

Intravascular atheroma monitoring: Past, present, and future of identifying vulnerable plaques

Suzanne A. Sorof, MD

There are approximately 2 million cases of acute coronary syndromes per year, with medical costs of \$100 billion. Aggressive medical therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, beta-blockers, aspirin, platelet inhibitors, and angiotensin-converting enzyme inhibitors are part of the treatment for this ever-growing problem of coronary atherosclerosis. As technology continues to evolve, there will be new techniques to assist the interventional cardiologist in identifying a plaque and determining its primary composition.

Coronary artery stenosis is generally asymptomatic until a lesion exceeds 70% to 80% of the vessel lumen. An acute coronary syndrome, however, is often due to the rupture of a 40% to 50% soft, lipid-laden plaque.^{1,2} When a plaque ruptures, a cascade of clotting factors occurs at the site, causing the formation of a thrombus.³ This review will discuss atheroma monitoring with conventional interventional techniques and new transcatheter techniques, as well as other adjunctive technology that could aid in the identification of soft, lipid-laden lesions. In addition, the combination of interventional and molecular biological techniques used to label and identify inflammatory proteins involved in plaque formation will also be discussed. Identification and treatment of these plaques before rupture may prevent loss of myocardium and sudden cardiac death.

Coronary artery disease

Coronary artery disease is a disease of the vessel wall caused by inflammation and leukocyte recruitment by dysfunctional vascular endothelium. Inflamma-

tory cells, especially macrophages, take up lipids and oxidize them, resulting in the formation of unstable plaques. When this vulnerable or unstable plaque ruptures, platelets adhere to the endothelium and activate such factors as endothelin-derived relaxing factor, prostacyclin, tissue plasminogen activator, and other factors, which are prothrombotic in nature.⁴

Vulnerable plaques

The fibrous collagen cap provides stability to the atherosclerotic plaque and extracellular matrix below. The unstable plaque has a thin fibrous cap and thrombus at the shoulder, many inflammatory cells, and a large lipid core.⁵ The atheromatous core makes up >40% of the plaque and is rich in cholesterol. The softer the core, the more vulnerable it is to rupture.

Because there is a significant amount of circumferential sheering stress on the atheroma, the softer plaques are prone to stress.⁶ Early in atherosclerosis, the external elastic membrane of the arterial wall undergoes positive remodeling, allowing the vessel size to enlarge and preserving the size of the lumen. As the atheroscle-

rotic plaque progresses, the plaque begins to encroach on the lumen. This remodeling, known as the Glagov phenomenon, causes intimal hyperplasia, dilation of the entire vessel with atherosclerosis, and, ultimately, obstruction of the vessel.⁷ As reported in a recent paper by Pasterkamp et al,⁸ 3 major interrelated determinants of a plaque's vulnerability to rupture include the thickness of the fibrous cap, the size and composition of the atheromatous lipid core, and inflammation within or adjacent to the fibrous cap.

Current interventional techniques

Angiography and intravascular ultrasound (IVUS) are routinely used to assess coronary vessels. With coronary angiography, atheroma monitoring is difficult because the contrast fills the lumen and the 2-dimensional (2D) images are only a rough estimate of the lesion underneath. Often, a complex plaque is an eccentric lesion and is associated with thrombosis. In addition, the lesion's length, diameter, and composition are difficult to accurately characterize. Lastly, angiography is approximately 50% sensitive in identifying calcium deposition.

Moreover, angiography does not determine if the lesion is a calcified plaque, a fibrocalcific lesion, a fibrofatty lesion, or a lipid-laden soft lesion. Therefore, adjunctive technologies have developed and are currently used to delineate further coronary arterial lesions and to measure, quantify, and qualify the underlying pathological atheroma.

