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CORONARY BALLOON ANGIOPLASTY AND VASCULAR RESPONSE TO INJURY.PERSPECTIVES FOR THE 1990'S

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In the past decade, coronary balloon angioplast" has had a major impact in the treatment of coronary artery disease, but the procedure has been associated with recurrence of stenotic lesions in a high percentage of cases'-4. In the last few years, several alternatives to balloon angioplasty have been proposed, but restenosis seems to be a common problem to most procedures tested in clinical practice thus far. More recently, great attention has been given to the cellular mechanisms involved in the process of restenosis, which is clearly a much more complex process than previously thought. Elucidation of such mechanisms will require detailed studies on the biology and pathology of the vessel wall, and major multidisciplinary efforts and interactions between cardiologists and several other disciplines will be necessary before the problem of restenosis can be solved. On the other hand, in order to improve the outcome of angioplasty (no matter which device or method is used for angioplasty), we must develop techniques to improve the diagnosis of atheroma, to improve recanalization of stenosed or occluded arteries, and more importantly, to improve our understanding of the cellular mechanisms involved in early and late vascular response to injury resulting from angioplasty.

Although coronary artery surgery still remains and will continue to be an important therapeutic option for many patients with severe coronary artery disease, it is unquestionable that **there is a greater tendency today towards catheter-based therapeutic interventions designed to either displace or prefer. rably remove atheroma from native blood vessels** rather than bypassing arterial lesions with surgical techniques. In this report we would like to emphasize some of the recent developments in this area, which we believe will be extensively investigated in the next decade and could radically change the current practice of coronary and peripheral artery angioplasty.

It is not known, at the present time, which factors are associated with acute complications following coronary angioplasty, particularly coronary artery dissection, thrombosis and spasm. It is likely that several factors may play an important role, such as the inherent characteristics of the atheroma itself, its morphology, platelet aggregation at the interventional site, and the magnitude of intimal damage and initial presence of partially occlusive thrombus, which in most cases cannot be detected angiographically. Conversely, it has been recognized that the intact endothelium has unique functional characteristics to prevent thrombus formation through release of endothelial surface enzymes, such as adenosine diphosphatases and heparans. Endothelium also produces prostacyclin, one of the most potent inhibitors of platelet adherence and aggregation and also a potent vasodilator. Endothelial integrity is important to produce vascular dilatation in response to acetylcholine, particularly in small vessels, through release of the endothelium-dependent relaxing factor (EDRF). Furthermore, atherosclerosis itself reduces EDRF synthesis and alters vascular reactivity. It is also recognized that coronary vessels with atherosclerotic lesions are more susceptible to spasm, all of which can play a role in acute complications following angioplasty.

Chronic complications following angioplasty, such as restenosis, are also poorly understood. We do not know the factors that will distinguish a poor outcome from those that determine a good outcome following angioplasty. For example, some types of lesions may be more suitable for a specific intervention. It is not difficult to imagine, for instance, that some very eccentric lesions consisting of atheroma and a very thin medial layers plus adventicia may not be appropriate for certain ablation techniques, and such lesions could be readily identif~ed prior to intervention. Therefore, more accurate diagnosis of obstructive lesions and knowledge of the pathogenesis of plaque instability and restenosis will be necessary for development and clinical implementation of improved angioplasty techniques and better long-term results.

1. IN VIVO MORPHOLOGY AND CONSTITUENTS OF ATHEROMA

There is preliminary data suggesting that intravascular imaging will allow us to identify in vivo the integrity of the blood vessel intima, the thickness of the arterial wall as well as its layers and components, the mass

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of atheroma, and the structure of the lesion such as the size of the necrotic core and thickness of the fibrous cap, and possibly the principal chemical constituents of atheroma. If this is possible, we will be able to assess the stability and instability of individual plaques prior to interventions and maybe identify the precursors of acute ischemic syndromes such as intimal disruption.

Coronary Artery Angioscopy

Coronary angioscopy has been used for analysis of the blood vessel internal surfaced, angioscopic findings have already contributed to our understanding of the pathophysiology of coronary syndromes5. Most fiberoptic angioscopes used today range in diameter from 0.35 mm to 3.0 mm and contain 3000 to 12000 imaging fibers enveloped in a flexible plastic. Illumination is provided by xenon light source and adjustments depend on the reflection of the vessel wall, diameter of the vessel, and the camera lens. Initial experience with this device for quantitation of coronary artery lumen diameter has been difficult, mostly due to problems with calibration and pin cushion distortion in the images. However, preliminary data in peripheral vascular surgery indicates that changes in intraoperative management occurred in approximately 30% of the cases based on angioscopic findings alone8. Angioscopy has also been used intraoperatively during coronary bypass surgery. The ultimate goal is to develop an angioscope for percutaneous use in the cardiac catheterization laboratory as well, and several prototypes have been successfully used in many centers. We believe that angioscopy will be of great value not only to guide surgical procedures but also in the, diagnosis of dynamic changes occuring in the internal surface and lumen of the blood vessel before and following CBA or pharmacologic interventions.

