FUTURE IN INTERVENTIONAL NEUROSURGERY/NEURORADIOLOGY

NEW ENGLAND CENTER FOR STROKE RESEARCH

Department of Radiology, Neurology and Neurosurgery
Division Neuroimaging and Intervention

Ajay K. Wakhloo, M.D., Ph.D., FAHA
Matthew J. Gounis, Ph.D.
I. Martijn J. van der Bom, Ph.D.
Juyu Chueh, Ph.D.

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Buenos Aires, Argentina

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DISCLOSURES

New England Center For Stroke Research

- Stryker Neurovascular (Consultant, Research Grant)
- Codman J&J (Consultant, Educational Grant)
- Covidien/ev3 (Consultant, Research Grant)
- Boston Biomedical Association (Consultant)
- Philips (MAB, Research Grant, Equipment support)
- Postgraduate Course Harvard Medical School (Speaker)
- Baptist Hospital, Miami, Florida (Speaker)
- NIH (ROI 1R21EB007767-01; 5R01NS045753-04:)
- 1-R21-NS061132-01A1

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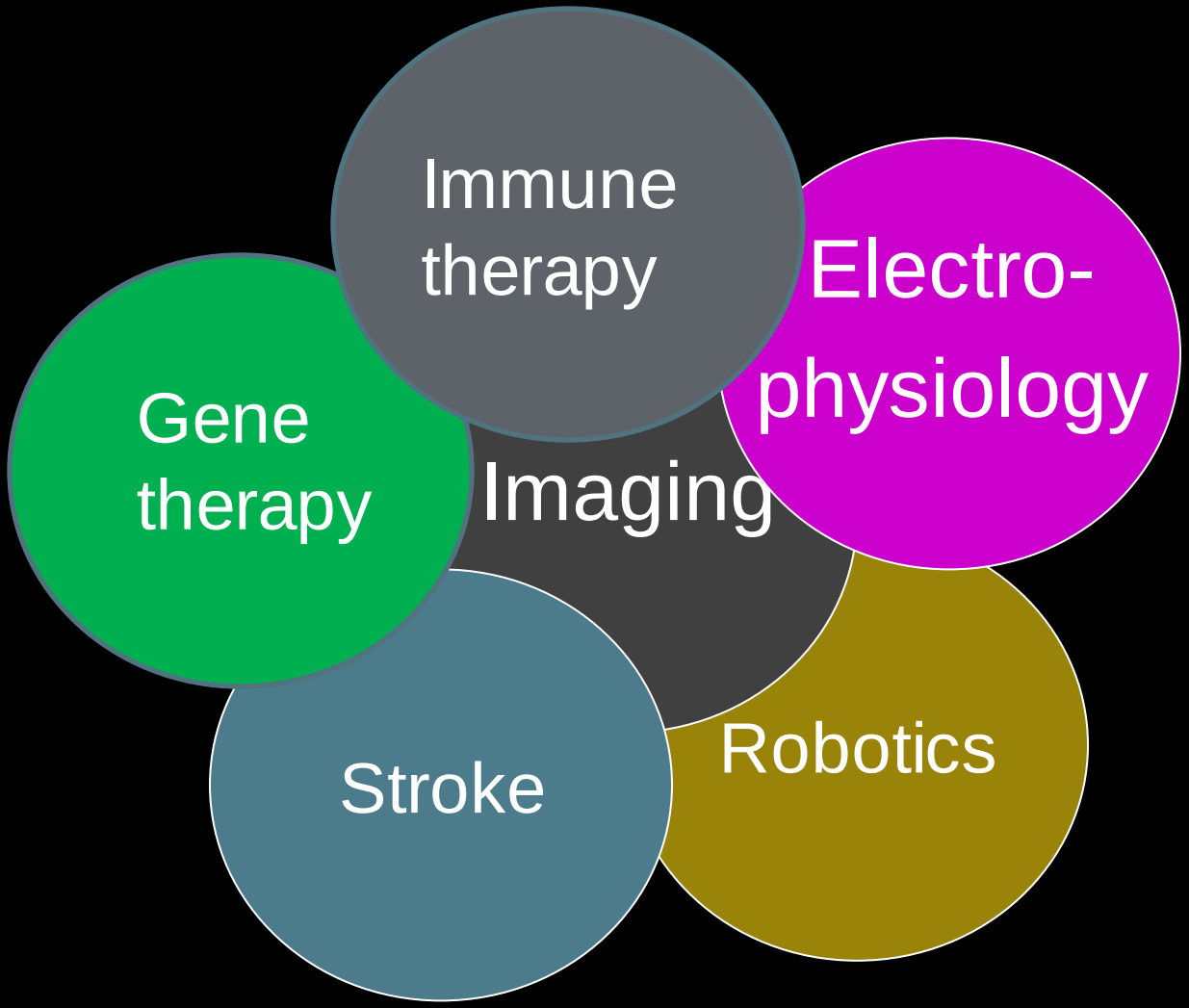
MAIN AREAS OF INNOVATION IN INTERVENTIONAL NEUROSURGERY



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RESEARCH FRONTIERS AND FUTURE IN INTERVENTIONAL NEUROSURGERY

OTHER AREAS ARE .....

- Pain Treatment
- Spine Intervention
- Training Standards in INS
- Politics of INS
- Changes in Healthcare and Impact on INS

…but our perspective and our ongoing Research and Future in INS…

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Innovation- the driving force

Starts generally in a well know environment
Motivation ("role model")
Different answers to same existing problems
Great changes begin with few supporters
Perseverance needed for execution
Ordinary people in extraordinary circumstances (self proof, alienation, poverty, minority, etc.)
Sensitivity (for observant, perceptive, understanding, connection, open-mindedness, etc.)
Inspiration (*inspīrō:* breath in)– the "divine dust"?

