Promises and Pitfalls of New Devices for Coronary Artery Disease

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In the past 2 years, there has been a precipitous availability of many new percutaneous coronary devices for investigational use, which are ultimately intended to assist, supplant, or integrate with balloon coronary angioplasty. Uniformly, these devices have attracted considerable attention from cardiologists based on recent journal articles,\(^1\)\(^2\) attendance at dedicated sessions during national meetings and regional interventional cardiology programs, new textbooks devoted to this field, and coverage by the media.\(^3\) The purpose of this report is to provide a brief overview of the many potential promises and pitfalls associated with these new coronary revascularization technologies.

**Promises**

**Management of Abrupt Closure**

Although many of the devices were not specifically designed to manage or prevent abrupt closure, this has been an exciting outgrowth of the experience.\(^4\) Recently, Detre et al\(^5\) summarized the incidence and complications of abrupt closure within the National Heart, Lung, and Blood Institute Coronary Angioplasty Registry II. An overall frequency of 122 of 1,801 patients (6.8%) was reported. Within the cohort of patients with documented closure, there was a cumulative 1-year mortality rate of 9% and in-hospital myocardial infarction rate of 40%.\(^6\) Clearly, even with the marked recent technological improvements in balloon angioplasty,\(^6\) there remains considerable potential for improvement in avoiding or treating iatrogenic coronary artery shutdown, the most dreaded technical complication of balloon angioplasty.

Using balloon technology but adding sideholes proximal and distal to the balloon, Stack and colleagues\(^7\) developed a catheter that permits passive autoperfusion to the myocardium during prolonged balloon inflations (as long as 20–30 minutes). Although a randomized controlled trial has not been completed, observational studies with this catheter have been encouraging for avoidance of emergency bypass surgery;\(^8\) it is commercially available and routinely being used as a method of managing acute coronary closure.

With respect to new treatment technologies, emergency stenting has been shown by Sigwart and colleagues to be a potential way of restoring coronary blood flow using the self-expanding stainless-steel Wallstent\(^8\) and by Roubin and associates\(^9\) using a coil design. In these patient studies, stent placement has led to a dramatic improvement in angiographic appearance of complex, propagated coronary dissection. Similarly, Spears et al\(^10\) have shown that laser balloon angioplasty may be effective in managing abrupt closure. Experimental studies performed by these investigators have suggested a "welding"-like effect of neodinium-YAG laser energy harnessed in this fashion. In 76 of 90 patients (84%), laser balloon angioplasty improved angiographic appearance, restored coronary blood flow, stabilized the patient, and prevented the need for emergency bypass surgery.\(^10\) Alternative less-expensive energy sources that achieve a similar heat-sealing effect, such as radiofrequency, are being pursued.

Although directional atherectomy has been used to manage abrupt closure,\(^4\) a recent case report by Seruys\(^11\) documents coronary artery perforation in this setting and raises caution about application of this particular technology to "salvage" balloon angioplasty. Despite this incident, the outlook for new device reduction of abrupt closure and its attendant serious complications is promising and deserves further study.

**Expansion to Complex Anatomical Subsets**

As an extension to more control or frank avoidance of abrupt closure, the new devices may permit a wider application for transcatheter approaches. Patients with complex angiographic lesions, such as excessive length, tortuosity, presence of thrombus, or marked ulceration, may be treated with new technologies. Directional atherectomy has demonstrated feasibility in debulking such lesions without the anticipated complication rate of balloon angioplasty.\(^12\) Patients with old (more than 8 years) saphenous vein grafts and diffuse disease have successfully undergone vacuum extraction atherectomy.\(^13\) These patients have traditionally been viewed as having high or excessive risk with balloon angioplasty.\(^14\) Similarly, stenting or laser technologies can be used to expand
the application of percutaneous techniques. Of particular note with the various new percutaneous techniques is that the postprocedure coronary artery segment often appears angiographically considerably better than with conventional angioplasty, as recently confirmed with matched-pair analysis; this is especially evident in lesions of type B or C morphology.

