to salvage the limb in patients with PAD and CKD.

Carbon dioxide (CO₂) has been used as a safe diagnostic contrast agent since 1914^[12]. CO₂ has been used in angiography since the 1950s and 1960s, and has been used to detect pericardial effusion^[13,14]. In the 1980s, digital subtraction angiography (DSA) was developed with CO₂ as a contrast agent for vascular imaging^[15]. Currently, CO₂ is used as an alternative to contrast medium in lower extremity vascular diagnosis and intervention, particularly in patients who are at risk from CIN^[16].

With advances in gas delivery systems and imaging technology, the use of CO₂ is rapidly increasing. In the United States, many centers have adopted a combination of CO₂ with iodine contrast to reduce the total amount of iodine injected^[17-20]. The use of CO₂ angiography has significantly reduced the incidence of CIN and is opening the way for patients with CKD to benefit from endovascular procedures^[17-20].

This review aims to highlight the current technological advances in the delivery of CO₂ in vascular angiography, resulting in reduced volumes of iodinated contrast medium, which may improve clinical outcome for patients with PAD and CLI that preserves both renal function and the lower limb.

CONTRAST-INDUCED NEPHROPATHY

CIN is an iatrogenic renal injury that follows the intravascular administration of radio-opaque contrast media and results in the impairment of renal function^[6,10,21,22]. Meta-analysis data have shown a 6% incidence of CIN following contrast-enhanced computed tomography (CT)^[23], and CIN following peripheral angiography has been reported to occur in 9% of patients^[24]. The administration of contrast medium can immediately affect the nephron by causing vasoconstriction, cell apoptosis, and oxidative stress resulting in impaired renal function^[6-9]. The level of cytotoxicity of contrast medium may be associated with the ionic strength, osmolality, or viscosity^[6,25]. CIN occurs in patients with and without CKD; however, patients with

CKD have reduced nephron capacity, which increases their risk of developing CIN^[6,22,26]. As a result, these patients are at a heightened risk of long-term renal function loss, cardiovascular events (*i.e.*, myocardial infarction), and death^[27].

CIN-associated renal impairment is defined as an increase in serum creatinine by $\geq 25\%$ (relative) or ≥ 0.5 mg/dL (absolute) within three days of injection of contrast medium^[28]. Serum creatinine levels will peak at 3-5 d after administration of contrast medium but typically return to or near baseline levels within 1-3 wk^[10,21]. Mortality rates have been reported to rise significantly when creatinine levels increased by more than 25% ($P < 0.0001$)^[28].

CONTRAST-INDUCED NEPHROPATHY PATHOGENESIS

The pathomechanisms of renal injury in CIN are poorly understood. Several different contributing factors, such as direct contrast media noxious effects, oxidative stress, vasoconstriction, and medullary ischemia are likely involved^[29-31]. The physiochemical properties of contrast media, along with vasoconstrictive and cytotoxic effects of contrast media contribute to the pathogenesis of CIN^[6-8]. Upon administration of contrast media, a transient release of nitric oxide is triggered, which induces endothelium-dependent vasodilation, leading to temporary renovascular dilation and increased renal blood flow within the renal vascular arcades. The contrast media is filtered through the fenestrated endothelium of the glomerulus and enters Bowman's capsule and the urinary space with exposure to the tubular epithelial cells, where it is re-absorbed. The contrast medium is cytotoxic to the tubular epithelial cells. As a result of a contrast medium osmotic diuresis, there is increased sodium delivery to the thick ascending limb and the macula densa resulting in adenosine is released from the macula densa, and increased tubule-glomerular feedback. Increased tubule-glomerular feedback is one mechanism of increased vasoconstriction and hypoxia. There is also a disturbance of the balance of vasoactive mediators - vasoconstrictive (adenosine, endothelin) *vs* vasodilatory (nitric oxide, prostacyclin) further resulting in vasoconstriction and hypoxia. The outer medulla is particularly vulnerable to hypoxia while increased sodium delivery to the thick ascending limb increases its metabolic requirement for oxygen further aggravating relative hypoxia in the region. Decreased renal blood flow also causes contrast media to accumulate in the renal medulla. As a result, the renal tubular cells are exposed to contrast media for a prolonged interval time period, resulting in more cellular injury and triggering the release of noxious vasoactive mediators, such as reactive oxygen species, that lead to prolonged vasoconstriction, apoptosis, and oxidative damage^[6,32]. Previous studies have illustrated contrast media to be trapped for several days, further propagating renal cell damage and death^[33].

INCIDENCE OF CONTRAST-INDUCED NEPHROPATHY AND ITS HEALTHCARE BURDEN

CIN is the third most common cause of acquired acute renal failure^[22], and the most common cause of acute kidney injury in hospitalized patients^[23]. In the general population, the prevalence of susceptibility to CIN is $> 2\%$ ^[22,24]; however, in several patient subsets, the prevalence becomes significantly higher, ranging from between $> 20\%$ and $> 30\%$ ^[22,24]. Patients considered to be at increased risk for the development of CIN typically have one or more pre-existing conditions, such as diabetes, congestive heart failure, chronic renal impairment, age ≥ 75 years, hypotension, the presence of an intra-aortic balloon pump, and anemia^[6,21,22,34]. Pre-existing renal insufficiency or underlying CKD is the most important risk factors for the development of CIN, with the incidence of CIN in patients with CKD ranges from 14.8%-55%^[35-37].

Previous studies have indicated decreased renal function and increased dose of contrast media are both risk factors for CIN, and, therefore, have been implicated as a prediction tool for the development CIN. In fact, the ratio of contrast volume to creatinine clearance (V/CrCl) is used as an independent predictor of CIN following angiography in patients with and without impaired renal function^[38-42]. A recent study consisting of 2308 patients that underwent coronary angiography and/or percutaneous coronary intervention evaluated the predictive power of the V/CrCl ratio. Overall incidence of CIN was 12.2% (281/2308) and a V/CrCl ratio > 6.15 was independently associated with an elevated risk of CIN. CIN occurred in 25.1% and 9.7% of patients with V/CrCl ≥ 6.15 and < 6.15 , respectively. This evaluation parameter was confirmed for diabetic and non-diabetic patients^[43].

