MRI Atherosclerotic Plaque Characterization

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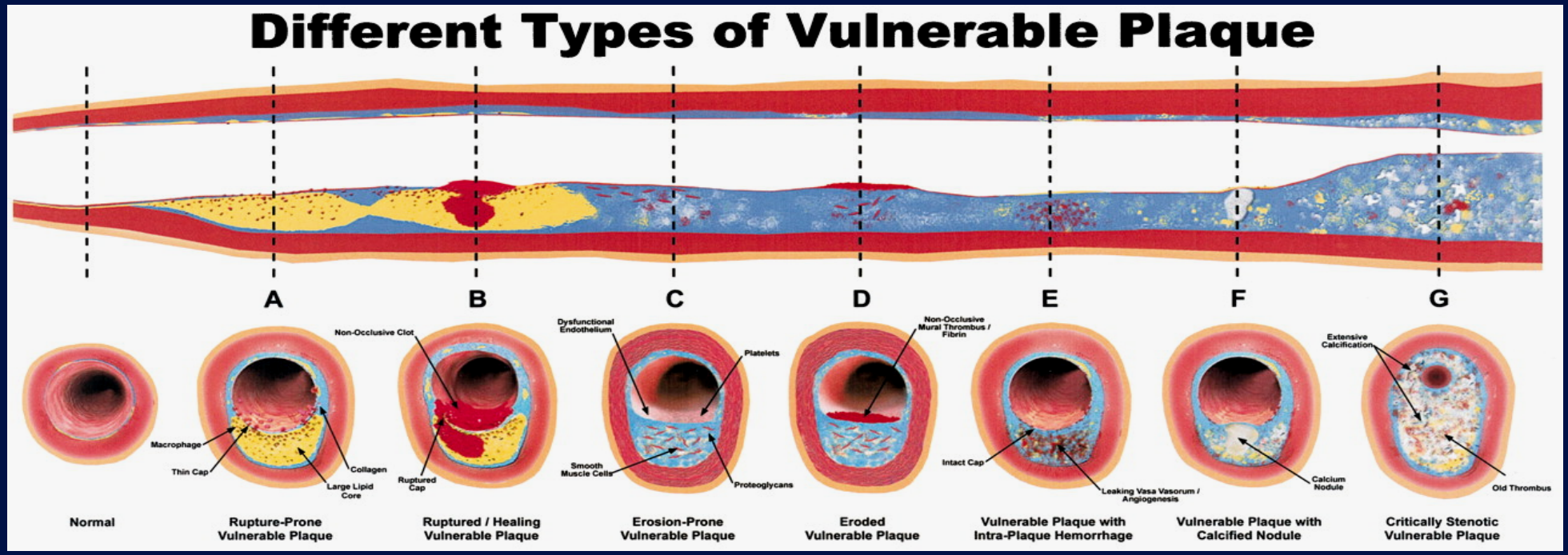
Vulnerable Plaque

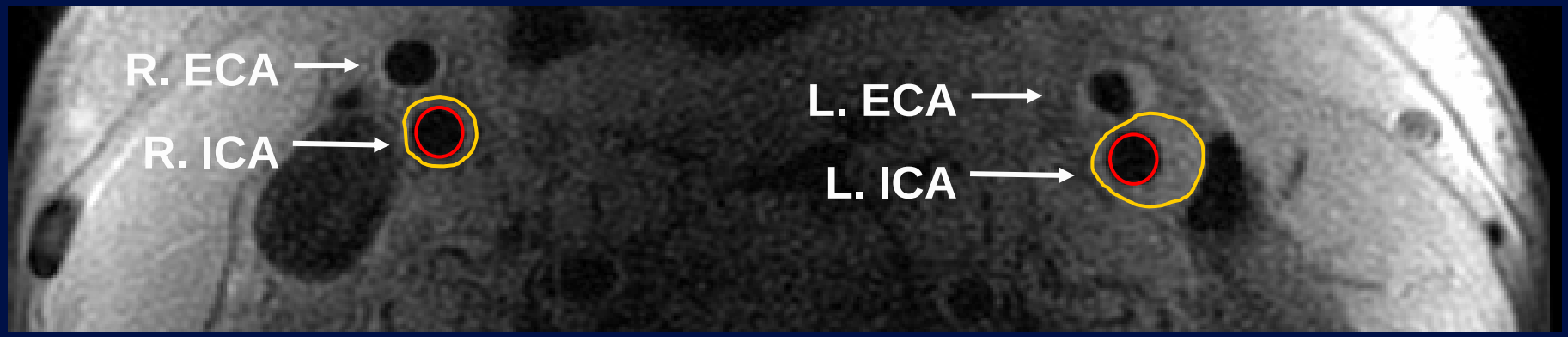


Naghavi et al, Circulation 2003

Need For Imaging

- **Detect asymptomatic patients**
  - High risk for future cardiovascular events
  - High risk for progression
  - Benefit from preventive or therapeutic interventions
- **Non-invasive**
  - Risk prediction
  - Follow up
- **Provide information of**
  - Vessel lumen and wall size
  - Tissue composition
  - Status of inflammation

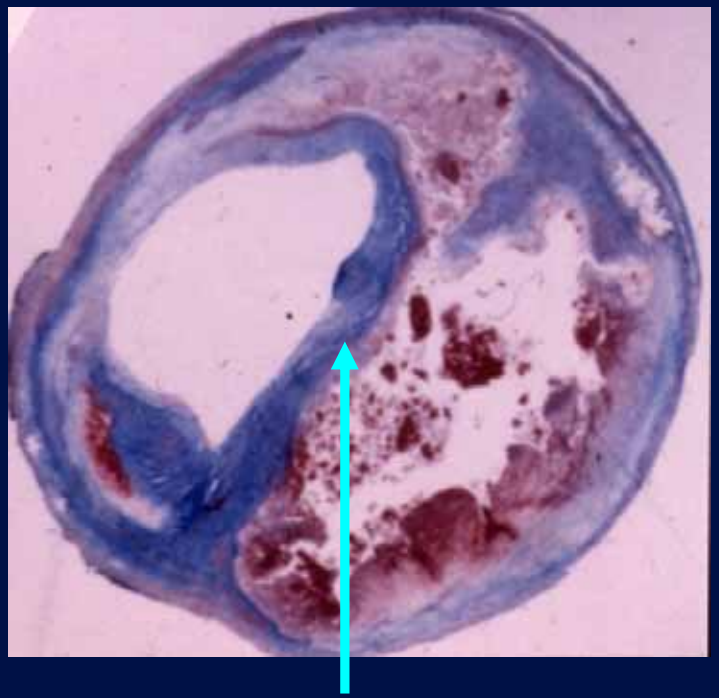
Imaging Goals I: Morphology



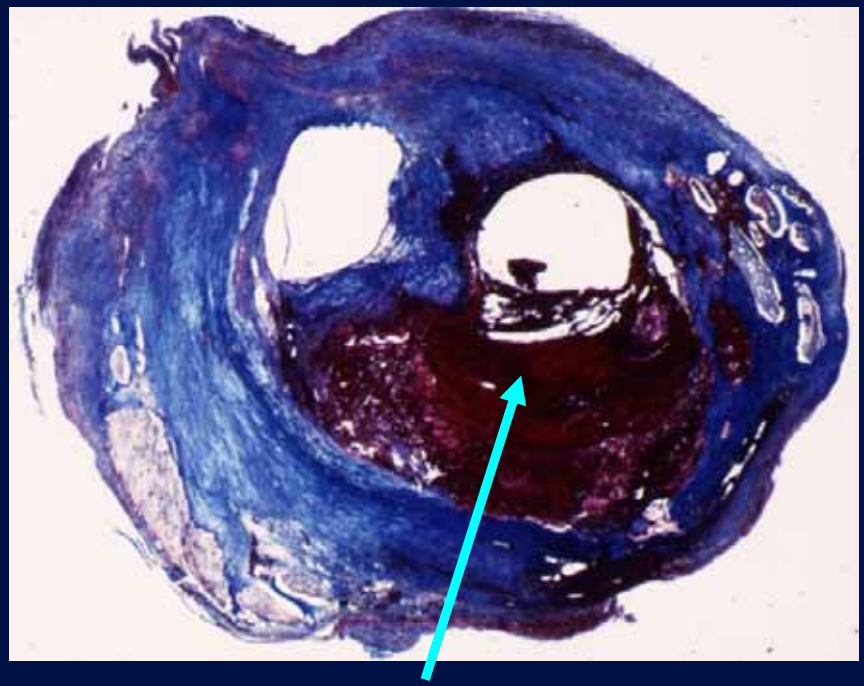
Lumen – Wall – Area – Volume
Wall thickness – Mean – Max/Min – IMT

Angiography Underestimates Plaque Burden

Imaging Goals II: Lumen Surface Characteristics



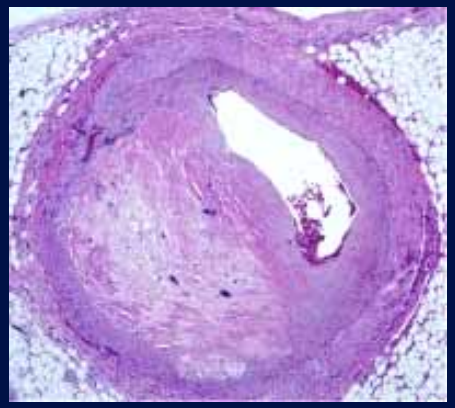
Intact, thick fibrous cap



Ruptured cap with intraplaque hemorrhage

Imaging Goals III: Tissue Composition

- Extracellular Matrix
- Intraplaque Hemorrhage
- Mural Thrombus
- Lipid Rich Necrotic Core
- Calcification
- Plaque neovasculature



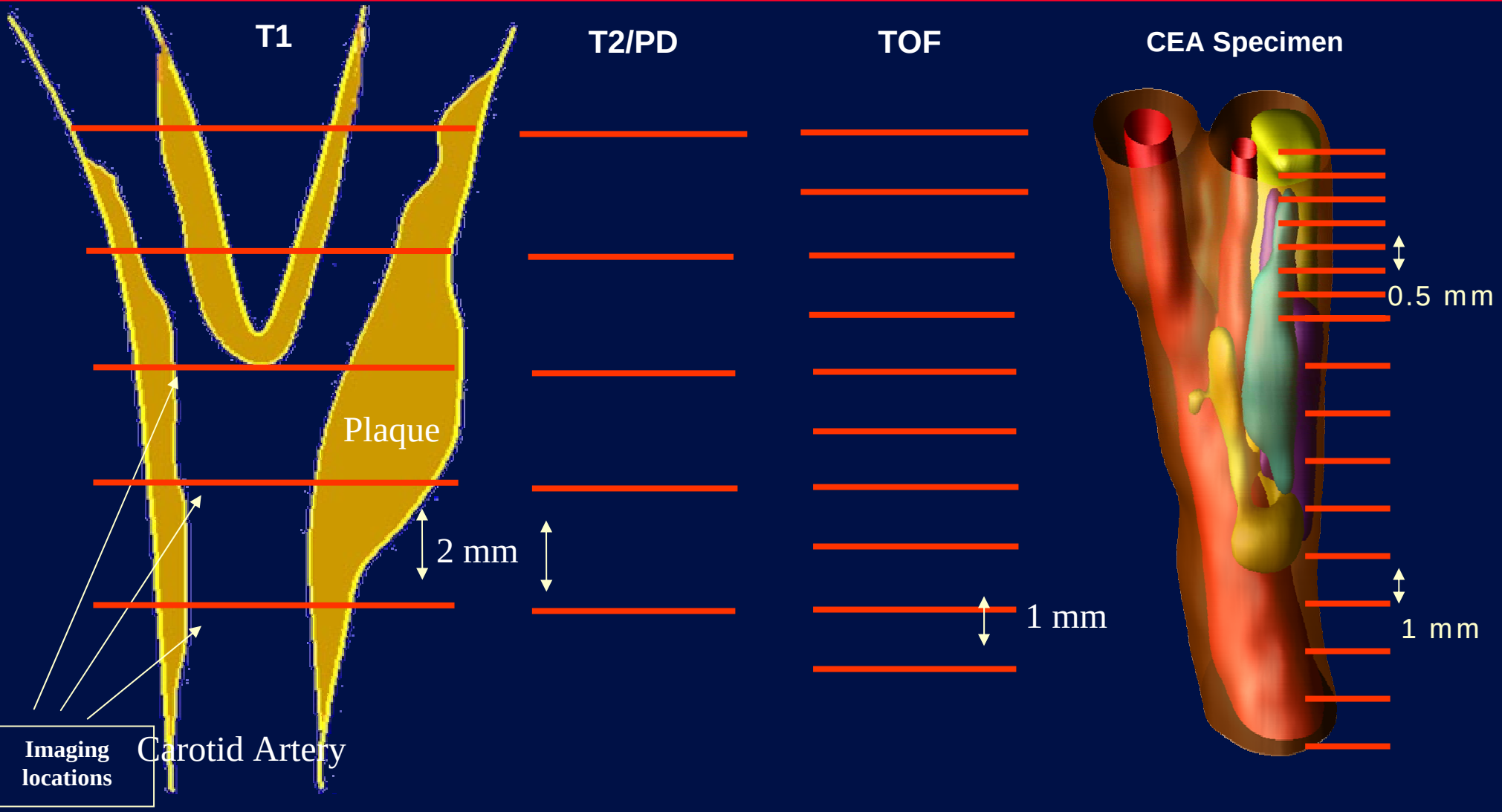
Coronary

Carotid

Carotid Artery Atherosclerosis

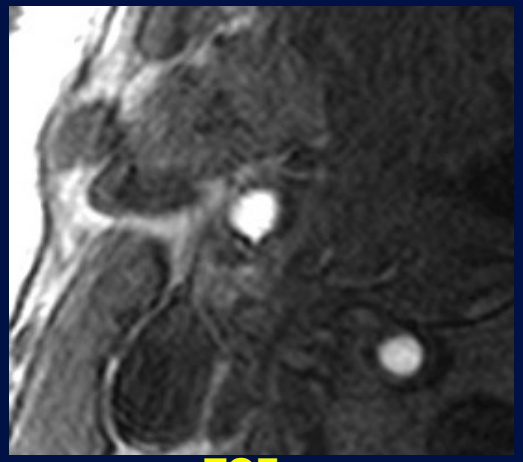
- Stroke/TIA
- Location
- Carotid endarterectomy (CEA)
  - Access to plaque specimen
    - In vivo and Ex vivo studies
    - Histology

MRI – Histology Matching Scheme

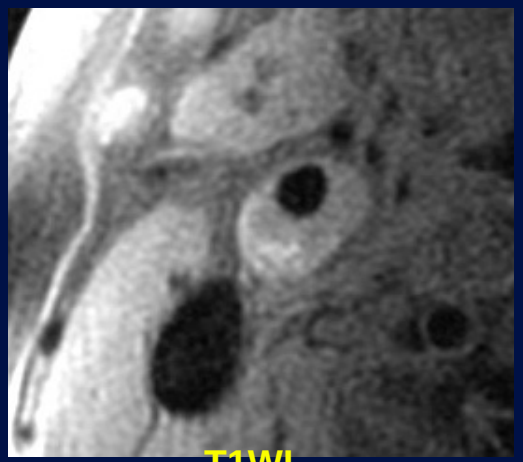


Yuan et al, Radiology, 2001.