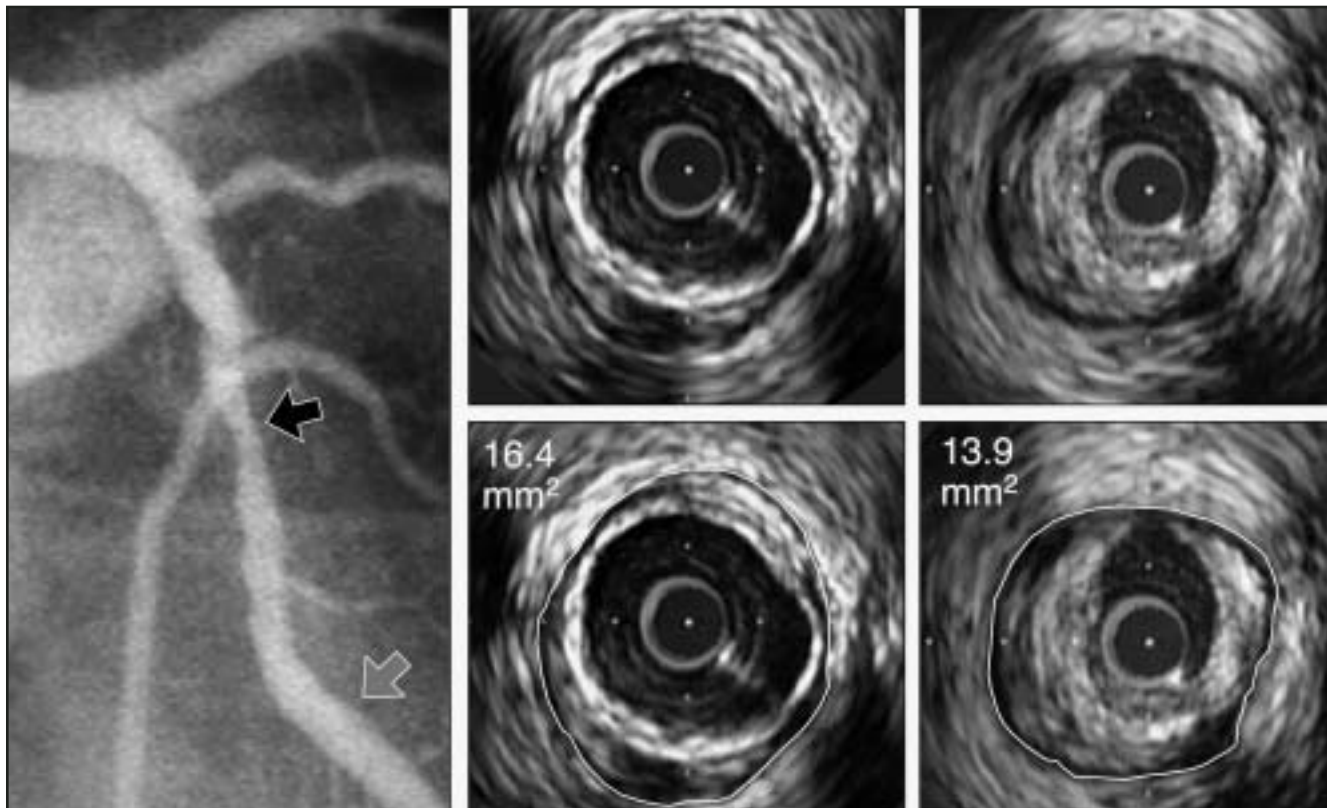


FIGURE 1. Intravascular ultrasound of a coronary vessel with disease showing ruptured plaque with positive remodeling. An angiogram (left) was obtained after thrombolysis for acute myocardial infarction. The black arrow indicates the occlusion site, and the gray arrow shows the proximal reference site. At the reference site, the external elastic membrane area is smaller (14.3 mm^2) than the area at the ruptured site (18.9 mm^2), indicating presence of positive remodeling. (Figure reprinted with permission from Nissen SE, Yock P. Intravascular ultrasound. Novel pathophysiological insights and current clinical applications. *Circulation*. 2001;103:604-616.¹⁵)

Intravascular ultrasound: The present

Intravascular ultrasound has characterized atheroma pathology since the mid-1980s, when cardiologists found a growing need to define the lesion morphology and length during angioplasty. It is a supplemental technique when performing angiography. The resolution of the ultrasound system is directly related to its frequency.

Using a 20- to 40-MHz transducer at the end of a catheter, clinicians can perform early atheroma monitoring. This technology provides 2D cross-sectional tomographic images of the arterial wall with an axial resolution of $150 \mu\text{m}$ and a lateral resolution of $250 \mu\text{m}$,⁹ resulting in an excellent histologic representation of the inner vessel wall. Intimal thickness increases with age, and this is a sign of early atheroma. Intravascular ultrasound can characterize plaque components, including the stiffness of the wall and the composition of the plaque. Because the

wall can be examined, the detection of the extent and severity of atherosclerotic disease is much more sensitive by IVUS than by angiography.

