Vascular Stents

Biodegradable Stents: Are They Finally Here?

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The concept of vascular stents dates back to the invention of angioplasty, when Charles Dotter described a metal coil that could hold the artery open after balloon angioplasty.[1] It took 24 years, however, before clinical studies confirmed the value of coronary stents.[2] Today, nearly 70% of patients undergoing angioplasty have stents placed as part of the interventional procedure. The popularity of stents is based on the recognition that stenting results in an immediately improved angiographic outcome (even in the setting of unfavorable coronary anatomy). In addition, physicians can manage coronary dissections successfully with stents, which can also reduce acute complications, with a significant reduction in the need for coronary bypass surgery. Finally, stenting also reduces restenosis by achieving a larger initial lumen diameter. While these attributes have led to increased popularity for stents, the risk of restenosis and the problems and management of in-stent restenosis remain serious.

Metal stents are permanent devices that can obstruct side branches and make it difficult to perform coronary artery bypass if it becomes necessary in the future. Biodegradable stents, on the other hand, may offer advantages over metal stents. Because they are not permanent devices, natural healing processes can take place in the vessel following their degradation. They could also be more easily impregnated with drugs or genes to promote optimal healing and further reduce restenosis. The idea of biodegradable stents is not new and has been actively pursued experimentally since metal stents were first introduced. Why, then, hasn't there been a viable degradable stent before now? The primary reason has been the difficulty of developing an adequate biodegradable material that is compatible with the vessel wall and does not evoke a significant inflammatory response, leading to worse restenosis than is caused by a metal stent.

Initial and 6-Month Results of Biodegradable Poly-*l*-Lactic Acid Coronary Stents in Humans

Tamai H, Igaki K, Kyo E, et al.
Circulation. 2000;102:399-404.

Tamai and colleagues report for the first time the successful deployment and favorable long-term outcome of use of a biodegradable stent. The stent was made of poly-*l*-lactic acid, a compound that has been studied previously. Unlike those used in previous studies, this stent was made from a high-molecular-weight form of the compound that resulted experimentally in a minimal inflammatory response compared with that seen in previous reports. The authors also discovered that stent structure was critical for ultimate success. They found that a zigzag coil design rather than a mesh design significantly improved outcomes experimentally. In this study, 25 stents were deployed successfully in 15 patients. No stent thrombosis or major cardiovascular events occurred within 30 days. At 6 months, restenosis occurred in 10.5% of patients and target lesion revascularization occurred in 6.7%. Subsequently, unpublished reports from the same group have shown similar results in another 15 patients followed for 6 months, with long-term follow-up of over 1 year in the original group showing no further complications.

These findings are remarkable and very exciting, particularly when compared with prior experimental studies. Stack and colleagues from Duke University were the first to develop a biodegradable stent.[3] A subsequent study by Zidar and associates at the same institution demonstrated minimal inflammation in a dog model,[4] but Van der Giesen and coworkers from the Netherlands demonstrated that with multiple formulations of the poly-*l*-lactic acid, a marked inflammatory response occurred in a porcine model.[5] Attempts by others to develop a biodegradable stent have likewise been discouraging.[6]

The favorable results in this study, albeit in a small number of patients from a single center, revive the concept that a biograda ble stent may be a viable and important new advance in coronary stenting. The next step is to demonstrate long-term clinical benefit in a randomized clinical trial. If this is successful, there is potential for drug-, radiation-, or gene-impregnated biodegradable stents that will even further reduce restenosis and improve long-term outcomes. Perhaps we will reach the ultimate goal of coronary stenting, namely, a reduction in restenosis to a level that approximates that currently obtained from coronary bypass surgery, with an early failure rate of no more than 5%.

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Stenting Plus Abciximab vs tPA in Acute Myocardial Infarction

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The increase in the use of primary angioplasty as compared with thrombolysis is based on a growing number of clinical trials that have shown improved short-term and long-term clinical benefit with the use of angioplasty.[1] The critics of these studies point to the relatively small number of patients who have been studied in primary angioplasty trials and to the fact that these trials are carried out in large centers and the procedures performed by highly experienced operators, which does not reflect the situation of the majority of centers where angioplasty is performed in the United States. Support of this concern comes from the National Registry of Myocardial Infarction (NMRI), with more than 27,000 patients, which shows that the majority of these patients underwent primary angioplasty more than 2 hours after presentation at the emergency department and that the success rates in these centers was significantly lower than those published in clinical trials.[2] In addition, the GUSTO IIb trial showed angioplasty to have only a minimal benefit over tPA.[3] GUSTO IIb, a multicenter trial in 57 centers, enrolling 1,138 patients, is the largest trial of primary angioplasty to date.

The enthusiasts for primary angioplasty point to the significant advances that have been made in the procedure with the current widespread use of coronary stents and glycoprotein IIb/IIIa agents. Stenting in most clinical trials has been shown to provide a better initial result and a decreased rate of restenosis. Glycoprotein IIb/IIIa agents, particularly abciximab, have been shown to reduce the incidence of acute complications and improve long-term outcomes in certain subgroups of patients, such as those with diabetes. In the RAPPORT trial, a study of abciximab in acute myocardial infarction and primary angioplasty, significant improvement in short-term outcomes was demonstrated.[4]

Coronary Stenting Plus Platelet Glycoprotein IIb/IIIa Blockade Compared with Tissue Plasminogen Activator in Acute Myocardial Infarction

Schömig A, Kastrati A, Dirschinger J, et al., for the Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators
N Engl J Med. 2000;342:385-391.