CIN is independently associated with increased length of hospital stay, increased

medical care costs, and unfavorable in-hospital outcome at one year^[10]. In the United States, more than one million radiocontrast procedures are performed annually, and there are approximately 150000 episodes of CIN per year^[44]. At least 1% of these cases of CIN require dialysis and are associated with an average stay in hospital of 17 d and an additional annual cost of \$32 million, compared with two days for patients that do not require dialysis^[44]. For patients requiring post-discharge dialysis, the cost has been estimated to be \$128000 per quality-adjusted life-year and \$51000 for dialysis treatment^[45]. The resulting annual cost of CIN is approximately \$180 million in the United States^[10,44]. Also, the results from a one-year outcome analysis showed that patients with CIN experienced higher rates of hospital death, out-of-hospital death, and major adverse cardiac events^[10,46].

RISK FACTORS FOR CONTRAST-INDUCED NEPHROPATHY

Several factors that increase the risk for the development of CIN are patient-related and can be identified from the clinical history, physical examination, and laboratory tests (Table 1). However, some risk factors are procedure-related and are modifiable. Previous studies have developed clinically useful multivariate predictive tools for assessing the risk of developing CIN and a list of contributing or risk factors have been developed^[21,47]. The risk factors for CIN include hypotension, diabetes, chronic heart failure, age > 75 years, anemia, increased baseline estimated GFR (eGFR), increased red cell distribution width, increased serum triglycerides, creatinine, total cholesterol, high-density lipoprotein, low-density lipoprotein, blood urea nitrogen (BUN), and sodium levels^[21,47]. Other risk factors include increased platelet count, international normalized ratio, blood glucose, the volume of contrast medium, and the requirement for intra-arterial balloon pump therapy before imaging^[21,47].

CLINICAL GUIDELINES FOR THE PREVENTION OF CONTRAST-INDUCED NEPHROPATHY

In 2014, the European Society of Cardiology established preventive guidelines for CIN and provided an outline of care for low, moderate, and high-risk patients^[48]. All patients undergoing a procedure involving the use of contrast medium should first be assessed for their risk of CIN, which includes the measurement of baseline serum creatinine levels and calculation of the eGFR^[48]. Patients are considered to be at increased risk of CIN if the serum creatinine level is > 1.4 mg/dL and the eGFR is < 60 mL/min/1.73m²^[2,6,48]. CIN has been defined as an increase from baseline in the serum creatinine of 0.5 mg/dL or 25% relative increase within 48 h following the administration of contrast medium^[47,48]. Current recommendations are that patients should be adequately hydrated before the procedure, and patients who are at risk should be given intravenous hydration with isotonic saline before, during, and after the procedure^[6,48]. Increased hydration works to counteract renal vasoconstriction^[30,49,50], prevents renal medullary hypoxia by increasing renal blood flow through the nephrons^[49,51,52], dilutes contrast media^[29,51,53], and reduces nephrotoxic effects on the tubular epithelium by decreasing how long contrast remains in contact with the kidney^[29,51,53]. Results from numerous experimental and clinical studies have supported the use of hydration to prevent CIN^[54-64]; however, no prospective trials have been conducted to determine the minimum effective treatment and optimal fluid composition of IV hydration^[65]. Patients who have diabetes are advised to discontinue the use of any nephrotoxic medication before the procedure and physicians should use the lowest possible volume of low-osmolar contrast medium (LOCM) or iso-osmolar contrast medium (IOCM)^[6,48]. Withholding nephrotoxic medications helps to minimize nephron injury by preventing nephritis^[53,66] and contrast accumulation in the proximal tubule cells^[66]; however, these medications should only be discontinued when clinically feasible, which is not the case for all patients^[52]. LOCM and IOCM are preferred because high-osmolarity elevate the viscosity of the agent and flow resistance in renal tubules^[31]. LOCM and IOCM have been found to reduce the incidence of CIN by 50%^[67]; however, they can still cause CIN^[68,69].

Table 1 Risk factors for the development of contrast-induced nephropathy

Risk factors for contrast-induced nephropathy
Increased age
Intravascular volume depletion
High volume or high osmolarity of contrast medium
Pre-existing chronic kidney disease (CKD)
Diabetes with CKD
The use of medications, including: calcineurin inhibitors, aminoglycosides, non-steroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors

NEW APPROACHES FOR THE PREVENTION OF CONTRAST-INDUCED NEPHROPATHY

Additional preventive treatments outlined by the European Society of Cardiology guidelines include the use of N-acetylcysteine (NAC) and high-dose statins^[48]. N-acetylcysteine has antioxidant and vasodilatory properties, which help to prevent the formation of free radicals in the renal tubules^[25], reducing the oxidative stress; however, it does not provide protection against CIN^[70]. In several clinical studies, high-dose statin therapy has shown to be effective in preventing CIN in statin-naïve patients^[6,48,71,72]. In 2015, Marenzi *et al*^[73] reported the findings from a meta-analysis of the effects of short-term and intensive treatment with statins before imaging on the reduction of CIN in patients with and without acute coronary syndrome undergoing coronary angiography and percutaneous coronary intervention. A systematic review of the literature identified nine clinical trials that included 5212 patients (age 65 ± 5 years), and meta-analysis supported the use of pre-treatment with statins in this patient population^[73]. Statin therapy is contraindicated for patients with decompensated cirrhosis or acute liver failure^[74].

CO₂ AS A CONTRAST AGENT

CO₂ is a negative contrast agent due to its low density and its ability to absorb X-rays to a lesser degree than the surrounding blood vessels and the vessel wall. Gaseous CO₂ is extremely buoyant, which allows it to float in the blood, and when using selective injection with reflux, the visceral arteries can be visualized^[75]. Because CO₂ does not mix with blood, it moves through the blood as an isolated bubble or bubbles and remains undiluted, which is significantly different from iodine contrast. The bubble of CO₂ has a characteristic parabolic flow pattern along the anterior part of the vessel, while the posterior portion remains filled with blood and free of CO₂. As a result, the vessels running anterior to the injection site produce more enhanced images^[75]. High-quality CO₂ DSA images of the lower extremity arteries can be obtained by overcoming the buoyancy limitation, which is done by positioning the patient in the Trendelenburg position, administering nitroglycerin by intra-arterial injection, and gas reflux by giving a distal injection^[16,75].

High-resolution DSA is required for CO₂ imaging. However, bowel gas, peristalsis, and movement due to respiration may interfere with DSA negative contrast image quality. These problems can be overcome by the use of rapid exposure with masked images, which eliminate these artefacts. The masked images allow for enhanced subtraction, pixel shifting, and image stacking^[75]. Several studies have shown that glucagon or hyoscine butylbromide (Buscopan) can reduce the effects of movement of the bowel to improve image quality^[19,76-78].