Intravascular ultrasound provides single cross-sectional areas of the arterial wall to enable the viewer to look at the length and thickness of the preintervention lesions. Intravascular ultrasound does not measure functional ability. Currently, it is the most commonly used imaging modality that provides images in which variations in arterial geometry and atherosclerotic plaque can be studied and monitored.^{10,11} Particularly with complex lesions and left main coronary atherosclerosis, IVUS has become an important adjunctive tool in the catheterization laboratory. After intervention, IVUS can also provide accurate images to ensure that stents are deployed correctly.

Intravascular ultrasound has allowed cardiologists to monitor plaques in the coronary arteries by allowing the observer

to see these layers of the artery at a level of 100 to $200 \mu\text{m}$. The intima, media, and adventitial layer can easily be discerned to give an estimation of the plaque burden present in the intimal layer. Ultrasound can detect the presence or absence of structural abnormalities of the vessel wall after mechanical interventions, including dissections, tissue flaps, intramural hematomas, perforations, and irregular surface features¹²⁻¹⁴ (Figure 1¹⁵). Limitations of IVUS include nonuniform rotational distortion (NURD). This distortion is caused by tortuous, calcified, or stenotic vessels and must be recognized. The operator must ensure that the catheter is not flexed and may need to change the direction of the guiding catheter to eliminate the distortion. Another limitation of IVUS includes decreased visualization of the layers of wall due to the backscatter of blood and components within the lumen.

A complication of IVUS is coronary spasm; the guidewire and catheter sys-

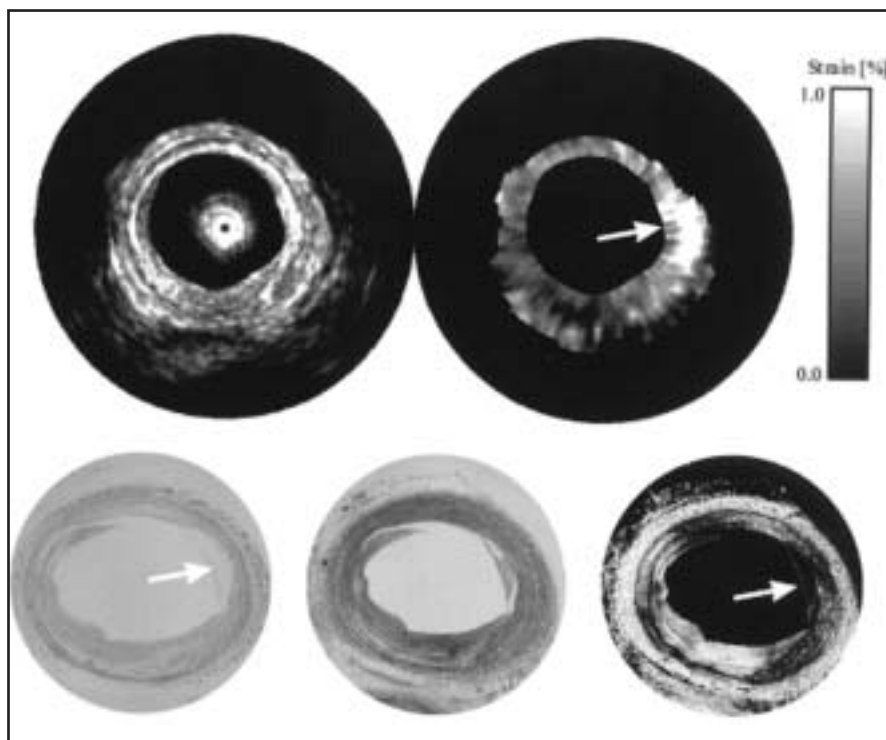


FIGURE 2. Intravascular ultrasound (upper panel, left) and elastogram (upper panel right) and histologic sections with alfa-actin stain, picro Sirius red stain without and with polarized light of a femoral artery. The ultrasound reveals an eccentric plaque between the 2 o'clock and 11 o'clock positions. The elastogram shows that the plaque can be divided into 2 sections: A low-strain part (4 o'clock to 11 o'clock) and a high-strain part (2 o'clock to 4 o'clock). The histologic study reveals that the material between the 4 o'clock and 11 o'clock positions is fibrous as opposed to the region between the 2 o'clock and 4 o'clock positions, which is more vulnerable with no smooth muscle or collagen. (Figure reprinted with permission from Pasterkamp G, Falk E, Woutman H, Borst C. Techniques characterizing the coronary atherosclerotic plaque: Influence on clinical decision making? *J Am Coll Cardiol.* 2000;36:13-21.⁹)