Inspiration leads to *Innovation* and is driven by unexpected observations and connections thereof

That's how I was doing angiograms…

New England Center For Stroke Research

Dr. Burt Lane, NYU in "The Exorcist"

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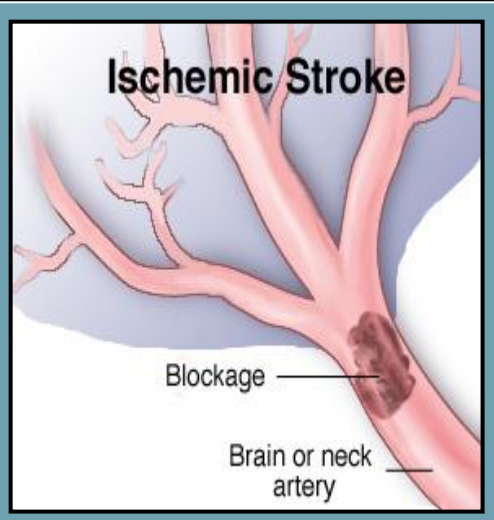
Major risk factors

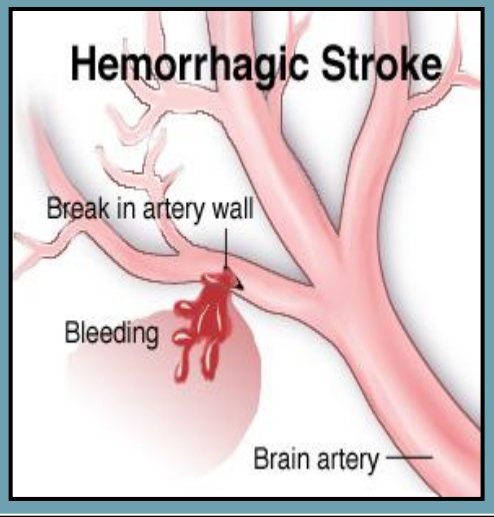
- Hypertension
- Atrial Fibrillation
- Carotid Artery Disease
- Intracerebral stenosis
- PFO
- CABG
- Aneurysms

Ischemic (blockage) 80-85%



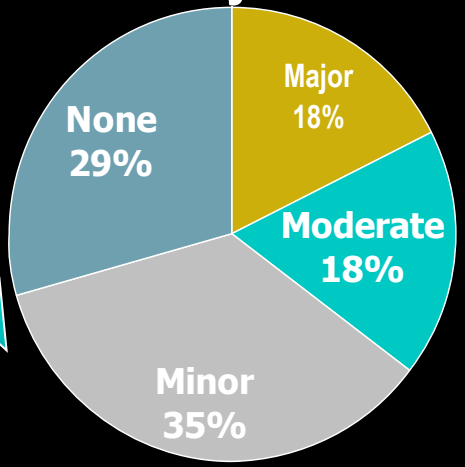
- 795,000 strokes annually
- 37,000 bleeds

Hemorrhagic (bleeding) 15-20%



7 M Stroke survivors: Level of disability

75-90%



10-25%

DEATH

MULTIMODALITY STROKE WORKFLOW

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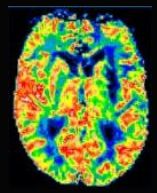
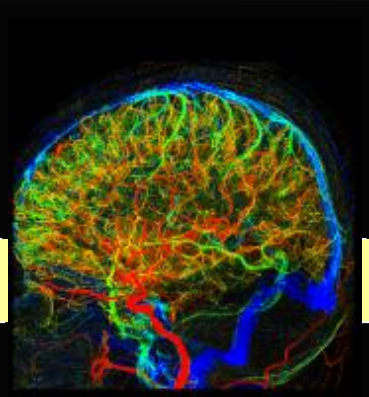
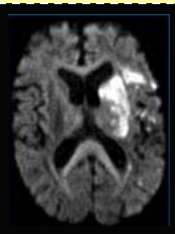
4-6 hours



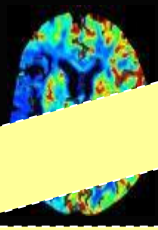


T1/T2, Perfusion, Diffusion MRI



Fluoroscopy, CE XperCT, XperCT, Perfusion X-ray

...IA Interventional Therapy



Stroke IV Therapy

...nological, Perfusion CT

Stroke Diagnostics

0-4.5 hours

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Envisioned Stroke Workflow

2D Fluoro
+ Rotational
Angiography

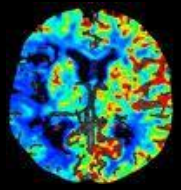
Xper CT

Hemorrhagic Stroke

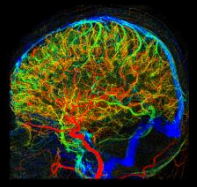
XperGuide For Ventricular Drainges

Xper CT

Ischemic Stroke



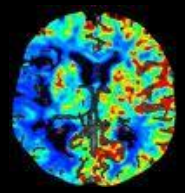
CBV



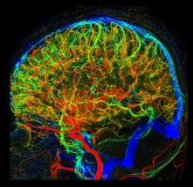
2D Perfusion

VasoCT

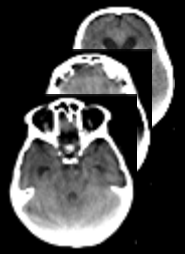
3D Roadmap on VasoCT



CBV



2D Perfusion



XperCT

Ischemic Stroke – “Singular Unit”

