

## Bring That Pioneering Spirit Back! A 25-Year Perspective on the Vascular Stent

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My personal perspective about intravascular stents has been for the most part very positive. From its humble beginnings in the late '70s the stent became a major therapeutic resource and has achieved worldwide application. However, some disappointments in the last few years dampened my early unbridled enthusiasm. In my view, during its third decade of life the stent evolution has been hampered by unfulfilled goals. I think this is related to a recent change in attitudes and perceptions by government, industry, the media, and people in general.

In regard to technological development, starting in the year 2000 the medical device industry has shown a pervasive reluctance to invest in new research and development. This has been a gradual change from the previous 15 years, when this industry invested boldly in new products, guided only by their instinct and everybody's expectation that there should be a change in the status quo. Reviewing the circumstances of those days compared to the present, it is apparent that the differences were global and not just limited to biotechnology. The innovative spirit of the '80s was evident in the wondrous technological achievements that arose during this decade. The launching of the first space shuttle and the deployment of the first permanently manned space station left us in awe, although they did not affect us personally. Conversely, the advent of practical personal computers,

compact discs, and cell phones did. The beginnings of the Internet were laid out by a burgeoning ARPANET and the introduction of the transmission control protocol-Internet protocol (TCP-IP) led to the World Wide Web. In medicine and biology the development of PCR (polymerase chain reaction) made possible a great expansion in DNA and gene research. Closer to our specialty, it was during the '80s that all major innovations in endovascular treatments developed. Andreas Gruntzig, who had done the first coronary balloon angioplasties in Zurich in 1977, moved to Atlanta, Georgia, and started a program of clinical research and teaching with unprecedented success. Under his leadership and inspiration the balloon angioplasty catheter got rapidly refined and the new technique achieved massive acceptance. During those years laser, rotational, and, later, directional atherectomy and the rapid exchange balloon catheter appeared, and so did stents. Unquestionably, a new revolution in vascular therapy had started then, with lots of new technologies and applications of these technologies in very innovative ways.

President Ronald Reagan, who reflected on innovation in his State of the Union Address before the U.S. Congress in February 1985 [1], said: "Let us begin by challenging our conventional wisdom. There are no constraints on the human mind, no walls around the human spirit, no barriers to our progress except those we ourselves erect." More interestingly, his comments on vascular therapy were quite foretelling of ongoing developments: "New laser techniques could revolutionize heart bypass surgery ... and hold out new promise for saving human lives."

The specialized medical press was quick to bring attention to the new trends and to prepare the public for the changes that occurred a few years later. The social impact was huge, as millions of patients got access to the new percutaneous techniques and, inevitably, open surgical

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treatments diminished. Endovascular equipment got increasingly refined and doctors' skills steadily improved. The new endovascular treatments changed from being the exclusive domain of primary referral centers to being available at smaller, peripheral hospitals. The competition between device manufacturers became fierce for an increasingly lucrative stent market opportunity.

### Recent Bad News

During the '90s the U.S. FDA made an effort to allow access to market to as many new products as possible. However, as questions about safety and effectiveness relative to established treatments arose, randomized clinical trials became commonplace, with their attendant large financial cost to the manufacturers. Because vascular intervention is closely tied to highly regulated endovascular devices, the endless questions about the safety and effectiveness of these devices created more restrictions in the product label recommendations, and this resulted in new boundaries to restrain interventional practice. Compared to our surgical colleagues, the practice of vascular intervention is becoming increasingly stifled by highly defined use regulations. In other words, freedom to practice is being curtailed.

The cost of bringing a new stent to market was also burdened by big investments in worldwide intellectual property protection and legal settlements, as litigation for infringement of patent rights raged. The cost of clinical trial evaluation and those associated with intellectual property protection may have curtailed the ability and willingness of the large device companies to invest in research and development of future projects. The typical 6- to 8-year time period to develop and bring a completely new product to patients got substantially shortened as companies shied away from new approaches to treat vascular disease and embarked on refining already established endovascular treatments. Invariably short-term projects with little innovation but a reasonable chance of succeeding replaced long-term projects carrying a higher risk of failure and cost but also having a chance of becoming disruptive technology. The result is evident at recent vascular meetings, where the presentation of new technologies and methods has given up center stage to late-breaking clinical trials.

Puzzling to me is the new trend of the specialized press to punish the stent, the stent industry, and interventional doctors. This is a change from the early days when the media trumpeted new therapeutic modalities with enthusiasm and optimism.

I was never an advocate of drug-eluting stents (DESs), as I was always concerned with incomplete healing and the

potential for delayed thrombosis. However, I definitely welcome their beneficial impact in treating patients with disease that was not previously the realm of the bare metal stent (BMS). As in so many areas of medicine, we are ready to accept new risks if the benefit is substantial. The early trials [2] and recent analysis of comparative trials of the DES and BMS [3] show similar survival rates for patients treated with either device but a definitely increased freedom from coronary revascularization with the DES. DES thrombosis, albeit delayed in time, is slightly increased compared to BMS thrombosis. Nonetheless, at 1.5% stent thrombosis, the balance of risk to benefit is unquestionably positive compared to the benefit afforded. Furthermore, a recent publication comparing percutaneous intervention and medical therapy in patients with stable coronary disease [4] has brought the message that perhaps too many angioplasties and stent placements are currently performed in patients with stable coronary artery disease [5].

All the recent negative news about angioplasty and stents has created an atmosphere of skepticism among people who have not been appropriately reminded of the benefits achieved thus far compared with, let us say, 30 years ago. Thus, it is the obligation of the medical community to educate the public to avoid damaging misconceptions in the public opinion. The notion that angioplasty devices are dangerous and that conservative treatment is just as effective as aggressive interventional therapy may cause many symptomatic patients not to seek prompt medical attention when they need it.

