Late Thrombosis After Radiation
Sitting on a Time Bomb

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Five years after Condado et al first treated human coronary arteries with brachytherapy, there is ongoing clinical investigation into its safety and efficacy in preventing restenosis. As with any novel technique, unexpected complications may dampen early high expectations and result in pessimism and skepticism. However, time, experience, and complete data analysis will determine the reality.

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Costa and coworkers may be reacting prematurely by reporting a new phenomenon in interventional cardiology entitled “late, sudden thrombosis after PTCA plus radiotherapy.” They report 6 (6.6%) of 91 patients who presented with late total occlusion/thrombosis at angiographic follow-up; these patients were enrolled into different radiation protocols using different β-emitters at different prescribed doses.

Late total occlusion or late thrombosis is a valid concern, especially when associated with acute myocardial infarction (MI). However, can we really draw any conclusion from 6 heterogeneous case reports taken from a small cohort of patients? Is this announcement based on too few data, and is it premature?

An editorial based on a Brief Rapid Communication mandates the editorialist to gather additional information, disclose his own insights, and provide the readers (the jury in this case) with as much information as possible.

Definition and Nomenclature

Acute thrombosis occurs during or early after intervention, and subacute thrombosis occurs within the subsequent 30 days. Both usually present with unstable symptoms and angiographic evidence of thrombus. However, the definition of late thrombosis may be problematic. It may not present with symptoms. It may be detected only when follow-up angiography shows a late total occlusion, which could also be the result of progressive intimal hyperplasia. Late total occlusion/thrombosis should be defined as any angiographically documented total occlusion >30 days after the procedure. For patients who have a patent treatment site at 6 months and subsequently develop a total occlusion, we propose the term “late late thrombosis.” Based on these new definitions, the investigators presented 4 patients with late thrombosis and 2 with late late thrombosis.

Is Late Thrombosis a Known Phenomenon After Conventional PTCA or Stenting?

The literature identifies patients at risk for late reocclusion after conventional PTCA. Total occlusions treated with stenting are reported to have a 7% rate of recurrence of late total occlusion at 6 months. Treatment of an infarct-related vessel is associated with a 30% reocclusion rate after thrombolytic therapy at 3 months and up to a 17% rate of reocclusion after PTCA at 6 months. The majority of these events were clinically silent, and the proposed causes were rethrombosis or progressive renarrowing. Patients treated with stents and ticlopidine rarely present with late thrombosis.

Late Thrombosis in Clinical Radiation Trials

The patients in the current series were not considered high-risk patients when they were enrolled in the radiation protocol, although 4 of 6 had contributing factors. The first question is whether late thrombosis occurs in other radiation clinical trials. Feasibility trials typically include highly selective small cohorts of patients, usually lack control groups, and have nonuniform anticoagulation/antithrombotic drug regimens; thus, complications that occur in <10% of patients can be easily missed. We reviewed the reported cases of late thrombosis/occlusion for each of the completed and published feasibility radiation studies.

Condado et al treated 21 patients with γ-radiation (192Ir after balloon angioplasty, with doses that exceeded 55 Gy to the near wall) and discharged all patients with aspirin and coumadin for a period of 3 months. Two patients developed silent thrombosis (at 30 and 38 days after treatment) without ECG evidence of MI. One of these patients had primary total occlusion and the other had a severe post-PTCA dissection before radiation. None of the other 19 patients had late total occlusion at 2-year angiographic follow-up.

Verin and coworkers treated 15 patients by application of β-radiation (90Y) after balloon angioplasty of de novo lesions. Patients were discharged with aspirin as sole antiplatelet therapy. At 6 months, none of the patients had clinical or angiographic evidence of thrombosis, but 1 asymptomatic patient had total occlusion.

In the Beta Energy Restenosis Trial (BERT), 23 patients with de novo lesions were treated with balloon angioplasty plus intracoronary radiation with 90Sr/Y (a pure β-emitter). Patients were discharged with no antiplatelet agent other than...
aspirin. At 6 months, only 1 patient presented with a late total occlusion. Conversely, in the middle of the Beta Cath study, a randomized study that used the same radiation system, prescription dose, and antiplatelet regimen as in BERT, the data safety monitoring committee advised a change in the antithrombotic regimen of the provisional stent arm to 3 months of ticlopidine due to an excess of late thrombosis.

In the SCRIPPS trial (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting),10 55 patients with restenosis were randomized to either placebo (29 patients) or 192Ir (26 patients) and were discharged with ticlopidine and aspirin for 3 months only if new stents were implanted. At 2 years, there were 2 MIs associated with deaths in the placebo group, whereas only 1 patient from the irradiated group developed stent thrombosis and MI at day 18 due to early cessation of ticlopidine.11

In the WRIST study (Washington Radiation for In-Stent Restenosis Trial), patients with in-stent restenosis were randomized to either placebo or radioactive 192Ir seeds after conventional treatment of in-stent restenosis. The anticoagulation protocol for all patients was aspirin and ticlopidine for 1 month. Late total occlusion (at 6 months) was documented in 5 (7.7%) of 65 patients in the irradiated group (2 were asymptomatic) versus 3 (4.6%) of 65 in the control group (all asymptomatic) (Waksman et al, unpublished data, 1999).