Schömig and colleagues compared coronary stenting plus abciximab to tissue plasminogen activator (tPA) in 140 patients with ST-segment elevation who presented within 12 hours of the onset of chest pain. The primary end point of this randomized, single-center study was myocardial salvage, as determined by technetium-99m sestamibi imaging done at baseline and at 1 week. The study demonstrated that patients receiving a stent and abciximab had greater salvage (57% vs 26%, $P = .001$) and smaller infarct size (14.3% vs 19.4% of the left ventricle, $P = .02$) than patients receiving tPA. In addition, 6-month outcomes were improved, with a lower incidence of death, reinfarction, and stroke in the stent plus abciximab group (8.5% vs 23.3%, $P = .02$). It should be noted that the study was small and that therefore individual end points, such as death, were not statistically different, although directionally consistent with the overall findings (3 deaths in the stent group vs 9 deaths in the tPA group).

This study differs from previous studies in that the primary end point was infarct size as determined by ^{99}mTc sestamibi rather than clinical events or mortality. Nevertheless, it adds further data to a growing body of information concerning the value of an interventional approach to the treatment of patients with acute myocardial infarction. The benefit of percutaneous coronary intervention (PCI) in this study is likely because of the high TIMI 3 flow rate achieved (95.8%), a rate higher than that seen in the GUSTO IIb trial. The value of abciximab is also inferred by the authors, who suggest that it reduced thrombotic occlusion and distal microembolization and that this may have further limited infarct size.

While this study supports the role of PCI over tPA, it was not specifically designed to compare balloon angioplasty with stenting or the use of abciximab with its omission in the setting of acute myocardial infarction. The larger multicenter, randomized trial CADILLAC addressed these issues specifically, but the results are not yet published.[5] Preliminary data suggest an extremely low overall mortality rate of 1.5% at 30 days in this study, without any significant difference between balloon alone, stenting alone, and the use of balloon or stenting with abciximab. If the final trial results confirm these preliminary results, then the routine use of stents and abciximab may need to be questioned. Improved outcomes, in both Schömig and colleagues' study and the CADILLAC trial, are more likely due to the rapid reperfusion that was achieved at these centers (within 60 minutes in the Schömig study) and the very high TIMI 3 perfusion rate (96% in Schömig, 98% in CADILLAC). The key message from this report and previous studies is that optimal reperfusion is the central element in obtaining maximum myocardial salvage and a low 6-month event rate, no matter how achieved.

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Angiogenesis

The Role of Nitric Oxide in Atherogenesis

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Nitric oxide (NO) is known to be important in the control of vasomotor tone and as an inhibitor of atherogenesis. Not until recently, however, has the role NO plays in angiogenesis been defined. A number of angiogenic factors up-regulate the expression of endothelial NO synthase (eNOS) and stimulate the release of NO. Vascular endothelial growth factor (VEGF) stimulates the release of NO, and secretion is enhanced by NO's precursor, L-arginine.

NO seems to play a critical role in angiogenesis. Endothelial cells, when stimulated by VEGF or fibroblast growth factor (FGF), release NO and form 3-dimensional capillary-like structures. These effects are blocked by the NOS antagonist N-nitro-L-arginine methylester (L-NAME). An endogenous antagonist to NOS, called asymmetric dimethylarginine (ADMA), has been discovered recently and has been shown to compete with L-arginine for NOS. Hypercholesterolemia is associated with the elevation of ADMA. This paper explores the role of ADMA as an endogenous antiangiogenic factor.

The experiment was performed in normal (E+) and in apolipoprotein E–deficient hypercholesterolemic (E-) mice using a subcutaneous implantable disk angiogenesis system. Fibrovascular growth was assessed as an index of angiogenesis after 2 weeks. Basal and FGF-stimulated angiogenesis was impaired in E-mice, a finding associated with an elevation in plasma ADMA level. This inhibition was reversed by oral administration of L-arginine. Direct addition of ADMA to the disk also inhibited angiogenesis in a dose-dependent manner.

Angiogenesis Is Impaired by Hypercholesterolemia: Role of Asymmetric Dimethylarginine

Jang JJ, Ho H-KV, Kwan HH, et al.
Circulation. 2000;102:1414-1419.

This basic science report brings together several pieces of information that shed light on the pathogenesis of angiogenesis, showing that hypercholesterolemia inhibits angiogenesis and that ADMA plays a key role. This observation firmly ties together the NO pathway and the ability of the vascular system to regenerate itself at times of ischemia. Exactly how NO can lead to angiogenesis is still largely unknown. Whether angiogenesis supported by NO leads to collateral vessel formation or angiogenesis in the vasa vasorum is under active investigation.

Suggested Reading
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