MISCONCEPTIONS OF CO₂ ANGIOGRAPHY THAT HAVE BEEN BARRIERS TO ITS USE

The use of CO₂ as a contrast agent has been documented over the decades but is not routinely used, as the use of iodinated contrast medium remains the gold standard for imaging techniques^[48]. Several misconceptions have resulted in the limited use of CO₂ angiography, including the belief that there will be poor image quality, fear of air embolism, lack of available CO₂ delivery systems or difficulties in their use, fear of explosive gas delivery, insufficient filling of arteries, and also lack of experience in

this technique. The development of new technology overcomes some of these limitations and has enabled CO₂ angiography to become increasingly used.

NEW SYSTEMS FOR CO₂ DELIVERY AND IMPROVED SAFETY

Older CO₂ delivery systems were typically homemade and consisted of large bulky tanks, CO₂ transport containers, and multiple valves^[19,79-81]. These older delivery systems caused concern regarding the development of an air embolism, intrapulmonary vapor lock due to air contamination, neurotoxicity resulting from injection of CO₂ into the cerebral circulation, hypoxia, or hypotension due to the use of an excessive volume of CO₂^[75]. The application of a CO₂ delivery system has been approved by the United States Food and Drug Administration^[82]. The delivery system holds 10000 mL of CO₂ and has valves to prevent mixing of CO₂ with room air, a 60 mL reservoir syringe, and a 30 mL injection syringe that delivers CO₂ into the angiography catheter^[82].

In our institution, recently developed pre-assembled portable medical CO₂ delivery systems are currently used and include the CO₂mmander® and the AngiAssist® Delivery System (AngioAdvancements Inc., Fort Myers, FL, United States) (Figure 1)^[83]. The new portable CO₂ delivery systems have been designed to remove the limitations and disadvantages of previous equipment and have the advantage of being user-friendly, safe, compact, and easy to move. The use of modified portable CO₂ delivery systems has overcome the reluctance of use of experienced and non-experienced operators and may increase the use of CO₂ as a contrast agent that benefits patients^[83]. The system consists of three main components that include a compact CO₂ medical gas cylinder, a portable, hand-held regulator, and a pre-assembled delivery system. The compact 10000 mL laboratory-grade cylinder is portable and disposable, making it easy to store in a convenient location. Also, there is unique threading that matches the regulator, which prevents the insertion of the wrong gas. Previous systems relied on large, bulky tanks that were never fully depleted of gas, allowing for the accumulation of contaminants, including bacteria, mold, carbonic acid, and rust^[83].

The CO₂ mmander® has a low-pressure regulator that converts medical grade liquid CO₂ in the cylinder to gas, which is then transferred to the delivery system. The low-pressure system can be regulated from 1-30 pounds-force per square inch, which prevents explosive delivery of the CO₂ gas^[83]. All components of the device, including the gauges and valves, are internalized and contained in a protective and durable aluminium shell^[83]. The AngiAssist® is a pre-assembled delivery system that consists of two one-way valves, a reservoir syringe, a delivery syringe, a K-valve, and afferent and efferent tubing^[83]. The design of each component prevents inappropriate connections and the direct transfer of CO₂ from the regulator to the patient^[83]. The included syringes (60 mL reservoir syringe and 30 mL delivery syringe) can be easily exchanged for other sizes, if required. A one-way valve is located at the end of the efferent tubing to prevent retrograde flow of blood into the system^[83]. The delivery catheter is attached to a three-way stopcock, which can be used to equalize the pressure of the delivery syringe to prevent explosive CO₂ delivery and excessive volume. Saline and contrast can also be delivered through the stopcock^[83].

Figure 2 shows the CO₂ angiography imaging findings from a recent case from our institution of a 71-year-old man with PAD that demonstrates the effective use of CO₂ in angiography-guided endovascular therapy.

SAFETY OF CO₂ IN PATIENTS UNDERGOING PERIPHERAL ANGIOGRAPHY

A recent meta-analysis investigated the safety of CO₂ in patients undergoing peripheral angiography with CO₂ and iodinated contrast medium^[84]. The meta-analysis included seven observational studies and one randomized controlled trial with 754 peripheral angiographic procedures for 677 patients. Patients undergoing CO₂ angiography experienced a higher incidence of minor, non-renal complications that included limb and abdominal pain (11 *vs* 0; *P* = 0.001), nausea and vomiting (9 *vs* 1; *P* = 0.006). Major adverse events attributable to CO₂ were rare^[84].

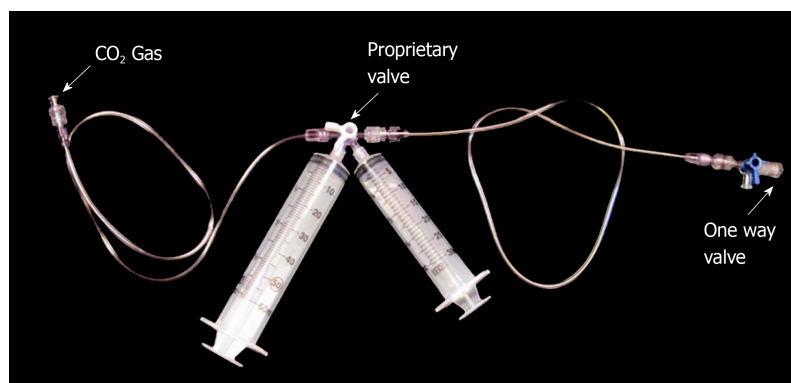


Figure 1 The pre-assembled portable medical AngiAssist® delivery system consisting of two one-way valves, a reservoir syringe, a delivery syringe, proprietary K-valve, and afferent and efferent tubing.

IMAGE QUALITY

In 2016, Palena *et al*^[80] reported the findings from a prospective, single-center study that evaluated the diagnostic accuracy of automated CO₂ angiography (ACDA) during the endovascular treatment of patients with diabetes and CLI with CKD of stage 3 or more. The study included 36 patients with a mean age of 74.8 ± 5.8 years. All patients underwent lower limb ACDA, followed by angiography with iodinated contrast medium and subsequent balloon angioplasty. Angiography was performed through the femoral artery using antegrade access. There were two experienced operators, and interobserver variability following independently reviewed DSA images was found to be very low ($\kappa = 0.89$). The diagnostic accuracy of ACDA was 89.9%, the sensitivity was 92.3%, the specificity was 75%, the positive predictive value was 95.5%, and negative predictive value was 63.1%. The difference in qualitative diagnostic accuracy between CO₂ angiography and the use of iodinated contrast medium was not statistically significant ($P = 0.197$), which supports the use of isolated CO₂ angiography for therapeutic evaluation and intervention of PAD in patients with CKD^[80].