tem may cause irritation or spasm to the coronary vessel. This can become a serious problem if the guidewire is advanced into a tight stenosis or a smaller distal vessel. Nitroglycerin prior to insertion of the instrument is advised to prevent spasm. Prompt withdrawal is recommended if there is resistance to the catheter to avoid dissection.

Since IVUS has been used in conjunction with stent deployment, there has been a decrease in restenosis rates. Trials have suggested a benefit of IVUS guidance. Colombo et al¹⁶ looked at 359 patients with IVUS after angiographically adequate stent implantation. The results showed that 30% of stents placed had optimal expansion after angiographic guidance; with IVUS guidance, there was an increase to 96%. The results of the SIPS trial¹⁷ indicated that with IVUS-

guided placement of stents, the 2-year target lesion restenosis rate was 17% compared with 29%. The AVID trial¹⁸ showed that 33% of angiographically expanded stents were actually underexpanded, which is a major cause of stent stenosis and/or thrombosis.

Other trials have also supported the use of stent placement using IVUS, including the MUSIC trial¹⁹ (1998) that showed that IVUS guidance could improve restenosis after stenting. The BEST trial²⁰ was a multicenter randomized trial that proved that IVUS-guided percutaneous transluminal angioplasty (PTCA) was not inferior to routine angiographically guided stent implantation. The results of the CRUISE²¹ trial showed that IVUS guidance significantly reduced lesion revascularization rates from 15.3% (angiographically guided) to 8.5% (IVUS-guided). The

OPTICUS²² trial was a neutral study that did not show any long-term angiographic or clinical benefit for IVUS.

Elastography is a new use for IVUS in monitoring atheromas. This technique is based on the principle that tissue components differ in hardness as a result of their histopathologic composition. The various tissues compress differently if a defined pressure is applied.²³ Elastography is able to discriminate between soft or hard material located in the vessel wall²⁴ and has the potential to identify plaque vulnerability in regions of high stress. Limitations of elastography are the artifacts caused by cardiac motion during the cardiac cycles (Figure 2⁸).

Optical coherence tomography

In the Fall of 2004, a new forerunner of imaging called optical coherence tomography (OCT) will emerge for coronary imaging. This is a technique used in ophthalmology²⁵ to assess the anterior chamber and retina of the eye with unprecedented resolution. It will become an important adjunct to angiography and IVUS and has the approval of the U.S. Food and Drug Administration for use in coronary artery disease.

Optical coherence tomography is based on fiber optics that produce a cross-sectional image using the optical reflectance properties of the underlying tissue.²⁶ Using infrared light and mirrors through a catheter, the histologic features of the plaque can be accurately depicted. Infrared wavelength (850 to 1300 Hz) is delivered into the artery, where the reflective backscatter on a mirror measures depth and position of the lesion. The intensity of the reflective light provides the signal intensity. Studies have shown that the properties of various cells and tissue have different reflective indexes and that when the cells take up collagen, fibrous material, or lipid, a different reflective index is obtained.²⁷

Optical coherence tomography will allow more exact definition of the plaque composition. The resolution with OCT at 4 to 10 μm is much better than the resolution with IVUS (100 μm). This high resolution allows for the inspection of the fibrous cap

