Pathological Mechanisms of Fatal Late Coronary Stent Thrombosis in Humans

Andrew Farb, MD; Allen P. Burke, MD; Frank D. Kolodgie, PhD; Renu Virmani, MD

Background—Coronary stent deployment is associated with a low incidence of acute thrombosis. However, late stent thrombosis (LST) has likely been underrecognized clinically, and pathological descriptions are lacking.

Methods and Results—LST was defined as an acute thrombus within a stent that had been in place ≥30 days. Cases of LST were selected from a registry of human coronary stents submitted for analysis. Thirteen cases of LST (9 men, 4 women) were identified. The mean duration from implantation to thrombosis was 3.6±3.5 months (range, 1 to 11.9 months). The causes of death were sudden cardiac death (n=10), acute myocardial infarction (n=2), and heart failure (n=1). The pathological mechanisms of LST were as follows: (1) stenting across ostia of major arterial branches (5 cases); (2) exposure to radiation therapy (3 cases); (3) plaque disruption in the nonstented arterial segment within 2 mm of the stent margin (2 cases); (4) stenting of markedly necrotic, lipid-rich plaques with extensive plaque prolapse (2 cases); and (5) diffuse in-stent restenosis (1 case). Twelve cases demonstrated a failure to form a completely healed neointimal layer overlying stent struts. Underlying in-stent restenosis was present in only 4 (31%) of 13 cases.

Conclusions—LST is a potentially fatal complication of coronary stenting. Stenting across branch ostia, disruption of adjacent vulnerable plaques, radiation therapy, and extensive plaque prolapse can precipitate LST. Impaired intimal healing (ie, the failure to form a complete neointimal layer over stent struts) extends the window during which stents are prone to thrombosis. (Circulation. 2003;108:1701-1706.)

Key Words: thrombosis ■ stents ■ restenosis ■ coronary disease

The incidence of acute and subacute coronary stent thrombosis, defined as stent thrombosis within 30 days of deployment, has been reduced to <1% to 2% as a result of improved deployment techniques that fully appose stent to vessel wall and the use of antiplatelet agents.1 Coronary brachytherapy focused attention on the issue of late stent thrombosis (LST), defined as thrombosis ≥30 days after stent deployment. There was a 6.6% incidence of late arterial occlusion 2 to 15 months after β-brachytherapy, of which 67% occurred in patients receiving stents.2 Limited data suggest a low frequency of nonbrachytherapy-related LST. There was a 0.8% incidence of LST in the nonbrachytherapy control arm of a recent γ-brachytherapy trial.3 Whether it occurs early or late, stent thrombosis is associated with either death or nonfatal myocardial infarction.4,5

Although the postulated mechanisms of LST in brachytherapy include delayed intimal healing and endothelialization, the cause of LST in nonbrachytherapy cases is unknown. To date, pathological analyses of LST are lacking. The objective of the present study was to evaluate the morphology of LST to gain insights into the mechanisms of this infrequent but clinically serious entity.

Methods

Source of Cases

From a registry of human coronary artery stent implants referred for diagnostic consultation, cases with histological evidence of an acute occlusive or nonocclusive mural thrombus within a coronary artery stent in place ≥30 days were selected. Stented arteries were fixed, processed for light microscopy, and stained with hematoxylin–eosin and Movat pentachrome as previously described.6 Clinical histories and cardiac catheterization reports were reviewed.

Results

Thirteen cases of LST were identified (8 men and 5 women; mean age, 59±15 years) from a group of 168 stented native coronary arteries (from 132 patients [9.8%]). At the time of coronary intervention, all patients had angiographically successful stent deployment with 1 stent deployed in 9 patients, 2 stents in 3 patients (2 with bifurcation stenting), and 3 stents in 1 patient. Stents had been deployed at 3.6±3.5 months (range, 1 to 11.9 months). The indication for stent placement was acute myocardial infarction (AMI) in 4 cases; unstable angina, non–Q-wave myocardial infarction, or post–myocardial infarction angina (3 cases); stable angina (5 cases); and unknown (1 case). Ticlopidine or clopidogrel in addition to...
aspirin were prescribed for all patients for whom a list of medications was available (7 patients). The cause of death was sudden cardiac death in 10 cases, AMI in 2, and heart failure in 1. Aspirin use at the time of death was confirmed in 10 patients; a list of medications was unavailable in 3 patients.

At autopsy, in-stent restenosis at the site of the thrombus (defined as a stent lumen area narrowing of >75% [equivalent to a diameter stenosis of >50%] by neointimal growth) was present in 4 of 13 cases. Stent thrombi were occlusive (or near occlusive) in 9 cases and nonocclusive in 4 cases. Thrombi consisted predominantly of platelets in 8 cases, mixed fibrin and platelets in 2 cases, and predominantly fibrin in 3 cases.