New developments in interventional CO₂ angiography of the lower limb include digital variance angiography (DVA). A recent study compared the qualitative and quantitative performance of DVA with standard DSA^[85]. The findings from this recent study showed that for CO₂ angiography of the lower limb, the use of DVA resulted in a higher signal-to-noise ratio and a significantly better image quality when compared with DSA^[85]. The development of lower limb CO₂ angiography using the new DVA image processing technique may increase the use of CO₂ angiography in clinical practice for patients with PAD and CLI who are at risk from CIN.

HYBRID ANGIOGRAPHY IS AN IMPROVED TECHNIQUE THAT REDUCES CONTRAST-INDUCED NEPHROPATHY

In conventional angiography, iodinated contrast medium is used to visualize smaller arteries and to confirm stenotic segments, particularly in vessels below the knee^[17,20]. Imaging of the aorta and large arteries, such as the iliac and femoral arteries, would require increased volumes of contrast. During conventional angiography, the use of iodinated contrast medium results in high-resolution images, but the patient is at increased risk for kidney damage^[19]. The image quality of CO₂ angiography alone has reduced resolution, but CO₂ is non-nephrotoxic and non-allergenic. However, hybrid angiography uses a combination of iodinated contrast medium and CO₂ to reduce the required volume of iodine and overcomes some of the problems associated with the use of iodinated contrast medium or CO₂ alone. Hybrid angiography reduces the required volume of iodinated contrast medium while providing the necessary image quality^[19].

Stegeman *et al*^[20] demonstrated the efficacy of hybrid CO₂ angiography in 191 patients with lower extremity claudication and CLI. Interventions were performed with iodinated contrast medium alone, or CO₂ combined with iodinated contrast medium (hybrid angiography), or CO₂ alone. All the patients underwent an extensive pre-interventional ultrasound exam to localize the flow-limiting stenosis and stent sizing. There were no severe complications reported and no significant differences

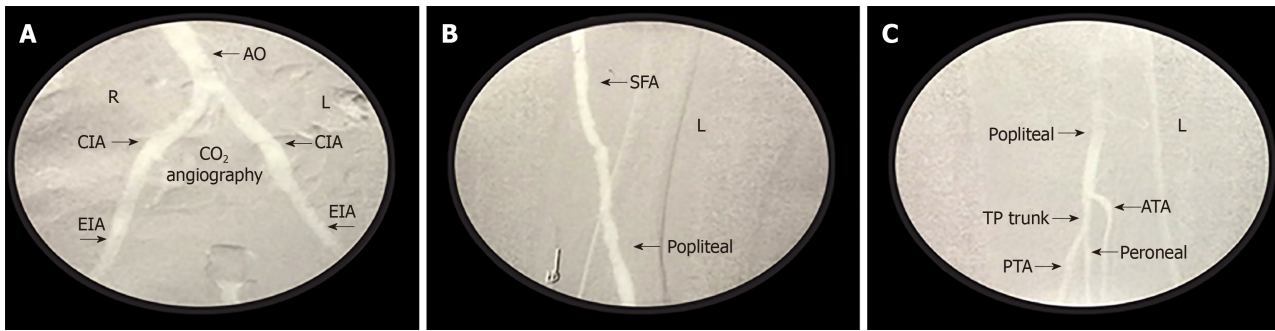


Figure 2 Carbon dioxide angiography imaging findings. A-C: Carbon dioxide angiography imaging findings of lower extremity vessels of a 71-year-old male with peripheral arterial disease. AO: Aorta; CIA: Common iliac artery; EIA: External iliac artery; SFA: Superficial femoral artery; TP Trunk: Tibioperoneal trunk; ATA: Anterior tibial artery; PTA: Posterior tibial artery.

between the technical success rate, total irradiation, and intervention time for the iodinated contrast medium and CO₂ groups. Patients in the CO₂ group exhibited significantly lower baseline renal function compared with the iodinated contrast medium group. The required volume of contrast and the incidence of CIN was significantly lower with CO₂ angiography for patients with both claudication and CLI ($P < 0.05$). Patients in the iodinated contrast medium group experienced a higher rate of CIN (19%; 29/154) compared with the patients in the CO₂ group (5%; 2/37; $P = 0.044$). Sub-group analysis that compared diabetic and non-diabetic patients in each therapy group further demonstrated the safety of CO₂ as a contrast agent. The incidence of CIN in diabetic (5%) and non-diabetic (6%) patients did not significantly differ in the CO₂ group, while diabetic patients in the iodinated contrast medium group experienced a markedly higher rate of CIN (25%) compared with the non-diabetic patients (13%)^[20].

COMPLICATIONS OF THE USE OF CO₂ ANGIOGRAPHY

Complications associated with the use of CO₂ are uncommon and are usually minor and transient. However, the clinician should be aware of two main complications that can arise from the use of CO₂ angiography, which are gas embolism and explosive gas delivery (Table 2). Gas embolism is the inadvertent mixing of air with CO₂ during delivery. CO₂ is highly soluble, which allows it to be safely and effectively injected into the arteries and veins below the diaphragm^[79]. The blood carries dissolved CO₂ to the lungs, where the gas is expired in a single pass before it reaches the coronary or cerebral circulation, which eliminates the possibility of gas embolism^[79].

The compressibility of CO₂ can significantly impact the patient experience and image quality of a CO₂ angiography. A physical characteristic of gases is that pressure is inversely related to the volume at a constant temperature. Therefore, as a force is exerted on CO₂ during its administration, its density and pressure increase, and the volume decreases. When CO₂ exits the catheter, the gas will expand, which explains the phenomenon known as explosive delivery. This effect may cause transient discomfort for the patient and poor image quality. This limitation of CO₂ as a contrast agent can be overcome by injecting 3-5 mL of CO₂ into the catheter to remove any fluid or blood, which decreases gas compression and explosive delivery^[73]. Movement can affect image quality, but this limitation can also be overcome. Palena *et al*^[80] reported treating patients with intra-arterial lidocaine before injection of CO₂, which completely resolved the patient's pain, preventing involuntary movement during repeat procedures.

There are minor complications associated with CO₂ angiography that are outweighed by the benefits. In 2015, in a multi-center prospective study, Fujihara *et al*^[17] showed that the technical success rate of CO₂ angiography-guided angioplasty of renal and iliofemoral artery disease was 97.9%. The incidence of CIN was 5.1% (5/98), but the prevalence of CO₂ angiography-associated complications was 17.3% (17/98). The complications were mainly minor from diarrhea, leg and abdominal pain (15/17), and a rare major complication was non-occlusive mesenteric ischemia (2/17)^[17].