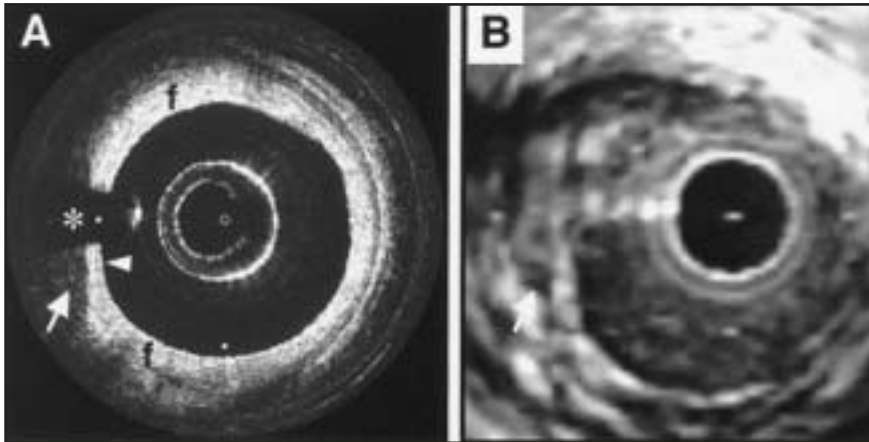


FIGURE 3. Fibrous coronary plaque imaged *in vivo* by (A) optical coherence tomography (OCT) and (B) intravascular ultrasound (IVUS). (A) An echolucent atherosclerotic plaque extends from 5 o'clock to 12 o'clock with regions of fibrous [f] (echo-dense) areas present. The arrowhead measures the plaque cap by OCT ($122 \mu\text{m} \pm 7 \mu\text{m}$). (B) In the corresponding IVUS image, the fibrous echolucent plaque (arrow) is also visualized. (Reprinted with permission from Jang IK, Bouma BE, Kang DH, et al. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: Comparison with intravascular ultrasound. *J Am Coll Cardiol.* 2002;39:604-609.²⁸)

of the atherosclerotic plaque to determine if there is infiltration of macrophages or inflammatory cell migration. Because activated macrophages are often found in patients having an acute coronary syndrome or sudden cardiac death, high-resolution technology with OCT would be extremely valuable in assessing which plaques are the most vulnerable and need treatment immediately. Limitations of OCT include the inability to see through blood. Also, because it is an optical reflective technique, its depth is only 2 mm. Therefore, one cannot see through to the adventitia when looking from the luminal surface (Figure 3²⁸).

Acoustic emissions: The future

During percutaneous coronary interventions, balloon angioplasty causes damage to the atherosclerotic lesion and to the arterial wall. Some of the arterial wall injuries