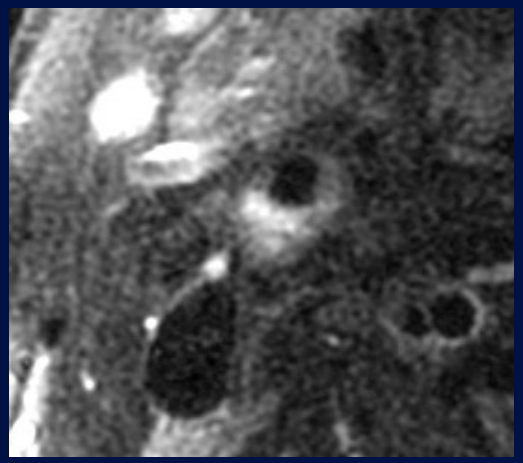
MRI Carotid Techniques:
Multi-Contrast Protocol



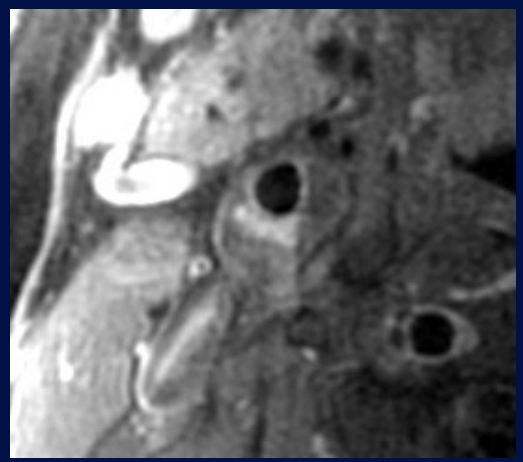
TOF



T1WI



T2WI

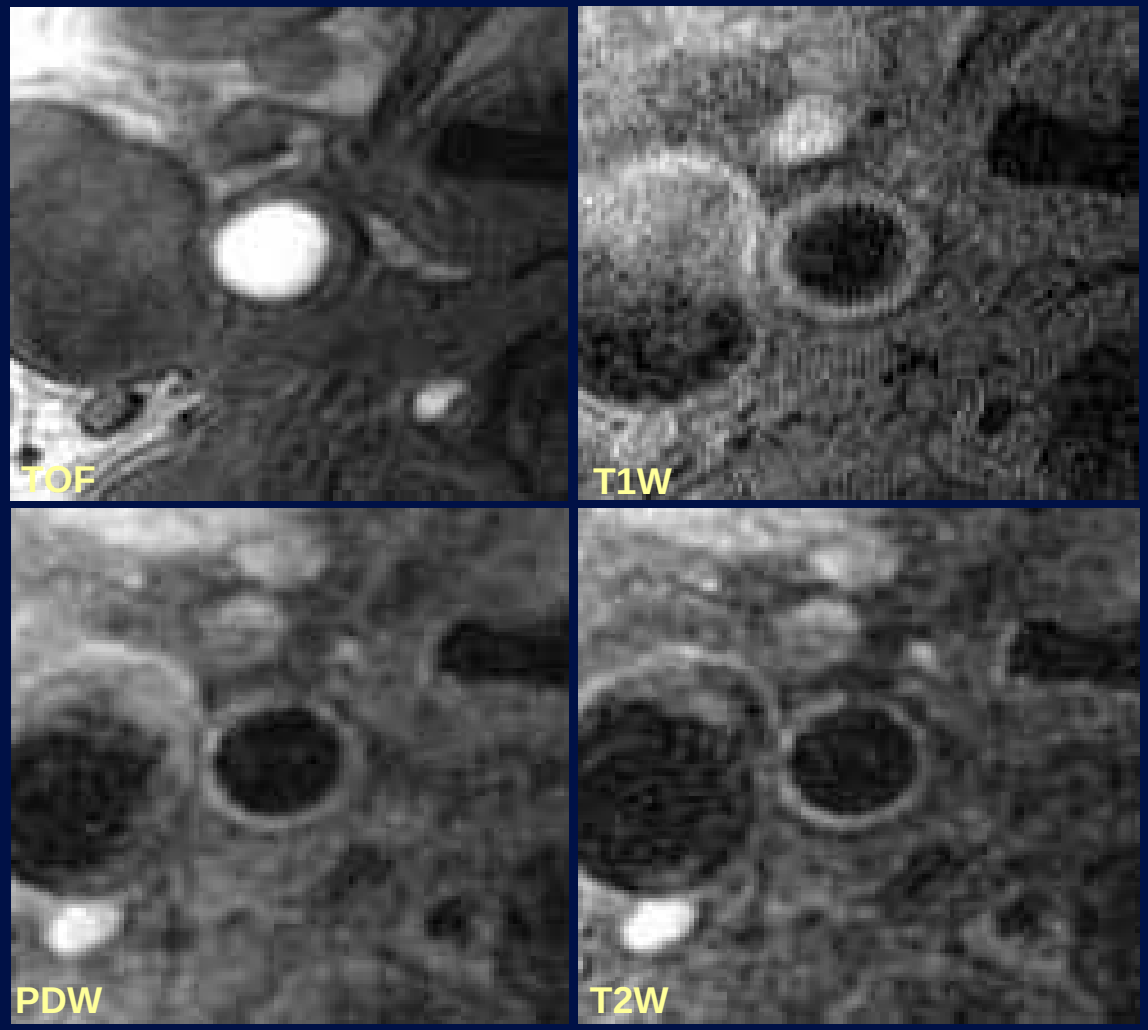


Post T1WI

- Bright/Black Blood
- MDIR/QIR sequences
- Contrast agent application
- Quantitative information
  - Lumen narrowing
  - Plaque burden
  - Tissue composition

Yarnykh et al. Current Protocols in MRI, Vol. 1. 2003:A1.4.1-A1.4.17.

MRI Based Lesion Type for the Carotid

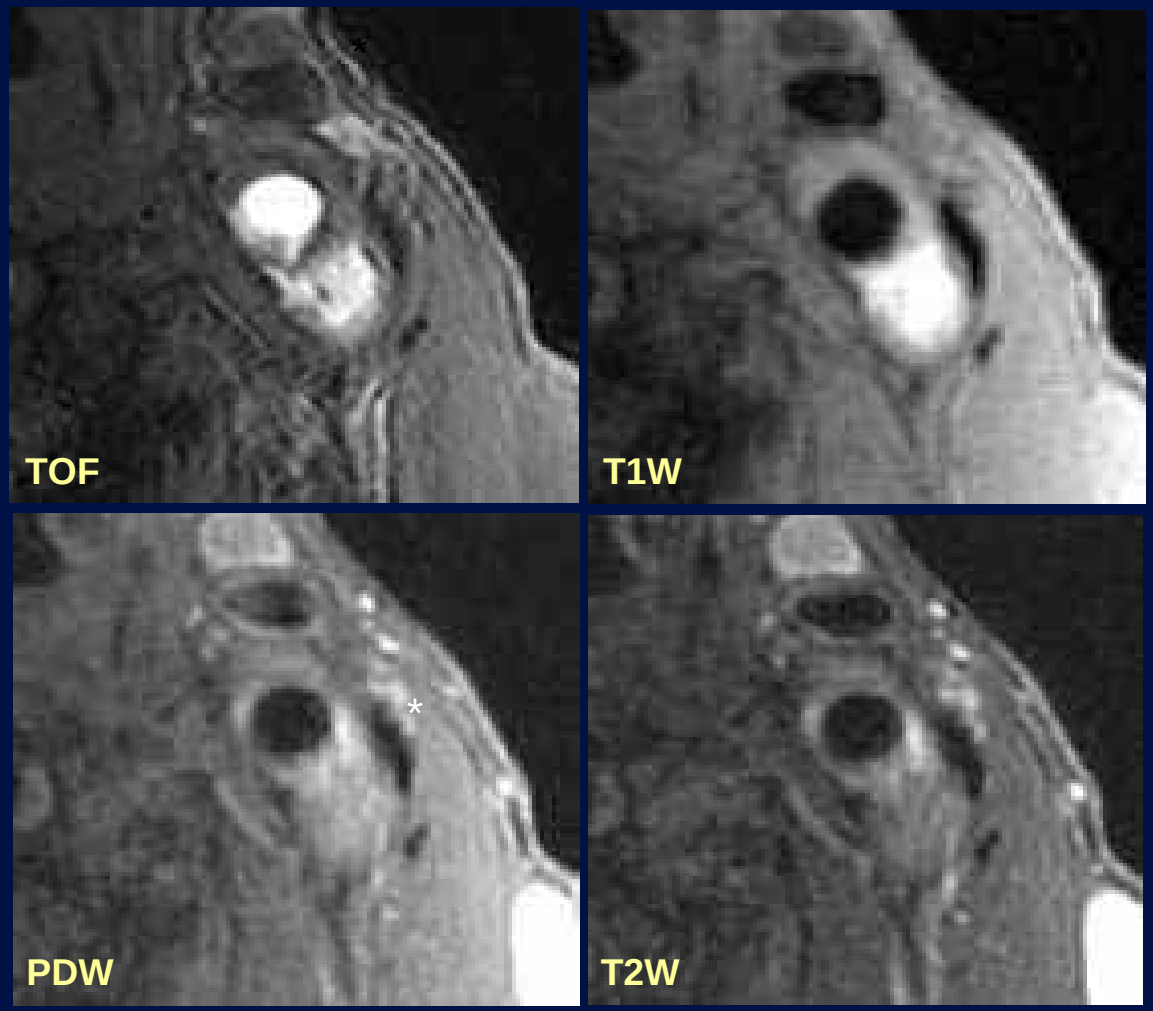


Normal - Early
Type I-II

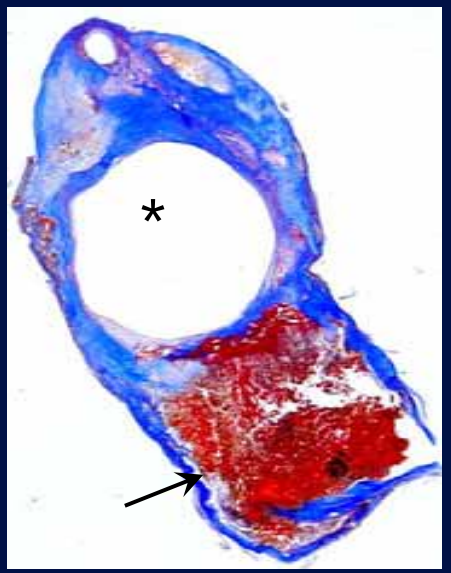
H&E

Cai JM, et al. Circulation, 2002; 106:1368-1373.