Avoidance of Restenosis

An underlying theme of designing new catheter technologies has been to reduce the problem of restenosis, the most important limitation of balloon coronary angioplasty. No pharmacological intervention has been reliably demonstrated to reduce the risk of restenosis after angioplasty. A review of preliminary data available for each of the new devices indicates that the overall rate of restenosis is quite similar to that of balloon angioplasty. This finding has been at least in part rationalized by the bias of patient selection, that is, applying the new techniques to patients with an excessive risk of recurrence, such as those who have developed restenosis two or three times. Additional explanations offered have been the prototypic status of many of the devices or the steep portion of the operator learning curve. It is clear that we are still in an early stage of understanding how the devices interact with the vessel wall, such as appreciating the simple mechanical dilating effect of the device per se or the balloon angioplasty effect of directional atherectomy. The relatively high rate of restenosis that pervades the early experience with these devices may reflect a common denominator of intimal injury. Overall, the data accrued so far are not particularly encouraging but have not ruled out the potential for new devices to have an impact on restenosis. The procedure that actually removes nearly intact pieces of plaque and luminal contents—directional atherectomy—may prove quite useful in elucidating the biology of restenosis via tissue culture, in situ hybridization, and thorough histopathological studies.

Foundation for Avant Garde Technologies

The many devices already under clinical investigation have laid the groundwork for further advances in transcatheter techniques. Examples of this building block concept include 1) the use of metallic stents seeded with the gene for tissue-type plasminogen activator, 2) the use of a dual-balloon catheter to transfer genes to a porcine artery, 3) endovascular drug delivery via a porous balloon, 4) impregnation of stents with heparin or other pharmacological agents, and 5) the use of biodegradable polymers that have the capacity to "pave" or "seal" the intima or serve as a reservoir for sustained release of a particular drug. Thus, many very specific, targeted approaches for the diseased vessel wall might be achieved without systemic pharmacological intervention. Vehicles such as stents or debulking with atherectomy may serve as pivotal steps requisite for effective endovascular drug delivery or, ultimately, gene transfer.

Pitfalls

New Complications

An aftermath of the new coronary artery procedures has been the emergence of a new set of complications. Examples of such complications include 1) coronary artery perforation that has occurred with laser angioplasty and the atherectomy procedures; 2) subacute thrombosis days after stent placement with all of the stents so far tested, with or without apparent adequate anticoagulation; and 3) the "no reflow" phenomenon after the high-speed drilling and emulsification process of rotational angioplasty, which presumably is related to distal showering of microparticles. Each of these is extremely serious, can lead to death or myocardial infarction, and represents new complications that are rarely if ever reported with the use of balloon angioplasty.

Refinements in technique and operator experience may reduce the risk of such dreaded complications. Guidance systems such as intravascular ultrasound or angiography may be incorporated into the atherec-tomy procedure to avoid removal of the media or adventitia vessel wall components. Fluorescence spectroscopy during laser treatment has the potential to direct plaque ablation. Alternatively, intraproce- dural techniques such as frozen section of tissue retrieved from atherectomy may indicate the level of resection and avoid unnecessary deep injury. It is already clear that atherectomy is capable of media and adventitial resection in a significant proportion of patients and that although not typically accompanied by immediate complication, deeper penetration appears to increase the risk of restenosis.

Similarly, the predisposition for stents to develop thrombosis has led to a very intensive polypharmacological regimen that includes preprocedural aspirin, dipyridamole and dextran, intraprocedural heparin (and urokinase for one stent), and postoperative coumadin, aspirin, and dipyridamole. The unexpected thrombosis of a stent days to a week after successful placement is fortunately unusual and may be avoided by newer stents coated with heparin, hirudin, or other thrombin or antiplatelet inhibitors.

With the no-reflow phenomenon after rotational angioplasty, a progressive increase in Burr size rather than the initial use of a large Burr may prevent the accretion of larger particulate matter and the sequelae of embolization. Integration with a technique such as vacuuming or filtering, which actually removes the particles or debris rather than relying on microemulsification, represents another alternative for avoidance of this complication.

Economic Impact

A generally unanticipated offshoot from the new devices will be a significant economic problem at various levels. Already there has been considerable charge to the investigators for use of the devices and support equipment. Currently, the charge to the
investigator for a single directional atherectomy catheter setup is more than $1,500, which includes the specialized guiding catheter, motor drive unit, and guide wire. The current stent charges range from $400 to $1,500 per device, and there is an incremental 2–3-day hospitalization period required to achieve adequate anticoagulation. These “single” catheter or devices charges are relatively small compared with those of the laser console and power source, which has cost between $100,000 and $300,000 to institutions performing laser system investigation.

The current policy of the Food and Drug Administration (FDA) device bureau is to allow the manufacturer to charge the investigator up to and including the anticipated approved and marketed price. This permits manufacturers, often small companies relying on venture capital, to charge considerable amounts for device use while the procedure is truly investigational, and has no safety or efficacy profile.