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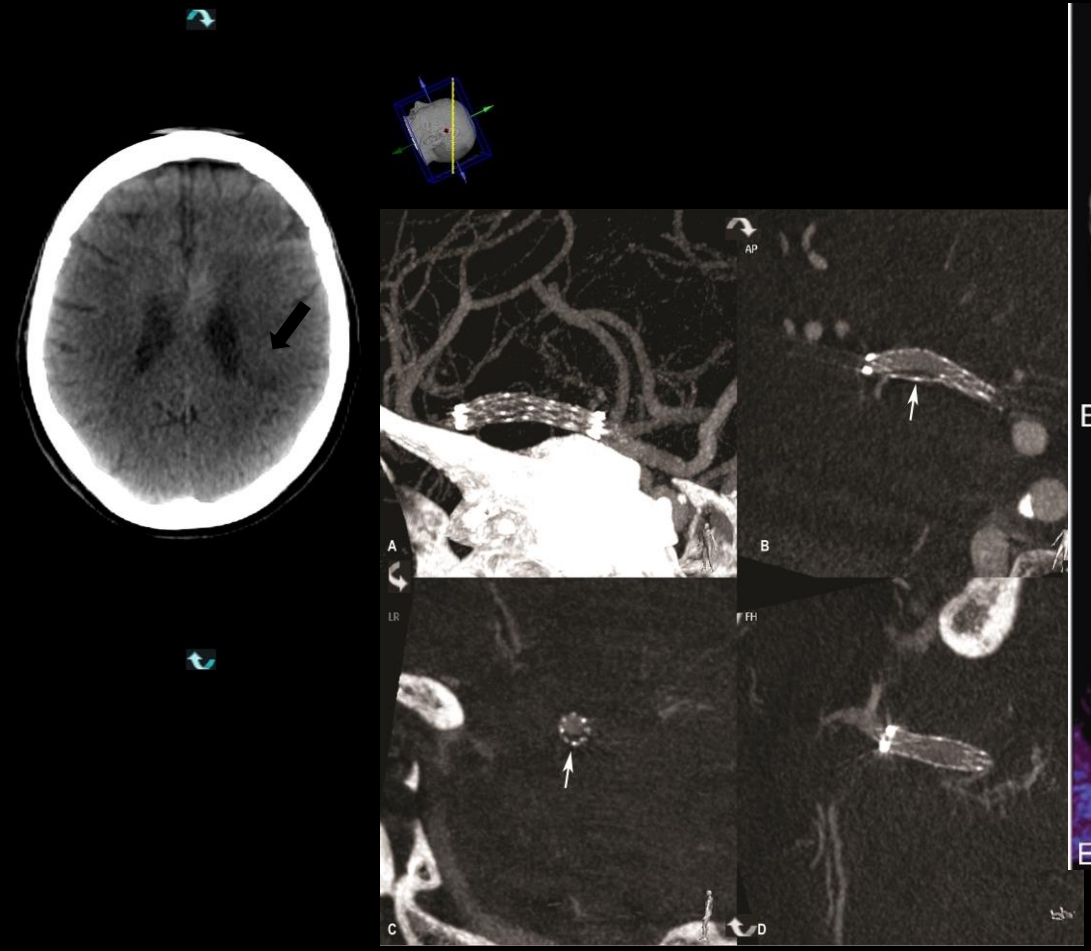
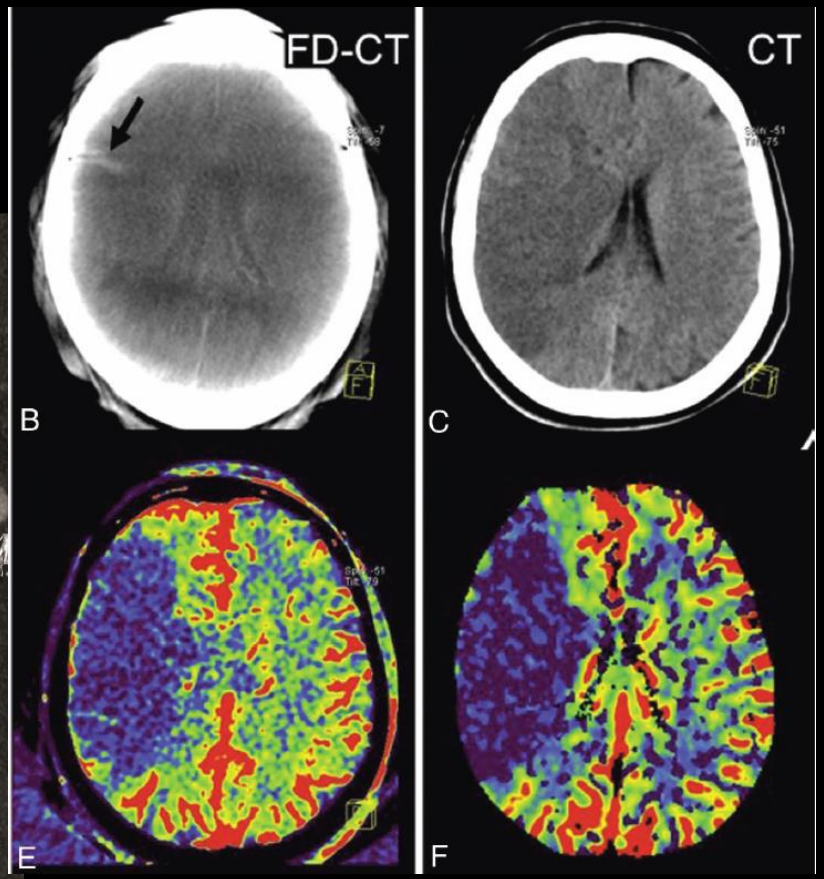
Imaging Integration: Flat-Detector (FD) Technology Enables *in situ:*

CT-like Imaging



High Resolution Stent Visualization

Functional Imaging



Struffert, Strother et al. AJNR, 2012

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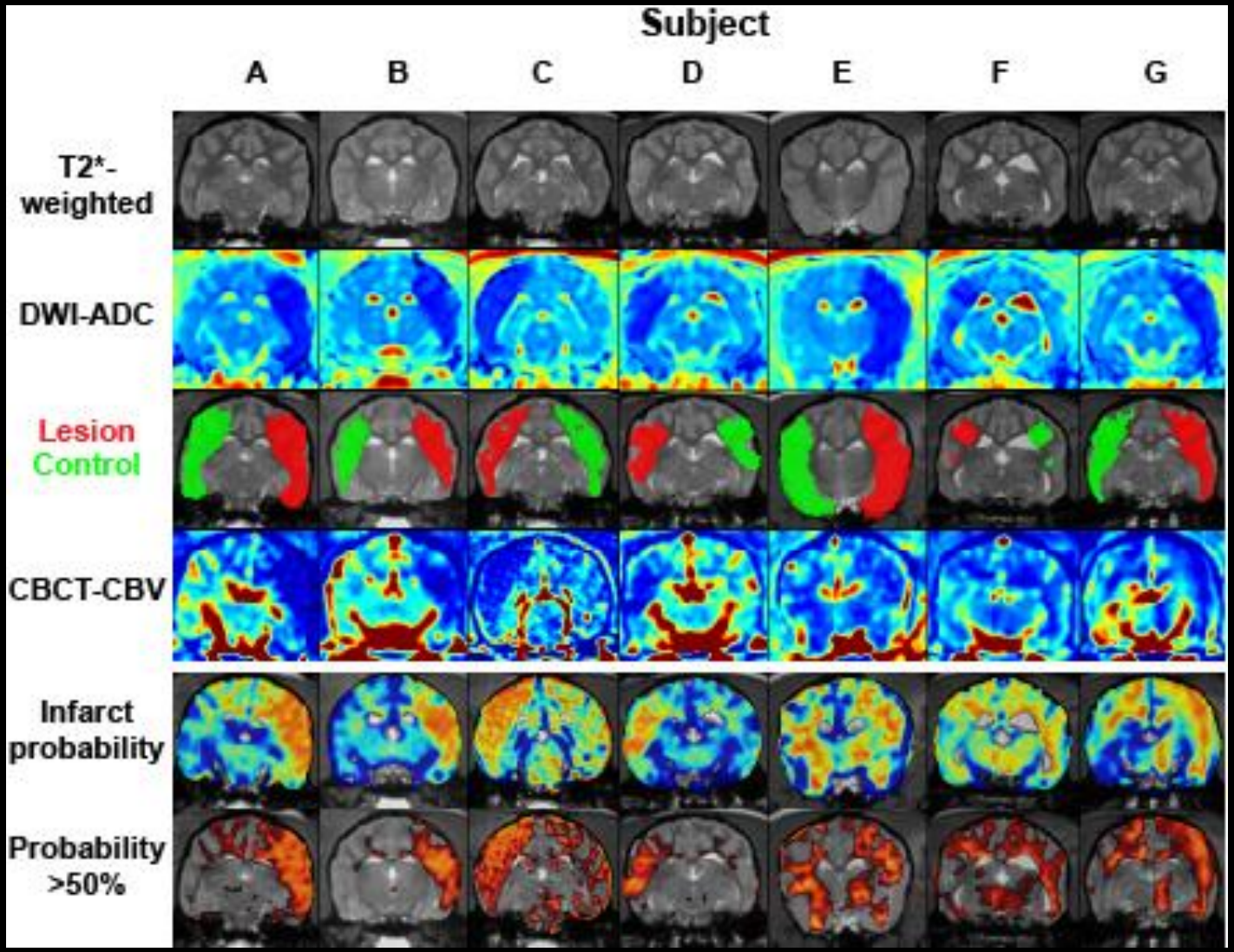
Voxel-Based Mapping of C-arm CT Cerebral Blood Volume to Infarct Probability in a Canine Model of Ischemic Stroke