Laser-luduced Fluorescence Spectroscopy (LIFS)

This technique uses a spectrograph to obtain spectra from tissue, and light detection is accomplished by using an intensified diode array detector coupled into an optical analyzer. Recently, several investigators have demonstrated that the morphology of spectra generated by LIFS can be used to differentiate normal from atherosclerotic blood vessels9, although the biological source or chemical species responsible for the LIFS signal are not known at the present time. This technique also has the potential for differentiating several chemical compounds within the atheroma, as long as their spectral lifetimes are different at a given wavelength. Furthermore, currently available laser can be used for excitation to induce fluoroescence, and the discriminatory power of LIFS can be enhanced by atheroma-specific agents such as tetraeycline and hematoporphyrini°. Therefore, LIFS re

search will possibly focus on studies to determine the chemical species responsible for the LIFS signal, different modes of excitation to help differentiation among chemical compounds of atheroma and fluorescent markers to enhance specificity of LIFS signals. Also, specific computer programs are now being developed for analysis of spectra generated by LIFS, such as neural networks, which may further enhance the discriminatory power of spectral analysis compared to currently available statistical methods. Hopefully, these studies will allow us not only to differentiate atheroma from thrombus and normal arterial wall, but also to possibly use spectroscoptically directed laser angioplasty.

Intravascular Diagnostic Ultrasound

Ultrasound imaging of coronary arteries has been performed intraoperatively using high-frequency transducers and epicardial imaging". More recently, catheter-based ultrasound for intravascular imaging has been developed and coronary artery imaging has been performed in vivo'2. Most systems available today us a 5 to 7 French ultrasound catheter with a distal guidewire advanced through a guiding catheter down the coronary artery to within and sometimes beyond the stenotic lesion to be dilated. The currently' used catheter is not an over-the-wire system but the distal guidewire permits steerability and it needs no flushing (ultrasound transmits well through blood medium) to image the artery. Insertion of the catheter is guided both by fluoroscopy and the two-dimensional image. The transducer (frequency ranging from 20 to 40 mHz) ensheated in the catheter yields two-dimensional realtime images with 360° display at a frame rate ranging from 7 to 25 per second.

Catheter-based intravascular ultrasound has great potential as a diagnostic technique for several reasons. There is already evidence from initial in vitro and in vivo studies that layers of the vessel wall can be discriminated by high-frequency ultrasound, including visualization of the internal elastic lamina'3. Arterial wall dynamics can be evaluated, as well as the effects of pharmacological and catheter-based intravascular interventions, and refinement of tissue characterization analytical programs may allow ultrasonic differentiation of the chemical constitutents of atheroma.

2. INTERVENTIONS TO REMOVE ATHEROMA MASS

This is an area of great interest in which catheter technology will play a major role. There is no doubt that continued efforts will be made to both improve existing technology and develop new techniques to displace and particularly to remove atheroma from coronary and peripheral arteries. New alternatives to balloon angioplasty have already been proposed and

initial studies are underway to determine feasibility, safety and efficacy of these techniques. There is reason

to believe that at least three modes of **energy sources that can potentially remove atheroma mass** win increasingly used and investigated in the next few years: the excimer laser, ultrasound and the radiofrequency thermal probe.

The excimer laser

A great deal of research and work has been done in the past five years to design the excimer laser for percutaneous application in human coronary artery disease. Several steps had to be overcome before this technique could be applied in humans'4. Perhaps the major problem encountered initially was the development of a flexible fiber optic capable of transmitting sufficient energy to ablate atheroma without being destroyed in the process. Forrester, Litvack and other of this Institution were able to overcome many of the early difficulties through a close collaboration with the NASA Program at the California Institute of Technology's Jet Propulsion Laboratory, using their laser to first develop the magnetic switching concept for excimer laser, which then led to the use of stretched pulses for laser angioplasty. The system used today is a highly flexible fiberoptic Over-the-wire" delivery system which can be inserted percutaneously and is capable of delivering to the coronary arteries high energy at 250 nanoseconds per pulse or more without destroying the fiber. One of the current limitations of this technique is the relatively small diameter of the catheter tip (up to 1.6 mm) compared to the larger internal diameter of the proximal coronary arteries. Although, theoretically, the vascular channel created by the excimer laser will not exceed the catheter-tip diameter, preliminary studies in man have demonstrated significant gain in coronary lumen diameter without supplemental baboon angioplasty'5. A third generation of excimer laser with a 2 mm catheter-tip diameter redesigned for vascular use is now being tested.

