Intravascular Ultrasound: A Histological Study of Vessels During Life
The New ‘Gold Standard’ for Vascular Imaging
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During the last several years, dramatic developments have taken place in the area of cardiac imaging techniques. From an era of imaging by silhouettes (chest roentgenography, fluoroscopy, angiography, angiography), we have emerged into an era of imaging by tomographic scanning (echocardiography, radionuclide and computed tomography, magnetic resonance).1-3 Two-dimensional intravascular echocardiography is one of these exciting new techniques capable of providing cross-sectional tomographic images of coronary arteries. Although visualization of the major epicardial coronary arteries by transthoracic or transesophageal echocardiography has been possible for nearly 15 years,4-17 intravascular ultrasound has, for the first time, allowed visualization of the coronary lumen and various normal and abnormal layers of the coronary arteries. In essence, intravascular echocardiographic imaging represents a histological study of the coronary artery during life. The usual three-layer structure (intima, media, adventitia) of muscular arteries such as the coronary artery system is acoustically distinctive, which permits ultrasound imaging. The relative echo lucency of the media compared with the intimal and adventitial layers permits visualization of this multilayer architecture first described in vitro by Meyer et al18 in 1988 and in vivo by Yock et al19 in 1989. The bright inner (luminal) lining of the ultrasound image in the normal coronary artery is caused principally by the internal elastic membrane separating the intima from the media.20-22 The intimal layer in the normal coronary artery is probably not thick enough to generate a distinct ultrasonic layer.3 Further refinement in the interpretation of images from the internal and external elastic membranes as well as the luminal surface of vessels is under way. Several in vitro and in vivo studies of arterial vessels (with and without histology) have confirmed the ultrasonic appearance of these arterial structures and have validated measurements of layer thickness and luminal cross-sectional area.23-35 Attention is now focusing on the clinical applications of intravascular echocardiography. At least three major areas of diagnostic and therapeutic use of intravascular ultrasound are under study: 1) assessment of vessel wall morphology and luminal characteristics (Figure 1), 2) assessment of acute and chronic vessel wall changes of various interventional therapies (Figure 2), and 3) assessment of the current “gold standard” of coronary imaging technique: angiography (Figure 3).

Vessel Wall Morphology and Luminal Characteristics

The ability to determine arterial wall morphology and the presence or absence of luminal narrowing has important applications in management of patients with cardiovascular disease (Figure 1). Intravascular ultrasound can significantly aid in the determination of normal versus diseased coronary vessels. This basic information in itself can markedly alter therapeutic decisions. After detection of disease, the intravascular ultrasound can further delineate the type (atherosclerotic, nonatherosclerotic), severity (diffuse, extensive, focal), and degree or amount (cross-sectional area luminal reduction, diameter reduction) of luminal obstruction.

Plaque Morphology

The type of atherosclerotic plaque (calcified or noncalcified, the presence or absence of associated thrombus, concentric versus eccentric) has major implications regarding the success or failure of various interventional procedures and provides information about the immediate prognosis of a patient with coronary artery disease. Heavily calcified atherosclerotic plaques may be less successfully treated with balloon angioplasty or atherectomy compared with minimally calcified or noncalcified plaques.36 Superimposed plaque thrombus has been associated with a higher frequency of abrupt closure at angioplasty sites compared with angioplasty sites without associated thrombus. Recognition of “soft” plaques (rich in intraplaque lipid pools and poor in fibrous tissue and calcium) versus “hard” plaques (rich in dense fibrous tissue and calcium and poor in lipids) can alter procedural aspects and ultimately the end result of balloon angioplasty. Discrimination of soft plaque from plaque with superimposed thrombus is currently a limitation of intravascular ultrasound. Computer-enhanced processing of raw ultrasound signals or higher image resolution may help solve this problem. With its capability of visualizing the three layers of the coronary artery, intravascular echocardiography can determine the presence of eccentric versus concentric plaques, one of the new concepts in atherosclerotic...
disease. Variation in the distribution of atherosclerotic plaques along the internal elastic membrane of coronary arteries results in these two major types of luminal shapes: 100% of the circumference covered by plaque (concentric) or a variable arc of circumference free of disease (eccentric). The presence of a segment of normal coronary arterial wall in the eccentric plaque (i.e., normal intima, media, and adventitia) has clinical implications regarding vessel spasm, stretching, and recoil. At necropsy, the frequency of eccentric plaques in human coronary arteries approaches 75%. Intravascular ultrasound will confirm or deny the importance and clinical implications of this morphological entity in the living patient.