Kajo van der Marel, Ju-Yu Chueh, Ajay K Wakhloo, Matthew J Gounis

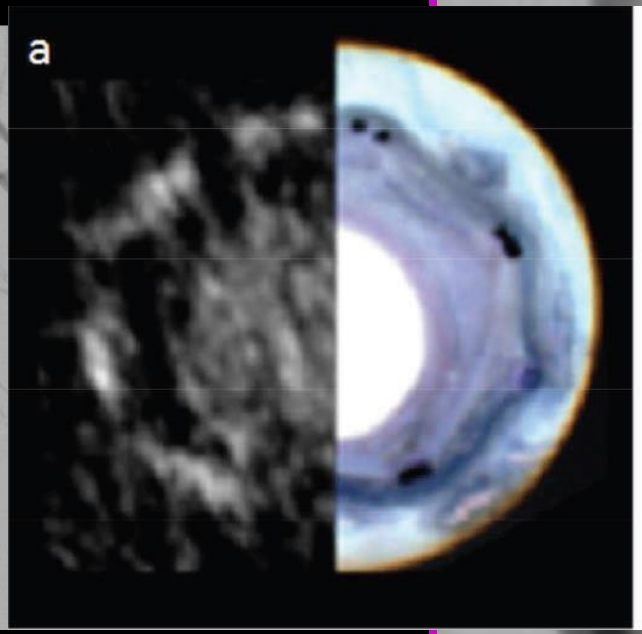


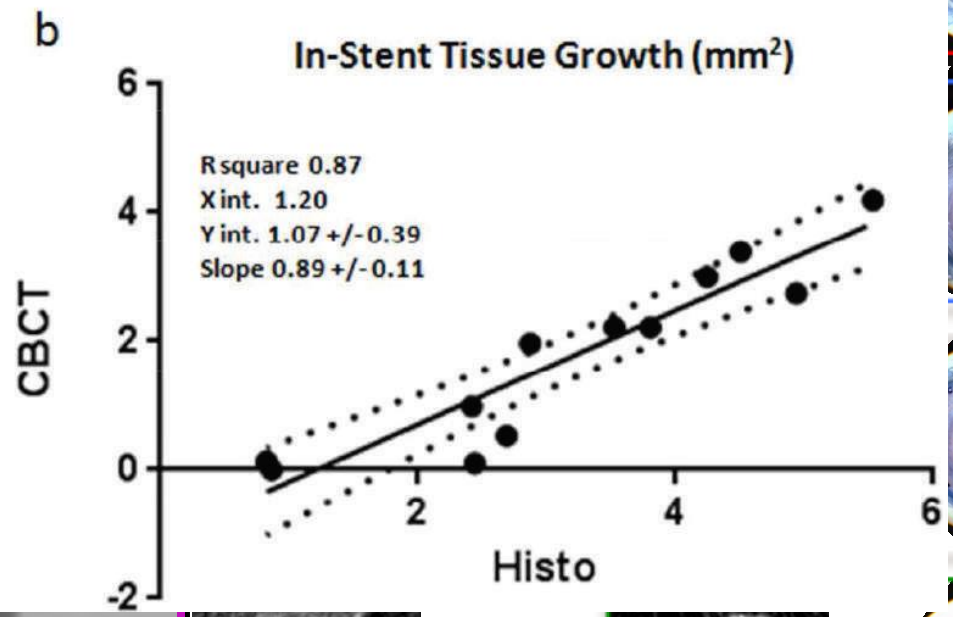
OPEN ACCESS

ORIGINAL RESEARCH

Quantitative analysis of high-resolution, contrast-enhanced, cone-beam CT for the detection of intracranial in-stent hyperplasia

Thomas F Flood,[1] Imramsjah M J van der Bom,[1] Lara Strittmatter,[2] Ajit S Puri,[1] Gregory H Hendricks,[2] Ajay K Wakhloo,[1] Matthew J Gounis[1]





High-Resolution Optical and Angiographic CT Imaging of Flow-Diverter Stents for Assessment of Vessel Wall Apposition

Kajo van der Marel, Matthew J. Gounis, Robert M. King, Ajay K. Wakhloo, Ajit S. Puri

New England Center for Stroke Research, Department of Radiology,
University of Massachusetts Medical School, Worcester, MA, USA

