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Severe, Diffuse Coronary Artery Spasm after Drug-Eluting Stent Placement

Brigitta C. Brott, MD, Andreas S. Anayiotos, PhD, Gregory D. Chapman, MD, Peter G. Anderson, DVM, PhD, William B. Hillegass, MD, MPH

ABSTRACT: Objectives. Three cases of severe, diffuse coronary artery spasm after drug-eluting stent placement at our institution prompted this review. **Background.** Drug-eluting stents have gained widespread use due to extraordinarily low rates of restenosis. Despite these generally superior clinical outcomes, the specter of rare idiosyncratic reactions remains a concern. **Methods.** We performed searches of Medline and the U.S. FDA Manufacturer And User facility Device Experience database (MAUDE) to identify and describe spasm after coronary stent placement. Searches included drug-eluting and bare-metal stents. Institutional cases are reviewed. Location, time course and outcome of cases are described. **Results.** Thirteen cases of spasm were identified after stent placement. Seven cases occurred after Cypher™ drug-eluting stent placement, 2 after Taxus® drug-eluting stent placement, 1 after BiodivYsio™ and 3 after bare-metal stents. Five patients experienced diffuse, multivessel spasm — 2 after Cypher, 2 after Taxus, and 1 after a Velocity™ stent. Of these 5 patients, 2 died. An additional 2 required intra-aortic balloon pump placement for cardiogenic shock. Another had persistent symptomatic diffuse coronary spasm documented by angiography at 1 year. **Conclusions.** We describe coronary spasm after stent placement, particularly after drug-eluting stents. Outcomes associated with diffuse severe spasm after stenting are poor, and the pathophysiology remains poorly understood.

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Drug-eluting stents have dramatically changed the care of patients with coronary artery disease, leading to decreased neointimal proliferation and clinical restenosis.[1] However, concerns have been raised regarding hypersensitivity reactions.[2] In addition, a case of localized hypersensitivity and late coronary thrombosis resulting in death has been described.[3] A recently published analysis demonstrates that there is abnormal vasomotion with vasoconstriction during exercise 6 months after Cypher™ stent *(Cordis Corp., Miami, Florida)* placement compared to normal preserved vasomotion with vasodilation after bare-metal stent placement.[4] We now report cases of severe symptomatic coronary vasospasm after predominantly drug-eluting stent placement. Three cases of severe, diffuse spasm after drug-eluting stent placement have occurred at our institution. These cases prompted a retrospective review of our experience, the published literature and reports to the U.S. Food & Drug Administration (FDA).

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Material and Methods

Case definition. Patients with spasm were identified as having severe coronary artery constriction without evidence of dissection or other mechanical obstruction. Cases of stent or vessel thrombosis were excluded. Cases were also excluded if spasm was associated with the use of another device, such as balloon dilation, balloon rupture or thromboatherectomy devices. A patient with a history of variant angina, for which she was being stented, was excluded. Cases were included from the FDA Manufacturer And User facility Device Experience database (MAUDE) database if: (1) there was angiographic evidence of spasm with patent stent(s); or (2) there was chest pain and electrocardiographic (ECG) changes or positive cardiac enzymes, and subsequent angiography after successful initial medical treatment showed patent stent(s) with no suggestion of thrombus or other significant angiographic abnormalities such as dissection to explain the episode.

Case identification. Cases were identified from a systematic literature review, reports to the FDA and our own institutional experience. A literature search was performed via Medline using the words: spasm, artery and stent. The articles identified and their references were reviewed for meeting the case definition. Cases were also identified from the U.S. FDA MAUDE database (2000–June 2005) using the term "spasm" crossed with "Cypher, Taxus, Pixel, Zeta, Penta, Tetra, Velocity, Nir, Express, Vision, Driver, and BiodivYsio". Institutional cases were obtained from review of catheterization laboratory procedures. Each case from this search was reviewed to determine whether it met the criteria listed above: (1) angiographic evidence of spasm with a patent stent; (2) the presence of chest pain with ECG changes; or positive cardiac markers with subsequent angiography after initial medical therapy showing no evidence of thrombus or dissection. Complete procedural details were not available from several of the MAUDE database cases. However, cases were included if there was adequate evidence of recurrent ischemia with no evidence of thrombus or dissection.

Results

Cases. A total of 13 cases were identified and are summarized in Table 1. Nine cases of spasm were identified in the MAUDE database. Two cases matched the description of institutional cases 1 and 2 described above that we had previously reported to the manufacturer. Of the remaining cases, an additional 4 involved Cypher stents (total of 6), 2 involved Taxus stents, and 1 involved a Bx Velocity™ stent

Table 1. Details of cardiac events related to spasm.