Extent of Disease

Discussion and debate continue as to whether coronary atherosclerotic plaque is a diffuse, extensive, or focal process. Intravascular echocardiography will provide further information on this topic in the living patient. As both the degree of luminal cross-sectional area reduction and the length of vessel stenosis play a role in determining the significance of a given coronary lesion, intravascular echocardiography will greatly assist in quantifying these two morphological factors and separating hemodynamically critical from noncritical coronary lesions.

Assessment of Acute and Chronic Vessel Changes After Various Interventional Techniques

Balloon Angioplasty

Catheter ultrasound images of acute angioplasty sites have already confirmed previous necropsy and angioscopy studies describing “cracking,” “breaking,” and “splitting” of atherosclerotic plaque with localized medial dissection as a major mechanism of balloon angioplasty (Figure 2). A recent issue of Circulation contained further intravascular echocardiographic observations in this area correlating depth and length of plaque splitting after balloon angioplasty with amount of residual lumen and the potential for restenosis.

Another major mechanism of balloon angioplasty appears to be stretching of the disease-free wall in the eccentric plaque. To date, this mechanism has been addressed in only a limited way by intravascular echocardiographic studies but represents an important topic for issues of acute closure (“spasm”), early restenosis (within hours or days) (elastic recoil), and chronic restenosis (weeks or months) (chronic recoil) after angioplasty. It seems clear that intravascular echocardiography will help solve issues of “stretch-recoil” at both acute and chronic angioplasty sites and provide morphological information on the intimal proliferation and chronic recoil types of restenosis.

Newer Interventional Devices

Experience is accumulating with intravascular ultrasound in association with directional atherectomy and intravascular stenting. Clinical experience with atherectomy devices suggests that optimal “debulking of plaque” may be difficult to achieve or recognize by angiography alone. Vessel perforation and a relatively high rate of restenosis have occurred with attempts at “remodeling” plaque by use of the directional atherectomy device. Anatomic factors associated with these atherectomy complications appear to be the depth of cutting and the amount of vessel media exposed. Both of these problem areas can be addressed and probably solved with the combined use of atherectomy and intravascular ultrasound (ultrasound-guided atherectomy) catheters. Given the echogenicity of metal, the present type of intravascular stent is easily visualized by intravascular ultrasound scans. Because of the tomographic cross-sectional views, ultrasound images of intravascular stents appear as a series of evenly spaced bright points along the luminal circumference (Palmaz-Schatz stent) or as intensely bright single bars seen alternating along the vessel circumference on serially imaged cross sections (Gianturco-Roubin stent). As with angioplasty
A. Balloon Angioplasty

**Acute**
- "Crack"
- Cracks, breaks or tears

**Restenosis**
- Intimal Proliferation (IP)
- Recoil

B. Atherectomy

**Acute**
- Inadequate Atherectomy
- Adequate Atherectomy

**Restenosis**
- Intimal Proliferation (IP)
- Thrombosis

C. Stent Placement

**Restenosis**
- Intimal Proliferation (IP)
- Thrombus

D. Chronic Vascular "Rejection" (Transplanted Heart)

**Procedural Costs and Time**

Use of intravascular ultrasound in conjunction with interventional procedures may lead to the use of specific devices for specific lesions and ultimately result in reduction in interventional procedural costs. Currently, the limitations of the coronary angiogram frequently result in the use of several types and sizes of balloon catheters and other interventional devices (atherectomy devices, stents) to arrive at a desired luminal configuration. Disposable equipment costs, not to mention operator time and energy costs, for these procedures can be staggering! With intravascular ultrasound, lesion-specific devices can be used initially as a direct result of knowledge of vessel luminal area and plaque morphology and can dramatically reduce procedural costs and time.

**Cardiac Transplantation**

A new area of intravascular ultrasound application involves coronary artery analyses in cardiac transplant...
recipients. The epicardial (and intramural) coronary vessels of the transplanted human heart may develop diffuse and concentric narrowing over time. This vessel change has been referred to by various names: chronic rejection, chronic vascular rejection, accelerated coronary disease of the transplanted heart, transplant atherosclerosis, but the specific cause is not known. This vascular process may involve as many as 50% of recipients 5 years after transplantation. In the past, the diagnosis has been established only at autopsy or clinically suspected in review of serial annual coronary angiograms. Because of its concentric and diffuse nature, the intimal proliferation is difficult to recognize angiographically but would be ideally suited for early diagnosis by intravascular ultrasound. “Cardiac transplant coronary disease” is also characterized by its preservation of the internal elastic membrane, in contrast to garden-variety atherosclerotic disease, which invades, fragments, or eliminates the internal elastic membrane. This characteristic feature of “transplant vascular disease” is uniquely detectable by intravascular ultrasound (Figure 2). Serial intravascular echocardiographic studies of coronary lumen and vessel wall morphology in cardiac transplant patients will lead to early detection of this disease and, we can hope, lead to a better understanding of its causes, treatment, and prevention.