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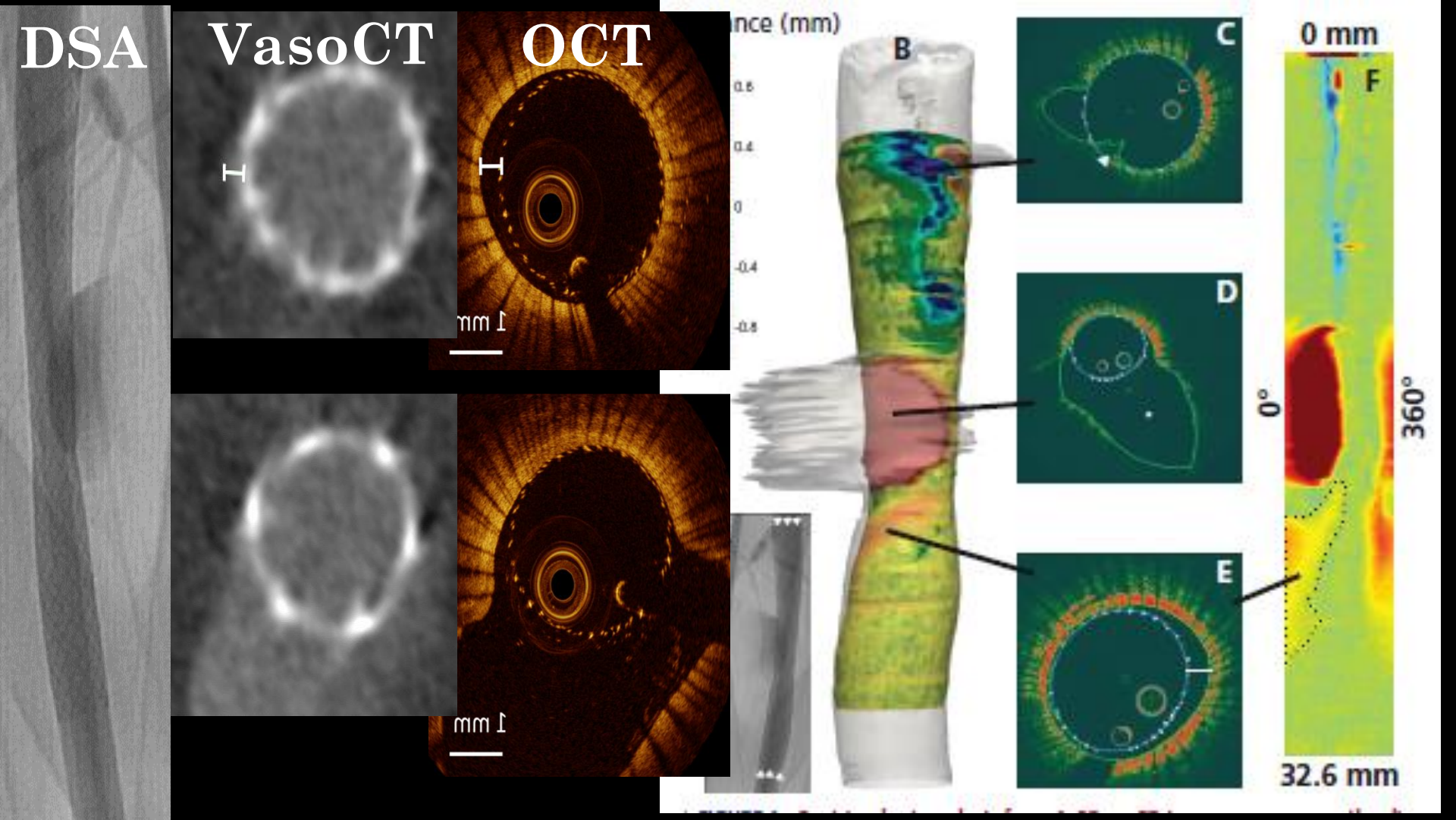
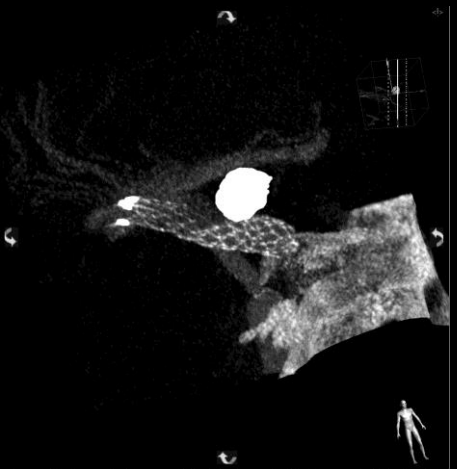
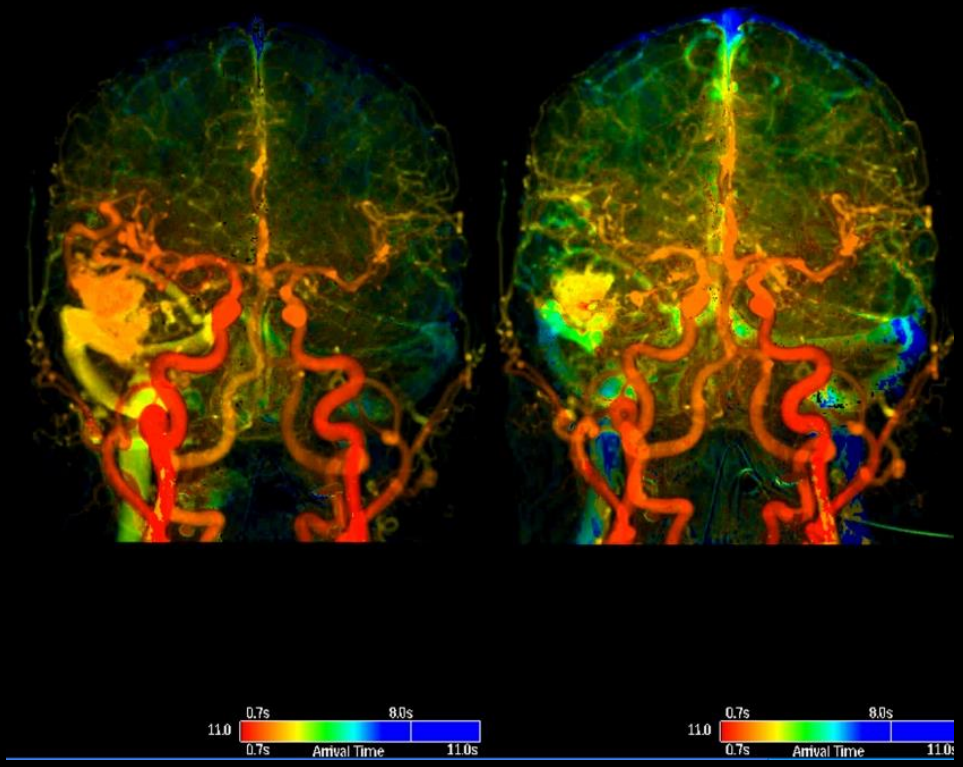