MRI Study of the Advanced Carotid Lesion



Hemorrhage - Recent (Type VI)



Mallory's Trichrome

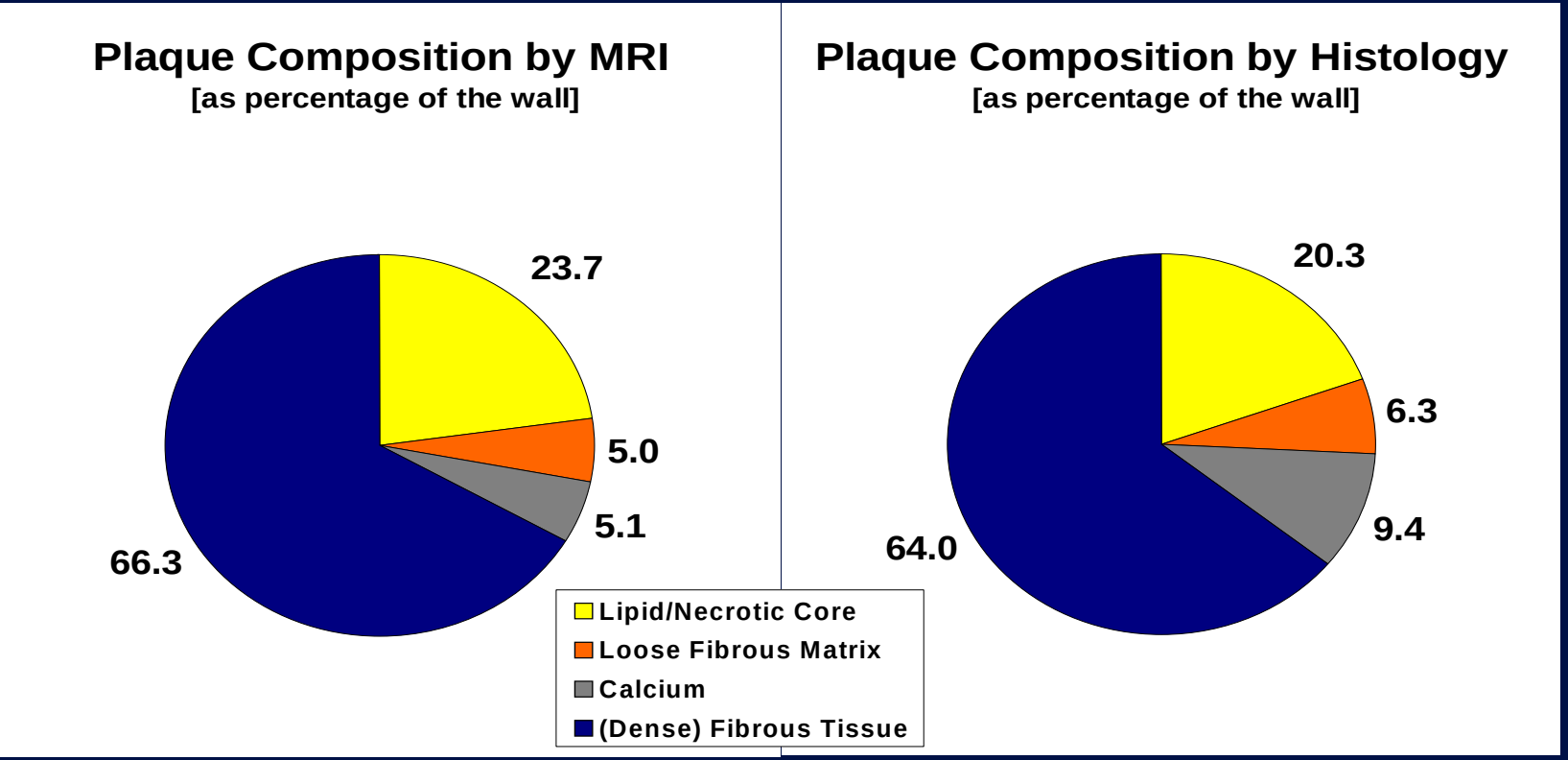
Cai JM, et al. Circulation, 2002.

MRI Accuracy

	Lipid-Rich Necrotic Core[1]	Fibrous Cap (thick vs. thin or ruptured)[2,3]	Intraplaque Hemorrhage[4]
Sensitivity	**85%**	**81%**	**96%**
Specificity	**92%**	**90%**	**82%**
Kappa	**0.69**	**0.83**	**0.82**

[1] Yuan, et al., *Circulation* 2001; 104:2051-6
[2] Hatsukami, et al, *Circulation* 2000; 102:959-64
[3] Mitsumori, et al., *JMRI* 2003 17:410-20
[4] Kampschulte, et al., *Circulation* 2004; 110:3239

Quantitative Evaluation of Plaque Composition by in vivo MRI



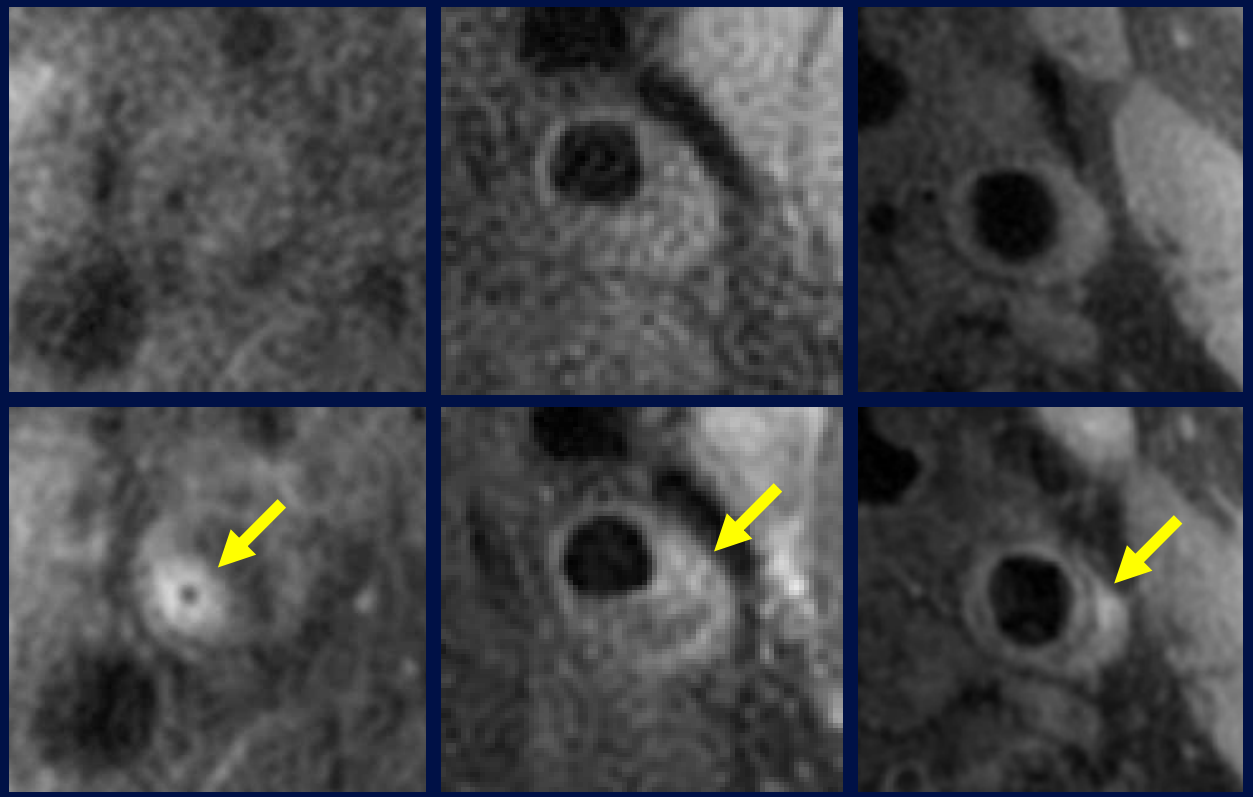
Lipid/Necrotic core MRI vs. Histology: p=.1
Loose Fibrous Matrix MRI vs. Histology: p=.1
Calcium MRI vs. Histology: p<.0001
(Dense) Fibrous Tissue MRI vs. Histology p=.4

Saam T et al. ATVB 2005; 25(1):234-239

Contrast Enhanced MRI

PRE:

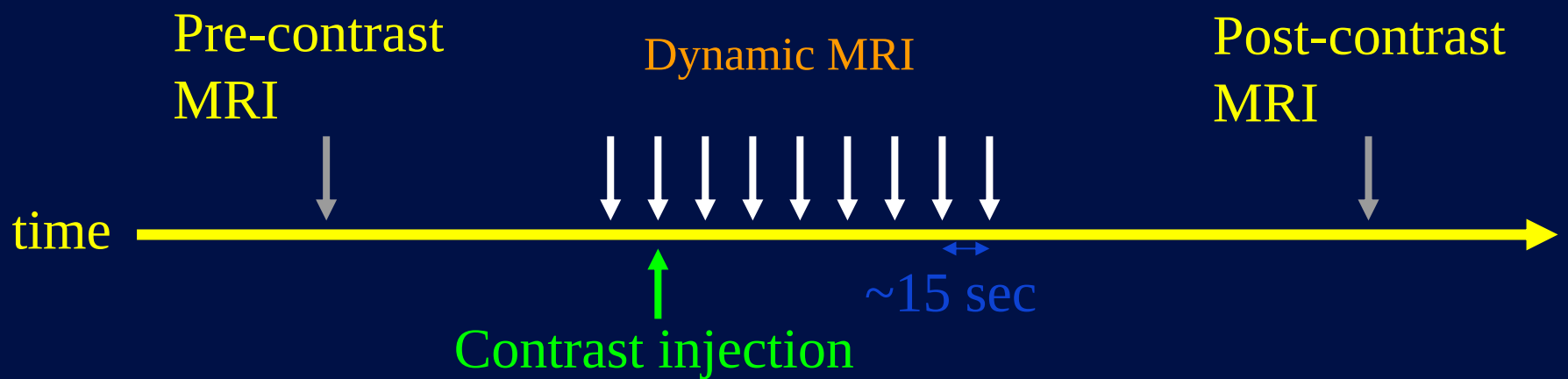
POST:

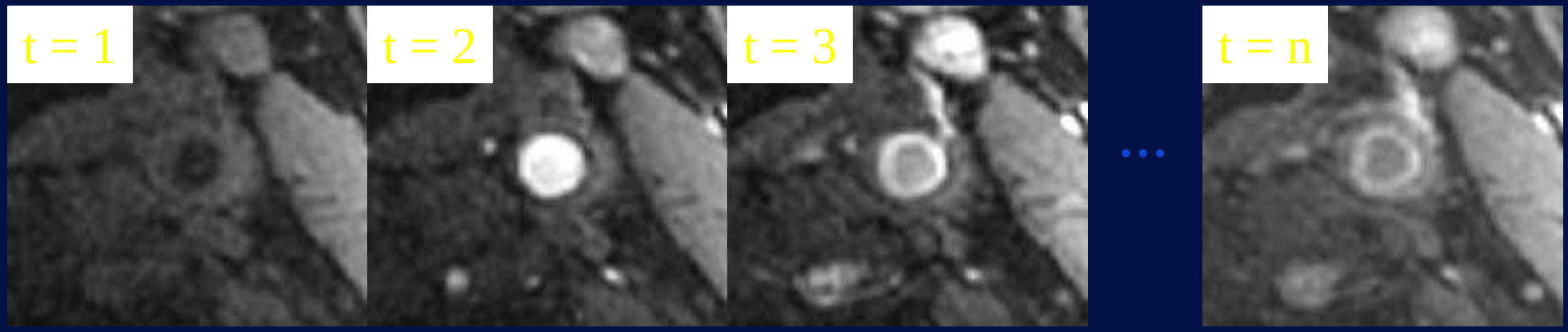


T1W Imaging – Black Blood

Yuan et al., *JMRI* 2002; 15:62-7
Wasserman et al, *Radiology*, 2002
Kerwin et al. *Circulation* 2003; 107:851-6

CE-MRI Protocol





- MRI: 2DSPGR (TR / TE = 100 / 3.5 msec)
- Contrast agent: 20 ml Omniscan (Gadolinium-based) administered at 2ml/sec

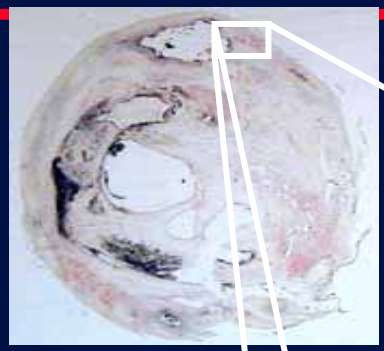
DCE Study: Histological Methods

Staining

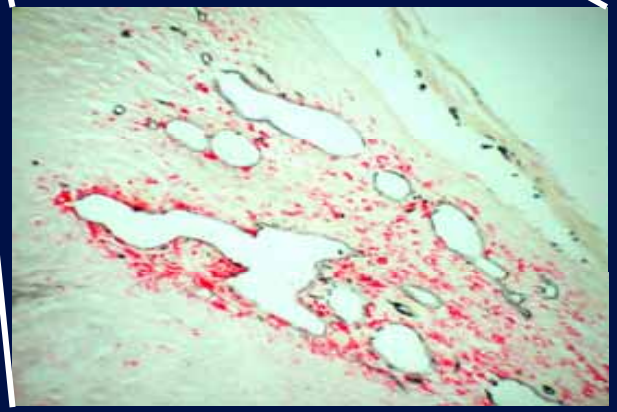
- HAM56 for macrophages (red)
- Ulex for endothelial cells (black/brown)

Quantification

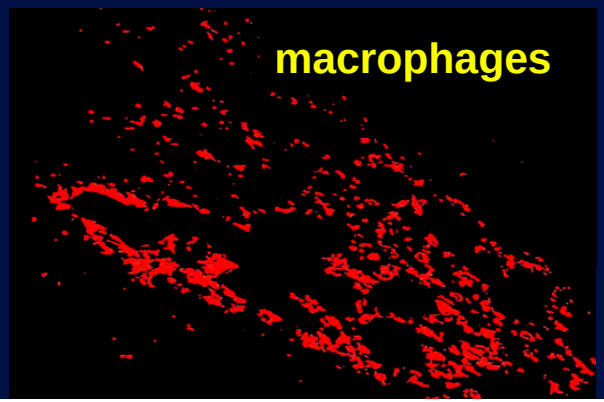
- Regions containing neovasculature / macrophages photographed at high power
- Measured HAM56 positive area
- Identified neovessel boundaries and measured area
- Normalized by total plaque area