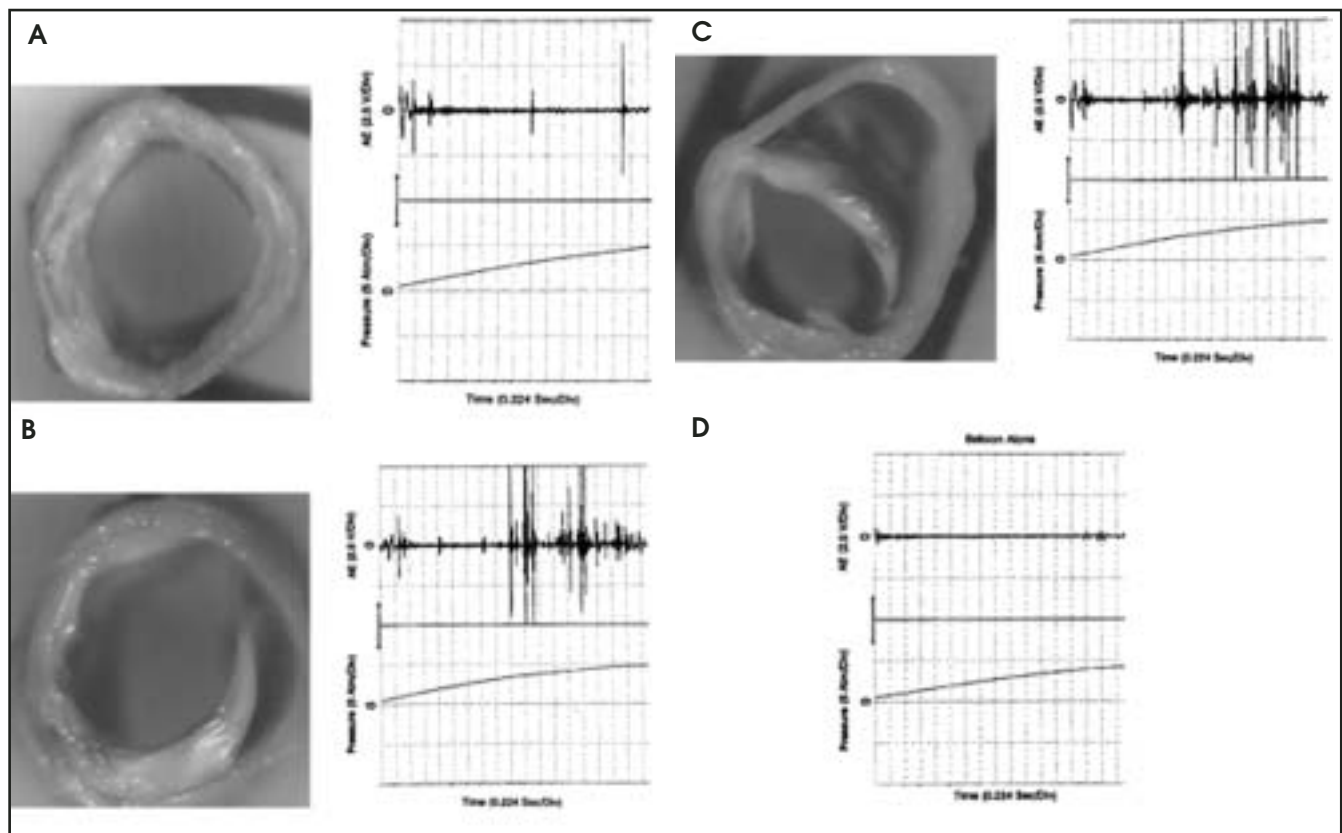


FIGURE 4. The sound waves generated from the dissection of coronary vessels. Composite figure depicts the postintervention tissue segments in which dissection was absent along with corresponding pressure data not suggesting sound emission. (A) Two segments exhibit progressively more traumatic dissections (B and C) along with simultaneous vascular acoustic emissions and pressure signals recorded during dilation of these specimens. (D) Vascular acoustic emissions and pressure signals collected from inflation of balloon without tissue specimen. This image shows significant dissections occurring following *in vitro* angioplasty, which can be postulated as a cause of the neointimal hyperplastic response following angioplasty. This has been postulated as a cause of restenosis.³⁹ (Reprinted with permission from Vonesh MJ, Mockros LF, Davidson CJ. *In Vitro* identification of angioplasty induced injury by use of vascular acoustic emissions. *Circulation.* 1997;95:1022-1029.³⁷)

include disruption of the intima, fracture of the atheromatous plaque, crack propagation, and stretching of the arterial tissue.²⁹⁻³² Crack propagation can lead to dissection of the artery, which ultimately leads to acute and chronic complications, including abrupt reclosure,³³ ongoing ischemia,³⁴ and chronic restenosis of the treatment site.^{35,36} Identification of balloon dissection may be used to identify patients at risk for future complications.³⁷

Vonesh et al³⁸ described the novel use of vascular acoustic emissions from post-mortem tissue. The vessels are subjected to in vitro balloon angioplasty, causing stress-induced structural damage, such as fracture. Simultaneously, acoustic emissions are obtained. When molecular bonds break, sound energy propagation occurs. This sound energy is also emitted when there is a change in molecular orientation. A monitor measures the acoustic emissions and converts the energy through the color spectrum; frequency and noise levels can be separated, allowing for identification of dissections versus plaque cracking. Because vascular injury is related to adverse outcomes, this could be a potential diagnostic modality to follow patients postangioplasty. This experimental model may identify those at risk for chronic restenosis due to dissection. This technique is experimental, so further evaluations and validation are needed (Figure 4^{37,39}).

Thermography: Thermal detection inside atherosclerotic plaques

Atherosclerosis is an inflammatory process with plaque rupture of the thin fibrous core, followed by macrophage infiltration of lipids. Macrophages have high metabolic activity.³¹ Because of their increased uptake of glucose and oxygen, there is a local rise in temperature. The thinner the fibrous cap, the higher the temperature the soft lipid core plaque emits. This results in an acidic environment in the area of the arterial lesion. Several studies have shown that the temperature heterogeneity is determined by the plaque composition and more specifically by the macrophage mass.⁴⁰ Stefanadis et al⁴¹ have done several studies that show that in

unstable angina and acute myocardial infarction, there is a higher temperature emitted from the lesions than in stable atherosclerotic lesions. There is also an elevation of C-reactive protein, one marker of inflammation, in the region of a vulnerable plaque. Both the elevated temperature and the elevated biomarkers indicate a poor prognosis in the setting of an acute plaque rupture.

Thermography is a catheter technique that measures temperature. Clinical trials are ongoing to assess its safety and reproducibility, as it may be another adjunctive technology to assess plaques in the near future.