Hemorrhagic Stroke

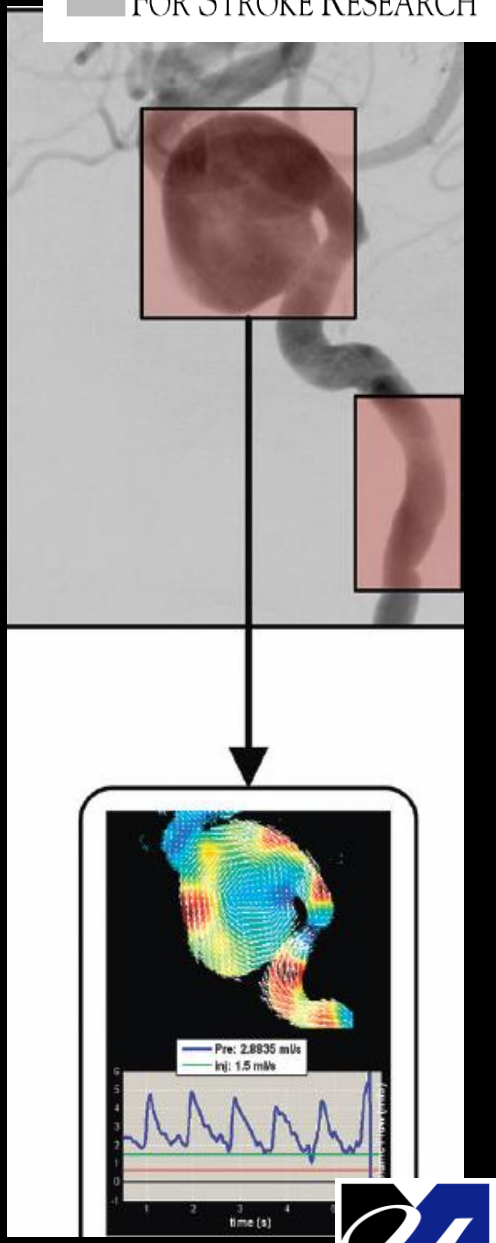
Flat-Detector Technology Enables *in situ:*

3D Angiography





Color-Coded DSA



Pereira et al. AJNR, 2012

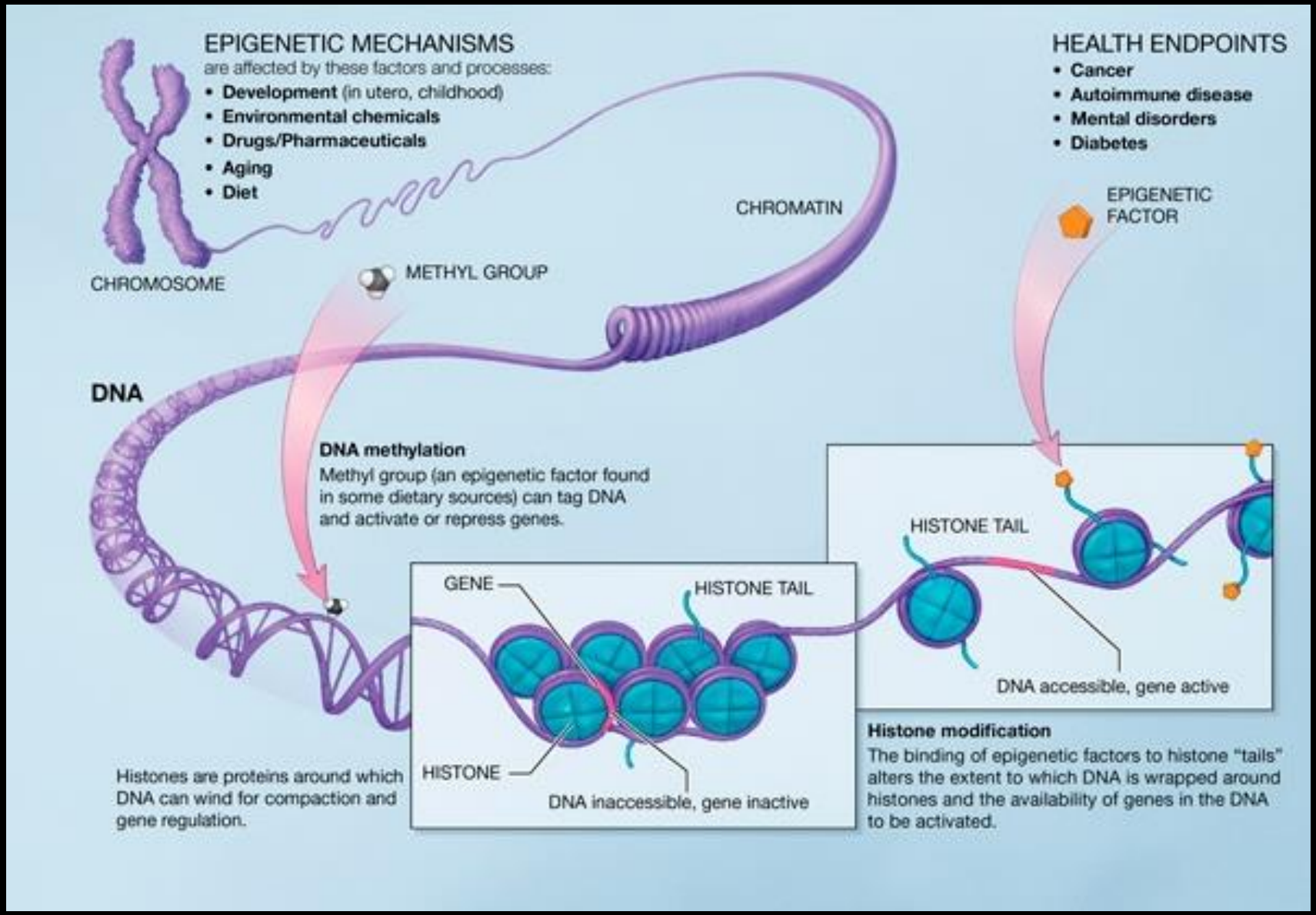
KEY QUESTIONS

- 1. what are our current tools in the angiography suite ?
-
- 2. what do we want to do with the angiography suite?

- 3. what are our limitations and how should the future Neurovascular Unit look like?


