

# How can we explore atherosclerotic plaque composition and regression?

**Borja Ibanez, MD, Giovanni Cimmino, MD, Juan J. Badimon, PhD, FAHA**

Cardiovascular Biology Research Laboratory - Mount Sinai School of Medicine - New York, NY - USA

*It used to be axiomatic that atherosclerosis was continuous, cumulative, and irreversibly associated with aging. However, since 1989, when the first evidence of treatment-induced lesion regression was obtained in animals, it has become increasingly apparent that the ultimate challenge—reversal of established atherosclerosis—is feasible. Intervention studies depend on accurate measurement not only of plaque dynamics, but increasingly of plaque composition and metabolic activity. It is important to be able to identify vulnerable plaques. In addition to intravascular ultrasound and its derivatives, merged modalities have been developed to provide valuable molecular and metabolic imaging, eg, using fluorodeoxyglucose positron emission tomography or ultrasmall superparamagnetic iron oxide nanoparticles and multi-detector computed tomography.*

**Keywords:** atherosclerosis; atherothrombosis; atherosclerotic plaque; intravascular ultrasound; molecular imaging; plaque composition; plaque metabolism; plaque regression

**Address for correspondence:**

Juan J. Badimon, One Gustave L. Levy Place, Box 1030, New York, NY 10029, USA (e-mail: juan.badimon@mssm.edu)

*Dialogues Cardiovasc Med.* 2007;12:253-259

**A**therosclerosis is a diffuse pathological process characterized by the deposition of lipid and other blood-borne material within the arterial wall of almost all vascular territories. Ensuing wall thickening may significantly compromise the lumen, leading to distal ischemia. The disease progresses silently with focal clinical manifestations due essentially to thrombosis complicating lesion rupture. The term atherothrombosis combines the two major components (atherosclerosis + thrombosis) in cardiovascular pathogenesis.

Until recently, atherosclerosis was seen as continuous, cumulative, and irreversibly associated with aging. However, new evidence indicates that plaque progression is not inevitable.<sup>1</sup> Plaques can be slowed, stopped, or even reversed.<sup>2-6</sup> The path toward effective plaque-regressing intervention is paved by a better understanding of the mechanisms underlying atheroma dynamics.

## PLAQUE GENERATION

Endothelial dysfunction is the initial hallmark of atherothrombosis. Triggered by pathologic conditions (risk factors, mechanical injury, etc), it is characterized by functional disruption of the protective endothelium, unleashing not only the internalization of cholesterol, but also the recruitment of inflammatory

cells into the vessel wall, initiating the atherosclerotic process. Endothelial function switches from anti- to proatherogenic mode.

The biological incompetence of the endothelium has two consequences. At systemic level, it facilitates the activation, adhesion, and aggregation of platelets to the dysfunctional area; the activated platelets serve as inflammatory mediators, expressing various receptors interacting with leukocytes and the activated endothelium, perpetuating the pathologic process. At vascular level, endothelial dysfunction is characterized by the synthesis and exposure of adhesive proteins that facilitate the homing and internalization of circulating monocytes

### SELECTED ABBREVIATIONS AND ACRONYMS

<b>ApoA1</b>	apolipoprotein A1
<b>FDG</b>	fluorodeoxyglucose
<b>IMT</b>	intima-media thickening
<b>IVUS</b>	intravascular ultrasound
<b>MDCT</b>	multidetector computed tomography
<b>MRI</b>	magnetic resonance imaging
<b>RCT</b>	reverse cholesterol transport
<b>USPIO</b>	ultrasmall superparamagnetic iron oxide

**How can we explore atherosclerotic plaque composition and regression?** - Ibanez and others

into the subendothelial space, where they become macrophages. Enhanced penetration of circulating lipids also occurs into the intimal layer.<sup>7</sup> Cholesterol accumulation plays a central role in atherogenesis. Low-density lipoprotein (LDL) cholesterol binds to the subendothelial space, where it undergoes oxidation. Being highly toxic, oxidized cholesterol is phagocytosed by the vessel wall macrophages (a normal body defense mechanism).

The oxidized lipids then trigger a series of proinflammatory reactions via different mediators, perpetuating the activation and recruitment of monocytes-macrophages and inflammatory cells. Macrophages engulf the lipid material and become foam cells. Secondary changes may

occur in the underlying media and adventitia, particularly in advanced disease stages. Lesions progress to fibroatheroma by developing a cap of smooth muscle cells and collagen (*Figure 1*).

