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Who Was Thrombogenic: The Stent or the Doctor?

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Editorials stents occlusions thrombosis

In 1986, when pioneers such as Jacques Puel and Ulrich Sigwart implanted the first coronary Wallstents, no guidelines were available to determine the treatment after stenting. From the experience acquired with mechanical prosthetic heart valves, it was inferred that chronic anticoagulation with coumarins was indicated. When the first cases of subacute occlusion were encountered, the anticoagulation regimen was further reinforced. The use of heparin, dextran, or thrombolytic agents during the procedure followed by warfarin, aspirin, sulphinpyrazone, and dipyridamole did not eliminate subacute thrombosis, which occurred in 18% of the first 117 stents implanted and was responsible for a higher incidence of hemorrhagic complications and prolonged hospital stay.[1]

When the first Palmaz-Schatz stents were implanted in the coronary arteries, Richard Schatz initially claimed that the sole treatment with antiplatelet agents was sufficient to prevent subacute occlusion (panel discussion, European Society of Cardiology Congress, Vienna, 1988). Unfortunately, a prohibitive early occlusion rate (18%) was observed with this regimen, so a stringent anticoagulation regimen was again recommended.[2] These two consecutive negative experiences identified coronary stents as highly thrombogenic foreign bodies and discouraged investigators from using coronary stenting as a primary treatment for coronary artery stenosis. Stenting was thus restricted to the treatment of acute complications after balloon angioplasty.

It is to the merit of Antonio Colombo and his group to have broken this vicious circle and focused the attention of the community of interventional cardiologists on the modalities of stent deployment, questioning the dogma of the intrinsic thrombogenic nature of the stents. Early experience with subacute stent occlusion despite optimal anticoagulation convinced Colombo and his coworkers that the key issue in the prevention of subacute occlusion was not the perfect control of hemostasis but the optimization of stent implantation (panel discussion, Rotterdam Stent Course, December 1994). The major critical contribution of these investigators was to assume that the normalization of the rheology inside the stent as well as at its inflow and outflow would render the anticoagulation treatment superfluous. Intravascular imaging played a pivotal role in revealing that most of the angiographically satisfactory stent implantations were in fact far from being optimal. Incomplete stent apposition, persistence of residual luminal narrowing due to incomplete or asymmetrical stent expansion, and presence of significant disease of the proximal and distal reference segment could not be easily detected with angiography, at least by visual assessment, and were revealed only by intravascular ultrasound imaging. These observations prompted investigators to elaborate an original strategy based on oversizing of the balloon and high-pressure dilatation in order to obtain an optimal stent deployment.

The possibility of sizing the stent on the original dimensions of the vessel, measured with intracoronary ultrasound, can be considered an important step forward in the search for the “holy grail” of the *restitutio ad integrum* of the atherosclerotic coronary vessel. The criteria proposed by Colombo to guide stent implantation (reduction of the residual plaque area to less than 40% of the total vessel area) corresponds to the area stenosis defined in pathology studies as the threshold above which a further plaque increase cannot be accommodated by the compensatory enlargement of the total vessel area, resulting in a progressive luminal narrowing. More than 5 years ago, one of the authors of this editorial (P.W.S.)[3] wrote that “Stenting may be regarded as the invasive cardiologist’s attempt to restore the ‘Glagovian’ balance between plaque and luminal area. . . .” Intracoronary ultrasound now offers to the interventional cardiologist the possibility of establishing whether this balance has been restored in all the cases treated. The achievement of a ratio between plaque and lumen below the critical level of 40% residual area stenosis appeared to be associated with a low incidence of subacute thrombosis and recurrence of symptoms, with a need for repeated balloon angioplasty in 13.1% of patients by 6 months.[4] Restenosis, however, was far from abolished in this study, suggesting that different methods of limitation of intimal hyperplasia are still required to overcome the inescapable biological phenomenon triggered by wall injury. Having recognized the important educational role of intracoronary ultrasound in the modification of the strategy of stent deployment, the concept that intracoronary ultrasound guidance is imperative in performing optimal stenting must nevertheless be questioned, since intravascular ultrasound is a time-consuming and costly investigation, with an inherent (although small) risk of complication. Although these limitations can be partially overcome by the use of a combined echo-balloon catheter for stent implantation and expansion,[5] in times of heavy financial constraints, the issue of cost-effectiveness must be specifically addressed and cannot be solved by a study that remains observational and uses only a visual assessment to define the angiographic end point.[4] The precise and accurate delineation of the angiographic contours provided by algorithms consistently validated for more than a decade[6] and now widely available on-line in the latest generation of digital angiographic systems can be seen as the “poor man’s alternative” to intravascular imaging. Automated edge detection in multiple views is the standard method used to detect the persistence of residual stenosis, but on-line videodensitometry also should be tested as a monitoring technique for stent deployment. Since for most stents the recoil after balloon dilatation is predictable, the on-line measurement of the dimensions of the balloon during inflation also can be used to optimize stent expansion. A moderate enhancement of the radiopacity of the stent struts—without hampering the detection of the opacified vessel lumen (for example, as for the tantalum stents)—may be sufficient to permit an accurate automated radiographic contour detection of the stent diameter without the need of contrast injections.