Table 2 Overcoming complications associated with the use of carbon dioxide angiography

CO ₂ associated complication	Preventive and / or therapeutic strategy
Gas embolism	Blood carries dissolved CO ₂ to the lungs, where the gas is expired in a single pass, eliminating the possibility of gas embolism ^[79]
Explosive gas delivery	Inject 3-5 mL of CO ₂ into the catheter to remove any fluid or blood, decreasing gas compression and explosive delivery ^[75] Administer intra-arterial lidocaine before CO ₂ injection to resolve patient's pain and prevent involuntary movement ^[80]

CONTRAINDICATIONS TO THE USE OF CO₂ ANGIOGRAPHY

When considering the use of CO₂ in interventional angiography of the lower limb in patients PAD and CLI, the clinician should be aware of the contraindications to its use and how they may be avoided (Table 3)^[48].

CO₂ arteriography performed above the diaphragm may result in cerebral air embolism if the patient has a left-to-right cardiopulmonary shunt. Intra-arterial supradiaphragmatic injections, which include thoracic aortography, coronary arteriography, and cerebral arteriography, risk developing a cerebral gas embolism due to an air block phenomenon^[75,81,86]. The findings from small animal studies showed that carotid injections of CO₂ were neurotoxic and associated with multifocal ischemic infarctions associated with disruption of the blood-brain barrier^[87,88]. In 2010, a clinical study reported by Kariya *et al.*^[89] showed that CO₂ could reflux into the thoracic aorta and cerebral circulation following CO₂ injection into the brachial artery, and this resulted in seizures and loss of consciousness (Table 3).

The concurrent use of nitrous oxide anesthesia and CO₂ should be avoided because the nitrous oxide may diffuse into the CO₂ bubbles, causing them to expand, which could lead to a pulmonary artery vapor lock (Table 3)^[75]. CO₂ should be avoided for use in the venous circulation of patients that have a right-to-left intracardiac shunt. If there is a critical requirement for CO₂ venography, the patient should be placed in the left lateral decubitus position to allow CO₂ to trap and dissolve in the right atrium (Table 3)^[90].

The relative contraindications to the intravenous use of CO₂ as a contrast agent include chronic obstructive pulmonary disease and pulmonary hypertension. Both of these conditions are sensitive to pulmonary arterial pressure changes, and because CO₂ increases pulmonary artery pressure, its use can exacerbate pulmonary hypertension^[75]. Therefore, the volume of intravenous injections of CO₂ should be reduced, while the interval between multiple injections should be increased to 3-5 minutes to avoid CO₂ accumulation and pulmonary artery vapor lock (Table 3)^[75].

IMPACT OF THE USE OF HYBRID CO₂ ANGIOGRAPHY IN OUR VASCULAR LAB

Real-world findings (unpublished) from the office-based laboratory service of our vascular lab illustrate the clinical impact following the use of hybrid CO₂ angiography in the management of patients with PAD and CLI who are at risk of CIN. We reviewed a random sample of 50 peripheral interventional procedures performed in patients with PAD who were Rutherford Class 3-6. The patients were between 57-92 years of age, and 98% had a history of hypertension, 67% had diabetes mellitus, 45% had coronary artery disease, and 21% had congestive heart failure. During interventional angiography, patients were given CO₂ in doses ranging from 35-500 mL, with the dose of iodinated contrast agents ranging from 8-80 mL. None of the patients developed acute renal failure or CIN after the procedure. The average amount of iodinated contrast medium used per procedure was 41 mL as compared to an average of 102 mL used before hybrid CO₂ angiography was used (Figure 3). This has had a significant impact on outcomes for our patients with CLI with concomitant CKD.

CONCLUSION

Recent advances in the delivery of CO₂ and imaging technology have increased the use of CO₂ angiography in patients with PAD who have CLI as a safe alternative to

Table 3 Contraindications for the use of carbon dioxide angiography

Contraindication	What the clinician should do
CO ₂ arteriography performed above the diaphragm may result in cerebral air embolism if the patient has a left-to-right cardiopulmonary shunt	Do not use CO ₂ arteriography in patients with cardiac septal defect, pulmonary arteriovenous malformation (AVM), or known left-to-right cardiopulmonary shunt. In cases of critical requirement for CO ₂ angiography, place the patient in the Trendelenburg position during imaging
CO ₂ can mix with nitrogen to reduce the solubility of CO ₂	Avoid the use of nitrous oxide sedation and anesthesia
CO ₂ should be avoided for use in the venous circulation of patients that have a right-to-left intracardiac shunt	Do not use CO ₂ venography in patients with a right-to-left intracardiac shunt, including tetralogy of Fallot. In cases of critical requirement for CO ₂ venography, place the patient in the left lateral decubitus position to allow CO ₂ to trap and dissolve in the right atrium
Delayed absorption of CO ₂ may occur in patients with chronic lung disease, such as chronic obstructive pulmonary disease (COPD), who have a high baseline CO ₂ level	Monitor and adjust the time interval between CO ₂ injections in patients with a high baseline CO ₂ level
CO ₂ increases pulmonary artery pressure and can exacerbate pulmonary hypertension	Check the pulmonary arteries for accumulation of CO ₂ gas dissipation within the initial 30-45 s following CO ₂ injection

CO₂: Carbon dioxide.

the use of iodinated contrast medium, resulting in the preservation of renal function and preventing limb amputations. Hybrid angiography, using combined CO₂ and reduced amounts of iodine, has reduced the incidence of CIN. The use of modern CO₂ delivery systems with advanced DSA techniques have improved diagnostic accuracy and have reduced morbidity and mortality rates.