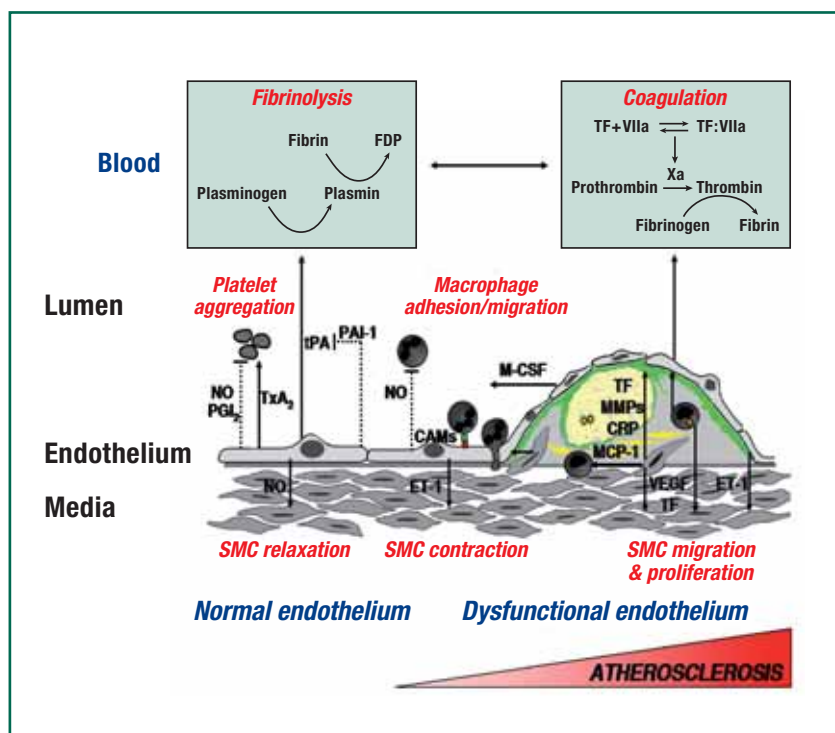
**FEASIBILITY OF PLAQUE REGRESSION**

The “discovery” that intravascular cholesterol deposition is not an irreversible process led to the concept of reverse cholesterol transport (RCT), in which cholesterol is transported back to the liver from the vessel wall (*Figure 2*).<sup>8,9</sup> Although it was once thought that high-density lipoprotein (HDL) cholesterol was the principal player in RCT, we now know that apolipoprotein A1 (apoA1) is responsible for the

metabolic fate of HDL cholesterol. ApoA1 is the major player in the process of removing cholesterol from the macrophages/foam cells in the vessel wall. Thus infusion of a cloned naturally occurring mutation of apoA1 (apoA1 Milano) induces vast plaque regression in under a week in animal models.<sup>10</sup> This suggests that atherosclerotic plaque regression is pharmaceutically feasible.

The ultimate challenge in treating atherothrombosis is to reverse established atherosclerosis. Our group provided the first preclinical evidence of feasibility in 1989 when we showed that HDL cholesterol infusion regressed preexisting lesions in a rabbit model of atherosclerosis.<sup>11</sup> Other LDL-lowering or HDL-elevating interventions corroborated this finding in different models,<sup>10,12,13</sup> while several HDL-elevating interventions have reduced atheroma volume in humans.<sup>14-16</sup>

