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DIAGNOSIS AND TREATMENT OF VULNERABLE PLAQUE

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EXECUTIVE SUMMARY

Rupture of atherosclerotic plaque with subsequent thrombosis is the primary cause of acute myocardial infarction. Vulnerable plaques are those coronary lesions with features known to be associated with rupture and arterial occlusion, such as a thin fibrous cap, a large lipid core, and the presence of inflammatory cells. Since vulnerable plaques cannot be identified by stress testing or angiography, new modalities such as intravascular ultrasound, intracoronary thermography, intravascular palpography, optical coherence tomography, intravascular radiation detection, magnetic resonance imaging, radionuclide imaging, and spectroscopy are under investigation. Prospective studies are needed to ascertain whether these technologies can reliably identify vulnerable plaques. If vulnerable plaques could be detected prior to their rupture, cardiologists could then identify patients at high risk of an impending acute coronary syndrome and target these patients with the most aggressive medical and device-related therapies.

Introduction

In 1912, Dr. J.B. Herrick associated the clinical presentation of acute myocardial infarction (MI) with thrombotic occlusion of a major coronary artery (1). Since that time, countless scientific studies have documented the intricate process leading to coronary arterial occlusion and acute coronary syndromes (ACS). The mechanism responsible for MI is atherothrombosis, an abrupt rupture or erosion of an atherosclerotic plaque leading to superimposed clot formation and arterial occlusion (2). Extensive progress has been made in identifying patient factors associated with atherothrombosis and in developing systemic therapies to reduce the risk of plaque rupture, such as antiplatelet therapy, statins, and ACE inhibitors (3). Despite this, acute coronary syndromes occur in over one million Americans annually. Moreover, recent clinical trials demonstrate that up to 10% of patients with an ACS event experience recurrent clinical events during the next year despite state-of-the-art medical and percutaneous therapies (4).

At the heart of the atherothrombotic process are so called “vulnerable plaques.” These are atherosclerotic lesions with characteristics that predispose to rupture and thrombus formation. Recent insights into the structural, cellular, and molecular basis for plaque instability have sparked intense efforts to identify vulnerable plaques, recognizing that early detection could prompt therapies aimed at preventing future coronary events. With knowledge of the pathology and natural history of vulnerable plaques, the field of vulnerable plaque detection is now burgeoning with ongoing observational studies of several promising modalities.

Vulnerable Plaque Characteristics

Atherosclerosis of the coronary arteries is a chronic inflammatory, fibroproliferative disease affecting primarily the intima of the major vessels (5,6). Atherosclerotic plaques consist of two main components, a lipid rich core and a collagen-rich fibrous cap. Numerous autopsy and animal studies have demonstrated that rupture or erosion of the fibrous cap leading to thrombosis and arterial occlusion is the proximal cause of myocardial infarction and many cases of sudden cardiac death (7).

Atherosclerotic plaques must obstruct approximately 70% of an artery lumen to become flow-limiting and cause coronary ischemia and symptoms of angina (8). Most plaques that lead to atherothrombosis, however, are not large enough to cause symptoms prior to rupture. For example, among patients in the Coronary Artery Surgery Study (CASS) registry with acute MI, the atherosclerotic lesion responsible for acute thrombosis and occlusion of the vessel was asymptomatic and obstructed less than 80% of the vessel lumen in 51 of 72 patients who had undergone coronary angiography prior to the event (9). Similar studies among patients with ischemic stroke have found that atherosclerotic lesion size is not predictive of plaque rupture and development of atherothrombosis (10). For this reason, most rupture-prone plaques are not large enough to be detected by stress testing and many are even invisible angiographically (11).

Plaque composition, on the other hand, has been shown to be correlated with rupture and thrombosis. Pathoanatomic studies have consistently identified three features associated with plaque vulnerability to rupture: size of the lipid rich core (12), degree of inflammation within the

plaque (13), and a thin fibrous cap (14). The thin cap fibro-atheroma (TCFA; ref. 15) is a specific lesion type that has been postulated as the precursor to atherothrombosis since it closely resembles the morphology of ruptured plaques (2,16).

