Overview

• How it worked for me
• Some philosophy
• Some images
Anatomy of a career (1)

• Moved from Montpellier France to US 1986
• BSEE – Bradley University 1989
  • Electrical Engineering
  • Math, Pre-Med, Economics
  • Dabbled in Biomedical research – Non-destructive testing of cartilage material properties using RadioFrequencies
• MS - Johns Hopkins 1991
  • Bioengineering/Med. School courses
  • Mentors (Elias Zerhouni, Bill Brody, Elliot McVeigh, Nitish Thakor)
  • Magnetic Stimulation - 1st hands-on experience with animal research
  • Cardiovascular Imaging (MRI) - 1st experience
  • Biomedical research - bug
Anatomy of a career (2)

• PhD – Penn 1996
  • MRI
  • Cardiovascular MRI (A-Z) - emerging field
    • Leon Axel
    • Nat Reicheck
    • Joao Lima
    • Victor Ferrari
    • Chris Kramer
  • Animal research
  • Human research
  • Imaging physics, instrumentation, image processing
  • Helped advisor renew successfully his NIH R01 grant
    • Painful, but excellent experience
• Met Jean-Francois Toussaint (fellow with Valentin Fuster at MGH) at an MRI meeting in 1994
• Most turning point lecture - SCMR 1995 Valentin Fuster on Atherosclerotic Plaque Classification
Anatomy of a career (3)

- Junior faculty - Dept of Radiology 1996-1997
  - Girlfriend (future wife) moved to NYU for MBA
  - Work on plaque imaging
    - Human in vivo carotids
    - Rabbits (Dan Rader) - few animals
  - Took the train from Philly to New York almost every w/e for six months
- Thru a faculty from Penn who left to Sinai met Valentin Fuster again
  - Started helping on imaging apoE-/- mice imaging at Penn
  - Visited Sinai few times to help with MRI
Anatomy of a career (3)

- Assistant Professor@ Sinai - 1997
- Traveled with the mice on a train from Sinai to Penn for imaging
  - Took them home for an evening stay in our bathroom loft in the West Village
  - Circ 1998 cover paper on mice imaging
- 2000 Installed our mice magnet
- 3 NIH grants on plaque imaging by Sinai team
- 2002 1st NIH grant R01, renewed 2005 - human imaging (MR, PET)
- 2002 Associate Professor
- 2004 2nd NIH grant R01 - molecular imaging (MR, CT, optical, PET)
- 2006 Professor
Anatomy of a career (4)

- Important Factors
  - Great support from mentor(s)
  - Excellent resources
  - Radiology/Cardiology cooperation
  - Lab talent recruitment and retention
  - Translational research (animal/human)
  - Good projects with strong collaborators
    - clinical
    - basic
Anatomy of a career (5)

• Other important factors:
  • The right fit
  • Good support
  • Opportunity to build
  • My program – credit or blame (independence)
  • Moved research program towards different directions (anatomy to molecular)
Tips and tricks (1)

Do: (Common sense stuff)
1. Choose the right mentor(s)
2. Choose the right research – you will be good at what you love
3. Novelty is important – where can you make an impact
4. Choose a technique – novel is good
5. Choose a disease process – preferably high impact disease
6. Focus – not always easy at this phase in life
7. Persistence
8. Determination
9. Pick good collaborators
10. Be proactive and take charge of your own career
11. Balance your lab budget and research portfolio
12. Learn fundraising
Tips and tricks (2)

Don’t: (Common sense stuff)
1. 53rd me too study
2. Old techniques – so what factor.
3. Too many projects/techniques at once
4. Choose the most difficult project
   • easy - quick success (papers, presentations, etc.)
   • medium - get attention
   • hard - nature medicine, NEJM
5. Give up and move on quickly
6. Collaborate with a “me” person
Don’t:

• Case reports
• Reviews (maybe 1 towards end of training)
• 8th author on 11 author manuscript
• Try to master several imaging techniques
• Get overwhelmed with clinical or administrative work
• Depend on others to move you ahead
Important steps

• Pick a mentor(s)
• Write protocols – IRB, animal
• Start planning a study from A to Z, better than jumping on in the middle
• Write a grant – good practice
  • AHA fellowships, ACC-Merck, etc.
  • Lead up to NIH K08/K24, ACC career grant
  • Transitional grants (K099 NIH, etc.)
First job

- Negotiate well
  - 0.3 days/week for research won’t work
  - research space
  - start-up funds
- Limit administrative/committee duties
- Just say NO when possible
- Find like-minded collaborators
  - Research is multi-disciplinary
  - NIH roadmap
- Look for hot areas – molecular imaging, vascular biology, stem cells
Conclusions