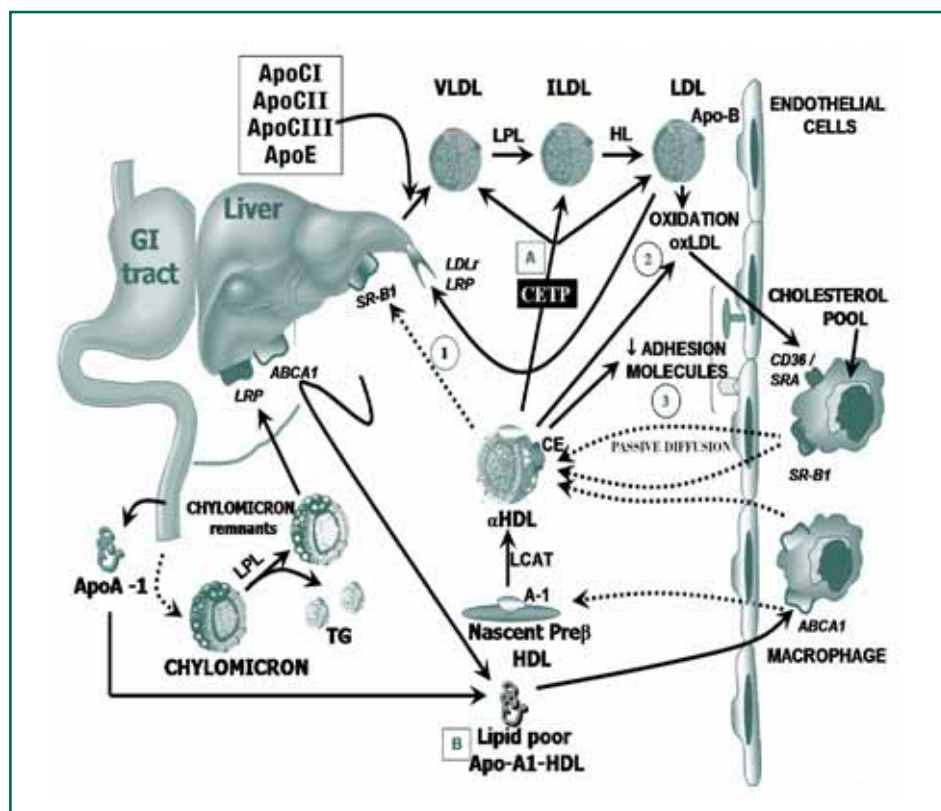
Aggressive LDL cholesterol lowering has two effects. On the one hand, it regresses atherosclerotic plaque: in low-risk patients, this requires protracted therapy (1 to 2 years) despite a demonstrable effect on circulating LDL cholesterol in just 6 weeks,<sup>3</sup> while in high-risk patients, regression is seen after only 6 months<sup>4</sup>; these results support the strategy of LDL cholesterol lowering and HDL cholesterol elevation with aggressive statin therapy.<sup>6</sup> On the other hand, separate studies using similar statin dose regimens have shown an association with a reduction in clinical events.<sup>17</sup> However, the evidence that plaque regression actually reduces clinical events remains indirect. Imaging parameters of plaque dynamics are for this reason coming increasingly to the fore as surrogate end points for new antiatherogenic therapies.<sup>18,19</sup>



**Figure 1.** Different mechanisms involved in atherosclerotic plaque generation.

**Abbreviations:** CAMs, cell-adhesion molecules; CRP, C-reactive protein; ET-1, endothelin-1; FDP, fibrin degradation products; M-CSF, macrophage colony stimulating factor; MCP-1, monocyte chemoattractant protein-1; MMPs, matrix metalloproteinases; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PGI<sub>2</sub>, prostacyclin; SMC, smooth muscle cell; TF, tissue factor; tPA, tissue plasminogen activator; TxA<sub>2</sub>, thromboxane A<sub>2</sub>; VEGF, vascular endothelial growth factor.

**Modified from reference 7:** Corti R, Badimon JJ. Biologic aspects of vulnerable plaque. *Curr Opin Cardiol.* 2002;17:616-625. Copyright © 2002, Lippincott Williams & Wilkins



**Figure 2.** Schematic view of cholesterol metabolism and reverse cholesterol transport. See text for further details.

**Abbreviations:** ABCA1, adenosine triphosphate binding cassette transporter A1; Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; GI, gastrointestinal; HDL, high-density lipoprotein; HL, hepatic lipase; ILDL, intermediate-sized low-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LDLr, low-density lipoprotein receptor; LPL, lipoprotein lipase; LRP, low-density lipoprotein receptor-related protein; oxLDL, oxidized low-density lipoprotein; SRA, scavenger receptor type A; SR-B1, scavenger receptor class B type 1; TG, triglycerides; VLDL, very-low-density lipoprotein.

**Modified from reference 8:** Choi BG, Vilahur G, Yadegar D, Viles-Gonzalez JF, Badimon JJ. The role of high-density lipoprotein cholesterol in the prevention and possible treatment of cardiovascular diseases. *Curr Mol Med.* 2006;6: 571-587. Copyright © 2006, Bentham Science Publishers.