Plaque location also influences the likelihood of rupture. Wang et al. analyzed 208 patients referred for urgent angioplasty for ST-elevation MI and mapped the location of the infarct-related lesion (17). Thrombotic lesions tended to occur in the proximal third of each of the major coronary vessels. Poisson regression showed that for each 10 mm increase in distance from the ostium, the risk of acute occlusion decreased by 13% for the right coronary artery, 30% for the left anterior descending artery, and 26% for the left circumflex artery. These findings have led some investigators to propose prophylactic stenting of the proximal coronary arteries in high-risk individuals (e.g., patients with diabetes or recent acute coronary syndromes) for prevention of future vascular events.

Detection of Vulnerable Plaques

Since vulnerable plaques are often asymptomatic and cannot be reliably visualized by current routinely used modalities, new methods for detecting such lesions are being developed. To date, no technology has been shown in a prospective manner to identify vulnerable plaques, but using knowledge of the composition and location of atherothrombotic plaques, several invasive and non-invasive imaging modalities hold promise and are currently under investigation.

Intravascular Ultrasound

Intravascular ultrasound (IVUS) images the coronary arteries through the use of a miniaturized ultrasound transducer at the tip of a catheter (18). With the transducer positioned over a guidewire in the coronary vessel, the ultrasound beam is directed perpendicularly through the course of the artery and cross-sectional images of the vessel wall are obtained. In contrast to coronary angiography, which can only visualize the vessel lumen, intravascular ultrasound visualizes both the lumen and the vessel wall. The morphology of plaque within the vessel wall can be characterized by the intensity of the signal. Areas of calcification and fibrosis, as well as plaque ruptures or ulcerations can also be visualized. Recent IVUS advances utilize mathematical transformation of the radiofrequency signal to produce color-coded images of plaque characteristics such as lipid, fibrous tissue, calcification, and necrosis of the core. These “virtual histology” images have shown good correlation with pathologic studies (19).

Intracoronary Thermography

Atherosclerotic lesions with high levels of inflammatory activity produce heat, most likely due to a combination of leukocyte metabolic activity, ineffective metabolism, and increased neoangiogenesis (20). Multiple animal and human experiments have shown that the surface temperature of atherosclerotic plaques correlates with the degree of plaque inflammation and is inversely associated with the thickness of the overlying fibrous cap (21). Several coronary temperature mapping catheters are under investigation such as the Volcano catheter (Volcano Corporation, Rancho Cordova, CA) and the ThermoCoil Guidewire (Imetrx, Mountain View, CA). These devices measure temperature at areas of atherosclerotic plaque and compare the recording to temperature within healthy vascular walls or within the bloodstream. “Hot spots”

are identified which are hypothesized to represent regions prone to plaque rupture and local thrombosis.

Intravascular Palpography

Arterial walls with vulnerable plaques have different mechanical properties than healthy vascular tissue (22). Thin fibrous layers, large lipid cores, and inflammatory cells can alter the stress-strain relationship of coronary vessels. Intravascular palpography involves determination of the mechanical properties of the vascular wall to identify vulnerable plaques. Using IVUS, images of the coronary artery are obtained at two different blood pressure points during the cardiac cycle. The change in pressure alters the lumen diameter and thickness of the vessel wall. Based on the change between these two images, as measured by the displacement of the radiofrequency signals, a strain level can be determined for each point along the artery lumen. Typically, color-coding of strain values is performed and superimposed on the IVUS image. Areas of high strain have been shown in pathoanatomic studies to represent vulnerable plaques.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a catheter-based method for intravascular imaging (23). Similar to ultrasound, it uses backreflection of waves to characterize arterial wall structures including vulnerable plaques. It differs from IVUS, however, by using infrared light rather than sound. This feature gives it several potential advantages including excellent image quality, acquisition rates at near video speed, and significantly lower catheter costs compared to IVUS. Several devices, such as the imaging guidewire from LightLab Imaging, Inc. (Westford, Massachusetts), are under investigation and have shown promise in pathoanatomic and animal studies.

Intravascular Radiation Detectors

Intravascular radiation detectors are in the very early stages of development with several prototypes being investigated (24). To detect vulnerable plaque characteristics, these radiation-sensitive catheters pick up radioactive tracers that localize to plaque components. Several tracers have been investigated including ^{18}F fluorodeoxyglucose (FDG) to detect metabolism, $^{99\text{m}}\text{Tc}$ monocyte chemoattractant peptide-1 to detect receptor expression, and $^{99\text{m}}\text{Tc}$ annexin V to detect apoptosis. Ex-vivo feasibility studies in mice have shown this technique to hold promise although mechanical refinements are needed to optimize the system for in vivo analyses.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an attractive diagnostic modality for imaging cardiac structure and function because it is non-invasive and does not utilize nephrotoxic agents. In addition, the ability of MRI to characterize soft tissue allows for a clear depiction of the various components of the atherothrombotic plaque. In excised and in vivo carotid artery studies, MRI has shown the ability to discriminate between adventitial and medial layers, as well as fibrous caps and lipid cores. Its ability to image plaques in the coronary arteries, however, is limited by a reduced spatial resolution for deep structures, the small size of coronary vessels, and motion effects (25).