**Atherosclerotic Plaque Regression or Modification**

Recent information suggests that atherosclerotic plaque “regression” can occur with the use of various antilipid agents. Conclusions reached in these studies rest solely on comparison of coronary angiographic studies—an indirect, “luminographic” technique. Intravascular ultrasound could confirm or deny the results of these studies by providing a direct imaging technique of target lesions before and after treatment to show actual loss of plaque (“regression”), loss of specific components of plaque (“modification”), or lack of change. Intravascular ultrasound also has the possibility of identifying plaque potentially more susceptible to regression or modification by pharmacological interven-

tion, such as soft, lipid-laden plaques rather than hard, densely fibrotic and calcified plaques.

**Assessment of Coronary Angiography: Verification, Underestimation, and Overestimation of Luminal Dimensions**

The coronary angiogram represents a silhouette study of the vessel lumen (Figure 3). As such, one measures luminal diameter reduction on the basis of a “peak-and-valley” effect of a diseased artery. Angiographically, one compares a site of maximal narrowing with an adjacent site of presumed normal coronary artery to determine the percentage of coronary diameter reduction. If coronary artery atherosclerosis is an extensive or diffuse process, then the angiographically presumed normal coronary segment used for comparison is actually a diseased segment. This process leads to underestimation of the amount of vessel disease. Variability in coronary luminal shape (eccentric plaque) represents another explanation for angiographic underestimation of vessel narrowing. Thus, a “normal” coronary angiogram may mean a normal coronary artery without luminal narrowing but may also represent a diffusely diseased artery composed of serial concentric or eccentric types of coronary lumen. Intravascular ultrasound will aid in verification of the coronary angiogram by confirming the presence of a normal vessel or diffusely diseased intimal layer (Figure 3A) and will help solve the problem of angiographic underestimation of coronary disease (Figure 3B). The intravascular ultrasound may also prevent overestimation of disease by angiography. As a luminogram, the coronary angiogram highlights the peak-and-valley effects of a diseased vessel wall. A marked variation in the height and depth of these peaks and valleys can produce the silhouette of a coronary aneurysm. Intravascular ultrasound can readily establish the presence of diffuse atherosclerosis masquerading as multiple aneurysms and also establish the correct diagnosis of coronary aneurysms, as in patients with Kawasaki disease.
Limitations of Intravascular Ultrasound

At present, many of the limitations of intravascular ultrasound appear to involve technical aspects and will be solved with future modifications and designs. The present relatively large catheter delivery systems limit intravascular echocardiographic access to distal segments of coronary arteries, including marginal and diagonal branches, which are frequently sites of interventional procedures. Reliable detection of thrombus (fresh and organized) and discrimination of thrombus superimposed upon plaque from soft, lipid-laden plaques also are limitations of the present imaging resolution and processing. Tortuosity of coronary vessels poses problems with catheter–vessel coaxial alignment, which can lead to overestimation or underestimation of disease and wall thickness by ultrasonic images. As with any new device or drug, initial equipment costs are high, which may deter early widespread use of the intravascular echocardiograph. However, the potential and real benefits of intravascular ultrasound far outweigh these present limitations.

The Future

There are a number of technical developments in catheter ultrasound currently under way that will enhance its usefulness in cardiovascular disease. Prototypes of combined balloon–imaging catheters, combined atherectomy–imaging devices, combined ultrasound–laser catheters, and combined Doppler–ultrasound catheters are being tested. Different imaging planes—if “funnel-forward” orientation and “direct forward-looking” sector scanners—are being developed. Three-dimensional image reconstruction is being actively pursued by a number of research groups. This reconstruction process will greatly enhance our understanding of vessel wall morphology in predicting results of interventional procedures. Rapid advances are continuing in the area of tissue characterization by intravascular ultrasound. Differentiating types of luminal narrowing (dendly fibrotic [hard] versus heavily lipid-laden [soft] atherosclerotic plaque, soft plaque versus thrombus, intimal proliferation versus thrombus or atherosclerotic plaque) will be feasible. Determination of luminal surface integrity will also be possible, which will lead to early detection of the “unstable plaque” (plaque fissures) now known to be the “missing link” between unstable angina, acute myocardial infarction, and sudden coronary death. In essence, intravascular ultrasound has a very exciting and promising use in the diagnosis and therapy of cardiovascular disease. If it is not already, intravascular ultrasound will become the new “gold standard” in evaluation of coronary artery disease.

References

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