The justification response from various manufacturers has been that there is a significant cost of device preparation and that there are a multitude of alternative investigators if one is not prepared to defray such expenses. These charges cannot be billed to the patient or third-party payor as there are strict guidelines against charging patients for investigational equipment or for the procedure itself. In some instances, like stenting, even the cardiac catheterization and preparatory angioplasty have been disallowed by third-party payors because of the association with an investigational device. For the active clinical investigator interested in pursuing this important area of research, a financial catch-22 situation is quite apparent: It is quite expensive to do the research, and there is no support mechanism.

These charges represent only those incurred during the investigational phase of device development; the anticipated costs after commercial approval will undoubtedly have a much larger impact. The incremental commodity and equipment charges for stents, atherectomy, laser catheters, additional days of hospitalization after the procedure for some devices, and corequisite medications and laboratory tests (particularly with stents) can represent as much as a 240% increase for cumulative in-hospital charges compared with the costs of conventional angioplasty. This margin does not take into account any potential increase in professional fees that may accompany such specialized procedures. The sales of balloon angioplasty catheters in the United States alone during 1989 exceeded $600 million; even a small increase in new device use has a formidable potential repercussion on national health-care expenditures.

Operator-Related Issues

When balloon coronary angioplasty was imported to the United States in the late 1970s, there was no prospective plan for education, training, or certification standards. The majority of current invasive cardiologists who perform balloon angioplasty have had no specific training other than attending a demonstration course, and most perform procedures infrequently. While this has been viewed as suboptimal by national committees, the difficulties may become markedly amplified in the upcoming era of multiple new devices. Each of the techniques, such as stenting or atherectomy requires specialized training and, as discussed above, has serious potential for complications. In the next few years, the anticipated application of these procedures is relatively restricted compared with the current balloon angioplasty procedure frequency, limiting the availability of large numbers of patients requisite for operators to progress along the learning curve. It would be helpful to prospectively develop acceptable standards for certification, provide operator surveillance, and, ideally, have regional interventional centers serve as educational resources. Fourth-year fellowship interventional training programs at several sites have offered formal teaching of multiple new coronary interventions.

Tied closely with the training problem are the overall lack of perspective and the anticipated operator exuberance. An example of this situation is the recent trend in balloon valvuloplasty, particularly for the aortic valve. Initial reports of relatively small numbers of patients confirmed feasibility and overall safety of aortic valvuloplasty. Enthusiasm led to overuse until adequate data in literally thousands of patients suggested that aortic valvuloplasty was accompanied by an excessive risk of restenosis in the first year after the procedure. With limited numbers of patients and, particularly noteworthy, limited follow-up (i.e., more than 6 months with coronary angiography), the hard facts about the new devices may become evident only after commercialization.

There are several latent motivating factors for such operator exuberance: the charm feature of a technique quite distinct from balloon angioplasty, the feeling of competition or inadequacy among operators not engaged in new procedures, the perceived need of each operator to maximize experience, the potential ability to use the new devices as a marketing ploy for patient referrals, and direct revenue or earnings based on performance of a highly specialized procedure. There has already been concern expressed in the medical literature about misdirected use of the new devices.

Industry Marketing

With the restricted number of investigational sites that can evaluate each device, the supply-to-demand ratio highly favors the position of the manufacturers. Several issues have arisen representing an outgrowth of this imbalance situation. First, the ability to capitalize, even in the premarketing phase of nearly every device, has led to substantial equipment charges to the investigator. Second, equipment manufacturers have at times used their position as a wedge to sell conventional balloon equipment in cases in which both prototypic and routine catheters are coupled. Examples are the restriction of clinical sites of a project to only those using the manufacturer’s ordi-
nary catheters or the promotion of a company’s current product line on the basis of its new technology profile. Third, the fundamental goal of each equipment company is to obtain commercial approval via a product marketing application and to sell the equipment. Instead of dedicating resources and time to rigorous randomized, controlled trials, the majority of companies have sought the most direct and rapid method of obtaining licensure.

**Lack of Randomized or Rigorous Trials**

Although randomized trials of new devices would be vital and relatively easy to perform using balloon angioplasty in the control group, there are several explanations for their conspicuous absence to date, including the prototypic nature of the equipment and likelihood of new-generation devices to become available in the midst of the trial, the relative lack of operator experience, the history of coronary angioplasty’s acceptance from 1977 to 1988 without a randomized trial ever having been performed in patients with angina pectoris, and referral of patients to a particular center for a specific device.