Case #	Type of Stent	Indication for Stent(s)	Location of Stent(s)	Method of Spasm Identification	Location of Spasm	Time to Spasm	Result
1	Cypher	Unstable angina	Proximal/mid LAD and diagonal	Chest pain, ST elevations, coronary angiography	Diffuse throughout LAD and LCx	3 hours after stents	Treated with NTG, nitroprusside, adenosine, IABP; Patient developed cardiogenic shock and died
2	Cypher	Angina	Mid LAD in-stent restenosis	Chest pain, coronary angiography	Diffuse throughout LAD and LCx	1 week after PCI	Treated with NTG with angiographic resolution; Continued CP as outpt despite NTG & diltiazem; Moderate diffuse spasm present on angiogram 1 year later
3	Cypher	Acute MI	LAD	Coronary angiography	LAD distal to stent	4 weeks after stent implantation	IC NTG with resolution
4	Cypher	Unstable angina	Distal LCx	Chest pain, ECG changes, coronary angiography	Proximal to stent	12 hours after PCI	Treated with bare-metal stent
5	Cypher	N/A	LAD via LIMA	Coronary angiography	Proximal and distal to stent	3 hours after PCI	Not relieved by NTG; Deployed another type of stent.
6	Taxus	N/A	LAD	Coronary angiography, ST elevations	Entire LAD and LCx system (entire left coronary system)	After stent deployed during procedure	Treated with IABP
7	Taxus	N/A	RCA, OM	Coronary angiography	RCA, OM, "total no flow" after OM stent deployed	After each stent deployed during procedure	Treated with "relevant drugs"; IIb/IIIa inhibitor; Pt expired 8 hours later of intracranial bleed
8	Velocity	Unstable angina	LAD	Cardiogenic shock, ST elevations, coronary angiography	Entire LAD and LCx system	After stent deployment	IABP, IC NTG, calcium channel-blocker with resolution
9	Cypher	+ Stress test	LAD	MI, chest pain, EKG changes	No catheterization performed during CP. Later cath showed patent stents and no significant lesion	11 days after PCI	Successfully treated with NTG
10	Cypher	N/A	Mid RCA	Chest pain, patent stents	CP resolved with NTG, diltiazem. Cath when asymptomatic - Patent stent	Within 11 days after PCI	Treated with isosorbide mononitrate, diltiazem
11	BiodivYsio	Non-Q-wave MI	Proximal LAD	Angina, ST elevation, spasm by angiography	LAD distal to stent	After stent deployment	CP and spasm resolved with IC NTG and IC verapamil
12	AVE	Stable angina	Proximal RCA	Chest pain, ischemic ECG, spasm by angiography	"Candy-wrapper" on either side of stent	After stent deployment	Resolved with IC NTG
13	Palmaz-Schatz	Post-MI angina and cardiogenic shock	Mid RCA	Hypotension requiring dopamine	Proximal and distal to stent	6 hours after stent deployment	Resolved; Treatment not outlined

Abbreviations: *Cath = cardiac catheterization; CP = chest pain; ECG = electrocardiogram; IABP = intra-aortic balloon pump; IC = intracoronary administration; LAD = left anterior descending artery; LCx = left circumflex artery; LIMA = left internal mammary artery; MI = myocardial infarction; N/A = not available; NTG = nitroglycerin; OM = obtuse marginal; PCI = percutaneous coronary intervention; Pt = patient; RCA = right coronary artery.*

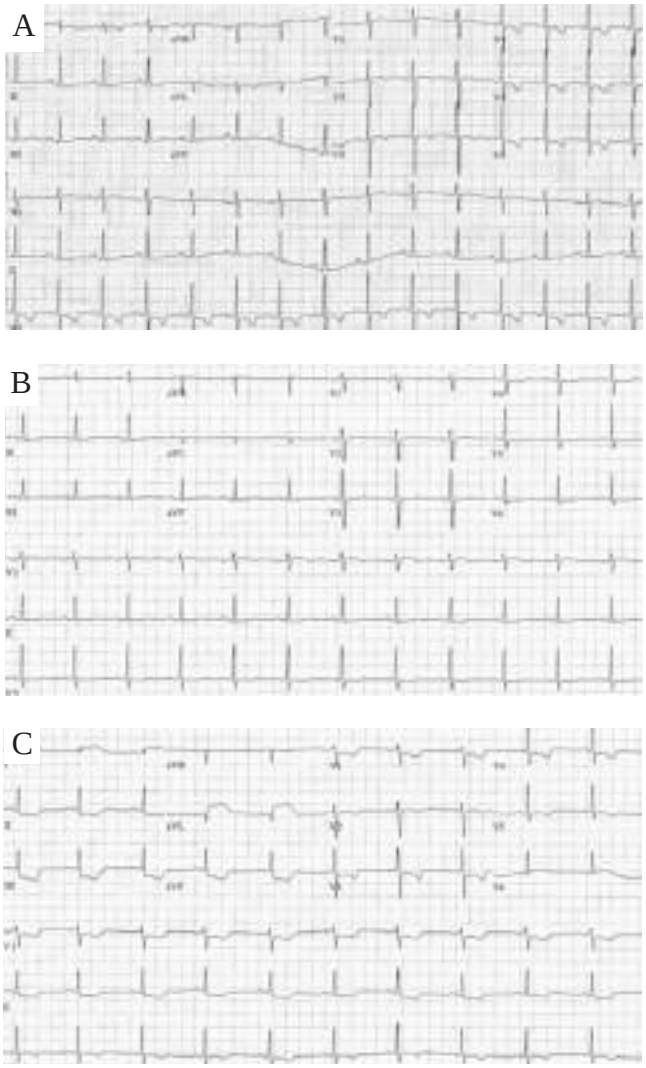

Figure 1. *ECGs for Case 1. Baseline ECG prior to procedure reveals anterior ischemia* (A). *ECG immediately after stenting reveals nonspecific anterior T-wave abnormality* (B). *ECG 90 minutes later with severe chest pain shows lateral ST-elevation with global ST-depression, indicating acute myocardial infarction* (C).