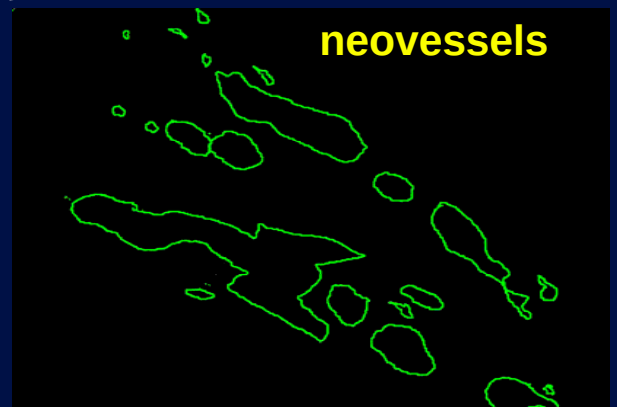


HAM56
ULEX

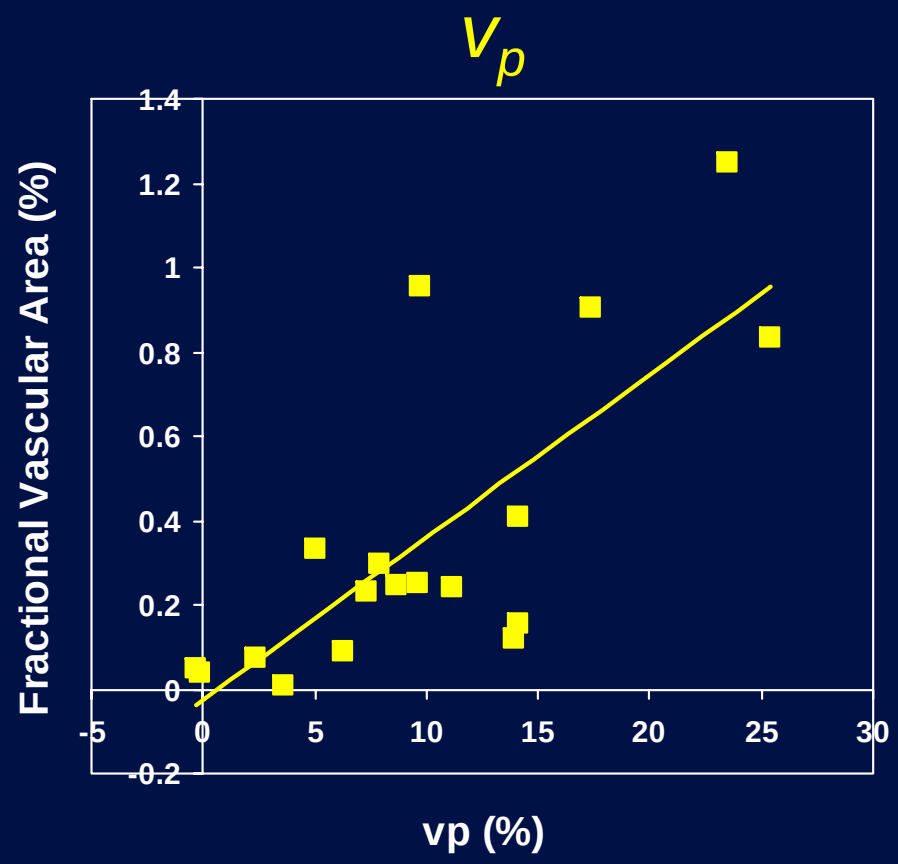


fMA
fVA





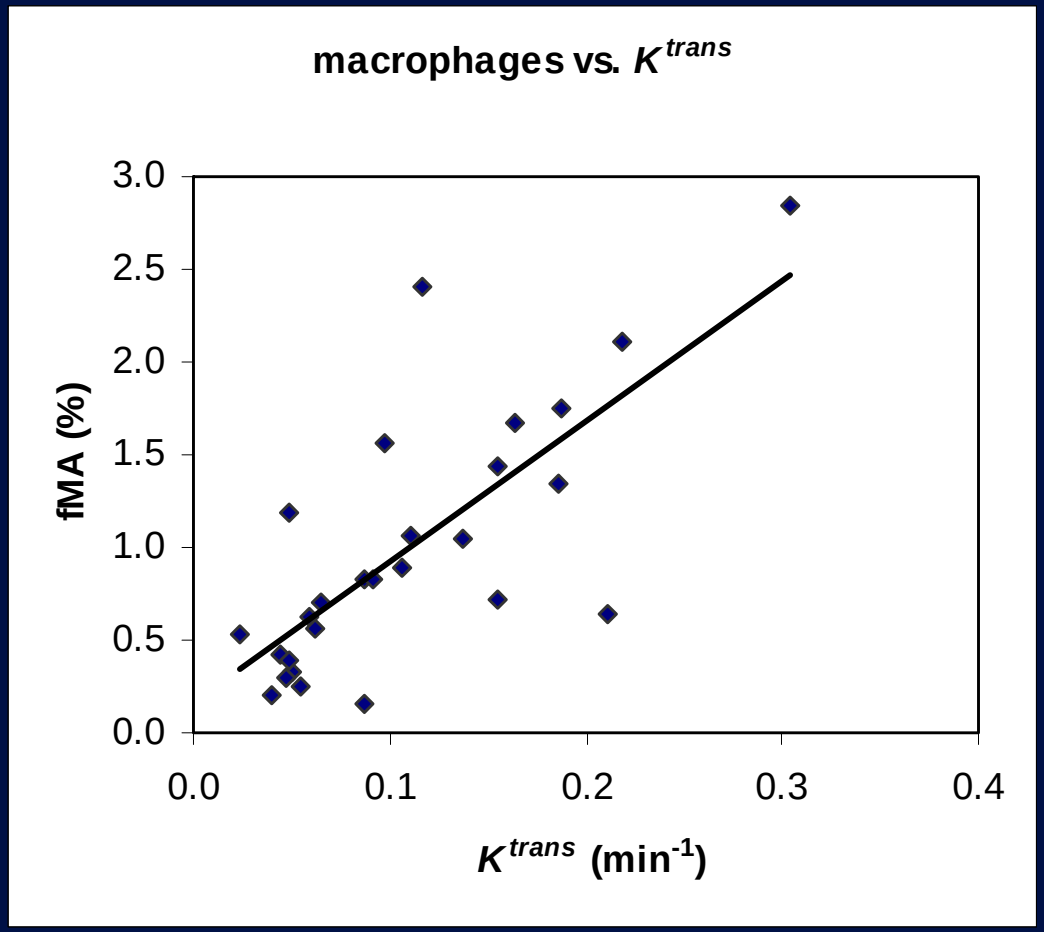
DCE-MRI and Neovasculature



r = 0.76
p = 0.0003

Kerwin WS, et al. Circulation, 2003; 107:851-856
Kerwin WS, et al. ACC, 2004.

Correlation Between K^{trans} (MRI) and Fractional Macrophage Area (Histology)



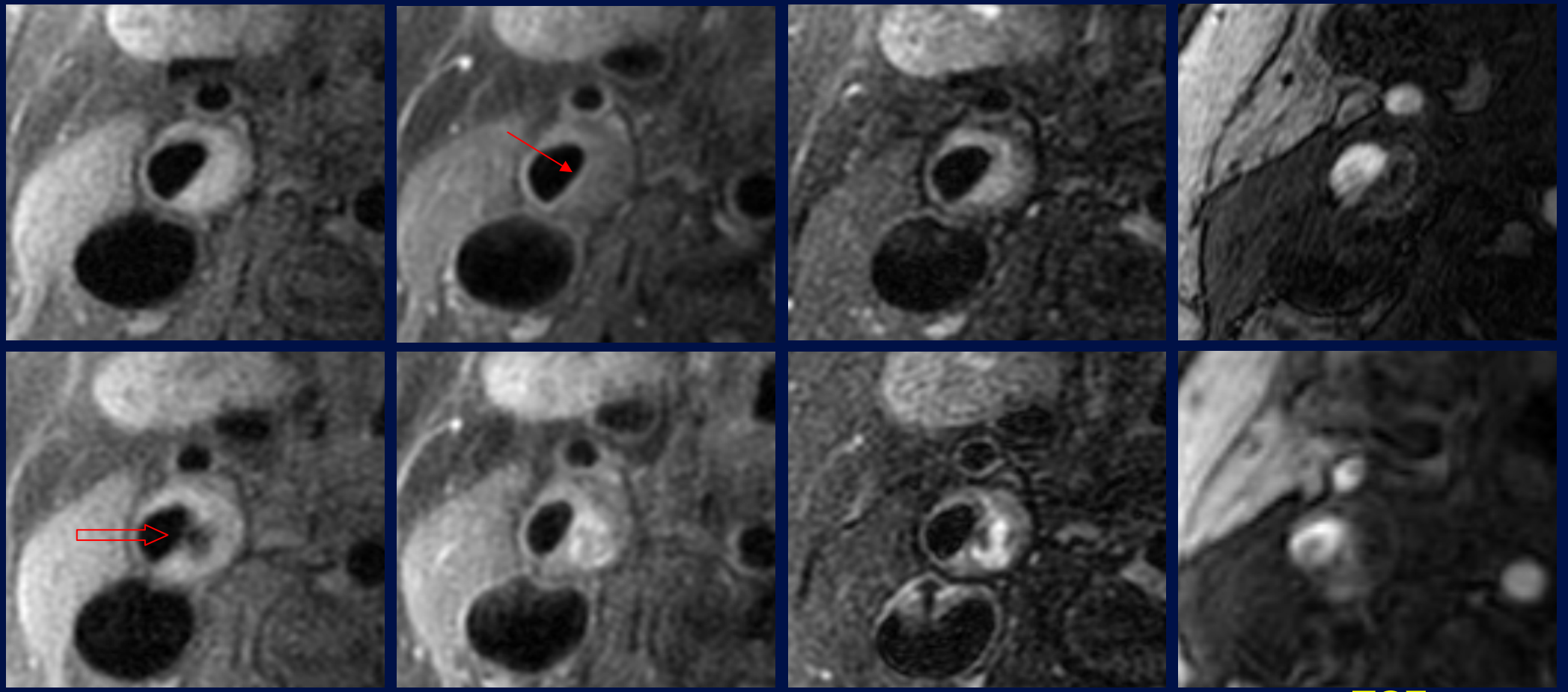
Elevated K_{trans} associated with:

Macrophage content

Smoking
Lower HDL

Kerwin et al, *Radiology, in press*

Serial Human Carotid Imaging - MRI

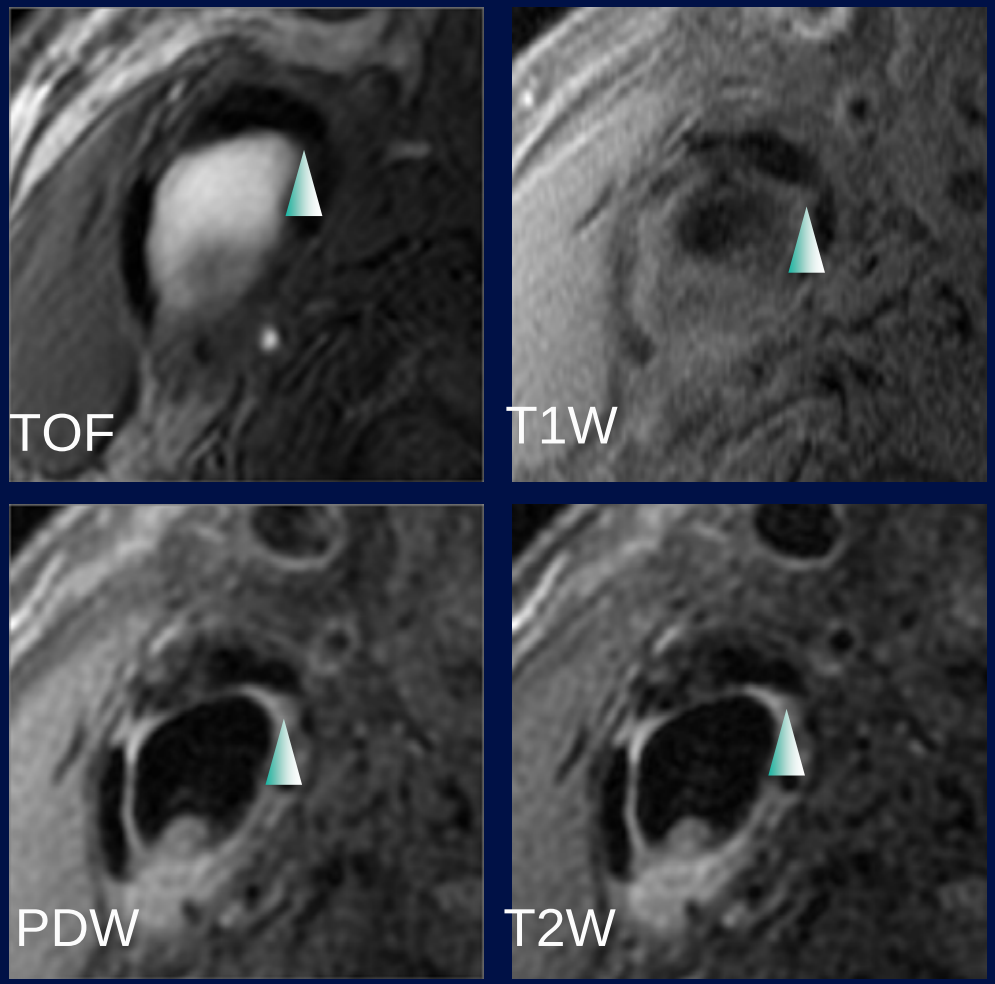


T1W CE-T1W T2W TOF

Fibrous cap rupture – 10 month follow up

BC Chu , et al . Circulation, 2006

Comparison of Patients from China and US with Recent TIA or stroke

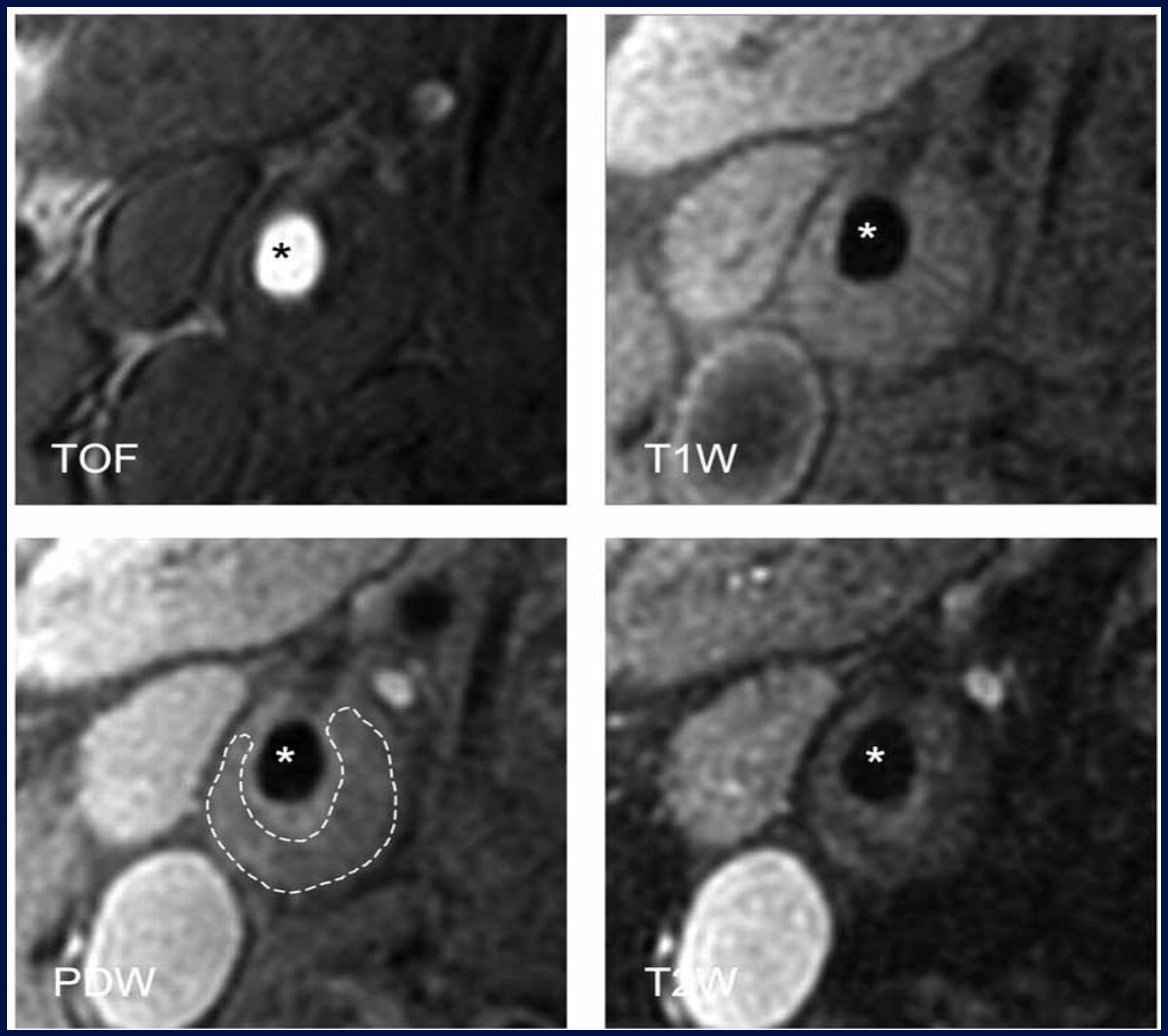


- Larger lipid cores in Chinese group (12.0 vs. 7.1 mm²; p = 0.01
- More calcification in US group (4.2 vs. 1.1 mm²)
- Lipid-lowering drugs in only 26% vs 63% in Chinese group

Calcified Lesion – US Patient

Saam T, et al. ATVB, 2005

Right CCA From a 59-year-old Chinese Patient



Saam, T. et al. Arterioscler Thromb Vasc Biol 2005;25:611-616

Imaging

Presence of Intraplaque Hemorrhage Stimulates Progression of Carotid Atherosclerotic Plaques

A High-Resolution Magnetic Resonance Imaging Study

Norihide Takaya, MD, PhD; Chun Yuan, PhD; Baocheng Chu, MD, PhD; Tobias Saam, MD; Nayak L. Polissar, PhD; Gail P. Jarvik, MD, PhD; Carol Isaac, RVT; Judith McDonough, BS; Cynthia Natiello, RN; Randy Small, HT; Marina S. Ferguson, MT; Thomas S. Hatsukami, MD

Background—Previous studies suggest that erythrocyte membranes from intraplaque hemorrhage into the necrotic core are a source of free cholesterol and may become a driving force in the progression of atherosclerosis. We have shown that MRI can accurately identify carotid intraplaque hemorrhage and precisely measure plaque volume. We tested the hypothesis that hemorrhage into carotid atheroma stimulates plaque progression.

Methods and Results—Twenty-nine subjects (14 cases with intraplaque hemorrhage and 15 controls with comparably sized plaques without intraplaque hemorrhage at baseline) underwent serial carotid MRI examination with a multicontrast weighted protocol (T1, T2, proton density, and 3D time of flight) over a period of 18 months. The volumes of wall, lumen, lipid-rich necrotic core, calcification, and intraplaque hemorrhage were measured with a custom-designed image analysis tool. The percent change in wall volume (6.8% versus −0.15%; $P=0.009$) and lipid-rich necrotic core volume (28.4% versus −5.2%; $P=0.001$) was significantly higher in the hemorrhage group than in controls over the course of the study. Furthermore, those with intraplaque hemorrhage at baseline were much more likely to have new plaque hemorrhages at 18 months compared with controls (43% versus 0%; $P=0.006$).

Conclusions—Hemorrhage into the carotid atherosclerotic plaque accelerated plaque progression in an 18-month period. Repeated bleeding into the plaque may produce a stimulus for the progression of atherosclerosis by increasing lipid core and plaque volume and creating new destabilizing factors. (***Circulation*. 2005;111:2768-2775.**)

Methods

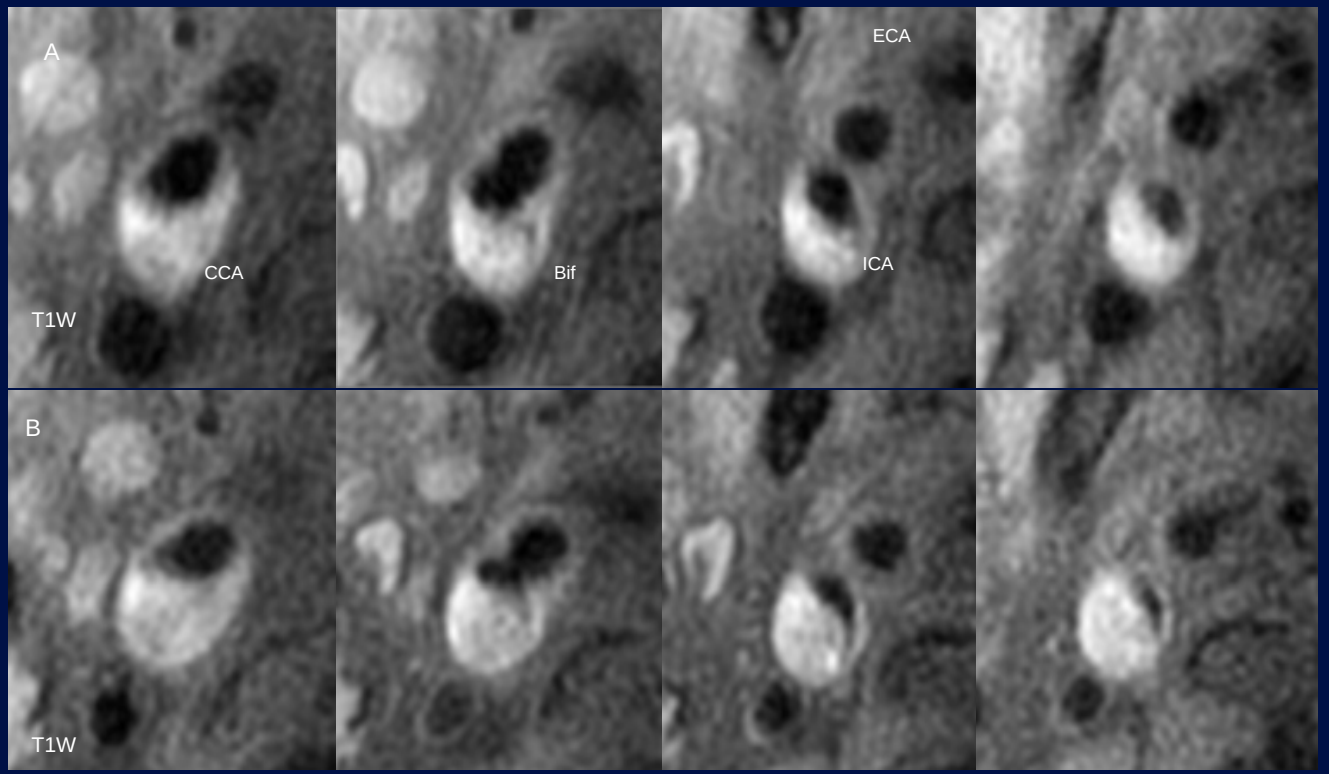
- Twenty-nine patients participating in a long term MRI progression study were divided into two groups:
  - 14 patients who had carotid plaques with intraplaque hemorrhage
  - 15 patients who had comparable plaques without intraplaque hemorrhage at the baseline MRI examination
- The volume of wall, lumen, lipid-rich necrotic core, and hemorrhage were measured at baseline and after 18 months

DoS2

Intraplaque Hemorrhage and Plaque Progression

Baseline

18 months



Takaya et al, *Circulation* 2005; 111:2768

DoS2 Dept of Surgery, 2004-11-24

Intraplaque Hemorrhage and Plaque Progression

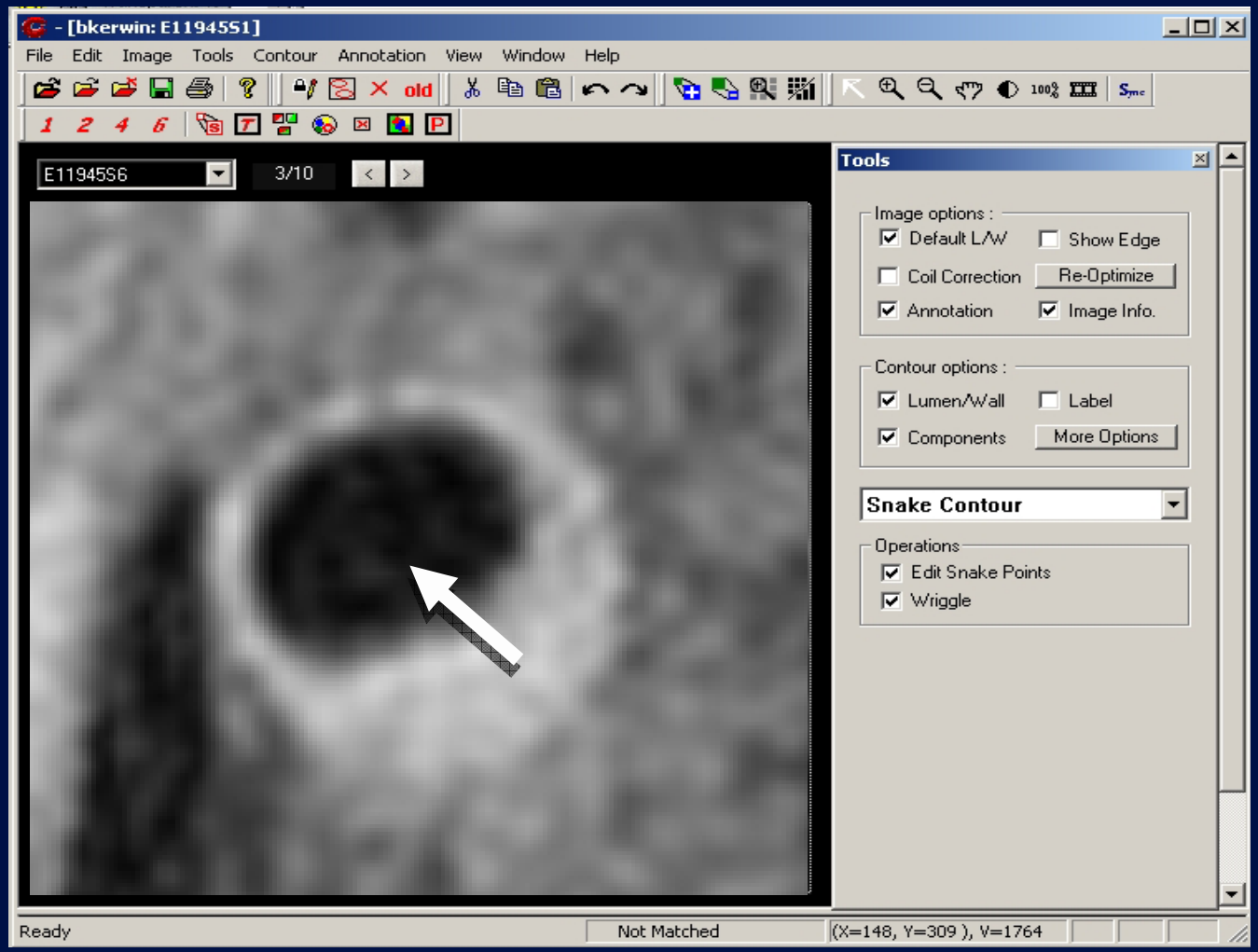
--% change in volume--

	IPH (n=14)	Control (n=15)	*P*
Lumen Volume	-8.5 ± 12.2	1.5 ± 7.9	0.014
Wall Volume	6.8 ± 7.9	-0.15 ± 5.1	0.009
LR/NC Volume	28.4 ± 29.7	-5.2 ± 17.3	0.001