## PLAQUE IMAGING

Traditionally, atherosclerotic lesions were described in terms of luminal stenosis. However, this neglects the real extent of atheroma, since plaque growth in the early stages follows an eccentric pattern, sparing the vessel lumen. We now also know that most cardiovascular events occur in areas of nonsignificant stenosis.<sup>20</sup> Thus, initial angiographic studies with lipid-lowering interventions associated the reduction in lipid levels with a reduction in clinical events, but with “surprisingly” little, if any, effect on the degree of stenosis.<sup>21</sup> This was often attributed to “unknown mechanisms.” Angiographic studies quantified changes in luminal size, but could not pick up changes in plaque volume. Today, however, imaging modalities are available for measuring the impact of interventions on plaque size.

Imaging techniques that evaluate the entire vessel wall (and not simply the lumen, as in contrast angiography) are mandatory for accurately monitoring the evolution of atherosclerotic lesions. More specifically, if an imaging modality can profile the composition and degree of inflammation of a plaque, it will identify those at high risk. Visualization of lesion composition has thus become a focus of intensive research, displacing simple measurement of the stenosis itself.

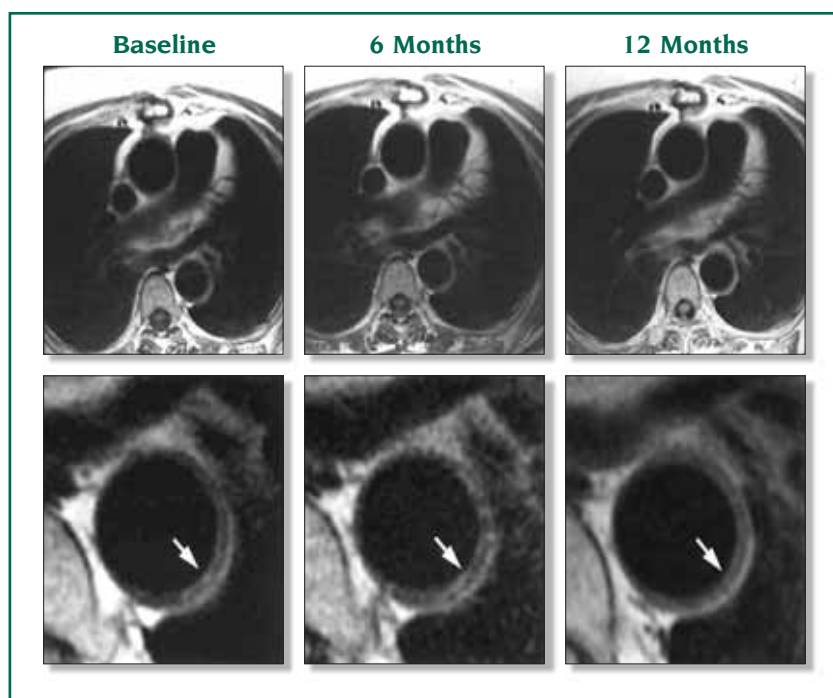
### Visualizing plaque progression and regression

Tracking change in atheroma volume not only facilitates risk stratification, but tests the efficacy of antiatherosclerotic intervention. Intravascular ultrasound (IVUS) is an invasive imaging tool that accurately measures not only luminal size, but also the thickness (and

even composition) of the entire vessel wall. It may reveal plaques undetected on contrast coronary angiography, including signs of recent disruption.<sup>22</sup> Serial IVUS in a pre-specified arterial segment has been used to monitor response to various therapies.<sup>6,16,18</sup>

Surface ultrasound measurement of carotid and aortic wall thickness is an accurate noninvasive technique that permits correlation with clinical events. Intima-media thickening (IMT) is a reliable parameter in the serial measurement of carotid plaque evolution, and is used as a marker of diffuse atherosclerotic vascular disease.<sup>23</sup> Changes in IMT have been used to monitor the response of atheroma volume to antiatherosclerotic therapy.<sup>19,24</sup>

Magnetic resonance imaging (MRI) can portray detailed arterial anatomy in almost all territories, although



**Figure 3.** Magnetic resonance cross-sectional images at the same level of the aorta in a patient treated with statins. Note that after 6 months of treatment the plaque volume is quite similar, revealing a halting in plaque progression. At 18 months there is plaque volume shrinkage.