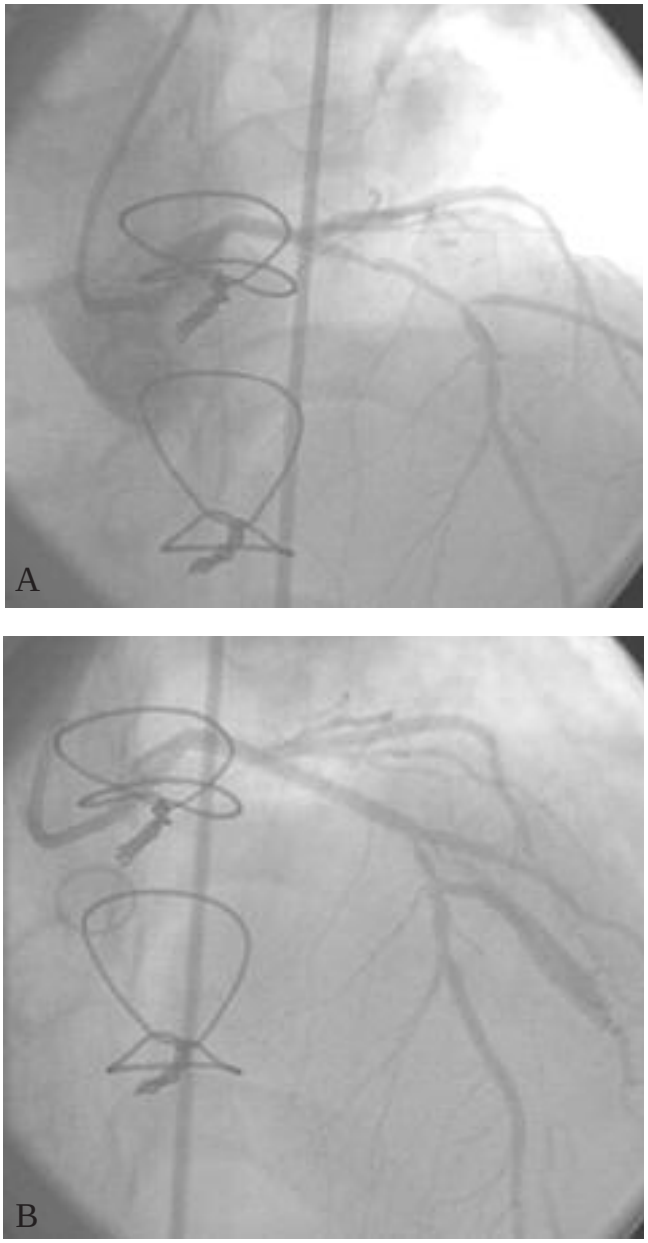

Figure 2. *Coronary angiography of patient in Case 1 interventional procedure. Initial angiography prior to stenting revealed severe lesion in LAD and ostial second diagonal branch* (A). *Angiography immediately after placement of 2 Cypher drug-eluting stents revealed a widely patent vessel with no residual stenosis at the lesion* (B).

(Cordis). There were no reported cases in the MAUDE database of spasm with Multi-Link Pixel® *(Guidant Corp., Indianapolis, Indiana)*, Zeta® *(Guidant)*, Nir *(Boston Scientific Corp., Natick, Massachussetts)*, Penta *(Guidant)*, Multi-Link Tetra *(Guidant)*, Express™ *(Boston Scientific)*, Multi-Link Vision® *(Guidant)*, Driver® *(Medtronic, Inc., Minneapolis, Minnesota)*, or BiodivYsio *(Biocompatibles, Galway, Ireland)* stents. The case of spasm associated with a Velocity stent is identical in events and descriptive language to a recently published case report.[5] Three additional cases were identified by Medline search: 1 with ByiodivYsio,[6] 1 with AVE[7] and 1 with Palmaz-Schatz[8] stents. We describe a final case from our institution that does not appear in the U.S. FDA MAUDE database. In Table 1, Cases 1, 2, and 3 correspond to Institutional Cases 1, 2, and 3 described below.

Analysis of cases. Of the 13 cases of spasm attributed to stents, 5 occurred while the patient was on the catheterization table (Table 1). Another 4 presented within 24 hours of the procedure. Of the final 4, two developed the described spasm within 2 weeks of stent placement. The time interval between stent implantation and development of symptomatic spasm is not reported in MAUDE for an additional patient. The final patient (Institutional Case 3) was asymptomatic, and spasm was identified by routine re-look angiography 1 month later, prior to staged intervention.

Among these 13 cases, severe diffuse spasm of multiple vessels occurred in 5. This resulted in death in 2: from cardiogenic

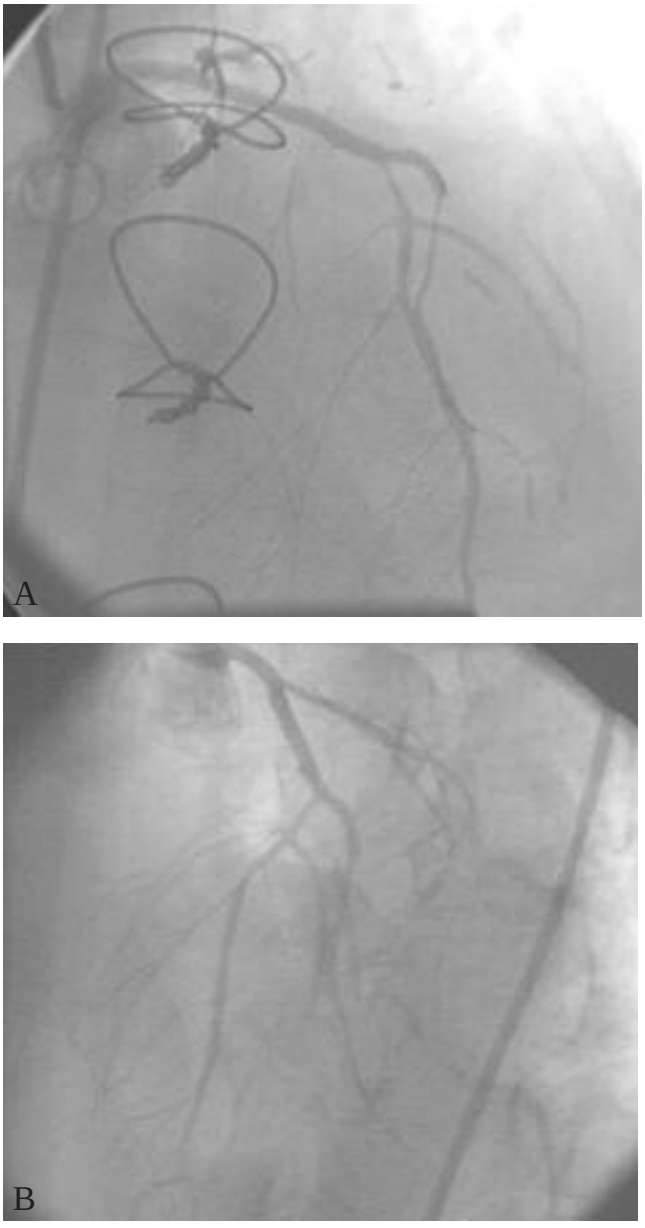

Figure 3. *Angiography in Case 1 approximately 3 hours after stenting during severe chest pain revealed widely patent stents with severe spasm of the diagonal* (A, B).

shock and from intracranial bleeding after aggressive anticoagulation. Two of the other multivessel diffuse spasm patients required intra-aortic balloon pump placement for severe ischemia or shock. Institutional Case 1, described below, is illustrative of Cases 6, 7 and 8 in Table 1. The remaining patient with multivessel diffuse spasm was Case 2 that we describe below. The patient required prolonged nitrates and calcium channel blockers. The presence of diffuse spasm has been described in patients receiving Cypher and Taxus stents and in the 1 patient who received a Velocity stent.