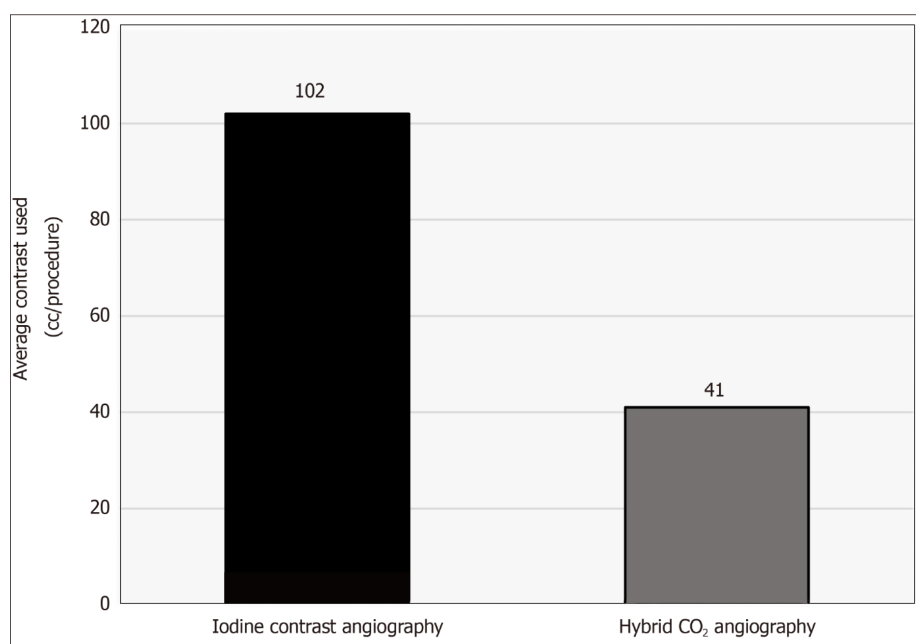


Figure 3 Average contrast used per endovascular procedure. Data from our Office Based Lab shows a reduction in Total Iodine Contrast used per procedure after adopting Hybrid CO₂ Angiography.

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Plaque herniation after stenting the culprit lesion with myocardial bridging in ST elevation myocardial infarction: A case report

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Author contributions: Ma J participated in the care of the patient throughout the hospitalization, collected clinical information, obtained informed consent for the publication of the manuscript and information, reviewed, edited and approved the manuscript; Gustafson GM performed the coronary angiography and primary percutaneous coronary intervention, initiated the discussion about myocardial bridging in STEMI care and plaque herniation; and reviewed, edited and approved the manuscript; Dai X initiated and proposed manuscript concept, participated literature search and review, wrote and revised manuscript as a senior author.

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Abstract

BACKGROUND

Myocardial bridging (MB) is increasingly recognized to stimulate atherogenesis, which may contribute to an acute coronary syndrome. Stenting the coronary segment with MB has been recognized to have an increased risk of in-stent restenosis, stent fracture and coronary perforation. The safety and efficacy of stenting the culprit lesion with overlaying MB in ST elevation myocardial infarction (STEMI) as primary reperfusion therapy has not been established.

CASE SUMMARY

We reported a patient who presented with inferior STEMI with a culprit lesion of an acute thrombotic occlusion in the right coronary artery and thrombolysis and thrombin inhibition in myocardial infarction 0 flow. After the stent placement during primary percutaneous coronary intervention, intravascular ultrasound revealed MB overlying the stented segment where heavy atherosclerotic plaque were present. Likely due to the combination of plaque herniation or prolapse caused by MB, as well as local increased inflammation and thrombogenicity, acute stent thrombosis occurred at this region, which led to acute stent failure. The patient required an emergent repeated cardiac catheterization and placing a second layer of stent to enhance the radial strength and reduce the inter-strut space.

CONCLUSION

Plaque herniation or prolapse after stenting a MB segment in STEMI is a potential etiology for acute stent failure.

Key words: Case report; ST elevation myocardial infarction; Myocardial bridging; Plaque herniation; Plaque prolapse; Intravascular ultrasound; Acute stent thrombosis

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Core tip: Stenting the coronary segment with myocardial bridging is known to have increased risks of in-stent restenosis, stent fracture and coronary perforation. Myocardial bridging is also increasingly recognized to be pro-atherosclerotic and potentially involved in acute coronary syndrome, including ST elevation myocardial infarction (STEMI). The safety and efficacy of stenting the culprit lesion with overlying myocardial bridging in STEMI as primary reperfusion therapy has not been established. Here we present a case where plaque herniation or prolapse occurred after stenting a culprit lesion in STEMI, where overlying myocardial bridging was recognized by post-stenting intravascular ultrasound. The plaque herniation at the stented segment with myocardial bridging contributed to acute stent thrombosis which required a second layer of stent deployment. This case highlighted that plaque herniation or plaque prolapse after stenting a segment with myocardial bridging in STEMI is a potential etiology for acute stent failure, and emphasized the important role of intravascular ultrasound in primary percutaneous coronary intervention.

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INTRODUCTION

Acute stent thrombosis after coronary artery stent placement is a rare but serious complication in percutaneous coronary intervention (PCI). Stenting culprit lesions in acute myocardial infarction has higher risk of acute stent thrombosis than stable coronary artery disease^[1]. Coronary dissection, stent mal-apposition, or inadequate antiplatelet/anticoagulation therapy have been considered as the most common causes of acute stent thrombosis, in addition to the local inflammation and thrombogenic environment. We report a patient who experienced acute stent closure after stenting the culprit lesion in the mid right coronary artery (RCA) of an inferior ST elevation myocardial infarction (STEMI). Intravascular ultrasound (IVUS) revealed myocardial bridging (MB) phenomenon overlaying the stented segment of the RCA, which likely promoted atherosclerotic plaque herniation (AKA, plaque prolapse) through the stent struts. We are suggesting that the herniated or prolapsed atherosclerotic plaque materials combined with the acute tissue inflammation contributed to the acute stent thrombosis.

CASE PRESENTATION

Chief complaint

Recurrence of chest pain 30 min after stent placement.

History of present illness

A 72-year-old woman with a history of hypertension, dyslipidemia, diabetes mellitus, and remote history of thyroid cancer status post thyroidectomy, who presented with acute onset substernal chest pain (CCS class IV angina pectoris) associated with nausea and diaphoresis. The 12-lead electrocardiogram (ECG) showed ST elevations in II, III and aVF with reciprocal ST depressions met the clinical diagnostic criteria of inferior STEMI (Figure 1A). The patient was pre-loaded with aspirin (325 mg) and P2Y₁₂ receptor antagonist (clopidogrel 600 mg) in the emergency department, and was brought to the cardiac catheterization laboratory for emergent coronary angiography followed by reperfusion therapy by primary PCI. An acute thrombotic occlusion in the mid RCA with thrombin inhibition in myocardial infarction 0 flow was identified as the culprit lesion (Figure 1B, white arrow). Diffuse atherosclerotic disease was also seen in the proximal RCA (Figure 1B, orange arrows). Weight-based direct thrombin inhibitor (bivalirudin) infusion (0.75 mg/kg IV bolus immediately followed by 1.75 mg/kg/h IV infusion) was used for anticoagulation during the primary PCI. Primary PCI was performed with initial aspiration thrombectomy and followed by the placement of two over-lapping drug eluting stents (3.0 × 28 mm drug