The study of Colombo et al proposes two elements of novelty in its strategy for stent implantation—ultrasound guidance and high-pressure intrastent dilatation—and it remains unclear which of the two is the key issue to virtually abolish the risk of subacute occlusion. As the authors recognize, an initial aggressive strategy of high-pressure dilatation can reduce the need for further interventions triggered by ultrasound after the “final” angiographic assessment from 88% to 40% of the cases.[4] The initial report from a large, observational, multicenter French trial conducted in 654 patients treated with ticlopidine and low molecular heparin after stenting supports this opinion, since a low subacute thrombosis rate was obtained without the use of ultrasound guidance using a strategy of stent deployment largely influenced by the Colombo approach.[7] In the evolving strategy of the Milan group, it appears that the current approach is based on the achievement of a vessel lumen of uniform caliber in the reference and in the stented segments with high-pressure dilatation of a noncompliant balloon matching the size of the angiographically normal segment. Intracoronary ultrasound can rapidly and accurately detect incomplete stent expansion, especially if the high-resolution ultrasound cross-sectional images are collected during a motorized pull-back of the ultrasound transducer, allowing the application of on-line algorithms of automatic lumen detection and three-dimensional reconstruction.[8] In most cases, however, the detection of a residual intrastent narrowing also appears possible with the use of quantitative angiography in multiple views. In diffusely diseased vessels, however, the sole use of angiography carries the risk of an inappropriate sizing of the stent on a falsely normal reference segment. A prerequisite for optimal stent implantation with high-pressure dilatation is that the implantation should cover the entire stenotic segment up to a relatively disease-free proximal and distal artery. Meticulous attention to the treatment of segments of residual narrowing adjacent to the most severe stenosis and potentially impairing the inflow and outflow of the stented segment is reflected by the use of multiple stents in 40% of the lesions.[4]

Although this study clearly demonstrates that the complete apposition and embedding of the metallic wires of the stent into the vessel wall minimize the stent thrombogenicity, other methods rendering the stent more thromboresistant are currently being explored. To date, the results of the pilot phase of the Benestent II trial (200 consecutive cases) indicate that no subacute

occlusion has occurred with a heparin-coated Palmaz-Schatz stent, although the optimization of the stent deployment was mainly achieved with on-line quantitative angiography (67% of the cases), and only in 8% of cases was intravascular ultrasound imaging used. The study of Colombo et al reports a large but single-center experience, so it seems dangerous to extrapolate results obtained in an optimally equipped research laboratory with the meticulous work of highly experienced operators to the daily practice of newcomers in the field. The work of Colombo et al demonstrates that it is the imperfect operator, and thus the surgeon, who is responsible for a large part of the cases of subacute occlusion, but it would be foolish to completely deny the thrombogenic nature of the stent, demonstrated in in vitro and in animal work. Therefore, it can be argued that a less thrombogenic stent, coated or biodegradable, eluting or not, may represent a safety net for the average interventionalist.

It remains to be demonstrated in large cohorts of patients that the strategy of the Colombo group can be applied to stents with different and less ideal scaffolding properties. In coil stents, high-pressure dilatation carries the risk of damaging the mechanically less resistant structure of the stent, facilitating the protrusion of plaque remnants.

The results of large randomized trials showing a significant reduction of recurrence of symptoms and late angiographic restenosis after stent implantation[9 10] and the initial reports of the Colombo group[11 12] bolstered the application of intracoronary stenting. The exponential rise that has made intracoronary stenting, in some major European centers, the primary modality of percutaneous treatment of coronary lesions would not have been possible without the elimination of the prolonged hospital stay and of the increased risk of complications associated with the use of anticoagulation. Intracoronary ultrasound has been instrumental in the development of a more effective strategy of stent expansion that has almost eliminated the incidence of subacute thrombosis, without the need of anticoagulation. It has been associated with a remarkably low incidence of recurrent angina and angiographic restenosis despite the inclusion of lesions longer than 15 mm (16%), lesions in vessels smaller than 3 mm (26%), chronic occlusions (8%), acute or threatened occlusion after balloon angioplasty (5%), and restenotic (12%) and unstable lesions (37%). Now that this strategy has been defined, the real and continued need of intravascular ultrasound for stent implantation cannot be established without randomized studies comparing the relative value of intracoronary ultrasound and on-line quantitative coronary angiography in favorably altering the early and long-term follow-up after stenting.

By the end of 1995, we will have results of three large multicenter trials aimed at the prevention of subacute thrombosis after stent implantation: MUSIC, applying in a multicenter study the ultrasound criteria proposed by Colombo et al; MUST, without intracoronary imaging and studying the effect of a combined treatment with ticlopidine and aspirin; and BENESTENT II, using a heparin-coated stent in combination with ticlopidine and aspirin. Assuming that all these trials will be successful in virtually eliminating the incidence of subacute thrombosis, the winner will certainly be the one whose technique is less expensive, more easily applied, and demonstrates a greater efficacy in the prevention of long-term restenosis.

Footnotes

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