Contrary to baboon angioplasty displacement of atherosclerotic plaques, excimer laser removes atherosclerotic tissue or thrombus by vaporization without causing the thermal injury seen with laser-heated probes. Nevertheless, several potential problems need to be investigated before this technique can be more widely used in clinical practice. Frequency of acute complications such as thrombosis, spasm, vessel dissection as weU as restenosis rates are not known and in fact may be related to a number of factors, including inappropriate laser dosimetry.

The Radiotrequency Thermal Probe

Hot tip laser angioplasty has been used as an adjunct to balloon angioplasty in peripheral arterial occluslve disease'°. With this technique, laser beams are

used to heat the catheter metallic tip, which ultimately results in thermal injury. However, the device used for energy source is complex and expensive. The radiofrequency generator uses a smaller power source, is portable, and has fewer maintenance requirements. Initial studies with this device were aimed at defining the relationship between energy input and catheter tip temperature, and subsequent,nvestigations were performed to study the relationship of energy input to changes in tissue temperature over time using thermal imaging chambers. Thermal characteristics of several metallic tips (brass, copper, gold, etc) have been tested as well as different tipo diameters, stainless steel wires and guiding catheters. Hot tip coronary angioplasty performed in animals was usually associated with coronary artery surface temperatures in excess of 60OC, whereas excimer laser induced temperatures of less than 37OC. The acute histologic response to the excimer laser and the thermal vascular injury associated with tip laser have been studied in animals using occular micrometry to quantify the depth of injury in relation to laser energy'5-'7. Infrared thermal imaging has also been used to correlate histologic injury with temperatures recorded at the impact site. It has been noted that following argon laser irradiation there is a central crater and a thick layer of fibrin and inflammatory cells with concentric zones of hypereosinophilic tissue and medial necrosis. In contrast, immediately following excimer laser irradiation, the crater usually extends to the media of the vessel wan without carbonization, hypereosinophilia or vacuolization. Several hours after excimer laser irradiation there is usually small amounts of fibrin and red blood cells in the crater as wed as scattered areas of necrosis in the media. Although it is not known which response is more desirable in terms of immediate or late outcome, thermal injury appears to be more frequently associated with greater histologic changes in adjacent tissue as well as more thrombus formation at the impact site. Coronary artery spasm seems to be more frequently seen with this device. Therefore, although hot-tip angioplasty may be an effective method to remove atheroma, we believe that this technique will be more suitable for interventions in large peripheral vessels.

Ultrasonic angioplasty

The potential of ultrasound to ablate atheroma has been recognized in the last few years. Research studies employing ultrasound are now at a position similar to laser angioplasty a few years ago. Several groups in this country and elsewhere are now beginning design tests for a vascular device to be initially used in animal models and later in human beings. As previously done with laser systems, early studies will focus on the capabilities of ultrasonic energy to recanalize peripheral vascular obstructions without trauma or perforations, and later on to develop a device for human coronary arteries.

Prototype devices have used ultrasonic frequency o approximately 20-25 mHz transmitted to the target areas by a ball-tipped wire probe with acoustic power output

ranging from 25 to 50 watts. This device operates in both pulsed and continuous mode and uses a potable generator. The ball-tipped wire probes range from 1.5 ho 2.6 French, are 30 to 90 cm long and are ensheated in 7 to 9 French catheters. Heating of the probe is prevented by continuous infusion of saline solution through the guiding catheter. Initial results using this device in animals after surgical insertion of external iliac artery atherosclerotic xenograM occlusions have demonstrated that ultrasound can be used to recanalize occluded arteries[18].

Thus, we believe that the above mentioned techniques will be intensively investigated in the next decade as potential energy sources to remove atheroma. Percutaneous transluminal coronary atherectomy'9 has been also investigated in recent years and it has some potential advantages as well as disadvantages compared to the above mentioned techniques. With this technique, tissue is mechanically resected by a rotating inner cup facing the stenotic lesion through a catheter side window. There is speculation that atherectomy might be more suitale for very eccentric as well as long coronary lesions and it may be associated with less acute complications such as coronary artery dissection and abrupt closures. On the other hand, depth of ressection is difficult to control with this technique, resulting not only in endothelial damage but also disruption of the internal elastic lamina and exposure of medial and sometimes adventitial tissue. Ne**vertheless, clinical experience with most of these methods is still limited** and implementation of these techniques will require more substantial data on feasibility, efficacy, acute complications and restenosis rate. There is aldo the need to **develop techniques to protect the ischemic myocardium distal to the intracoronary interventional site** to minimize the effects of myocardial ischemia caused by prolonged interruption of coronary blood flow during the procedure, particularly in patients with high-risk anatomy. One such technique that has been extensively studied in animals and is now undergoing clinical validation studies during angioplasty is synchronized coronary venous retroperfusion of autologous arterial blood[20].