eluting stents deployed at 12 ATM, and 3.25 mm × 12 mm NC balloon for 18 ATM post-dilatation), which achieved 0% residual stenosis and thrombin inhibition in myocardial infarction 3 flow angiographically (Figure 1C). The patient's symptoms and ST elevations on ECG completely resolved after this primary PCI. Pre-stenting IVUS was not performed. Serial post stenting IVUS studies were performed which revealed heavy atherosclerotic plaque burden at the stented area (Figure 1E, blue arrows). The IVUS images demonstrated that there was overlying MB with the typical IVUS appearance of echo-lucent area overlying the stented segment (the "half-moon phenomenon") (Supplement Video 1; Figure 1E, orange arrows; Figure 1C, boxed area, arrows). IVUS also confirmed fully expanded and well apposed stent. With the recognition of the stent in a segment with overlying MB, there was some concern and discussion, but no further prophylactic action was taken. At the conclusion of the primary PCI, bivalirudin infusion was discontinued. The patient was subsequently transferred to the coronary care unit (CCU) for further post-STEMI monitoring.

Shortly after her arrival to the coronary care unit (30 min after the discontinuation of bivalirudin infusion), the patient experienced recurrent chest pain. Again, the pain was substernal, 9-10 out of 10 in pain scale. It was associated with nausea and diaphoresis. The patient appeared to be in significant distress although, vital signs were stable. She had mild shortness of breath associated with the chest pain, denied of palpitations, and any neurological symptoms. She did not have hypotension, nor evidence of tamponade on bedside transthoracic echocardiography. Other review of systems were negative except detailed above.

Immediate bedside 12-lead ECG revealed the re-appearance of the inferior leads ST elevations, which was previously confirmed to have resolved after stenting the mid RCA. An acute stent failure/thrombosis leading to acute occlusion of the stented RCA was suspected. The patient returned to the CCL immediately for repeat coronary angiography and primary PCI.

History of past medical and surgical history

Hypertension, hyperlipidemia, diabetes mellitus, thyroid cancer status post thyroidectomy on thyroid hormone replacement therapy.

Physical examination

Vital signs: Temperature 36.9 °C, heart rate 58 bpm, respiratory rate 15 per minute, BP 105/68 mmHg, SpO₂: 93% on room air. The patient appeared in mild distress, skin was mildly moisture suggestive for mild diaphoresis. Alert awake oriented × 3. There was no significant evidence of jugular vein distention, mild crackles in the bilateral lung bases without wheezing. There was no significant murmur audible. The right femoral access site for the previous emergent catheterization was clear without evidence of hematoma. Peripheral pulses were intact bilaterally. Other physical examinations were unremarkable.

Laboratory examinations

Labs were drawn at her initial emergency department presentation with returned results by the time when she returned to the CCL with recurrent chest pain. Her complete blood count results were white blood cell, 9.16 K/ μ L, Hb 11.2 g/dL; Hct 34.1%, platelet 160 K/ μ L; her basic chemistry panel showed: Na⁺ 131 mEq/L, K⁺ 4.1 mEq/L, Cl⁻ 95 mEq/L, HCO₃⁻ 24 mmol/L, blood urea nitrogen 18.5 mg/dL, Mg²⁺ 2.3 mEq/L, Troponin 3.48 ng/mL. Her liver function panel were within normal range.

Imaging examinations

12-leads ECG: Sinus bradycardia at 53 beat per minutes, with ST segment elevations > 0.1 mV in II, III and aVF and reciprocal ST depressions in leads I and aVL.

Transthoracic echocardiography (post-PCI): Mild segmental left ventricular systolic dysfunction, estimated EF 50%. The basal to mid inferior wall is hypokinetic. The inferolateral wall appears mildly hypokinetic. Normal right ventricle size and function. No significant valvular abnormalities. No evidence of pericardial effusion. No evidence of pulmonary hypertension.

Chest X-ray (post-PCI): Increased interstitial markings throughout both lungs, which may represent pulmonary edema. No pleural effusions. No pneumothorax.

FINAL DIAGNOSIS

Acute stent thrombosis due to plaque herniation after stenting a STEMI culprit lesion with overlying MB.

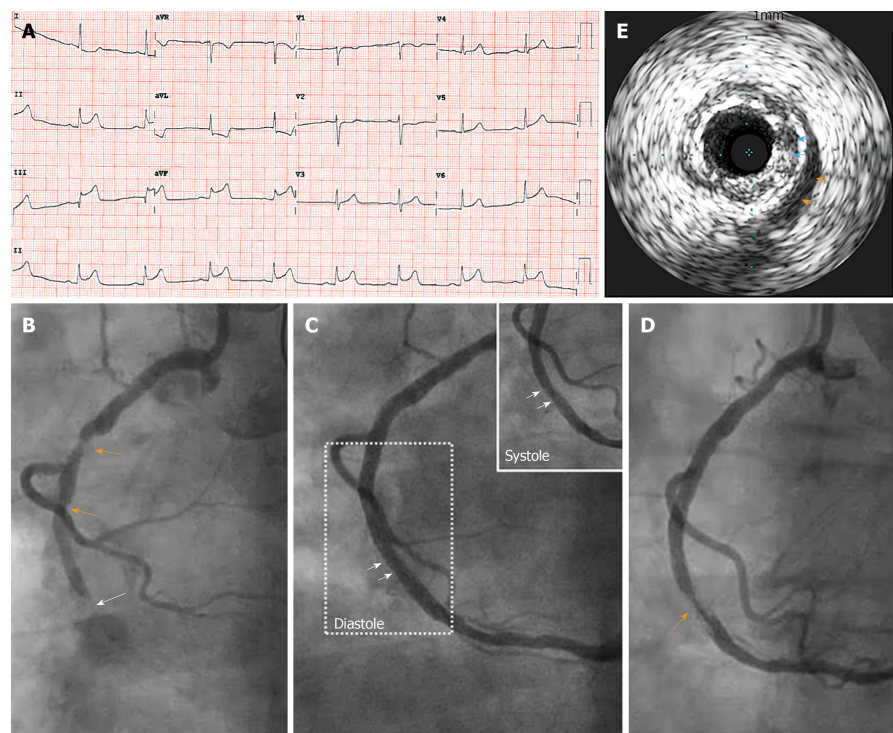


Figure 1 Images of the recurrence of inferior ST segment elevation myocardial infarction and intra-procedural findings during reperfusion therapy. A: Presenting 12-lead electrocardiogram showed ST elevation in inferior leads; B: Culprit lesion in the mid right coronary artery (RCA) (white arrow) and diffuse atherosclerotic lesions in the proximal RCA (orange arrows); C: Initially stented RCA with systolic narrowing (insert, systolic phase of the dashed area in C) showed mild compressions of the stented lumen (white arrows); D: Circumferential filling defect in the stented segment (orange arrow); E: Intravascular ultrasound evidence of myocardial bridge with echo-lucent half-moon sign (orange arrows) and plaque between stent and myocardial bridge (blue arrows).