In hopes of overcoming these limitations, several novel MRI techniques for identifying vulnerable plaques are under investigation. These include intravenous targeting agents that

localize to components of atherosclerotic plaque and enhance by MRI. One such agent is gadofluorine M, which in animal models has shown strong uptake in the extracellular matrix of plaques, with particular enhancement of the lipid rich component. Also, intravenous nanoparticles called ultra-small particles of iron oxide (USPIO) were demonstrated to localize to intra-plaque macrophages and enhance by MRI. Lastly, a dual-labeled contrast agent, PTIR267, with fluorescent and gadolinium-based components, was found to provide in vivo detection of LDL receptors.

Intravascular MRI techniques can obtain detailed images of atherosclerotic plaques from within the coronary vessels and avoid many of the limitations of external-field MRI. Investigators have studied the insertion of an intravascular MRI coil to enhance image quality of external-field detectors. This method is limited, however, due to heating effects of the coil. Others have studied self-contained intravascular MRI probes. Recently, Schneiderman et al. (26) reported the successful use of an intravascular MRI probe to detect thin-capped fibroatheroma in excised human coronary arteries.

Radionuclide Imaging

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) detect vulnerable plaques in the coronary arteries through the use of tracer compounds that localize to inflammatory plaque components (27). Since highly inflammatory plaques are more prone to rupture, radionuclide compounds have been developed which selectively target components of plaque inflammation such as macrophage recruitment, foam cell generation, matrix metalloproteinase production, and macrophage metabolism. After intravenous injection of the tracer compound, the coronary arteries are imaged and quantified in terms of degree of inflammation in the vessel walls. Areas of greater inflammatory activity are hypothesized to be more prone to rupture and thrombosis. A major advantage of this modality is that it is non-invasive, giving it the potential to be used for ambulatory screening purposes with low risk to the patient.

Near Infrared Spectroscopy

Near-infrared (NIR) spectroscopy is a technique commonly used in physics to determine chemical compositions. This modality takes advantage of the principle that different substances absorb and scatter NIR light to different degrees. The return signal from a NIR emitter can be plotted to show light absorbance at varying wavelengths, with spikes in absorbance representing different chemical compounds. Recent studies of aortic and coronary autopsy specimens have demonstrated that NIR can reliably detect lipid-rich, thin-capped fibroatheromas (28). Through creation of a chemogram, NIR depicts an analysis of the arterial wall that can serve as an index for vulnerability. Studies on human subjects have been limited because the beating heart is a difficult environment for performance of spectroscopy. Very recently, coronary artery catheters containing fibers to deliver and collect NIR light have been developed. Early human testing is currently underway.

Conclusions

Each of the emerging modalities for vulnerable plaque detection takes advantage of differences between rupture-prone plaques and stable atherosclerotic lesions. Although some of

these techniques have been confirmed pathoanatomically to identify plaques with vulnerable features—thin fibrous caps, large lipid cores, presence of inflammatory cells—none have been prospectively studied for the ability to identify patients who will experience clinical events. Key issues at this stage relate to the number and distribution of vulnerable plaques, the duration of vulnerability, and the absolute level of risk conferred by specific pathoanatomic features. Ongoing clinical research is mainly in the form of “natural history” studies that will help to define these key parameters and their relationship to traditional cardiovascular risk factors and other patient characteristics. Ultimately, if one or more of these diagnostic modalities proves to be both accurate and reliable, cardiologists may be able to safely identify vulnerable plaques prior to rupture and treat their patients with either aggressive medical plaque stabilization, drug-eluting stent implantation, or regional therapies such as local drug delivery, in order to prevent a coronary event. Such an achievement would represent a fundamental shift in our approach to managing coronary artery disease, with the potential to dramatically alter treatment patterns and improve patient outcomes.

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