Of the patients who did not have multivessel diffuse spasm, 1 developed spasm proximal to the previously placed drug-eluting stent, which was treated with a bare-metal stent. The patient in Institutional Case 3 had asymptomatic diffuse spasm distal to a Cypher stent placed 1 month previously. This was successfully treated with intracoronary (IC) nitroglycerin (NTG). Another patient developed diffuse spasm throughout the drug-eluting stent-treated artery, and this patient was treated with another type of stent. A third had spasm throughout the vessel, distal to a polymer-coated BiodivYsio stent.[6] Two more had spasm in the peri-stent region of bare-metal stents.[7,8] These were treated with IC NTG. The reports of the remaining 2 patients were obtained from the MAUDE database describing spasm after Cypher stent placement. They do not provide significant detail, and the diagnosis of spasm was based on recurrent symptoms, positive cardiac markers or ECG changes, with widely patent stents by angiography.

Institutional Cases

Case 1. *A 59-year-old female with a history of coronary artery bypass grafting (CABG) in October 2001 presented with severe angina in November of 2003. Her baseline ECG revealed evidence of anterior ischemia (Figure 1A). Diagnostic catheterization at another institution revealed a patent left internal mammary graft (LIMA) to the left anterior descending artery (LAD), and a patent saphenous vein graft (SVG) to the second diagonal. The left circumflex (LCx) and right coronary artery (RCA) were without angiographically significant disease. There was a 70% stenosis in the proximal LAD and an 80% stenosis at the origin of the first diagonal (D1), which was not grafted (Figure 2A). She had a history of a rash related to aspirin, and did not receive aspirin prior to the intervention.*

Percutaneous intervention (PCI) of the proximal LAD and D1 was performed after administration of heparin and abcximab. The lesions were predilated with a 2.0 x 15 mm balloon. Next, a 2.5 x 18 mm Cypher drug-eluting stent was deployed at the D1 lesion, and a 2.5 x 23 mm Cypher drug-eluting stent was deployed in the proximal LAD in an overlapping fashion. They were dilated to 14 and 16 atm. This resulted in a 0% residual with normal flow (Figure 2B). Her postprocedure ECG revealed nonspecific anterior T-wave abnormalities (Figure 1B).

After the procedure, the patient was initially asymptomatic, conversing with her family. Approximately 3 hours later, she developed sudden onset of severe chest pain and anterior and inferior ST-depressions with lateral ST-elevation (Figure 1C). This did not respond to sublingual or intravenous (IV) NTG, morphine sulfate or an IV heparin bolus. She rapidly became cold, clammy and hypotensive, not responsive to normal saline fluid boluses. IV dopamine 5 mcg/kg/minute was administered, with continued hypotension. The patient was brought emergently to the cardiac catheterization laboratory. Because of persistent hypotension, metaraminol 0.2 mg was administered IV. She also received IV solumedrol and diphenhydramine to treat a possible anaphylactic reaction. Coronary angiography revealed that the stents were widely patent. However, there was severe spasm of the LAD and D1 distal to the Cypher stents, as well as severe, flow-limiting spasm of the mid and distal LAD and LCx systems (Figures 3B, 3B). This included severe spasm of the second diagonal, as seen by injecting the vein graft that supplied the second diagonal. Angiography of the RCA,

taken after administration of IC nitroprusside to the left coronary system and the initial metaraminol dose, did not reveal spasm. The left coronary system spasm did not respond to nitroprusside intracoronary (IC) in divided doses.[9] An intra-aortic balloon pump was placed, a temporary pacing wire was placed for profound bradycardia and the patient was intubated. A bedside echocardiogram revealed no pericardial effusion. Adenosine, in divided doses, was administered via the left main artery without improvement in spasm. Under fluoroscopy, minimal cardiac motion became apparent. Single doses of IV epinephrine and atropine were administered for refractory hypotension. Despite very prolonged efforts at resuscitation, the patient expired.

There was no drop in hematocrit or hemoglobin drawn at the start of the emergency catheterization after the onset of chest pain. Routine serum markers for myocardial infarction were not elevated after completion of the procedure, prior to the onset of severe chest pain and hypotension. Post-mortem examination revealed that the Cypher stents were widely patent without thrombosis. There was no evidence of proximal or distal dissection in the LAD or D1, though there was evidence of mild acute hemorrhage within the adjacent epicardial fat. Occasional inflammatory cells were observed in the tunica adventitia of the LAD and D1, but cell numbers were no greater than in other artery sections examined. A Giemsa stain for mast cells with positive control revealed a few scattered mast cells within the tunica adventitia of the LAD.

Case 2. *A 53-year-old female with a history of previous mid LAD and distal OM1 stenting, diabetes and hypertension presented with increasing chest pain in July 2003. She had initially received a bare-metal stent in her mid LAD in June 2002. She developed in-stent restenosis in November 2002, which was treated with cutting balloon dilatation. In April 2003, she received a 2.25 x 13 mm Pixel bare-metal stent in her distal OM1. She did well until she developed worsening chest pain in the beginning of July 2003. A nuclear stress test revealed significant LAD ischemia, with evidence of RCA ischemia. Repeat coronary angiography revealed 70% diffuse in-stent restenosis of the LAD and moderate restenosis of the distal OM1 (Figure 4A). There was slight left main spasm with catheter engagement, which resolved with IC NTG. It was elected to treat the distal OM1 lesion medically and to stent the mid LAD lesion with a Cypher drug-eluting stent. The lesion was predilated and a 3.0 x 23 mm Cypher drug-eluting stent was deployed. This resulted in a 0% residual stenosis (Figure 4B).*

Approximately 3 days after discharge, the patient felt poorly, as though she were developing an upper respiratory tract infection, and she received a prescription for azithromycin. The next day, she developed intermittent chest discomfort both with exertion and rest, associated with heaviness, tightness, shortness of breath, nausea and diaphoresis. She was admitted to the hospital, and serum markers for myocardial infarction were negative.