Takaya et al, *Circulation* 2005; 111:2768

CASCADE

- One-click detection of lumen / wall boundaries



CASCADE

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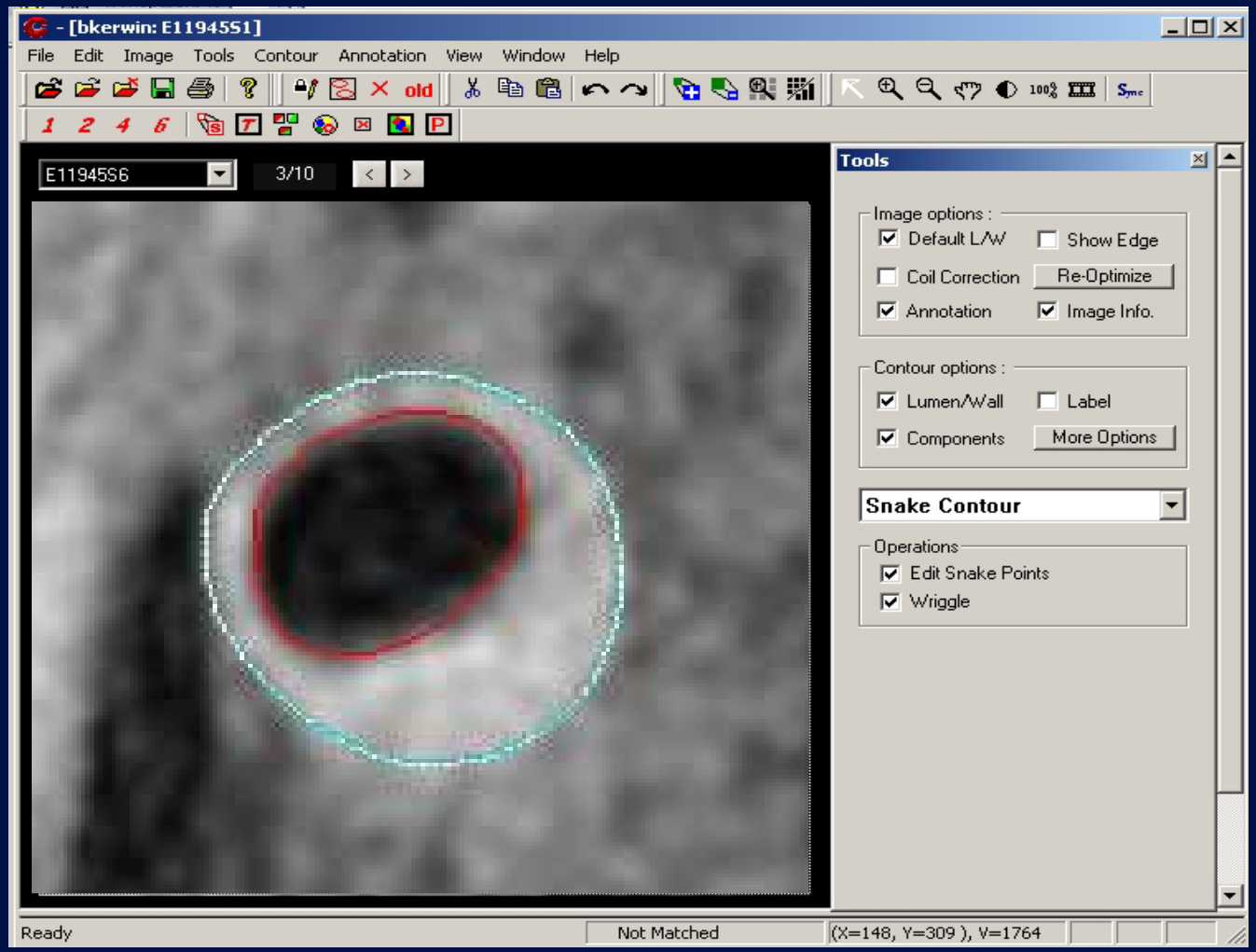
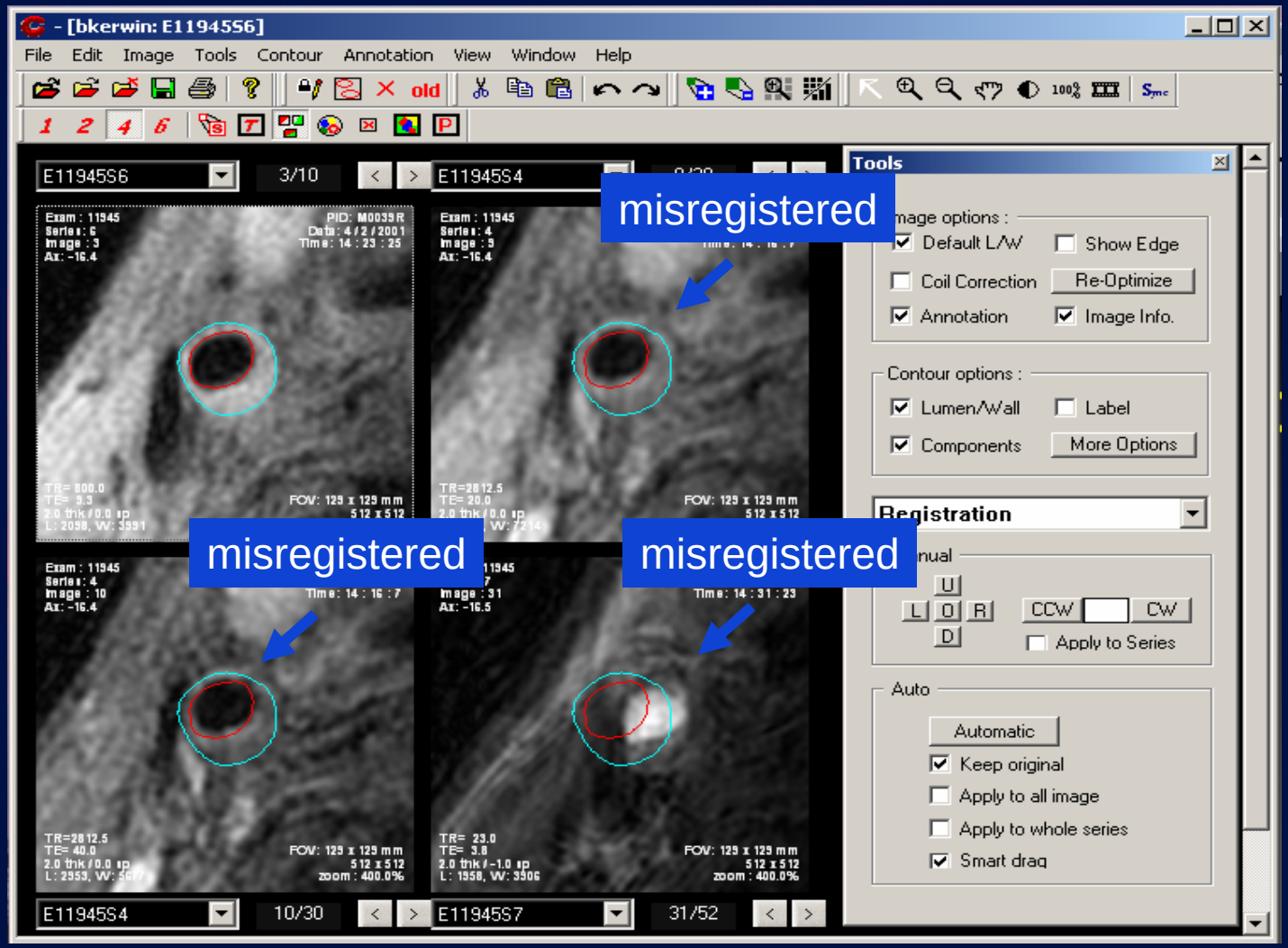


CASCADE

- One-click detection of lumen / wall boundaries
- Automated multi-contrast image registration



CASCADE

- One-click detection of lumen / wall boundaries
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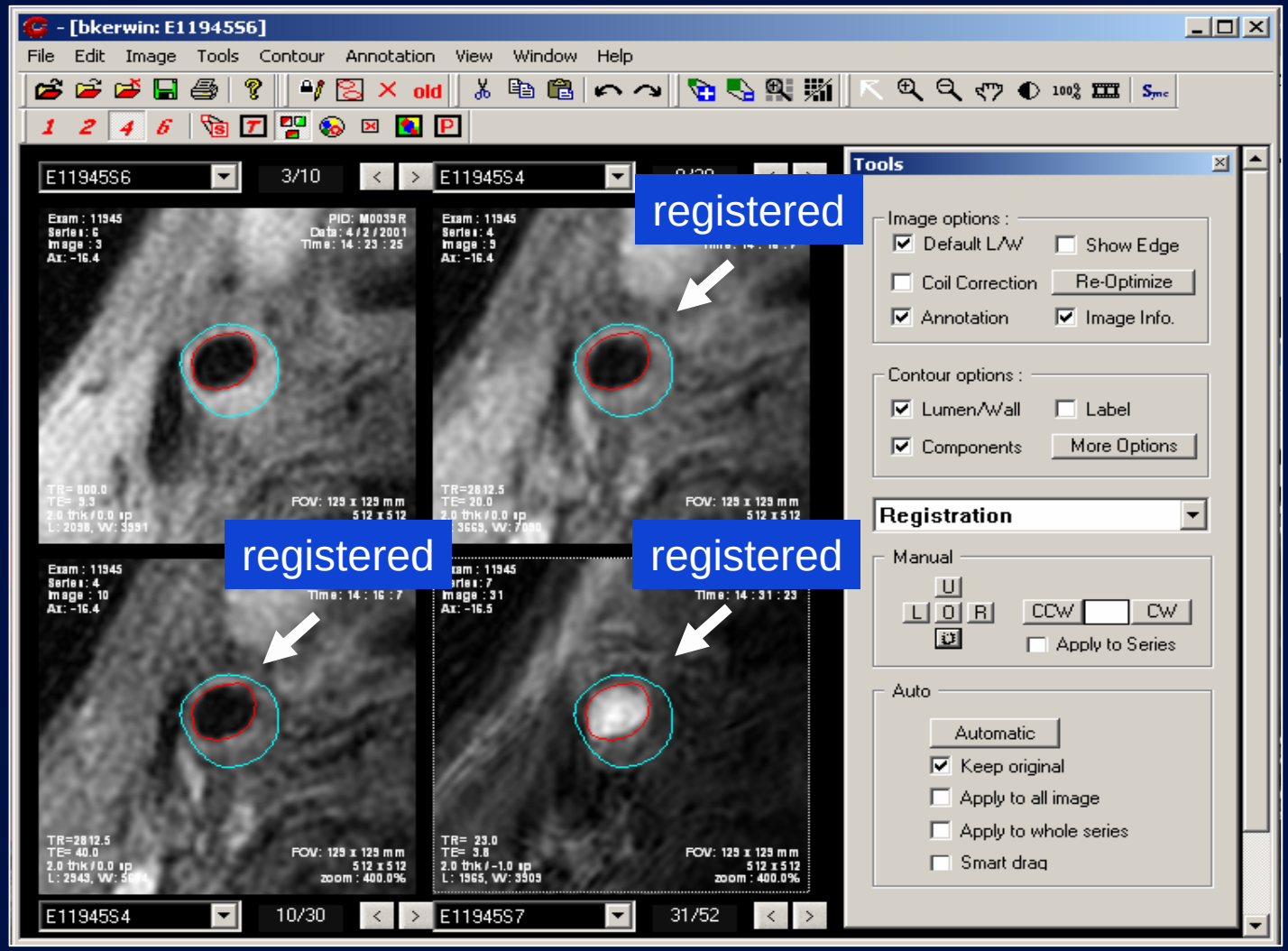
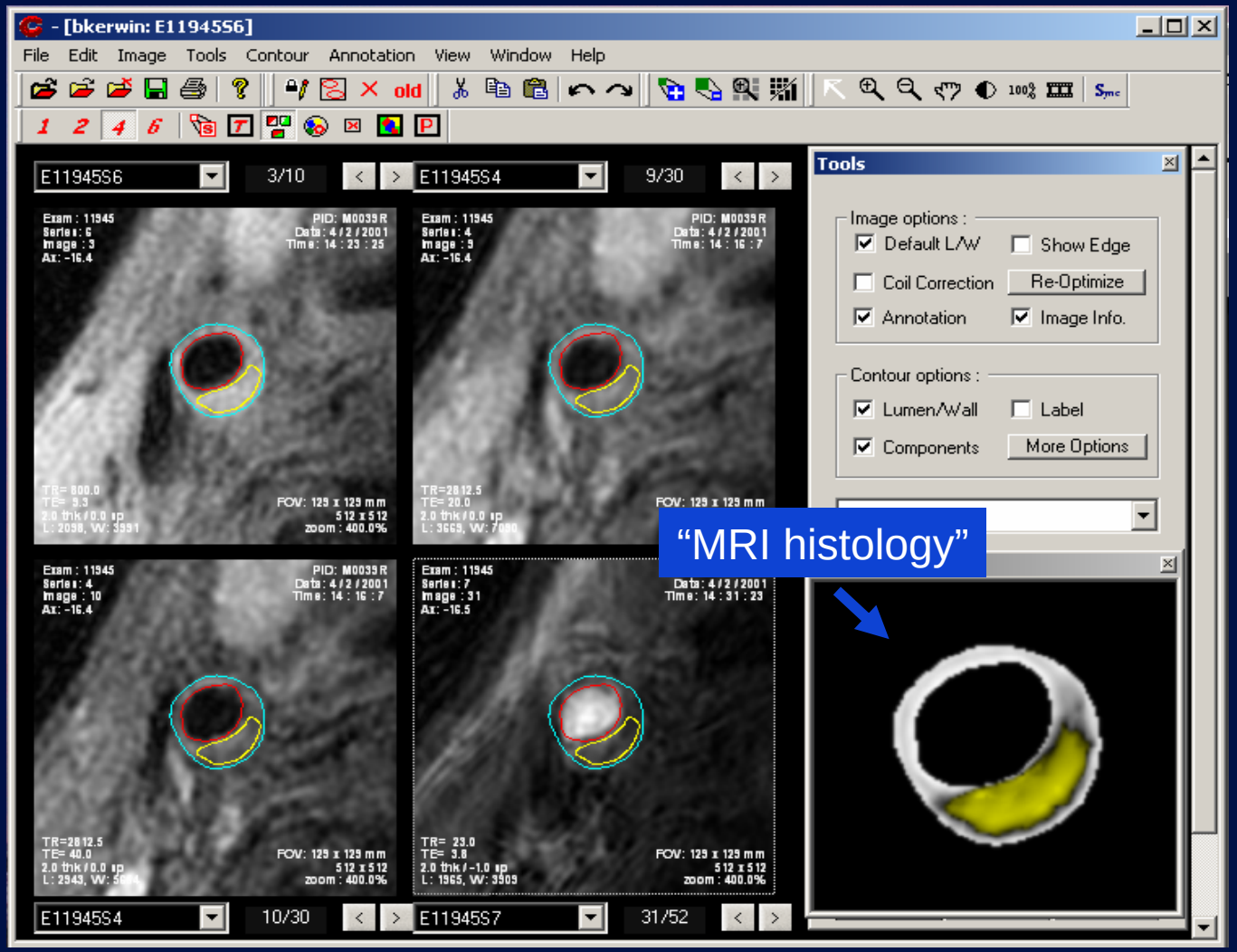