Beyond the lack of randomized trials is the lack of rigorous quality of the observational studies. Data have yet to be quality assured by manufacturers, as would be expected with a new pharmaceutical agent, including source documentation of case report forms or handling of the data coordination and verification by an independent institution or agent. Many of the presentations and initial reports have not even incorporated the use of a core angiographic laboratory but instead used the on-site clinical investigator’s visual interpretation of technical results, which has a high probability of being unreliable. 30 Although clinicoangiographic data assurance and verification require considerable resources, time, and expense, it would markedly bolster our confidence in interpreting observational studies of new technologies. Furthermore, subgroup analyses, although frequently performed, have been done on a post-hoc basis to identify a particular patient group that may have derived benefit from the new device or technique. This involves multiple statistical comparisons with relatively small patient numbers, which in itself produces the potential for a spurious result.

The lack of data collected with utmost scrutiny may be especially troubling for the FDA as its representatives consider application for marketing of new devices. Given the current minimal requirements associated with approval of a pharmaceutical, including pivotal randomized, controlled clinical trials, it remains unclear what will be the standards for approving a new coronary interventional device. At recent FDA Circulatory System Devices Panel hearings, the committee recommended directional coronary atherectomy and excimer laser coronary angioplasty for approval and requested new data to be obtained from a randomized trial of the coronary retroperfusion device. 37 Unfortunately, neither of the two newly approved devices had any control patients, core laboratory angiographic review of the results, or quality assurance of the data collected.

**The Inventor-Investigator**

Each of the devices has an inventor who frequently is intimately involved with the clinical research project and presents original papers on the behalf of the study group at national meetings, authors papers in peer review journals, and stands to derive financial benefit if the device proves successful. Although current inventors have in general gone to excessive lengths to be accurate and comprehensive in reporting data, there must be full disclaimer provisions according to recently developed standards of conflict of interest. 38

**Composite Perspective**

During the coming years, it is likely that a number of devices will become commercially available, and the actual scenario of how each strategy will be incorporated into practice remains speculative. One possible scenario for such devices based on preliminary data is outlined in Table 1. With such an extensive armamentarium, the interventional cardiologist may have an array of newly developed equipment from which to select. With controlled trials,

### Table 1. A Possible Scenario of New Device Use in the Next Few Years

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Niche therapeutic use</th>
</tr>
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<tbody>
<tr>
<td>Directional atherectomy</td>
<td>Proximal left anterior descending de novo lesion</td>
</tr>
<tr>
<td></td>
<td>Complex, ulcerated lesions not suitable for balloon angioplasty</td>
</tr>
<tr>
<td>Transluminal extraction catheter</td>
<td>Degenerated saphenous vein grafts</td>
</tr>
<tr>
<td>Rotational angioplasty</td>
<td>Calcified or tortuous vessels not amenable to angioplasty or other techniques</td>
</tr>
<tr>
<td>Palmaz, Wall, Gianturco stents</td>
<td>Chronic total occlusion with guide wire across lesion but inability to cross with balloon</td>
</tr>
<tr>
<td>Laser balloon angioplasty</td>
<td>Abrupt closure</td>
</tr>
<tr>
<td>Excimer laser angioplasty</td>
<td>Refractory restenosis after conventional methods</td>
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</tbody>
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each strategy may be proven beneficial for a patient subset, such that each device will have a niche. Another level of complexity in clinical research within this field will be to define the appropriate use of different technologies that can be used for the same indication. For example, a comparison of stenting versus laser balloon angioplasty for abrupt closure needs scrutiny in future trials. For patients at high risk, integration with the new support devices, including percutaneous cardiopulmonary bypass, catheter-mounted left ventricular assist device, or retroperfusion, will need sorting out. Novel approaches to chronic total occlusion constitute another group of devices that are in the early phase of development. The number of combinations and permutations of all the new devices is clearly formidable. Without question, the new device era for coronary revascularization is an exhilarating one with prodigious capacity for growth and application in the future. Maintaining an awareness of the multiplicity of problems and deficiencies will hopefully facilitate meaningful progress in this vital field.

References


Topol New Devices 693
37. Food and Drug Administration Circulatory Systems Devices Advisory Panel minutes, January 29, June 8, and October 29, 1990, Bethesda, Md.
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