In the BETA WRIST (Beta Radiation for WRIST),12 50 patients with in-stent restenosis in native arteries were treated with β-radiation (90Y) and discharged with the same anticoagulation therapy as in WRIST. At 6-month angiographic follow-up, late total occlusion was documented in 5 patients (10%); 2 were asymptomatic. Information from other radiation trials (eg, GAMMA1, LONG WRIST [Long Lesions for WRIST], SVG WRIST [Saphenous Vein Grafts for WRIST], and PREVENT [Proliferation Reduction With Vascular Energy Trial]) suggest that late occlusion is present as well. However, the rate, timing, and clinical presentation are not defined yet.

In the study by Costa et al,2 the late thrombosis rate reported was 6.6%. However, a substantial number of patients did not complete the 6-month angiographic follow-up. Thus, an additional number of patients may develop symptomatic or silent late thrombosis that will be detected by angiography, unopposed to the vessel wall.

Delays in the late thrombosis rate may be related to the dose. Our studies13 showed luminal thrombi after radiation consisting mostly of fibrin, less organized than thrombus found in nonirradiated arteries after vascular injury. Furthermore, thrombi present in irradiated arteries lacked cells thought to be involved in the healing response to arterial injury (monocytes, lymphocytes, and macrophages); this may prolong the platelet residence and delay thrombus organization.14 Others16 demonstrated a dose-dependent recruitment of platelets at the site of injury and irradiation.

Stents may increase the risk of late thrombosis by being more thrombogenic, and radiation may further delay complete reendothelialization. Delayed healing was seen at 12 weeks with the radioactive stent.17 It is possible that the new endothelium may be dysfunctional, causing arterial spasm and flow impairment.

Unhealed dissections were also seen (both angiographically and by intravascular ultrasound at 6-month follow-up) in some patients who were treated with balloon angioplasty and intracoronary radiation.18 A different explanation is required for the striking phenomenon of late late thrombosis seen many months after a patent artery was documented at 6-month angiographic follow-up. At this time, we don’t know what the incidence, timing, and mechanism of this new phenomenon are or how to prevent it.

Is it possible that a gradual erosion of tissue surrounding the stent, leaving the stent unopposed to the vessel wall, will serve as a nidus for thrombosis? The intravascular ultrasound studies of patients who underwent radiation in the WRIST studies demonstrated reduction of in-stent neointimal tissue at follow-up in >50% of patients. This could be paralleled by a reduction in the peri-stent tissue, causing the stents to become unopposed to the vessel wall.

### Clinical Implications and Therapeutic Strategy

There are advantages to the rapid identification of complications of a new technique, because therapeutic strategies to prevent these complications may be included in the early pivotal trials. In the past, adjunct antiplatelet therapy with ticlopidine proved to be effective in reducing acute and subacute thrombosis in the STent arterial AntiCoagulation Regimen Study (STARS).19 Now, the important questions are (1) whether prolonged antiplatelet therapy for patients treated with intracoronary radiation will be effective, and (2) what should be the duration of prolonged antiplatelet therapy?

### Potential Causes of Late Thrombosis After Radiation

| 1. Delayed reendothelialization |
| 2. Fibrin deposition and platelet recruitment |
| 3. Impaired vasoreactivity and spasm |
| 4. Tissue erosion around the stent |
| 5. Unhealed dissection |
Currently, we are studying whether 6 months of clopidogrel may significantly reduce the rate of late thrombosis. So far, none of the patients in our study have developed late thrombosis.

Late thrombosis after radiation therapy is like sitting on a time bomb. You don’t know if or when it will happen. Prolonged antiplatelet therapy may affect the cost-effectiveness of brachytherapy for preventing restenosis. Alternative therapeutic approaches may become important, including agents that enhance vascular healing (such as nitric oxide donors) and limiting stent use in conjunction with radiation.

Final Comments and Conclusions

New technologies continue to surprise us with unexpected events that need to be disclosed fully and evaluated carefully. Describing a true new phenomenon from only 6 cases is like shooting in the air and hitting the right bird with the first bullet. Costa and his coworkers should be congratulated. However, we still don’t know why the bird was there, where it came from, and what its final destination was. It therefore becomes essential to define the true incidence and origin of late thrombosis, as well as the factors that contribute to it. Multivariate analysis of larger patient cohorts will be required to determine clinical and angiographic predictors of late thrombosis, and clinical therapeutic strategies will be found to prevent it. The control of late thrombosis will strengthen vascular brachytherapy, and the winner will be the patient, who will be able to enjoy the honey without feeling the sting.

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References


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