Mechanisms of LST
Stenting Across Ostia of Major Arterial Branches (5 Cases)
LST occurred between 1 and 4 months after stent deployment (Table; Figures 1 and 2). There were 4 sudden deaths and 1 death soon after an AMI. All thrombi were platelet rich and occlusive, and thrombi extended beyond the branch artery ostium in 4 of 5 cases. Three cases involved thrombosis of a left anterior descending (LAD) stent (2 of which also had bifurcation stenting of a left diagonal [LD] branch), and the remaining 2 stents were in the left circumflex. In the 2 bifurcation stenting cases, the LD artery stent protruded back through the arterial ostium into the LAD artery. In all cases, there was evidence of ongoing thrombosis in the neointima overlying stent struts, characterized by focal fibrin deposition interspersed with smooth muscle cells and extracellular matrix. Bare stent struts (ie, no neointimal coverage) were focally present at the ostium of the major side branches in 3 of 5 stents. Underlying in-stent restenosis was present in 2 cases, only 1 of which involved the arterial segment at the side branch ostium.

Radiation Therapy (3 Cases)
Two cases of LST were associated with vascular brachytherapy. In 1 previously reported patient, a right coronary artery balloon angioplasty restenosis lesion was treated with stenting plus 18 Gy $\beta$-radiation delivered via a catheter-based system. Ticlopidine was stopped after 18 days, and the patient died suddenly 70 days after stenting. A second case of brachytherapy-associated LST was observed in a patient who died suddenly 19 weeks after undergoing balloon angioplasty, rotational atherectomy, and 14 Gy $^{92}$Ir brachytherapy for right coronary artery in-stent restenosis (with 3 stents placed 6

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<th><strong>Age (years),</strong> Gender</th>
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<th><strong>Stented Stents</strong></th>
<th><strong>No. of Stents</strong></th>
<th><strong>Stent Length, mm</strong></th>
<th><strong>Time to Stent Thrombosis, d</strong></th>
<th><strong>Presentation/In-Stent Thrombosis</strong></th>
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| **AMI** indicates acute myocardial infarction; **CHF**, heart failure; **ISR**, in-stent restenosis; **LCX**, left circumflex coronary artery; **LOM**, left obtuse marginal branch; **PCI**, percutaneous intervention; **RCA**, mid-right coronary artery; **SCD**, sudden coronary death; and **UAP**, unstable angina pectoris.
| *Bifurcation stenting of LAD and LD coronary arteries.
| †Nonoverlapping.
months before brachytherapy). The patient was taking aspirin and clopidogrel at the time of his death. LST associated with radiation was observed in 1 patient treated with external beam radiation therapy for lymphoma (Figure 3).

Histologically, all 3 LST cases associated with radiation showed impaired neointimal healing. Fibrin-rich thrombi were present in all cases, and 1 brachytherapy case had an additional occlusive platelet-rich thrombus. The majority of stent struts were uncovered by neointima in 2 cases (1 brachytherapy and 1 external beam radiation case). The other brachytherapy case showed diffuse in-stent restenosis; the neointima was focally disrupted with variably thick layers of fibrin-rich thrombus.

Figure 1. A 31-year-old man died suddenly 3 months after left circumflex coronary (LCX) stenting. Postmortem radiography (A) shows a MULTI-LINK stent crossing the ostium of the left obtuse marginal (LOM) branch. B and C are low- (B) and high- (C; box in B) power views of an occlusive platelet-rich thrombus (t) at the ostium of the LOM. Stent struts across the ostium (t) are not covered by neointima. Struts in contact with the LCX plaque are covered with alternating layers of neointima and fibrin (arrow in B). A deeper section (D) demonstrates in-stent restenosis, a neointima with layered fibrin overlying the LOM ostium (arrowhead), and an occlusive luminal thrombus (B through D: Movat pentachrome; scale bars 0.36 mm in B and D and 0.18 mm in C).

Figure 2. A 64-year-old man underwent bifurcation stenting of the LAD (AVE stent) and LD (NIR stent) coronary arteries after an AMI. Sudden death occurred 31 days after stenting. Postmortem radiography (A) shows protrusion of the proximal portion of the LD stent into the LAD. Thrombosis of the bifurcation is demonstrated in B (low power, struts indicated by *); the box in B (high power in C) shows an organizing neo-intima with smooth muscle cells in a proteoglycan-rich matrix (arrow) and platelet-rich thrombus around an uncovered strut (t) (B and C: Movat pentachrome; scale bars 0.23 mm in B and 0.20 mm in C).