• Enjoy your work
• Enjoy your family and friends
• Be well-rounded – music, athletics, art, whatever you like to do outside of work
• Always do what you like inherently, not what is expected
Noninvasive In Vivo High-Resolution Magnetic Resonance Imaging of Atherosclerotic Lesions in Genetically Engineered Mice

Zahi A. Fayad, PhD; John T. Fallon, MD, PhD; Meir Shinnar, PhD, MD; Suzanne Wehrli, PhD; Hayes M. Dansky, MD; Michael Poon, MD; Juan J. Badimon, PhD; Sherri A. Charlton, MS; Edward A. Fisher, MD, PhD; Jan L. Breslow, MD; Valentin Fuster, MD, PhD

**Background**—The pathogenesis of atherosclerosis is currently being investigated in genetically engineered small animals. Methods to follow the time course of the developing pathology and/or the responses to therapy in vivo are limited.

**Methods and Results**—To address this problem, we developed a noninvasive MR microscopy technique to study in vivo atherosclerotic lesions (without a priori knowledge of the lesion location or lesion type) in live apolipoprotein E–knockout (apoE-KO) mice. The spatial resolution was 0.0012 to 0.005 mm. The lumen and wall of the abdominal aorta and iliac arteries were identified on all images in apoE-KO (n=58) and wild-type (n=58) mice on chow diet. Images obtained with MR were compared with corresponding cross-sectional histopathology (n=58). MR accurately determined wall area in comparison to histopathology (slope=1.0, r=0.86). In addition, atherosclerotic lesions were characterized in terms of lesion shape and type. Lesion type was graded by MR according to morphological appearance/extent and by histopathology according to the AHA classification. There was excellent agreement between MR and histopathology in grading of lesion shape and type (slope=0.97, r=0.91 for lesion shape; slope=0.94, r=0.90 for lesion type).

**Conclusions**—The combination of high-resolution MR microscopy and genetically engineered animal models is a powerful tool to investigate serially and noninvasively the progression and regression of atherosclerotic lesions in an intact animal model and should greatly enhance basic studies of atherosclerotic disease. (*Circulation.* 1998;98:1541-1547.)
In Vivo Magnetic Resonance Evaluation of Atherosclerotic Plaques in the Human Thoracic Aorta
A Comparison With Transesophageal Echocardiography

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Background—The structure and composition of aortic atherosclerotic plaques are associated with the risk of future cardiovascular events. Magnetic resonance (MR) imaging may allow accurate visualization and characterization of aortic plaques.

Methods and Results—We developed a noninvasive MR method, free of motion and blood flow artifacts, for submillimeter imaging of the thoracic aortic wall. MR imaging was performed on a clinical MR system in 10 patients with aortic plaques identified by transesophageal echocardiography (TEE). Plaque composition, extent, and size were assessed from T1-, proton density-, and T2- weighted images. Comparison of 25 matched MR and TEE cross-sectional aortic plaque images showed a strong correlation for plaque composition ($\chi^2=43.5, P<0.0001; 80\%$ overall agreement; $n=25$) and mean maximum plaque thickness ($r=0.88, n=25; 4.56\pm0.21$ mm by MR and $4.62\pm0.31$ mm by TEE). Overall aortic plaque extent as assessed by TEE and MR was also statistically significant ($\chi^2=61.77, P<0.0001; 80\%$ overall agreement; $n=30$ regions).

Conclusions—This study demonstrates that noninvasive MR evaluation of the aorta compares well with TEE imaging for the assessment of atherosclerotic plaque thickness, extent, and composition. This MR method may prove useful for the in vivo study of aortic atherosclerosis. (Circulation. 2000;101:2503-2509.)

Key Words: atherosclerosis ■ magnetic resonance imaging ■ aorta ■ echocardiography ■ plaque
Noninvasive In Vivo Human Coronary Artery Lumen and Wall Imaging Using Black-Blood Magnetic Resonance Imaging

Zahi A. Fayad, PhD; Valentin Fuster, MD, PhD; John T. Fallon, MD, PhD; Timothy Jayasundera, MD; Stephen G. Worthley, MD; Gerard Helft, MD; J. Gilberto Aguinaldo, MD; Juan J. Badimon, PhD; Samin K. Sharma, MD

**Background**—High-resolution MRI has the potential to noninvasively image the human coronary artery wall and define the degree and nature of coronary artery disease. Coronary artery imaging by MR has been limited by artifacts related to blood flow and motion and by low spatial resolution.

**Methods and Results**—We used a noninvasive black-blood (BB) MRI (BB-MR) method, free of motion and blood-flow artifacts, for high-resolution (down to 0.46 mm in-plane resolution and 3-mm slice thickness) imaging of the coronary artery lumen and wall. In vivo BB-MR of both normal and atherosclerotic human coronary arteries was performed in 13 subjects: 8 normal subjects and 5 patients with coronary artery disease. The average coronary wall thickness for each cross-sectional image was 0.75±0.17 mm (range, 0.55 to 1.0 mm) in the normal subjects. MR images of coronary arteries in patients with ≥40% stenosis as assessed by x-ray angiography showed localized wall thickness of 4.38±0.71 mm (range, 3.30 to 5.73 mm). The difference in maximum wall thickness between the normal subjects and patients was statistically significant (P<0.0001).