Seven days after deployment of the Cypher drug-eluting stent, she underwent repeat coronary angiography. Prior to engagement of the left main with any diagnostic catheter, flush angiography was performed, revealing a widely patent left main without spasm but severe diffuse spasm of the LAD, except the stented segment,

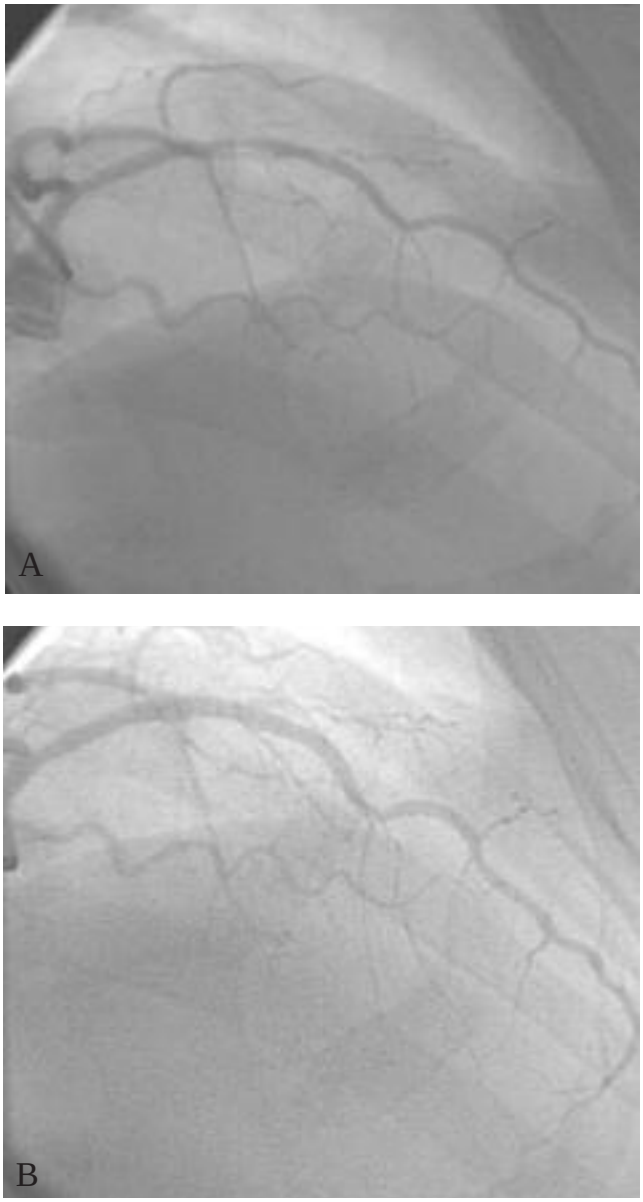

Figure 4. *Coronary angiography of patient in Case 2. Initial angiography prior to stenting revealed 70% in-stent restenosis of bare metal stent in LAD* (A). *Angiography immediately after placement of Cypher drug-eluting stent revealed widely patent vessel with no residual stenosis* (B).

and severe spasm of the entire LCx system. Selective left coronary angiography then confirmed a widely patent mid LAD stent with severe diffuse spasm of the entire LAD and LCx systems (Figures 5A, 5B). The spasm resolved after administration of IC NTG (Figure 5C). There was slight spasm of the ostial RCA with catheter engagement, which resolved with IC NTG.

The patient was followed in general medicine and interventional cardiology clinics for the following year. She has had persistent symptoms of frequent chest pain, despite increasing calcium channel-blocker doses and nitrate administration. Without her NTG patch, she has disabling anginal chest discomfort. Repeat angiography 1 year after placement of the drug-eluting stent