CASCADE

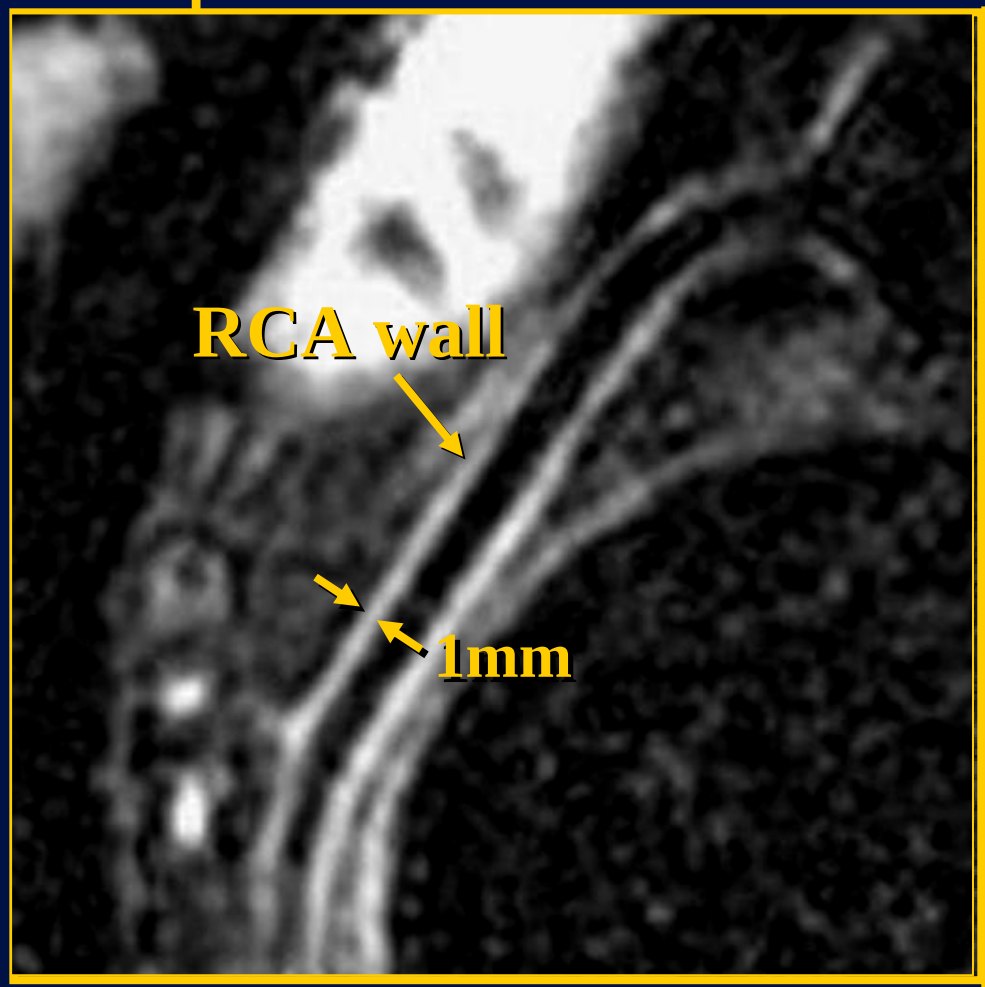
- One-click detection of lumen / wall boundaries
- Automated multi-contrast image registration
- Morphology Enhanced Probabilistic Plaque Segmentation (MEPPS)

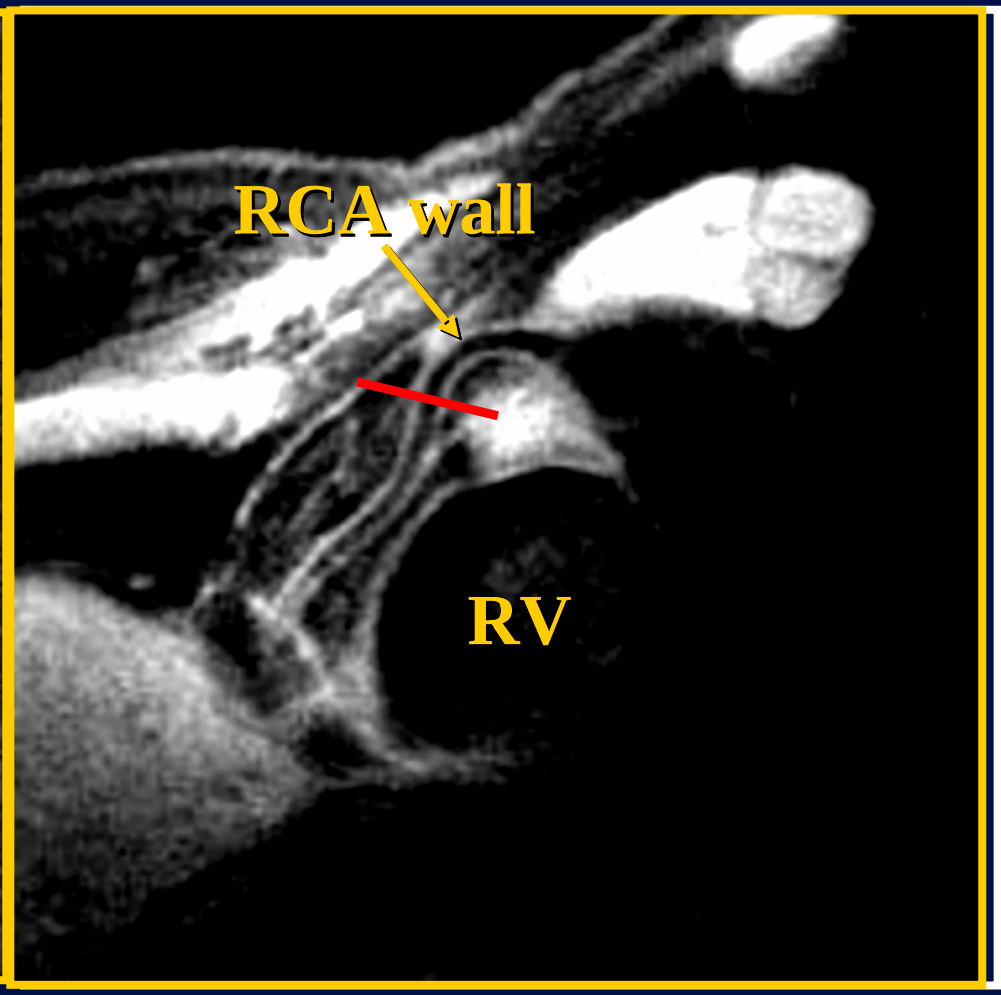


Liu, et al. *MRM*, 2006; 55:659

Coronary Imaging

3D spiral

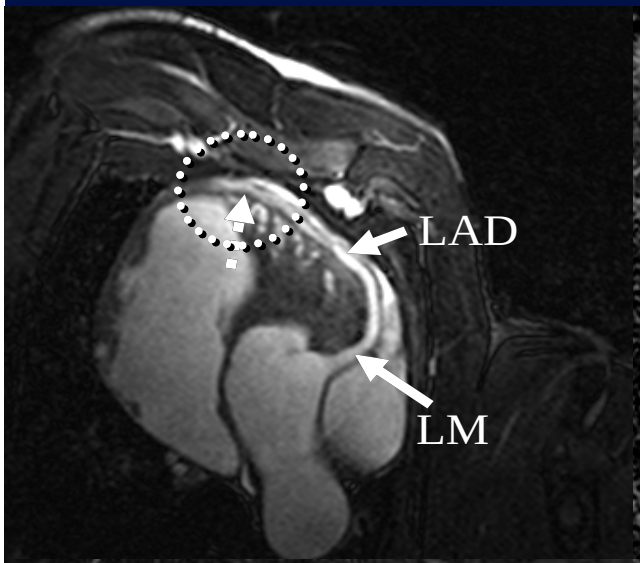


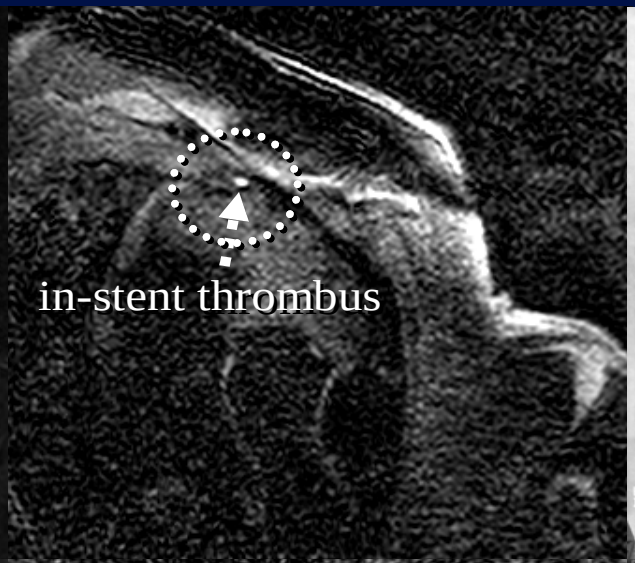


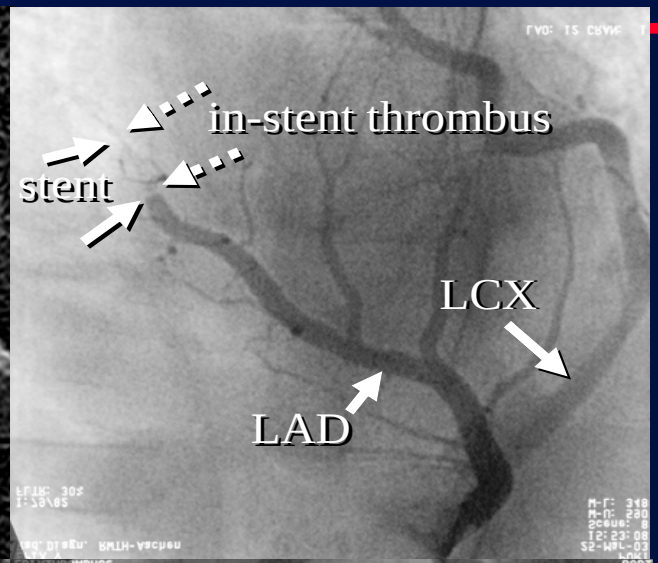
Healthy subjects

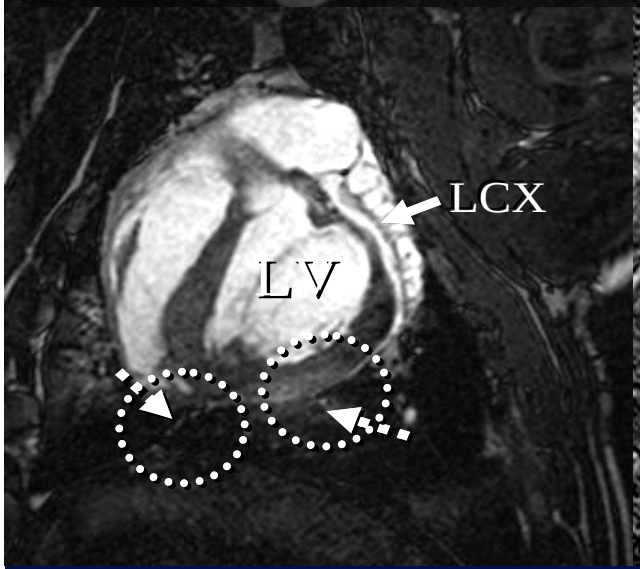
Botnar RM, Kim WY, Boernert P et al.: Magn Reson Med 46(5); 848-854 (2001)