**Reproduced from reference 3:** Corti R, Fuster V, Fayad ZA, et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging. *Circulation*. 2002;106:2884-2887. Copyright © 2002, Lippincott Williams & Wilkins.

it continues to be challenged by the coronary tree. The combination of multicontrast sequences has been proposed as a technique for visualizing plaque anatomy and composition, based on differences in the biophysical and biochemical properties of the plaque components.<sup>25</sup> As a noninvasive technique with high spatial resolution, it has been used to monitor plaque regression after lipid-lowering treatment (Figure 3).<sup>2-4</sup> The technique can also be merged with positron emission tomography (PET) to measure inflammation within the vessel wall.<sup>26</sup>

Multidetector computed tomography (MDCT) has recently attracted much attention for measuring luminal stenosis, coronary calcium, and even noncalcified plaque volume.<sup>27-29</sup> However, only its ability to monitor changes in atheroma vol-

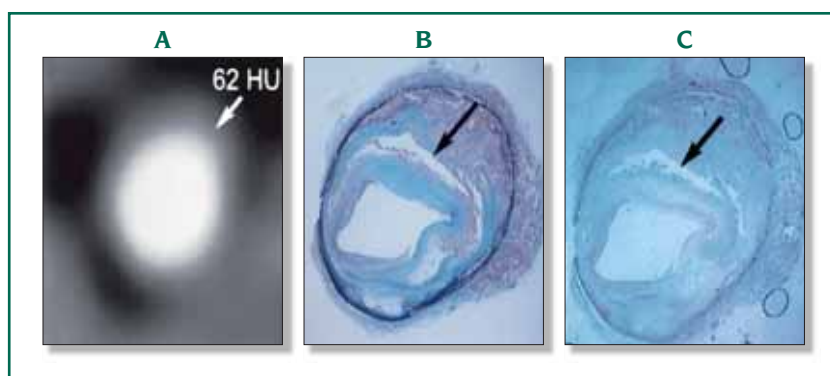
ume has been fully evaluated so far. MDCT is being investigated for its ability to determine plaque composition in terms of the differential densities (measured in Hounsfield

units) of plaque and vessel wall (Figure 4).<sup>30</sup> It can also be merged with PET for metabolic studies of vascular lesions.<sup>31</sup>

### Future trends: molecular imaging

Despite sharing a hypothetically identical origin, not all atherosclerotic lesions are equal. For example, those more prone to rupture—"vulnerable" plaques—are generally eccentric, mildly stenotic, macrophage-rich, and covered by a thin fibrotic cap separating their necrotic lipid core from the bloodstream. It is widely accepted that plaque composition, rather than volume or luminal stenosis, is the major determinant of atherothrombotic events. Hence the intense research interest in the in vivo techniques available for characterizing plaque composition:

- IVUS, an invasive tool that differentiates calcium-containing plaque from soft lipid-rich plaques and fibrotic lesions, has long been considered the gold standard for studying not only vessel wall anatomy, but also lesion composition.<sup>32</sup>
- Palpography, an IVUS-derived technique, provides information addi-



**Figure 4.** Plaque characterization images: **A**, multidetector computed tomography, showing 62 Hounsfield units (HU) attenuation of cross-sectional image; **B**, combined Masson's elastin-stained histopathologic section; **C**,  $\alpha$ -actin stained histopathologic section. Arrows: lipid.

**Reproduced from reference 30:** Viles-Gonzalez JF, Poon M, Sanz J, et al. In vivo 16-slice, multi-detector-row computed tomography for the assessment of experimental atherosclerosis: comparison with magnetic resonance imaging and histo-pathology. *Circulation*. 2004;110: 1467-1472. Copyright © 2004, Lippincott Williams & Wilkins.



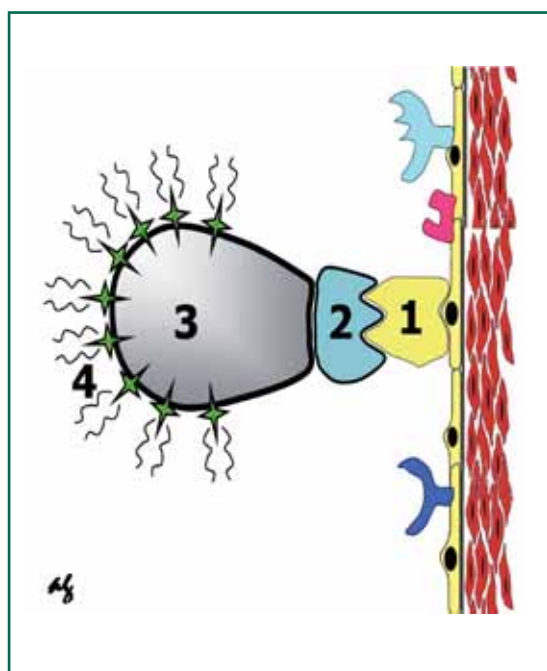
tional to conventional IVUS; by differentiating between deformable and nondeformable tissue, it can detect vulnerable plaques with a positive predictive value.