3. VASCULAR RESPONSE TO INJURY

Although the predisposing factors and mechanisms of acute complications associated with angioplasty need to be more carefully investigated, restenosis is the major problem and a critical limitation to the use of coronary as well as peripheral artery balloon angioplasty today. It is likely that restenosis will also be a problem with laser and other ablation techniques such as ultrasound, because **these procedures are also associated with endothelial surface damage.** The sequential histologic events following

balloon angioplasty have been well documented both in animal models and in man2i 23. Immediately following endothelial injury, platelet aggregation occurs at the site of injury. A few days later, endothelial cell proliferation is prominent and smooth muscle cells (SMC) appear in the subintima. SMC, which under normal conditions have a very slow replication rate, now migrate and proliferate within the subintimal layer, which is the hallmark of atheroma development after endothelial injury24.

Although vascular SMC proliferation is a key component of restenosis following transluminal angioplasty24 the cell signals and molecular events that trigger the phenomenon of restenosis are poorly understood. Replication of smooth muscle cells occurs in vitro in response to platelet-derived growth factor (PDGF), which is one of the growth-factors released by platelets upon aggregation25. It has been postulated that PDGF may be responsible for initiation of the local vascular response to injury26. However, these events seem to be more complex than previously thought. For example, studies have indicated that SMC proliferation continues to occur long after platelet interaction with the vessel wall has eased. Also, in vitro studies have suggested that PDGF requires the presence of other growth factors to induce SMC proliferation, such as insulin-like growth factor 1 (IGF-1), in order to induce DNA synthesis and cell division[27].

IGF-1 is a mitogenic polypeptide structurally similar to proinsulin, which is present in large amounts in serum and is a mediator of the grow-promoting effects of growth hormone. The main source of circulating IGF-1 is the liver23, but its production has been demonstrated in other tissues as well, although the contribution of serum (endocrine) and locally produced (autocrine) IGF- 1 to the bioactivity of this peptide is not clear. On the other hand, tissue IGF-1 gene expression seems to be regulated by systemic factors, such as pituitary growth hormone29, and tissue-specific factors, such as in tissues undergoing compensatory hypertrophy, in which selective induction of IGF-1 messenger RNA content has been demonstrated30. Experimental studies in rats after balloon denudation of the aorta have shown marked induction of IGF-1 messenger RNA as well. Since PDGF is a very powerful stimulator of mesenchymal IGF-1 gene expression, continued SMC proliferation after endothelial injury may result from the combined effects of PDGF and endogenous IGF-1. Therefore, elucidation of the mechanism of restenosis will require studies of the biosynthesis of growth factors and possibly other mediators, and how these factors are regulated after an arterial injury. Other mechanisms such as abnormal extracellular matrix formation by myofibroblasts may also play a role. Only after these cellular and subcellular mechanisms are better understood, it will be possible to minimize the problem of restenosis by early application of pharmacologic interventions designed to stop or reduce the response to vascu

lar injury. There has been already evidence from experimental studies that the PDGF antagonist trapidil

(triazolopyrimidine), previously shown to prevent myointimal proliferation in injured rat carotid arteries31 can reduce restenosis after angioplasty in atherosclerotic rabbits[32].

In summary, in spite of major technological advances in angioplasty techniques, **restenosis still remains a significant problem** and acute complications associated with coronary angioplasty are not negligible. Improved diagnosis of the atheroma mass and its constituents, detection of the integrity of the endothelial surface, as well as better understanding of interactions between components of the vessel wall, platelets, and other coagulation factors are essential to reduce acute complications. The problem of restenosis may be even a more difficult one to solve. In addition to the above mentioned factors, which may also affect the long term results of angioplasty, the cell signals and molecular events preceding the release of growth factors, which are responsible at least in part for intimal hyperplasia and restenosis following angioplasty, are poorly understood. Therefore, much research needs to be done in this area.

There is reason to believe, however, that before the end of this century, leading cardiology centers will be able to evaluate and manage patients with documented myocardial ischemia, particularly those with unstable angina, in a more comprehensive stepwise approach. We can envision that in many cases **angiograph,ic** localization and quantification of stenotic lesions in the epicardial coronary arteries will be followed by **angioscopic** evaluation of the atheroma surface and blood vessel lumen, and a **diagnostic test** to define the anatomy of the atheroma and the blood vessel wall as well as the constituents of the atheroma mass, possibly with the use of intravascular ultrasound and/or LIES. Based on those findings, the appropriate pharmacologic, catheter-based or surgical intervention, or a combination best fitted for each particular case can be proposed. Such advances, combined with better understanding of the pathogenesis of atherosclerosis and clinical implementation of preventive measures, will certainly bring renewed hope for patients with coronary artery disease in the next decade.

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