Disruption of Vulnerable Plaques Just Proximal or Distal to the Stent (2 Cases)
Both cases were sudden cardiac deaths, one of which was exercise related. In 1 case (Figure 4), there was a rupture of a lipid-rich vulnerable plaque with an acute occlusive thrombus in the arterial segment within 2 mm of the distal margin of the stent. The necrotic core of the ruptured plaque was in continuity with the core deep to the stent; the destabilized intrastent core ruptured, resulting in plaque prolapse between struts and lumen thrombosis. In the second case, there was a plaque rupture within 2 mm proximal to the stent associated with a large platelet-rich thrombus in the proximal portion of the stent. Only mild neointimal thickening was present in the thrombosed stent segment.

Stent Deployment in Highly Necrotic Atherosclerotic Plaques With Extensive Plaque Prolapse (2 Cases)
One patient died suddenly 33 days after coronary stenting (Figure 5) and the other died suddenly 48 days after stenting (and 12 days after presenting with an AMI in the distribution of the stented artery). The plaques in these cases had large

Figure 3. A 53-year-old woman presented with an AMI and underwent LAD coronary artery stenting 18 weeks antemortem. Mediastinal adenopathy was noted at the time of stenting, and she was diagnosed with stage IIIb Hodgkin’s disease (treated with chemotherapy and 20 Gy mediastinal radiation therapy). Fourteen days antemortem, she presented with an AMI and cardiogenic shock; angiography showed LAD stent occlusion, which was treated with balloon angioplasty. The patient died secondary to multiorgan failure. At autopsy, a MULTI-LINK stent was present in the proximal LAD (A). A fibrin-rich nonocclusive mural thrombus is shown in B and was focally present between the stent and the underlying vessel. Most stent struts were uncovered by neointima except for those indicated (t in C, a high power of box in B) (B and C: Movat pentachrome; scale bars 0.30 mm in B and 0.11 mm in C).
necrotic cores (occupying 38% and 47% of the total plaque area). Impaired neointimal healing was associated with necrotic core prolapse between struts with strut penetration deep into the lipid core. There was impaired healing overlying the stent characterized by the failure to form a confluent smooth muscle cell–rich proteoglycan and collagen matrix. The thrombi were composed of layered platelets and fibrin, were focally occlusive, and were present along the entire length of the stent. Neither stent demonstrated restenosis.

LST Associated With In-Stent Restenosis
In 1 case, a 67-year-old man died secondary to heart failure and bradycardia. He had 2 nonoverlapping AVE stents in the mid and distal LAD coronary artery (placed 300 days antemortem), and both stents showed diffuse in-stent restenosis. A subocclusive fibrin-rich thrombus was present in the proximal stent, and there was focal hemorrhage in the atherosclerotic plaque underlying the stent.

A diagram of the postulated mechanisms of LST associated with impaired neointimal healing is shown in Figure 6.

Discussion
In the present study, LST was associated with major adverse clinical events (AMI and sudden cardiac death), and the following morphological substrates were observed: (1) stenting across major arterial side branches, (2) radiation therapy, (3) plaque disruption in the arterial segments adjacent to stents, (4) stenting of necrotic lipid-rich plaques with plaque prolapse, and (5) diffuse in-stent restenosis. A common pathological finding of all of these clinical events, except for 1 diffuse in-stent restenosis case, was incomplete neointimal healing.

Pathology of Stent Healing
Experimental animal studies and analysis of postmortem human coronary artery stents demonstrate an "injury-and-repair" response to arterial stenting.8,9 In the first 24 hours after stenting in humans, there is platelet and fibrin deposition with neutrophil infiltration associated with stent struts.9 Chronic inflammatory cells are also observed early and may persist indefinitely. Fibrin deposits organize and vascular smooth muscle cells are recognized in the emerging neointima by 2 weeks. A compact neointima containing smooth muscle cells in a proteoglycan/collagen extracellular matrix covering stent struts has been identified in stents in place 30 days.9

The endothelium plays an important role in preventing thrombus deposition, and catheter-based revascularization procedures invariably produce severe endothelial injury. The time required to establish complete stent endothelialization in humans is unknown but probably requires at least 3 months.10 Although arterial healing leads to restenosis when neointimal growth is excessive, an endothelialized smooth muscle cell–
rich neointima that seals the thrombogenic components in the underlying artery (metallic stent, lipid core, fibrin) from the lumen likely provides protection against LST.

A unifying morphological finding in 12 of 13 cases of LST in the present study is impaired neointimal healing, defined as delayed development of a endothelialized layer of smooth muscle cells and extracellular matrix that completely covers the stent.