- Thermography uses temperature heterogeneity as a marker of intra-plaque metabolism, suggesting an association between temperature elevation and vulnerable plaque.
- Optical coherence tomography is a new, catheter-based, high-resolution technology that produces images from backscattered echoes similar to IVUS, but using a high-bandwidth infrared light source instead of an ultrasound-emitting crystal. The resulting high resolution (P15 mm vs P150 mm with IVUS) provides optimal plaque identification.
- Virtual histology is the spectral analysis of the radiofrequency ultrasound backscatter signals.<sup>33</sup> Virtual histology IVUS has P90% in vitro accuracy in identifying different types of atherosclerotic lesions, making it a very promising tool for plaque characterization.

Noninvasive modalities are headed by MRI and MDCT, with their excellent ability to identify lipid-rich tissue. They have been used to characterize potentially vulnerable plaques, primarily in fixed structures such as the carotid arteries. Although they have been able to discriminate between different plaque compositions in preclinical studies,<sup>30,34</sup> their clinical utility remains unproven. Their noninvasive nature and high spatial resolution have led them to be merged with novel techniques for visualizing plaque anatomy, activity, and composition. The result—molecular imaging—can be considered an in vivo equivalent of immunohistochemistry. The aim is to identify different molecules and/or cells using radiolabeled markers that enhance the signal wherever they are deposited. The contrast agent

should identify the target not only with high specificity, but also with a signal intense enough to be detected and differentiated from unlabeled zones (Figure 5).<sup>35,36</sup> Best results are obtained with nanoparticles combining high binding affinity for the target zone with the ability to transport sufficient paramagnetic contrast agent. Those most widely employed are liposomes and fluorocarbon-based lipid emulsions. Preclinical models have shown that ultrasmall superparamagnetic iron oxide (USPIO)

promising for the noninvasive evaluation of plaque components. Imaging derived from the detection of positron emission by certain radionuclides such as <sup>11</sup>C and <sup>18</sup>F gives PET great potential for visualizing atherosclerotic plaques. Deoxyglucose “competes” with glucose as an energy substrate for metabolically active cells, accumulating incrementally with the level of metabolic activity. Combination with <sup>18</sup>F to form fluorodeoxyglucose (FDG) permits “visualization” of cellular metabolic activity.<sup>31,40</sup>



**Figure 5.** The principle behind molecular imaging: the molecule of interest (receptor, integrin, adhesion molecule (1) is recognized by a ligand (2), usually a monoclonal antibody, that has previously been bound in vitro to signal-transmitting substances (4) via a vehicle (3) that binds specifically to both.

**Reproduced from reference 36:** Ibanez B, Pinero A, Orejas M, Badimon JJ. Novel imaging techniques for quantifying overall atherosclerotic burden. *Rev Esp Cardiol.* 2007;60:299-309. Copyright © 2007, Ediciones Doyma, SL.

nanoparticles are “attracted” by the macrophages predominating in “vulnerable” plaques.<sup>37</sup> The same observation applies in human carotid arteries where USPIO accumulates in the macrophage-rich zones of unstable plaques.<sup>38</sup> Most recently, a 64-slice CT scanner was able to detect macrophages present in animal atherosclerotic plaques after the intravenous injection of an iodinated contrast agent that specifically binds these cells.<sup>39</sup> Although such results are only preliminary, these merged modalities are highly

In confirmation of several animal studies, recent work with FDG-PET in humans suggests that “activated macrophages” are responsible for the observed FDG uptake. Moreover, a combination of PET and CT in patients with transient ischemic attacks has shown that the culprit plaques exhibited more marked FDG uptake than contralateral plaques. Should this be confirmed, the technique could transform high-risk plaque detection, as well as the monitoring of treatment response (to lipid-lowering drugs, etc).