### Tracing Back the Development of Stent Technology

Vascular stent evolution has gone, in my opinion, through three main phases. The first and perhaps the most significant is the mechanical phase. During this phase, the need to achieve flexibility and a low profile for ease of use was the first motivation to evolve and develop [6–10]. Later, recognition of the injury effect to the arterial wall produced by stent deployment [11] led to design changes aimed at decreasing the “footprint” of the stent struts by making more elaborate cell designs [12]. The appearance of scores of new stent designs covered just about all iterations in this respect [13], practically exhausting further development of the mechanical phase.

The second phase began with an interest in the effect the stent materials could have on blood and the arterial wall, independent of the stent design. This phase led to exploration of alternative metals and alloys as well as surface texture modifications and surface coatings able to influence thrombogenicity and cell coverage [14–23]. Unfortunately, this phase did not progress too far because of the advent of

the third phase, that of the DES [24]. The DES introduced profound changes in the healing mechanism of the stent, almost completely suppressing neointimal formation. This implicated that the late luminal loss became negligible and the prevention of repeat revascularization was significantly improved compared to that with the BMS. Interestingly the designation BMS, adopted for comparative purposes with the DES, relegated all non-drug-eluting stents to a unified and rather pedestrian category, reflecting the general feeling that a BMS is just a stent that has no special properties. The appearance of the DES almost eliminated interest in stent materials research and focused all new development on the quest for new drugs and/or drug release mechanisms. Part of this new trend is due to economic incentive and part to an attempt to harness the powerful and potentially dangerous effects of the DES.

From the perspective of an interventional radiologist, the almost-obsessive pursuit of treating vascular disease with DESs seems rather futile. To anybody who has examined the histological reaction to stents in vessels of various sizes, it is apparent that the larger the vessel, the less restenosis becomes an issue. In fact, in large vessels such as the thoracic aorta, the lack of healing seen many months after implantation may represent a problem. Poor tissue incorporation seems to affect all large vascular devices such as endovascular bypass, septal occluders, atrial appendage occluders, and transluminal valves, causing leaks and dislodgement. In fact, lack of tissue incorporation and its attendant thrombogenic effects doomed the mechanical heart and ventricular assist devices to a thwarted evolution [25].

It seems to me that the premature demise of the interest in stent material biocompatibility caused by the DES constitutes the loss of an opportunity to have unraveled more than one mystery. Had we found a truly biocompatible stent surface, we should have solved the issue of poor tissue incorporation of large devices and perhaps even given the mechanical heart another chance.

### **Nanotechnology: A Way of the Future?**

Who knows? However, nanotechnology has made amazing changes in our lives by allowing the development of incredibly smart, small, and inexpensive electronic devices. It seems to have tremendous potential in the pharmaceutical industry, and this is quite logical [26]. The reason to look into nanotechnology is practical and compelling. How can we effect a profound biological change without addressing it at the molecular level? A coronary stent may weigh a few milligrams but the features on its surface such as crystals and boundary areas can be larger than cells. Studies with surface sensitive equipment such as XPS and

TOF-SIMS demonstrate enough chemical heterogeneities throughout the surface of commercial stents to assure that proteins dispersed in blood would not have equal interaction from point to point on the device surface [27]. The same applies to cells interacting with ligands of such adsorbed proteins [28, 29]. Yet we seem to be interested only in what happens at the microscopic level, without paying attention to the fact that biological phenomena are based on events starting at dimensions two to three orders of magnitude smaller than cells. The earliest interaction at time zero during stent placement is with water and electrolytes, followed in seconds to minutes by protein adsorption, ligand exposure, and cell interaction. Until we control what happens at the atomic level we will not have a chance to uniformly affect molecular interaction and, even less, cell interaction. Controlling a surface at the atomic level means that we control feature size and its homogeneous distribution throughout the surface. Once we identify a feature with a desirable property, such as affinity for a certain target molecule or lack thereof for an undesirable molecule, we must assure that it is homogeneously distributed throughout the device surface. This should assure a uniform and predictable biological response. Today vascular implantable devices are of “medical quality” because they are free of allergens, carcinogens, pyrogens, and microorganisms and have a clean, smooth surface to the eye and to the microscope. However, the biological reaction they induce is “chaotic” viewed from the perspective of surface biocompatibility. This means a haphazard and disorganized reaction with the molecular components of blood and tissues, potentially leading to unpredictable and undesirable results. The surface properties of the most varied implantable materials such as polymers and metals are surprisingly similar because contaminants on the surface are remarkably alike. This may explain the disconcerting similitude in tissue reaction to materials believed to have very different properties.

Just as it happens with nanoelectronics, where the quirky quantum phenomena trick investigators with unexpected effects, dealing with nanomanufactured surfaces may bring unsuspected powerful biological effects, and this would be a fascinating challenge to face. Unfortunately, nanotechnology research is not cheap and requires extensive collaboration with disciplines far removed from biotechnology. The electronics industry invests many billions of dollars annually in nanotechnology to research products that will be a practical reality many years from now, and this is their formula for success. Pharmaceutical industries are also investing significantly in this area. I would surmise that, today, the device industry is not investing in any meaningful way in nanotechnology. This may be a mistake, as I believe that this may be the most viable way out of the technological slump we are currently in. I would dare to say that if the

leaders who showed us the way in the '80s were alive today, they would recommend that we devote major efforts to high technology as the only alternative for the future.

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