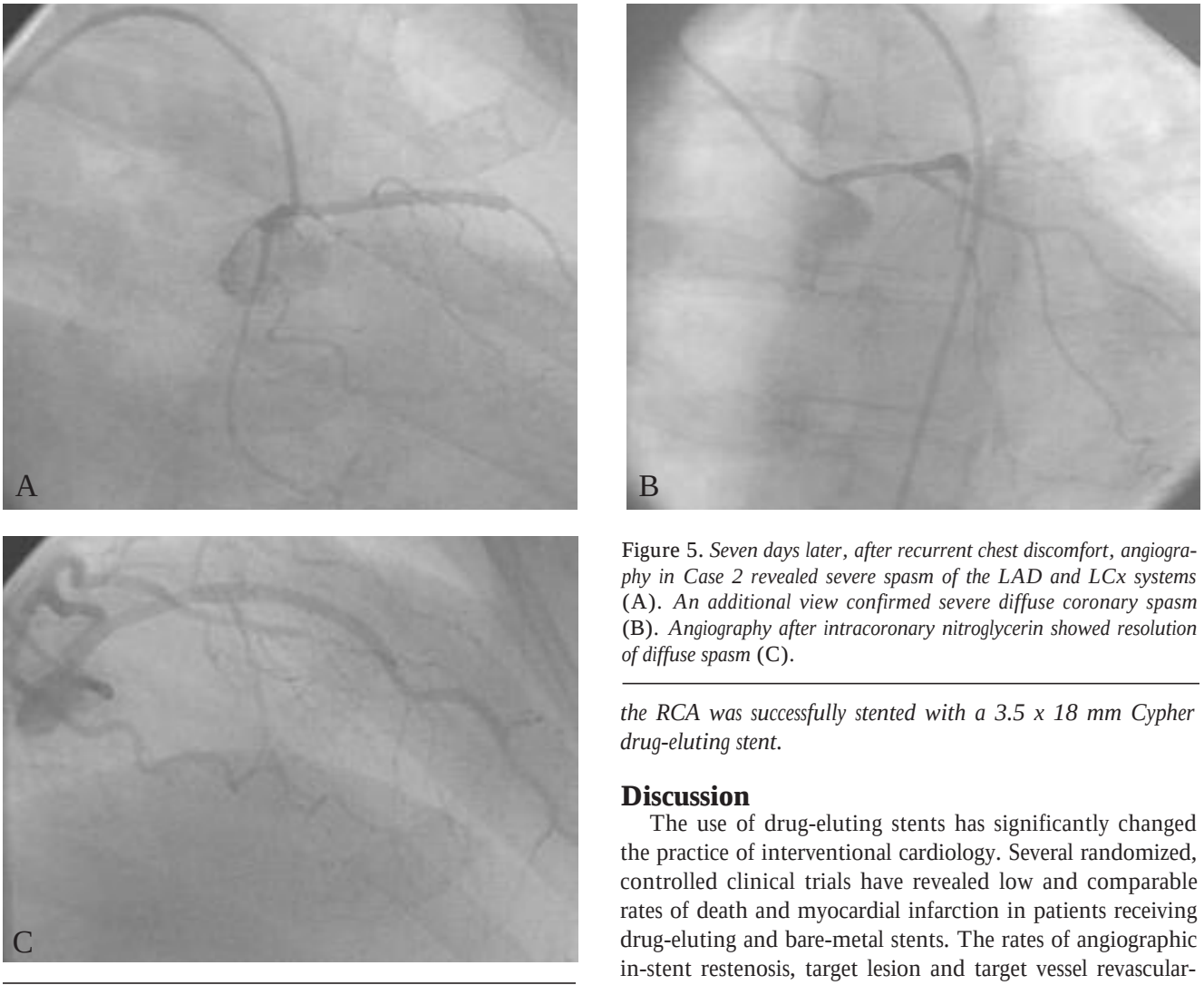

Figure 5. *Seven days later, after recurrent chest discomfort, angiography in Case 2 revealed severe spasm of the LAD and LCx systems* (A). *An additional view confirmed severe diffuse coronary spasm* (B). *Angiography after intracoronary nitroglycerin showed resolution of diffuse spasm* (C).

revealed diffuse moderate spasm of the left coronary system that was responsive to IC NTG.

Case 3. *A 47-year-old male without a prior medical history presented with an anterolateral ST-segment elevation myocardial infarction. He was treated with thrombolytic therapy and transferred for catheterization. Emergent catheterization revealed a 90% mid LAD lesion and an 80% mid RCA lesion (Figure 6A). The LAD was predilated with a 2.5 x 15 mm balloon and then stented with a 2.5 x 23 mm Cypher drug-eluting stent, resulting in a widely patent vessel with no residual stenosis and normal flow (Figure 6B). Subsequent cardiac echocardiography revealed normal ventricular function.*

Four weeks later, the patient returned for staged percutaneous intervention of the RCA. Since discharge, he had experienced occasional chest discomfort. He had completely quit smoking. Coronary angiography of the left system revealed severe diffuse spasm of the LAD distal to the previously placed stent (Figure 6C). The stent was widely patent. The diffuse spasm resolved with IC NTG (Figure 6D). The association of this case with the other cases of diffuse spasm after drug-eluting stent placement was not made until after completion of the procedure. Therefore, the RCA was successfully stented with a 3.5 x 18 mm Cypher drug-eluting stent.

Discussion

The use of drug-eluting stents has significantly changed the practice of interventional cardiology. Several randomized, controlled clinical trials have revealed low and comparable rates of death and myocardial infarction in patients receiving drug-eluting and bare-metal stents. The rates of angiographic in-stent restenosis, target lesion and target vessel revascularization are significantly lower with drug-eluting stents.[1,10–16] However, the specter of serious, rare idiosyncratic reactions to stents, particularly drug-eluting stents with polymer and active pharmacologic constituents remains a concern. To date, documented vascular compatibility issues include rare hypersensitivity reactions[17] and persistent abnormal vasomotor responses in the drug-eluting stented vessel.[4] Based on our own experience, published case reports and the U.S. FDA database, the data assembled from these sources raises the additional concern that severe coronary spasm (with significant morbidity and occasional fatality) may also be a rare idiosyncratic reaction to stent placement, particularly drug-eluting stents.

To our knowledge, this report is the first description of severe, diffuse coronary spasm after drug-eluting stent placement in a series of patients. Our observations of 3 institutional patients are consistent with the additional cases reported in the MAUDE database. During the past 5 years, there has been 1 case of diffuse spasm with a bare-metal stent reported to the FDA, compared with 8 involving drug-eluting stents. Whether this represents a reporting bias where adverse events are more likely to be reported with more recently approved