**Conclusions**—In vivo high-spatial-resolution BB-MR provides a unique new method to noninvasively image and assess the morphological features of human coronary arteries. This may allow the identification of atherosclerotic disease before it is symptomatic. Further studies are necessary to identify the different plaque components and to assess lesions in asymptomatic patients and their outcomes. (*Circulation. 2000;102:506-510.*)
Effects of Lipid-Lowering by Simvastatin on Human Atherosclerotic Lesions
A Longitudinal Study by High-Resolution, Noninvasive Magnetic Resonance Imaging

Roberto Corti, MD; Zahi A. Fayad, PhD; Valentin Fuster, MD, PhD; Stephen G. Worthley, MD; Gerard Helft, MD; James Chesebro, MD; Michele Mercuri, MD; Juan J. Badimon, PhD

Background—This study was designed to investigate the effects of lipid-lowering by simvastatin on human atherosclerotic lesions.

Methods and Results—Eighteen asymptomatic hypercholesterolemic patients with documented aortic and/or carotid atherosclerotic plaques were selected for the study. A total of 35 aortic and 25 carotid artery plaques were detected. Serial black-blood MRI of the aorta and carotid artery of the patients was performed at baseline and 6 and 12 months after lipid-lowering therapy with simvastatin. The effects of the treatment on atherosclerotic lesions were measured as changes in lumen area, vessel wall thickness, and vessel wall area, a surrogate of atherosclerotic burden. Simvastatin induced a significant (P<0.01) reduction in total and LDL cholesterol levels at 6 weeks that was maintained thereafter. At 6 months, no changes in lumen area, vessel wall thickness, or vessel wall area were observed. However, at 12 months, significant reductions in vessel wall thickness and vessel wall area, without changes in lumen area, were observed in both aortic and carotid arteries (P<0.001).

Conclusions—This in vivo human study demonstrates that effective and maintained lipid-lowering therapy by simvastatin is associated with a significant regression of atherosclerotic lesions. Our observation suggests that statins induce vascular remodeling, as manifested by reduced atherosclerotic burden without changes in the lumen. (Circulation. 2001; 104:249-252.)
Computed Tomography and Magnetic Resonance Imaging for Noninvasive Coronary Angiography and Plaque Imaging
Current and Potential Future Concepts

Zahi A. Fayad, PhD; Valentin Fuster, MD, PhD; Konstantin Nikolaou, MD; Christoph Becker, MD

Atherothrombosis is a systemic disease of the vessel wall that causes distinct clinical manifestations, depending on the affected circulatory bed and the characteristics of the individual lesions. These lesions may be quite heterogeneous. Thus, the clinical manifestations of atherothrombosis of the coronary arteries, of the arteries supplying the central nervous system, of the aorta, and of the peripheral circulation can be significantly different.

Disruption-prone plaques in the coronary arteries, the so-called "vulnerable plaques," tend to have a thin fibrous cap (cap thickness ~65 to 190 μm) and a large lipid core (American Heart Association [AHA] plaque type IV-Va). Acute coronary syndromes often result from disruption of a modestly stenotic vulnerable plaque, not visible by x-ray angiography, which results in a thrombotic complication (AHA plaque type VI). During its evolution, a type Va plaque may also become fibrotic (AHA plaque type Vc) or calcified (AHA plaque type Vb). In contrast, coronary artery vulnerable plaques characterized by high lipid content and a thin fibrous cap, high-risk plaques of the coronary arteries tend to be fibrotic and severely stenotic.

Imaging of Atherothrombotic Disease

Because there is striking heterogeneity in the composition of human atherothrombotic plaques, even within the same individual, reliable noninvasive imaging tools that can detect early atherothrombotic disease in the various regions and characterize the composition of the plaques are clinically desirable. Such imaging tools would improve our understanding of the pathophysiological mechanisms underlying atherothrombotic processes and allow us to better risk-stratify the disease. Additionally, such tools may permit optimal tailoring of treatment and allow direct monitoring of the vascular response.

Currently, a number of imaging modalities are employed to study atherosclerosis; most identify luminal diameter or stenosis, wall thickness, and plaque volume. Two noninvasive imaging modalities, computed tomography and MRI, have been introduced to the study of atherothrombotic disease.

Computed Tomography

Methods

The cardiovascular system can be imaged with the use of two different computer tomography (CT) modalities: one employs nonmechanical movement of the x-ray source (ie, electron beam CT) and the other involves the motion of the x-ray source and table, combined with multiple detectors to acquire the data in spiral or helical fashion (ie, multidetector-row CT).