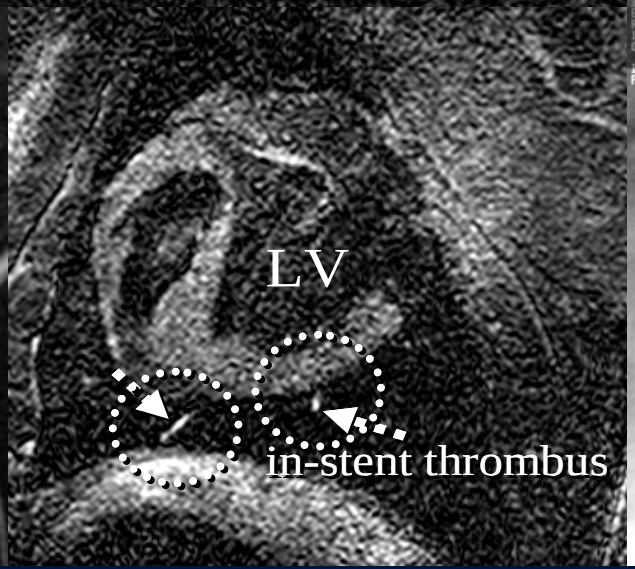
Fibrin binding Gd-labeled Contrast Agent

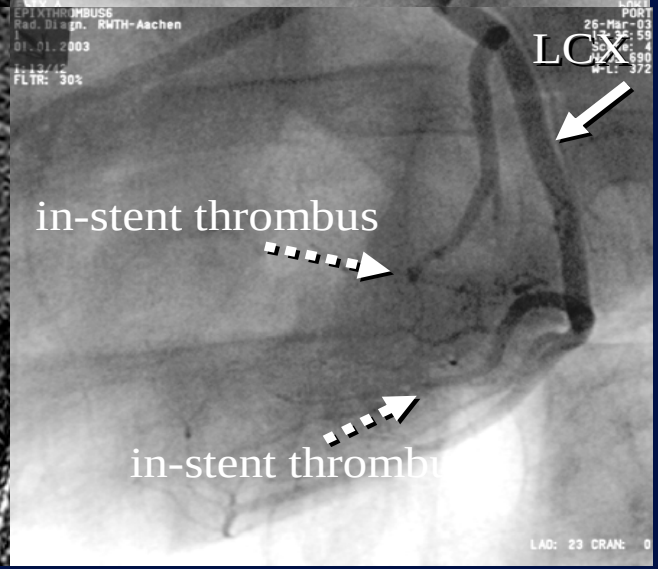








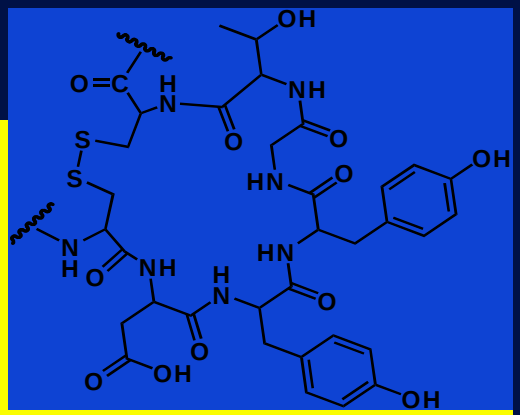




Botnar, Buecker, Wiethoff et al. Circulation 2004

EP-2104R (EPIX Medical Inc.)

Thrombus - Fibrin-targeted MR CA

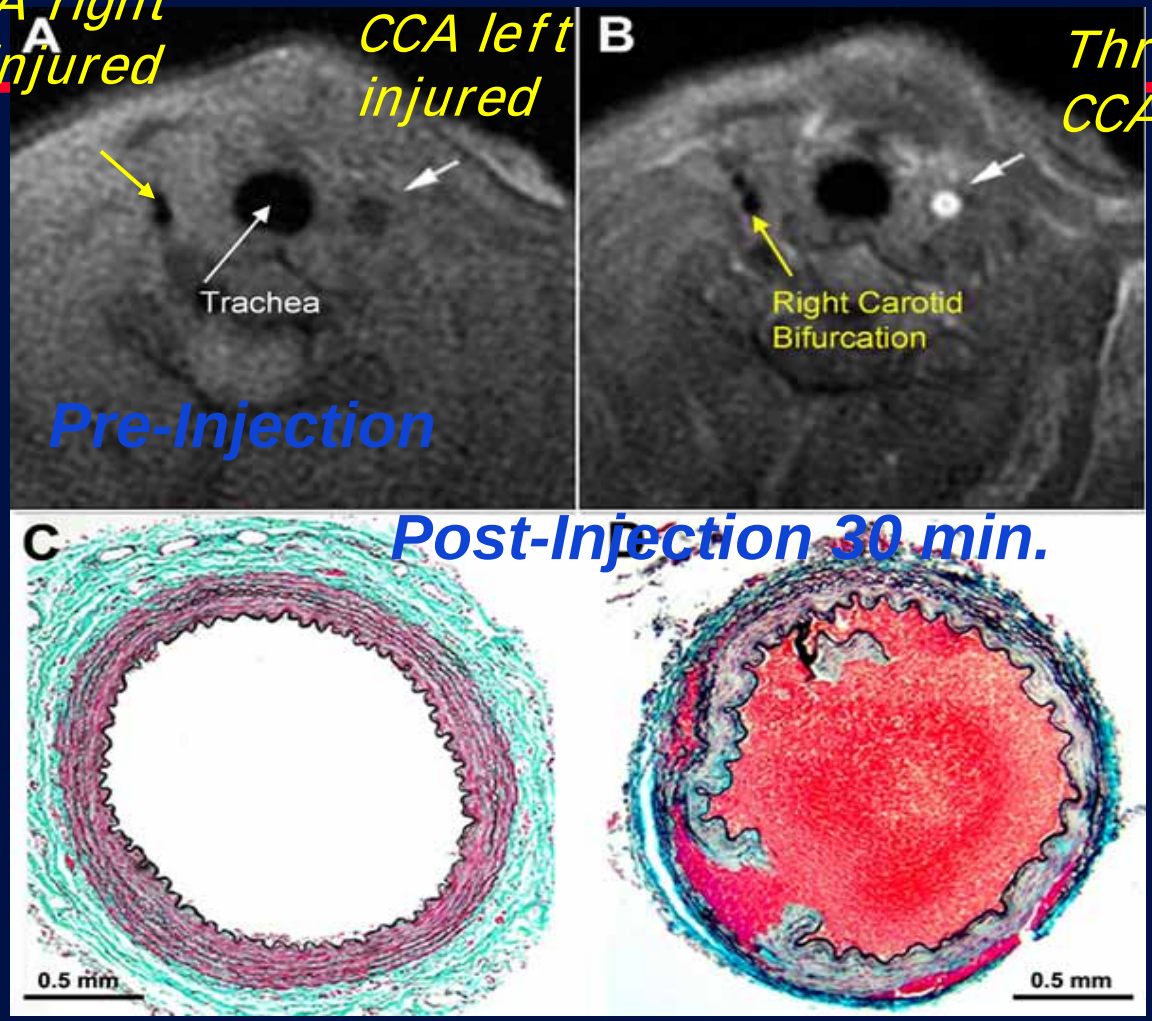


Fibrin specific
Cyclic peptide (EPIX)

CCA right uninjured

CCA left injured

Thrombus CCA left



Pre-Injection

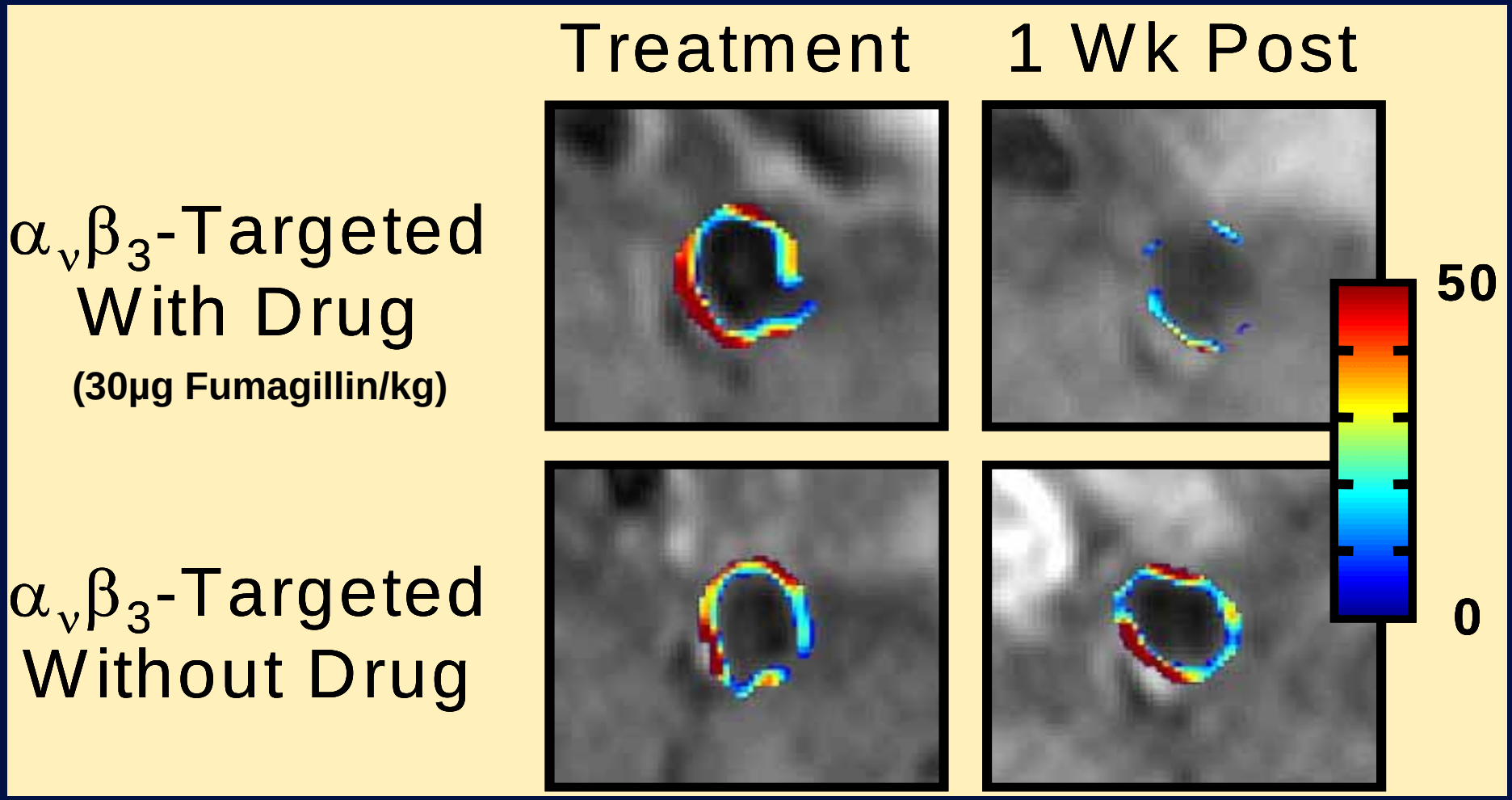
Post-Injection 30 min.

Sirol M; Fayad ZA et al. *Atherosclerosis* 2005:182:79-85

MOUNT SINAI SCHOOL OF MEDICINE

Imaging Science Laboratories

Anti-angiogenic Effects of Fumagillin Nanoparticles in Atherosclerotic Rabbits



Winter et al.

MR Atherosclerosis Imaging

- **Current status**
  - Soft tissue contrast
  - Safe
  - Depicts vessel wall/burden
  - Tissue characterization
  - Serial studies
- **Future**
  - Atherosclerosis progression
  - High resolution coronary imaging
  - Relationship of systemic atherosclerosis
  - Targeted contrast enhancement