The future of monitoring atheroma

The future of atheroma monitoring lies in using a combination of catheter-based and molecular biology techniques. Many studies are evaluating new ways to use label proteins within the artery wall, including inflammatory cells, enzymes, and metalloproteinases to enable the study of plaques at a molecular level. Bioluminescence, or molecular tagging of cellular structures, is being evaluated to determine which lipid cores are prone to rupture to trigger the coagulation cascade.

Another novel method is IVUS-guided transvascular delivery of liposomal-based imaging agents. Injections of labeled proteins (antibodies and peptides) are used to highlight and target plaque components. This technique may also help to delineate the more vulnerable lipid-laden plaques. Through color coding, calcium, fatty macrophages, and fibrotic material can be visualized. As technology becomes advanced, the ability to detect vulnerable plaque will become more sensitive. A combination of illumination techniques and specialized catheters will be the future of this field.

REFERENCES

- Falk, E, Shah, PK, Fuster, V. Coronary plaque disruption. *Circulation*. 1995;92:657-671.
- Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery coronary syndromes. *N Engl J Med*. 1992;326:242-250.
- Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol*. 1988;12:56-62.

- Sambola A, Osende J, Hathcock J, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. *Circulation*. 2003;107:973-977.
- Heistad, DD. Unstable coronary artery plaques. *N Engl J Med*. 2003;349:2285-2287.
- Loree HM, Tobias BJ, Gibson LJ, et al. Mechanical properties of model atherosclerotic lesion lipid pools. *Arterioscler Thromb*. 1994;14: 230-234.
- Glagov S, Weisenberg E, Zarina C, et al. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316:1371-1375.
- Pasterkamp G, Falk E, Woutman H, Borst C. Techniques characterizing the coronary atherosclerotic plaque: Influence on clinical decision making? *J Am Coll Cardiol*. 2000;36:13-21.
- Schoenhagen P, Nissen S. Understanding coronary artery disease: Tomographic imaging with intravascular ultrasound. *Heart*. 2002;88:91-96.
- Hermiller JB, Tenaglia AN, Kisslo KB, et al. In vivo validation of compensatory enlargement of atherosclerotic coronary arteries. *Am J Cardiol*. 1993;71: 665-668.
- Losordo DW, Rosenfield K, Kaufman J, et al. Focal compensatory enlargement of human arteries in response to progressive atherosclerosis. *Circulation*. 1994;89:2570-2577.
- Rioufol G, Finet G, Ginon I, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome: A three vessel intravascular ultrasound study. *Circulation*. 2002;106:904-908.
- Fitzgerald PJ, Ports TA, Yock PG. Contribution of localized calcium deposits to dissection after angioplasty. *Circulation*. 1992;86:64-70.
- Sheris SJ, Canos MR, Weissman NJ. Natural history of intravascular ultrasound-detected edge dissections from coronary stent placement. *Am Heart J*. 2000;139:59-63.
- Nissen SE, Yock P. Intravascular ultrasound. Novel pathophysiological insights and current clinical applications. *Circulation*. 2001;103:604-616.
- Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation*. 1995;91:1676-1688.
- Frey AW, Hodgson JMcB, Muller C, et al. Ultrasound guided strategy for provisional stenting with focal balloon combination catheter: Results from the randomized strategy for intracoronary ultrasound guided PTCA and stenting (SIPS) trial. *Circulation*. 2000;102:2497-2502.
- Russo RJ, Nicosia A, Teirstein PS, for the AVID investigators. Angiography versus intravascular ultrasound directed stent placement [abstract]. *J Am Coll Cardiol*. 1997;29:369A.
- DeJaegere P, Mudra H, Figulla H, et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 month clinical and angiographic results from the Multicenter Ultrasound stenting in Coronaries study (MUSIC study) *Eur Heart J*. 1998; 19:1214-1223.
- Schiele F, Meneveau N, Gilard M, et al. Intravascular ultrasound guided balloon angioplasty compared with stent: Immediate and 6 month results of the multicenter randomized Balloon Equivalent to Stent Study (BEST study). *Circulation*. 2003;107:545-571.
- Fitzgerald PJ, Oshima A, Hayase M, et al. Final results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. *Circulation*. 2000;102: 523-530.
- Mudra H, DiMario C, DeJaegere P, et al. Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce