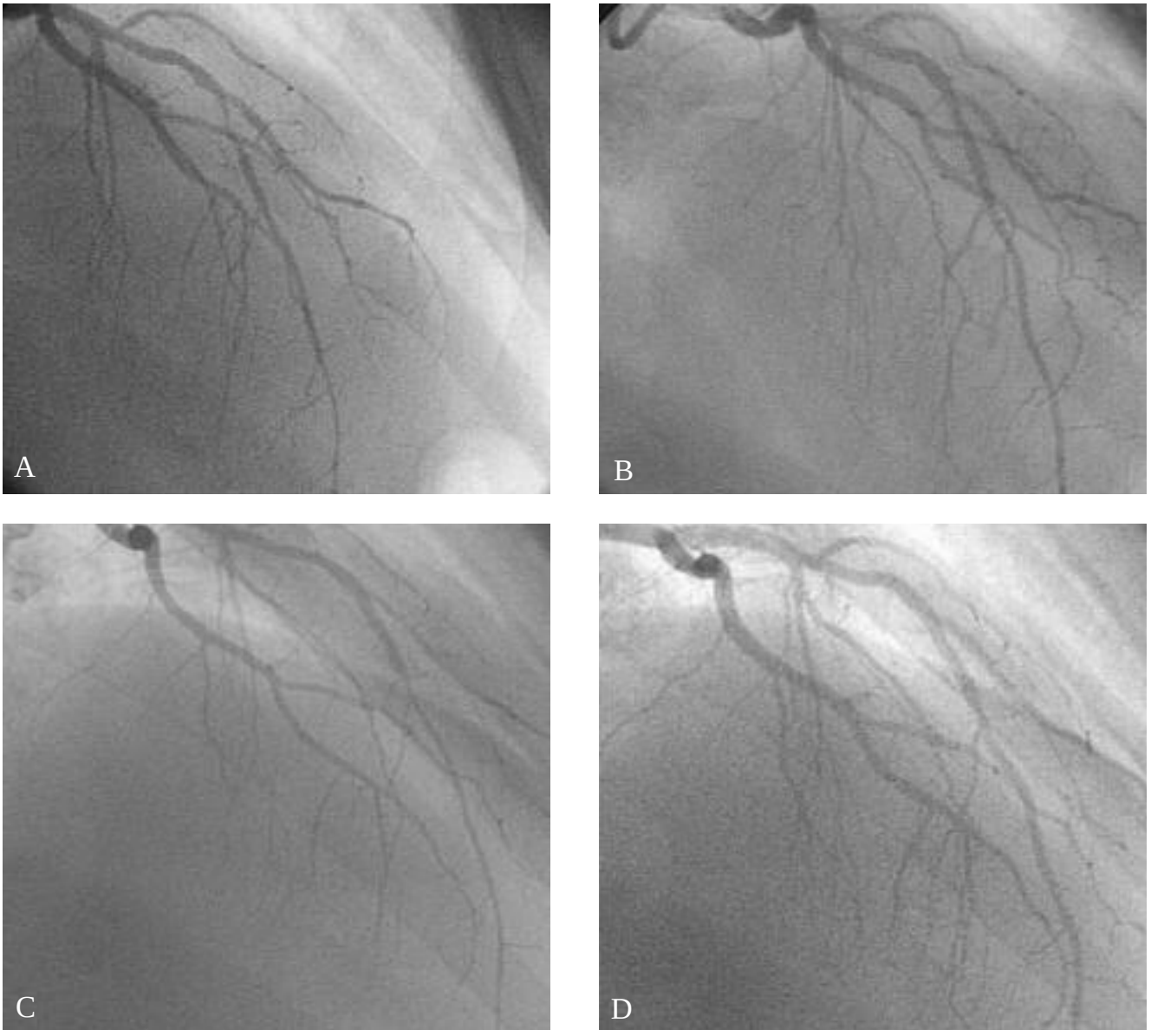

Figure 6. *Coronary angiography in Case 3. Initial angiography prior to stenting 90% LAD stenosis* (A). *Immediately after stenting, angiography reveals widely patent vessel* (B). *Two weeks later, repeat angiography shows diffuse spasm distal to the LAD Cypher stent* (C). *Spasm resolved after intracoronary nitroglycerin* (D).

devices or an increased risk of idiosyncratic reactions to drug-eluting stents with drug and polymer constituents is uncertain. Review of our institutional experience with bare-metal stents from January 2000 to June 2005 revealed no similar cases of diffuse spasm as we have observed with the 3 drug-eluting stent cases. Review of the guide catheters, wires, anticoagulation regimen, periprocedural care and patient characteristics/medical histories did not reveal alternative etiologies for these patients' coronary spasm. The paucity of reports in the medical literature, MAUDE database and our institutional experience with bare-metal stents implies that clinically significant spasm after bare-metal stenting appears to be a very rare event. In fact, there are only 5 case reports identified in Medline describing coronary spasm after stenting.[5–8,18] Two of these reports describe spasm adjacent to a bare-metal stent.[8,18] Another describes arterial spasm distal in a vessel stented with a polymer-coated BiodivYsio stent.[6] Another case report describes a patient undergoing stenting for variant angina who developed spasm in another artery during the procedure. This case was not included in the analysis for this paper.[18] A final case is the one described above in the medical literature and the MAUDE database involving a Velocity stent.[5] All the above cases describe successful treatment of spasm with nitrates or calcium channel-blockers. In particular, these reports suggest that diffuse, multivessel coronary spasm after bare-metal stent implantation is extremely uncommon.

Another possible etiology of the cases we report is that the patients' true underlying condition was variant angina in the

setting of coexisting fixed atherosclerotic disease, and the spasm component became manifest at the time of or shortly after stent implantation. None of the institutional cases or reported cases had clinical histories to suggest the clinical syndrome of variant angina. Furthermore, multivessel spontaneous coronary vasospasm (in the absence of PCI) is thought to be rare, with only 6 cases reported in the medical literature.[19–24] Two of these patients had diffuse multivessel spasm.[21,22] Four reports describe cases of focal multivessel spasm.[19,20,23,24] All of these cases resolved with intracoronary therapy and were successfully treated with long-term nitrates and/or calcium channel-blockers. Another theoretical explanation we cannot exclude is that the patients were also exposed to a contaminant such as latex, talc or new medications when the stent was implanted. None of the institutional or reported patients had a history of known allergy or intolerance to these substances or to the periprocedural medications.

If the drug-eluting stent system is the cause of the spasm, it could potentially be a reaction to the stainless-steel stent platform, the polymers or the released medications. It is unlikely to be the stainless-steel platform, given the large number of bare-metal stents deployed worldwide and the paucity of similar reports of diffuse spasm. Additionally, the second patient we describe had undergone bare-metal stent placement twice without difficulty prior to developing diffuse spasm after drug-eluting stent placement.