Electron-Beam CT

The necessity for very short image acquisition times to virtually freeze cardiac motion urged the development of a cardiac-dedicated CT system in 1982, on the basis of a nonmechanical movement of the x-ray source and fixed detector arrays. The electron-beam CT (EBCT) uses a single, curved anode with 4 tungsten targets underneath the patient, and a focused electron beam that is rapidly swept across these targets to produce an x-ray fan beam detected by 2 detector rows above the patient (Table 1).

Multidetector-Row CT

Mechanical multidetector-row CT (MDCT) systems were introduced in 1998, and allow for scanning with one x-ray tube and 4 detector rows in a single gantry rotating twice per second around the patient. Continuous gantry rotation and table movement causes the projection data to be obtained along a spiral or helical path (Table 1).

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The online figure is available in an online-only Data Supplement at http://www.circulationaha.org

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

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Sudden fibrous cap disruption of ‘high-risk’ atherosclerotic plaques can trigger the formation of an occlusive thrombus in coronary arteries, causing acute coronary syndromes. High-risk atherosclerotic plaques are characterized by their specific cellular and biological content (in particular, a high density of macrophages), rather than by their impact on the vessel lumen. Early identification of high-risk plaques may be useful for preventing ischemic events. One major hurdle in detecting high-risk atherosclerotic plaques in coronary arteries is the lack of an imaging modality that allows for the identification of atherosclerotic plaque composition with high spatial and temporal resolutions. Here we show that macrophages in atherosclerotic plaques of rabbits can be detected with a clinical X-ray computed tomography (CT) scanner after the intravenous injection of a contrast agent formed of iodinated nanoparticles dispersed with surfactant. This contrast agent may become an important adjunct to the clinical evaluation of coronary arteries with CT.

Macrophages are an essential component of the immune system but are also involved in several pathological processes, including atherosclerosis and autoimmune diseases. Acute coronary syndromes (unstable angina, acute myocardial infarction and sudden death) are caused, in about two-thirds of patients, by the fibrous cap disruption of so-called ‘high-risk’ or ‘vulnerable’ atherosclerotic plaques. The sudden exposure of the underlying atheromatous content of plaques to blood triggers the formation of a thrombus, which can occlude the coronary artery, leading to myocardial ischemia and necrosis. These high-risk atherosclerotic plaques are characterized by their specific cellular and biological composition rather than by their impact on the vessel lumen. Macrophages play a key role in acute plaque destabilization and thrombus formation. They secrete proteases that digest the extracellular matrix and weaken the protective fibrous cap covering the atheromatous core, and they release in atherosclerotic plaques large amounts of tissue factor that accelerate thrombus formation following plaque rupture. Moreover, macrophage density measured by immunohistochemistry was found to be higher in atherosclerotic plaques obtained from patients with recent acute coronary syndromes as compared to plaques from patients with stable cardiovascular disease. Therefore, atherosclerotic plaques with high macrophage densities could be at a higher risk of rupture and subsequent arterial thrombosis.

On the basis of the assumption that early identification of high-risk atherosclerotic plaques could preclude ischemic events, both invasive and noninvasive imaging techniques aimed at detecting the composition of atherosclerotic plaques are growing at a rapid pace. One of the most promising techniques for noninvasive imaging of coronary arteries is contrast-enhanced multidetector computed tomography (CT). Owing to the faster rotation times and increasing number of detectors, the spatial and temporal resolutions of CT scanners are continuously improving. An intravenous bolus of small iodinated molecules, effective in absorbing X-rays, is injected simultaneously to the acquisition of CT coronary angiography. Hence the X-ray absorption of the vascular lumen is temporarily decreased, allowing for an optimal discrimination by CT between the arterial lumen and surrounding tissues. Using contrast-enhanced CT, stenosis of the coronary arteries, caused by atherosclerotic plaques protruding into the arterial lumen, are detected with increasing accuracy when compared to the results obtained with invasive angiography. Furthermore, recent studies have shown the potential of CT to directly measure the size of atherosclerotic plaques in coronary arteries. Atherosclerotic plaques can be characterized on CT as hypo-dense, dense or calcified by measuring their X-ray absorption values (densities expressed in Hounsfield units (HU)). Low densities detected in hypo-dense atherosclerotic plaques could be related to the lower X-ray absorption of lipids present in the atheromatous core and have been suggested as a marker of high-risk plaques as assessed by CT. However, densities of atherosclerotic
Atherosclerosis Imaging with Novel Nanoparticles
18Fluorodeoxyglucose Positron Emission Tomography Imaging of Atherosclerotic Plaque Inflammation Is Highly Reproducible

Implications for Atherosclerosis Therapy Trials

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