## CONCLUSION

Atherosclerosis is a systemic disease with focal manifestations. Of the various modalities available for quantifying its burden in the different vascular territories, only IVUS, IMT, and aortic and carotid MRI are also capable of accurately monitoring plaque progression and regression. Assessment of plaque composition is a subject of intensive research. Invasive IVUS techniques can discriminate between different components of atherosclerotic lesions, but their clinical impact remains undetermined. Most effort is centered on noninvasive modalities, in particular the fusing of data sets acquired by different modalities, such as MRI-CT plus PET or targeted contrast media, thus combining high spatial resolution with a snapshot of physiological plaque activity and providing important clues to plaque composition. A proven high-performance imaging modality would not only be critically important in the direct assessment of disease severity, it would also be an invaluable tool in proof-of-concept studies to demonstrate the efficacy and/or mechanism of action of new antiatherosclerotic interventions prior to launching large, long and expensive phase 3 trials.

## REFERENCES

**1. Ibanez B, Vilahur G, Badimon J.**

Plaque progression and regression in atherothrombosis.

*J Thromb Haemost.* 2007;5(suppl 1):292-299.

**2. Corti R, Fayad ZA, Fuster V, et al.**

Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging.

*Circulation.* 2001;104:249-252.

**3. Corti R, Fuster V, Fayad ZA, et al.**

Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging.

*Circulation.* 2002;106:2884-2887.

**4. Lima JA, Desai MY, Steen H, Warren WP, Gautam S, Lai S.**

Statin-induced cholesterol lowering and plaque regression after 6 months of magnetic resonance imaging-monitored therapy.

*Circulation.* 2004;110:2336-2341.

**5. Nissen SE, Tuzcu EM, Schoenhagen P, et al.**

Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial.

*JAMA.* 2004;291:1071-1080.

**6. Nissen SE, Nicholls SJ, Sipahi I, et al.**

Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial.

*JAMA.* 2006;295:1556-1565.

**7. Corti R, Badimon JJ.**

Biologic aspects of vulnerable plaque.

*Curr Opin Cardiol.* 2002;17:616-625.

**8. Choi BG, Vilahur G, Yadegar D, Viles-Gonzalez JF, Badimon JJ.**

The role of high-density lipoprotein cholesterol in the prevention and possible treatment of cardiovascular diseases.

*Curr Mol Med.* 2006;6:571-587.

**9. Cuchel M, Rader DJ.**

Macrophage reverse cholesterol transport: key to the regression of atherosclerosis?

*Circulation.* 2006;113:2548-2555.

**10. Ibanez B, Vilahur G, Pinero A, et al.**

Rapid change in plaque size, composition and molecular footprint following recombinant apoA-I Milano (ETC-216) administration. Magnetic resonance imaging study in an experimental model of atherosclerosis.

*J Am Coll Cardiol.* In press.

**11. Badimon JJ, Badimon L, Fuster V.**

Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit.

*J Clin Invest.* 1990;85:1234-1241.

**12. Shah PK, Kaul S, Nilsson J, Cercek B.**

Exploiting the vascular protective effects of high-density lipoprotein and its apolipoproteins: an idea whose time for testing is coming, part I.

*Circulation.* 2001;104:2376-2383.

**13. Corti R, Osende J, Hutter R, et al.**

Fenofibrate induces plaque regression in hypercholesterolemic atherosclerotic rabbits: in vivo demonstration by high-resolution MRI.

*Atherosclerosis.* 2007;190:106-113.

**14. Nissen SE, Tsunoda T, Tuzcu EM, et al.**

Effect of recombinant apoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial.

*JAMA.* 2003;290:2292-2300.

**15. Taylor AJ, Lee HJ, Sullenberger LE.**

The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3.

*Curr Med Res Opin.* 2006;22:2243-2250.

**16. Tardif JC, Gregoire J, L'Allier PL, et al.**

Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: A randomized controlled trial.

*JAMA.* 2007;297:1675-1682.

**17. Cannon CP, Braunwald E, McCabe CH, et al.**

Intensive versus moderate lipid lowering with statins after acute coronary syndromes.

*N Engl J Med.* 2004;350:1495-1504.



**18. Nissen SE, Tardif JC, Nicholls SJ, et al.**

*Effect of torcetrapib on the progression of coronary atherosclerosis.*

*N Engl J Med.* 2007;356:1304-1316.