TREATMENT

With the presumed diagnosis of acute stent thrombosis which led to the recurrent presentation of inferior STEMI, the patient was brought back to the CCL emergently for a repeat reperfusion therapy. Repeat angiography confirmed a filling defect with subtotal occlusion in the mid portion of the stented segment (Figure 1D, orange arrow), where overlying MB had been recognized on IVUS in the earlier study. MB induced plaque herniation was thought to be the likely contributing factor for the acute thrombotic closure, where the stent had been well expanded and apposed on IVUS at the end of previous procedure. In order to enhance radial strength and reduce the inter-strut spaces to minimize plaque herniation through the stented MB segment, a second layer of DES was deployed with additional post dilatations. Repeat IVUS study confirmed an improved stent expansion and luminal gain without evidence of acute plaque herniation. Since the acute stent thrombosis occurred only 30 min from the discontinuation of the bivalirudin (less than one half-life), and the P2Y12 inhibitor (clopidogrel) was loaded approximately 2 h earlier, we considered that an ineffective dual antiplatelet therapy was less likely to be the major contributor to the event. Nevertheless, the patient's P2Y12 antagonist was changed to ticagrelor to enhance antiplatelet therapy.

OUTCOME AND FOLLOW-UP

The patient did well after the second procedure, and was discharged to home after 3 d of uneventful hospitalization. A pre-discharge echocardiography showed mild segmental left ventricular systolic dysfunction (EF 50%) with hypokinesis of the basal-to-mid inferior and inferolateral walls. She was doing well at 30-d follow up.

DISCUSSION

MB is a coronary anomaly in which a segment of epicardial coronary artery coursing

under a “bridge” of overlying myocardium^[2]. This phenomenon was initially discovered in autopsy. Coronary artery angiography, coronary computer tomographic angiography (CCTA) and IVUS are now commonly used imaging modalities to identify MB. In general population, the prevalence of MB reported by autopsy series was roughly 25%, similar by CCTA and lower in coronary angiography series (0.5%-12%)^[2]. Angiographically, MB is most commonly seen in the mid segment of left anterior descending artery, followed by left circumflex and least common in RCA. However, some CCTA and autopsy series found similar involvement of left circumflex and RCA in MB^[3-6]. The overlying myocardial fibers often lead to vessel compression during systole in cardiac cycle. Depending on the depth of MB, location of the MB, with or without myocardial hypertrophy, as well as systemic and coronary hemodynamic status, MB may result in clinical symptoms such as angina, myocardial ischemia or even ventricular arrhythmias. The first line of therapy of stable symptomatic MB remains medical treatment with beta-blockers and non-dihydropyridine calcium-channel blockers, while nitrates provides less consistent effects.

Stenting a coronary artery segment with overlying MB is associated with an increased risk of in-stent restenosis, stent fracture and coronary perforation. Therefore, stenting the coronary artery with MB is generally not recommended for management of ischemic symptoms in stable patients. MB is also increasingly recognized to be pro-atherosclerotic, especially at the peri-bridge edges, due to endothelial dysfunction, thickened intima and turbulent flow dynamics^[7-9]. Rupture of atherosclerotic plaque in the segment of MB could result in acute thrombotic occlusion and STEMI presentation^[10]. Primary PCI with stent placement remains the treatment of choice in the acute STEMI setting with or without the recognition of MB by angiography or IVUS. How often an overlying MB is involved in STEMI culprit lesion is not known. In our case, the MB overlying the stented segment involved in the culprit lesion of STEMI was recognized by post stenting IVUS during the initial primary PCI. Although concerns were raised during the initial primary PCI after the recognition of MB, and options such as empirically deploying a second layer of stent was discussed, there was no clinical evidence to guide this prophylactic use of second layer of stent against acute stent failure in this setting. In retrospect, potential adverse consequences after stenting coronary segment with overlying MB, such as acute plaque herniation, recoiling, and re-thrombosis had been underestimated. Plaque herniation or prolapse after stenting occurs up to 25% of stent placement in acute MI by IVUS imaging^[11,12]. It is associated with worse clinical outcome including stent thrombosis^[13]. Like the case presented here, in the setting of acute STEMI with the culprit lesion in a coronary artery segment with an overlying MB and heavy atherosclerotic plaque burden, stenting of this lesion resulted an increased risk of plaque herniation through the stent struts. With the combination of local inflammation, and the thrombogenic nature of the disrupted atherosclerotic plaque, acute stent thrombosis and closure occurred which required repeat revascularization. It's a perfect storm. In our case, placing a second layer of stent to improve radial strength and also reduce the space between struts especially in open-cell designed stents was performed to minimize plaque herniation.

IVUS is an important imaging modality to identify MB. On IVUS, the tunneled segment of coronary artery underneath the overlying myocardium demonstrates systolic vessel compression and highly specific echo-lucent “half-moon” appearance as shown in **Figure 1E** (orange arrows). The use of IVUS in primary PCI is a valuable technique to provide information to recognize overlying MB and plaque herniation, which can promote the consideration of approaches of prophylaxis of acute stent failure after stenting MB segment^[14,15]. We now felt strongly that pre-stenting IVUS may provide potential MB information before stent placement, which may change clinical decision making. When MB phenomenon identified by post-stenting IVUS, then empirically deploying an additional layer of stent may be advantageous after the recognition of MB and significant plaque burden and herniation in the stent on IVUS. This case further emphasizes the value of IVUS (pre- and post- stenting) during primary PCI.

CONCLUSION

The risk related to MB in the STEMI culprit lesion was under-recognized. Stenting the culprit lesion with overlying MB may result in plaque herniation, leading to acute stent failure. IVUS study in primary PCI is an useful tool for detecting MB. Empirical treatment with double layered stents may be necessary to prevent acute stent failure.

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