- stent stenosis (OPTICUS study). *Circulation*. 2001;104:1343-1349.
23. Vavuranakis M, Stefanadis C, Toutouzas K, et al. Impaired compensatory coronary artery enlargement in atherosclerosis contributes to the development of coronary artery stenosis in diabetic patients. An in vivo intravascular ultrasound study. *Eur Heart J*. 1997;18:1090-1094.
24. De korte CL, Cespedes EI, van der Steen AF, et al. Intravascular ultrasound elastography: Assessment and imaging of elastic properties of diseased arteries and vulnerable plaque. *Eur J Ultrasound*. 1998;7:219-224.
25. Huang D, Swanson EA, Lin CP et al. Optical coherence tomography. *Science*. 1991;254:1178-1181.
26. Brezinski ME, Tearney GJ, Bouma BE, et al. Optical coherence tomography for optical biopsy. Properties and demonstration of vascular pathology. *Circulation*. 1996;93:1206-1213.
27. Tearney GJ, Brezinski ME, Southern JF, et al. Determination of the refractive index of highly scattering human tissue by optical coherence tomography. *Opt Lett*. 1999;24:531-533.
28. Jang IK, Bouma BE, Kang DH, et al. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: Comparison with intravascular ultrasound. *J Am Coll Cardiol*. 2002;39:604-609.
29. Casteneda-Zuniga WR, Formanek A, Tadavarthy M, et al. The mechanism of balloon angioplasty. *Radiology*. 1980;135:565-571.
30. Block PC, Myler RK, Stertz S, Fallon JT. Morphology after transluminal angioplasty in human beings. *N Engl J Med*. 1981;305:382-385.
31. Waller BR. Crackers, breakers, stretchers, drillers, scrapers, shavers, burners, welders and melters: The future treatment of atherosclerotic coronary artery disease? A clinical morphological assessment. *J Am Coll Cardiol*. 1989;13:969-987.
32. Tobis JM, Mallory JA, Gessert J, et al. Intravascular ultrasound cross-sectional arterial imaging before and after balloon angioplasty in vitro. *Circulation*. 1989;80:873-882.
33. Leimgruber PP, Roubin GS, Anderson HV, et al. Influence of intimal dissection on restenosis after successful coronary angioplasty. *Circulation*. 1985;72:530-535.
34. Agarwal R, Kaul U, Dev V, et al. The morphology of coronary arterial dissection occurring subsequent to angioplasty and its influence on acute complications. *Int J Cardiol*. 1991;31:59-64.
35. Essed CE, Van Den Brand M, Becker AE. Transluminal coronary angioplasty and early restenosis: Fibrocellular occlusion after wall laceration. *Br Heart J*. 1983;79:1374-1387.
36. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: A time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1,2,3 and 4 month. *Circulation*. 1988;77:361-371.
37. Vonesh MJ, Mockros LF, Davidson CJ. In vitro identification of angioplasty induced injury by use of vascular acoustic emissions. *Circulation*. 1997;95:1022-1029.
38. Vonesh MJ, Mockros LF, Davidson CJ, et al. Relationship of angioplasty-induced vascular trauma to released acoustic emission energy content [abstract]. *Circulation*. 1995;92(suppl):I-400.
39. Nobuyoshi M, Kimura T, Ohishi H, et al. Restenosis after percutaneous transluminal coronary angioplasty: Pathologic observations in 20 patients. *J Am Coll Cardiol*. 1991;17:433-439.
40. Verheye S, De Meyer GR, Van Langenhove G, et al. In vivo temperature heterogeneity of atherosclerotic plaques is determined by plaque composition. *Circulation*. 2002;105:1596-1601.
41. Stefanadis C, Diamantopoulos L, Vlachopoulos C, et al. Thermal heterogeneity within human atherosclerotic coronary arteries detected in vivo. A new method of detection by application of a special thermography catheter. *Circulation*. 1999;99:1965-1971.

THE AUTHOR



Suzanne A. Sorof, MD

Dr. Sorof is a second-year Cardiology Fellow at the MetroHealth Medical Center of Case Western Reserve University, Cleveland, OH. She graduated from Baylor College of Medicine, Houston, TX, in 1998. Following residency at the Baylor Affiliated Residency Program, she worked as a hospitalist at St. Luke's Hospital/Texas Heart Institute, Houston, for 2 years prior to beginning her cardiology training.