Another possibility is a response to the released medications from the stent. Drug-release data suggest that approximately 70–80% percent of the sirolimus is eluted from the Cypher stent in 28 days, as is the majority of the paclitaxel available for release from the Taxus stent.[25–27] A recently published report, however, suggests that after Cypher stent placement, asymptomatic vasoconstriction and abnormal vasomotion with exercise may be present 6 months after stent deployment. Abnormal vasomotion was noted both proximal and distal to the drug-eluting stents. Vasoconstriction was not seen in the bare-metal stent control group in this study.[4] The authors speculate that the impaired vascular response is a result of the sirolimus. This is supported by an *in vitro* porcine coronary model in which sirolimus caused significant impairment in vascular relaxation.[28] Paclitaxel was not evaluated in this model. Impairment of endothelium-dependant relaxation from the medication may contribute to vascular spasm. Another etiology could be delayed endothelialization after stent placement, leading to abnormal vasomotion. This may be a contributing factor in patients with delayed spasm. Prior studies have shown that local delivery of paclitaxel has been associated with delayed endothelialization and chronic inflammation.[17,29,30]

The polymer coating on stents may be a possible cause of arterial constriction. Early studies evaluating biodegradable and nonbiodegradable polymers in porcine coronary arteries suggested a significant inflammatory reaction to the several polymers evaluated.[31] Vascular response to the polymer on the Taxus drug-eluting stent, poly(styrene-b-isobutylene-b-styrene),[27] is not publicly available. Data regarding the local vascular response to the specific polymer used in the Cypher stent (a poly-n-butyl methacrylate and polyethylene-vinyl acetate copolymer) in animal models are conflicting. In a porcine model, with greater polymer thickness, there tended to be greater arterial inflammation than bare-metal stents, although the arterial injury score also tended to be greater with the thicker polymer. In contrast, there was no relationship between the presence of polymer or polymer thickness with neointimal area or inflammation in a canine model.[32] There was also no increase in neointimal area in a rabbit iliac model in the presence of polymer compared with bare-metal stents.[26]

Components of the Cypher polymer coating have been evaluated in animal models as well. The monomer (n-butyl methacrylate), a component of the polymer coating on the stent, has been infused in a rabbit model. This resulted in a dose-related decrease in mean blood pressure and increased central venous pressure. Particles of the polymer poly(ethyl methacrylate) n-butyl methacrylate placed in the subcutaneous tissues of rats resulted in the presence of macrophages and foreign body giant cells in the adjacent tissue.[33] In addition, implantation of ethlyene-vinyl acetate copolymer has been reported to be associated with sterile abscesses in 25% of rabbits.[34]

The mechanisms of clinical coronary spasm remain unclear. Isolated focal coronary spasm generally occurs at the site of atherosclerotic plaque, and is usually responsive to calcium channel-blockers and nitrates.[35] Mechanisms may include endothelial dysfunction, alterations in autonomic tone, reactive oxygen species, smooth muscle hypercontractility or inflammation and allergic responses. Allergic reactions have been reported to induce chest pain with ST-elevations in patients with angiographically normal coronary arteries or angiographically mild coronary artery disease.[36,37] The release of histamine from mast cells may trigger coronary spasm in these cases.[34] Intravenous infusion of histamine has been used to provoke coronary artery spasm in patients with nonexertional chest pain and nonobstructive coronary artery disease. In these patients in whom spasm was induced by histamine, the spasm was inhibited by preadministration of cimetidine.[38] In the cases reported, it is possible that the patients developed an allergic reaction to a component of the stent system, leading to diffuse spasm perhaps mediated by histamine release.

Reports of early and late hypersensitivity to components of drug-eluting stents have prompted an FDA notification to physicians.[2,39] The described reactions include: pain, rash, respiratory alterations, hives, itching, fever and blood pressure changes. However, some reactions have been severe, including anaphylaxis. Additionally, Virmani et al[3] describe a case of localized hypersensitivity vasculitis after Cypher stent placement, resulting in fatal stent thrombosis 18 months after stent implantation. This well-documented case raises the possibility of long-term hypersensitivity to the stent, resulting in extensive inflammation, aneurysmal dilation and stent thrombosis. Fortunately, localized hypersensitivity vasculitis appears to be quite rare or not severe since it has not been described in the randomized trials and large registries. Work by Togni et al[4] clearly establishes unique functional changes in the vasomotion of at least the target coronary vessel with

drug-eluting stents compared to bare-metal stents. This abnormality includes a mild chronic resting vasoconstriction as well as paradoxical vasoconstriction to exercise challenge. While the patients Togni et al studied were asymptomatic, we hypothesize that a very small subset of patients may be more profoundly affected, leading to the more severe refractory spasm and clinical events we have observed.

Study limitations. This is a descriptive review of the available literature and the MAUDE database, as well as our institutional experience. The possibility of significant reporting and publication biases cannot be excluded in this retrospective, observational series. The incidence of severe spasm, for instance, cannot be accurately established without population-based data. Underreporting of adverse events in the literature and to the FDA is a well-known phenomenon. Understandably, this is due to the operators' lack of time and information on how to file a report, as well as the natural tendency to harbor the concern that one's own underperformance caused the event. Inexplicable adverse events tend to be rare without raising concern until a cluster precipitates a broader review. The diagnosis of coronary spasm can be particularly difficult if it has resolved with medical therapy prior to diagnostic angiography. Intravascular ultrasound (IVUS) was not performed in our cases. While IVUS interrogation of these arteries may have helped to more definitively rule out dissection, the angiographic appearance in the cases did not suggest dissection, and dissection was not present at autopsy in the fatal case. If other operators have observed similar cases, perhaps this description of a possible association between severe diffuse coronary spasm and stent placement, particularly drug-eluting stent placement, will stimulate further reports to improve our understanding and management of this apparently infrequent periprocedural event. Clearly, drug-eluting stents have substantially improved interventional cardiovascular care. However, these rare cases of severe, diffuse spasm indicate the need for continued vigilance and perhaps further improvement in the vascular compatibility of drug-eluting stents.

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