**Stenting Across Ostia of Arterial Branch Points**

Stenting across side branches is usually associated with a low incidence of acute or late side branch occlusion. However, LST can be associated with impaired healing and the absence of full neointimal coverage over struts at branch-point ostia. Arterial branch points are foci of low shear and low flow velocity and are sites predisposed to the development of atherosclerotic plaque, thrombus, and inflammation. In addition, flow disturbances and changes in shear at arterial branches, augmented by the presence of a semirigid stent, increase the likelihood of local thrombus deposition. These low-flow velocity areas increase local fibrin and platelet deposition. Nevertheless, these physiological properties do not prove a cause-and-effect relationship between stenting across side branch ostia and LST.

**Radiation Therapy**

Damage to the endothelial lining of capillaries, arterioles, and arteries that occurs after radiation exposure is associated with increased vascular permeability, inflammation, and thrombus deposition. Initial studies of coronary brachytherapy demonstrated a high incidence (9.1%) of late arterial occlusion, mostly in patients treated with stents. Aspirin and clopidogrel treatment for 12 months after ir brachytherapy for in-stent restenosis lowered the rate of LST to 3.3%. Currently, antiplatelet therapy for at least 6 months is recommended after brachytherapy for in-stent restenosis.

Potential mechanisms of late arterial thrombosis after coronary brachytherapy include impaired endothelialization, persistent fibrin deposition leading to continuous platelet recruitment, positive arterial remodeling producing stent malapposition, and unhealed arterial dissection. Preclinical studies of arterial brachytherapy have demonstrated delayed neointimal healing characterized by persistent fibrin and platelet deposition on nonconfluent areas of matrix, incomplete endothelialization, and increased intimal cellular proliferation.

**Plaque Disruption Proximal or Distal to the Stent**

In one clinical study of LST, angiograms were suggestive of intimal dissection in the nonstented arterial edges in 75% of cases. Coronary atherosclerosis is often a diffuse disease, and the number of vulnerable thin-cap atheromas increases with the presence of multiple coronary risk factors. A plaque rupture that occurs in close proximity to a stent can extend to the adjacent stented segment and present as LST. The occurrence of plaque disruption outside the stent leading to stent thrombosis underscores the need for continuous aggressive coronary risk factor modification.

**Stenting of Highly Necrotic Plaques**

Underlying plaque morphology affects the rate and completeness of healing and endothelialization. Neointimal growth and reendothelialization occur via the migration and proliferation of vascular smooth muscle and endothelial cells from the noninjured arterial edges, adjoining arterial branches, and vasa vasorum. In highly necrotic plaques, stent struts penetrate deeply into the lipid core and are not in contact with the vessel wall (either arterial media or fibrocellular plaque). A stent placed in an artery with a large lipid core with significant plaque prolapse could have a delayed
development of a compact endothelialized neointima as a result of the relative paucity of migrating and proliferating smooth muscle cells in close proximity to the stent.

Clinical Studies of LST
There have been few reports of LST not associated with brachytherapy. Danenberg et al identified 8 of 994 (0.8%) patients with coronary stents presenting with AMI >1 month after stenting (with the stented segment as the culprit lesion). The mean time from stent to AMI was 141 days (range, 35 to 400 days). Angiography demonstrated an intimal flap (dissection) at one of the stent edges in 6 of 8 patients. The authors speculated that during the cardiac cycle, high deformation stress is generated between the stented arterial segment and nonstented segments, increasing the likelihood of plaque rupture.

Heller et al observed LST (AMI >30 days after implantation) in 12 patients (0.65% incidence of the population studied). No particular coronary angiographic finding at the time of initial stenting or specific stent type was linked to LST. Patients presented 73±23 days (range, 33 to 270 days) after stenting. LST was associated with significant mortality and morbidity: 2 of 12 (17%) patients died, and of the 10 patients with initially successful percutaneous interventions, 4 patients developed abrupt or threatened arterial closure (leading to coronary bypass surgery in 2), 1 experienced a stroke, and there was 1 late death. Finally, Wang et al reported LST in 9 of 1191 patients (0.76%) with a mean presentation at 109 days (range, 39 to 211 days). There were no differences in clinical characteristics or angiographic variables in patients with LST versus control subjects without stent thrombosis. Notably, only 3 of 9 patients had clinical symptoms suggestive of in-stent restenosis. These 3 clinical studies likely represent an underestimate of the incidence of LST because all patients survived to the point of being able to undergo angiography.

Clinical Implications
Although the incidence of LST is expected to remain low, the present study suggests that continued efforts to identify plaque morphologies at increased risk for this potentially fatal event are needed. When stenting across the ostia of major side branches and in bifurcation stenting, careful attention should be paid to assure full stent apposition at the origin of the side branch and to avoid free stent protrusion into the main artery. Improved imaging techniques could help identify vulnerable plaques at the stent edges. These data suggest that, in addition to stents subjected to radiation therapy, the use of prolonged antiplatelet therapy should be considered when stents are deployed in highly necrotic, lipid-rich plaques.

References
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