**19. Kastelein JJ, van Leuven SI, Burgess L, et al.**

*Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia.*

*N Engl J Med.* 2007;356:1620-1630.

**20. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ.**

*Compensatory enlargement of human atherosclerotic coronary arteries.*

*N Engl J Med.* 1987;316:1371-1375.

**21. Jukema JW, Bruschke AV, van Boven AJ, et al.**

*Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS).*

*Circulation.* 1995;91:2528-2540.

**22. Ibanez B, Navarro F, Cordoba M, Marcos-Alberca P, Farre J.**

*Tako-tsubo transient left ventricular apical ballooning: is intravascular ultrasound the key to resolve the enigma?*

*Heart.* 2005;91:102-104.

**23. de Groot E, Hovingh GK, Wiegman A, et al.**

*Measurement of arterial wall thickness as a surrogate marker for atherosclerosis.*

*Circulation.* 2004;109(23 suppl 1):III33-III38.

**24. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA.**

*Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins.*

*Circulation.* 2004;110:3512-3517.

**25. Fayad ZA, Fuster V.**

*Clinical imaging of the high-risk or vulnerable atherosclerotic plaque.*

*Circ Res.* 2001;89:305-316.

**26. Davies JR, Rudd JH, Fryer TD, et al.**

*Identification of culprit lesions after transient ischemic attack by combined <sup>18</sup>F fluorodeoxyglucose positron-emission tomography and high-resolution magnetic resonance imaging.*

*Stroke.* 2005;36:2642-2647.

**27. Achenbach S, Giesler T, Ropers D, et al.**

*Detection of coronary artery stenoses by contrast-enhanced, retrospectively electrocardiographically-gated, multislice spiral computed tomography.*

*Circulation.* 2001;103:2535-2538.

**28. Achenbach S, Moselewski F, Ropers D, et al.**

*Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound.*

*Circulation.* 2004;109:14-17.

**29. Leber AW, Becker A, Knez A, et al.**

*Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound.*

*J Am Coll Cardiol.* 2006;47:672-677.

**30. Viles-Gonzalez JF, Poon M, Sanz J, et al.**

*In vivo 16-slice, multidetector-row computed tomography for the assessment of experimental atherosclerosis: comparison with magnetic resonance imaging and histopathology.*

*Circulation.* 2004;110:1467-1472.

**31. Rudd JH, Warburton EA, Fryer TD, et al.**

*Imaging atherosclerotic plaque inflammation with [<sup>18</sup>F]-fluorodeoxyglucose positron emission tomography.*

*Circulation.* 2002;105:2708-2711.

**32. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG.**

*Coronary plaque classification with intravascular ultrasound radiofrequency data analysis.*

*Circulation.* 2002;106:2200-2206.

**33. Moore MP, Spencer T, Salter DM, et al.**

*Characterisation of coronary atherosclerotic morphology by spectral analysis of radio-frequency signal: in vitro intravascular ultrasound study with histological and radiological validation.*

*Heart.* 1998;79:459-467.

**34. Corti R, Osende JI, Fallon JT, et al.**

*The selective peroxisomal proliferator-activated receptor-gamma agonist has an additive effect on plaque regression in combination with simvastatin in experimental atherosclerosis: in vivo study by high-resolution magnetic resonance imaging.*

*J Am Coll Cardiol.* 2004;43:464-473.

**35. Choudhury RP, Fuster V, Fayad ZA.**

*Molecular, cellular and functional imaging of atherothrombosis.*

*Nat Rev Drug Discov.* 2004;3:913-925.

**36. Ibanez B, Pinero A, Orejas M, Badimon JJ.**

*Novel imaging techniques for quantifying overall atherosclerotic burden.*

*Rev Esp Cardiol.* 2007;60:299-309.

**37. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT.**

*Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture.*

*Circulation.* 1994;90:775-778.

**38. Kooi ME, Cappendijk VC, Cleutjens KB, et al.**

*Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging.*

*Circulation.* 2003;107:2453-2458.

**39. Hyafil F, Cornily JC, Feig JE, et al.**

*Noninvasive detection of macrophages using a nanoparticulate contrast agent for computed tomography.*

*Nat Med.* 2007;13:636-641.

**40. Rudd JH, Myers KS, Bansilal S, et al.**

*<sup>18</sup>Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials.*

*J Am Coll Cardiol.* 2007;50:892-896.