GAP
SFCA

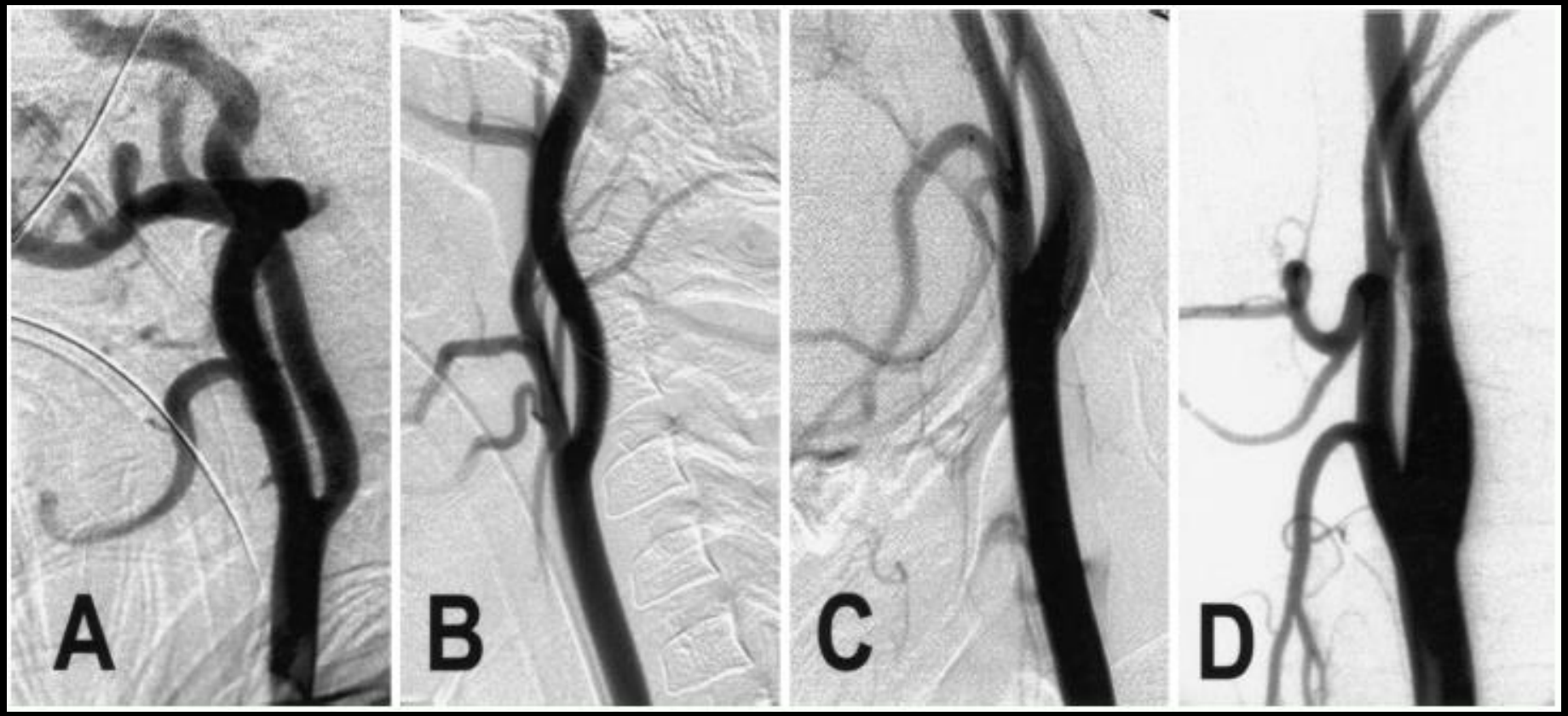
EPIGENETICS



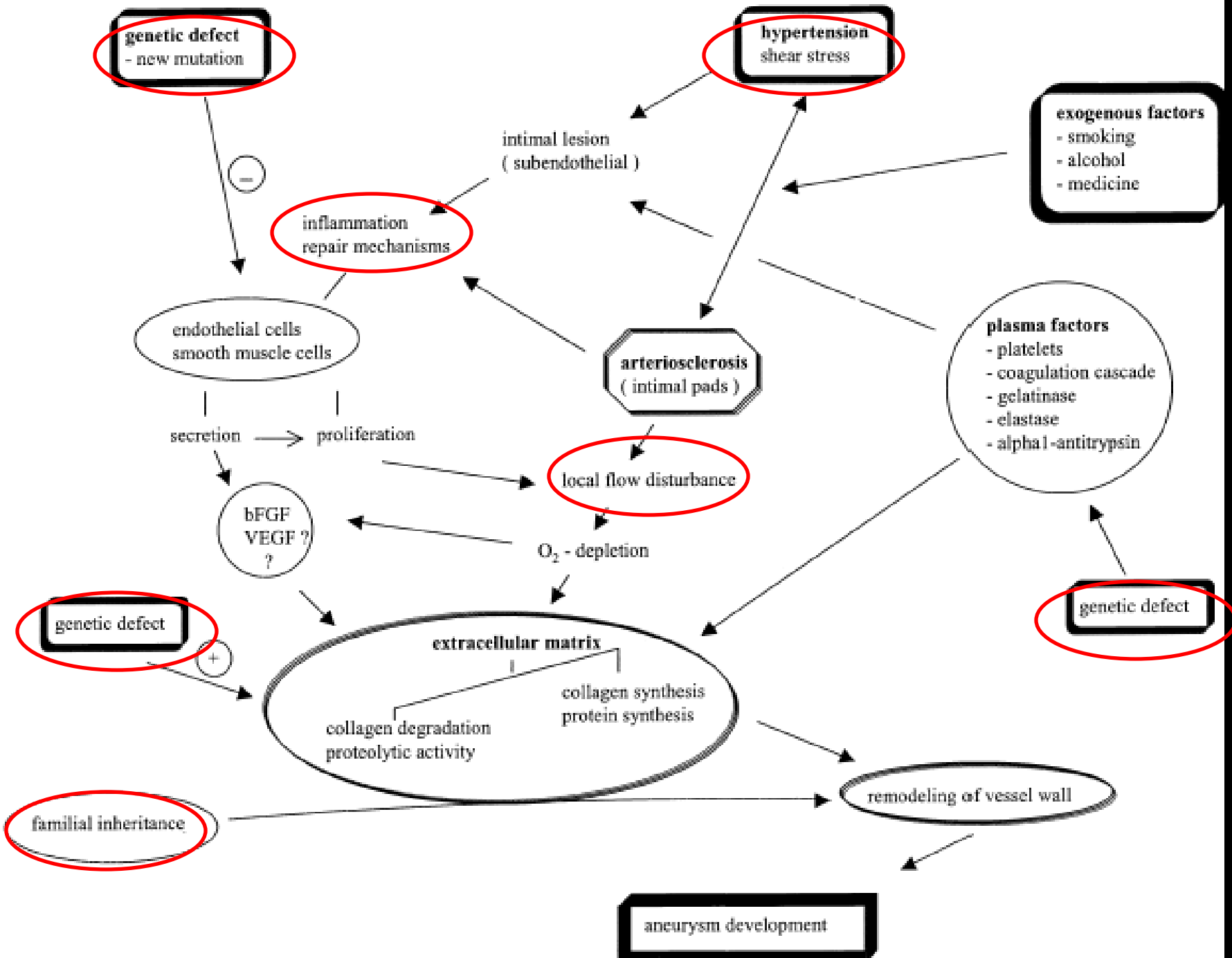
Source: Wikipedia April 2012

MORPHOLOGICAL AGE-DEPENDENT DEVELOPMENT OF THE HUMAN CAROTID BIFURCATION

1-y-o-m 5.5-y-o-m 15.7-y-o-m 33-y-o-m



Seong J, Lieber BB, Wakhloo AK. J Biomech Eng 38:453-465, 2005


genetic defect
- new mutation
hypertension
shear stress
exogenous factors
- smoking
- alcohol
- medicine
intimal lesion
(subendothelial)
inflammation
repair mechanisms
endothelial cells
smooth muscle cells
arteriosclerosis
(intimal pads)
plasma factors
- platelets
- coagulation cascade
- gelatinase
- elastase
- alpha1-antitrypsin
secretion
proliferation
local flow disturbance
bFGF
VEGF ?
?
O_2 - depletion
genetic defect
genetic defect
extracellular matrix
collagen synthesis
protein synthesis
collagen degradation
proteolytic activity
familial inheritance
remodeling of vessel wall
aneurysm development

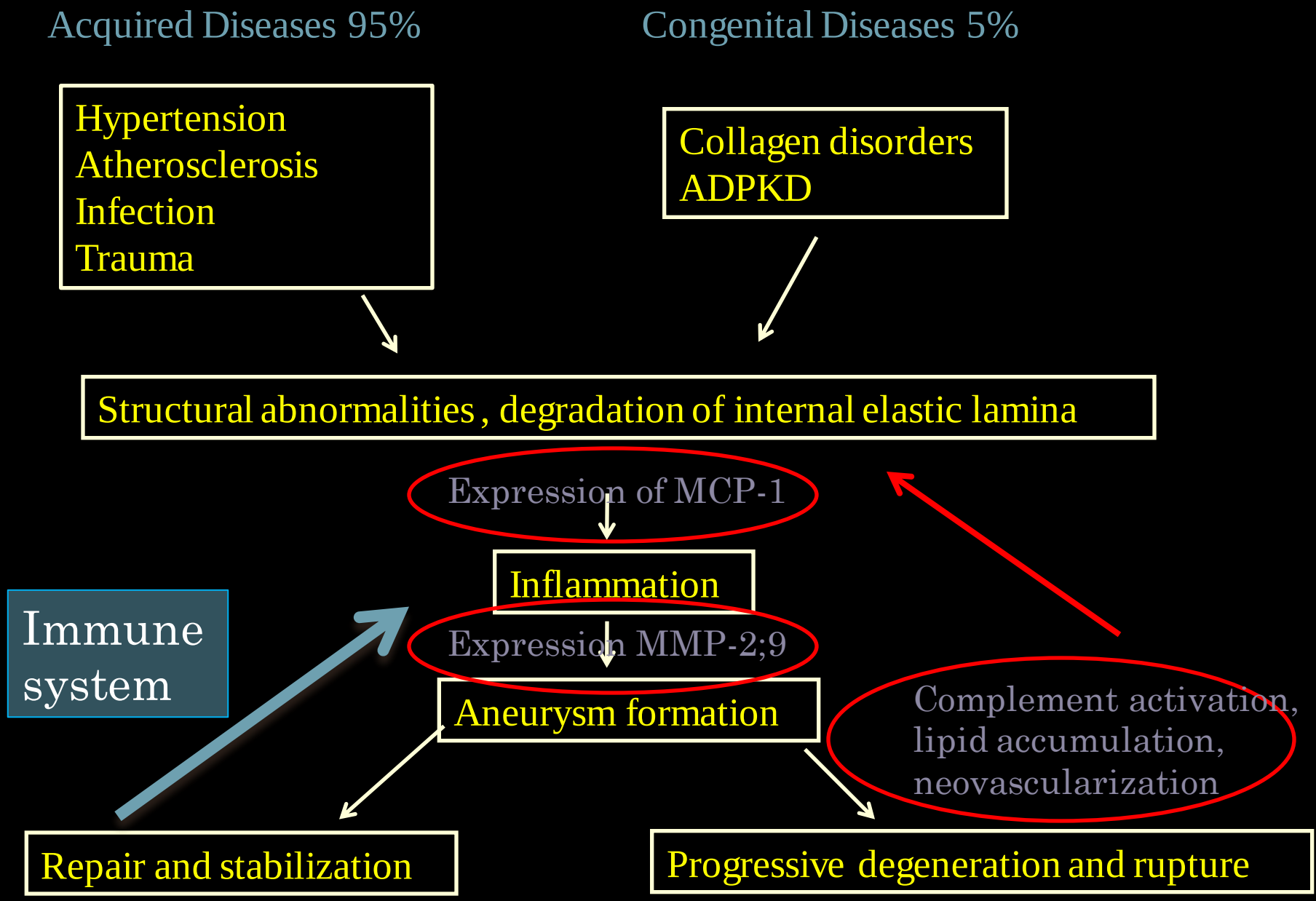
WHERE ARE WE TODAY WITH ATHEROSCLEROSIS?

- ATVB in focus life after GWAS: Functional genomics in vascular biology – Recent studies of the human chromosome 9p21 locus, which is associated with atherosclerosis in human population. *Arteriosclerosis, Thrombosis, and Vascular Biology. 2012;32:196-206*

- Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque. *Nat Genet. 2011;43:940-7*

- A gene expression signature that classifies human atherosclerotic plaque by relative inflammation status. *Circ Cardiovasc Genet. 2011;4:595-604*

- Carotid plaque and candidate genes related to inflammation and endothelial function in hispanics from Northern Manhattan. *Stroke.2011;42:889-896*


Acquired Diseases 95%
Congenital Diseases 5%
Hypertension
Atherosclerosis
Infection
Trauma
Collagen disorders
ADPKD
Structural abnormalities , degradation of internal elastic lamina
Expression of MCP-1
Inflammation
Expression MMP-2;9
Aneurysm formation
Immune system
Complement activation, lipid accumulation, neovascularization
Repair and stabilization
Progressive degeneration and rupture

MONOCYTE CHEMOATTRACTANT PROTEIN-1 (MCP-1)

Impact of Monocyte Chemoattractant Protein-1 Deficiency on Cerebral Aneurysm Formation

Tomohiro Aoki, MD; Hiroharu Kataoka, MD, PhD; Ryota Ishibashi, MD; Kazuhiko Nozaki, MD, PhD; Kensuke Egashira, MD, PhD; Nobuo Hashimoto, MD, PhD

Background and Purpose—Recent studies have suggested that chronic inflammation actively participates in cerebral aneurysm (CA) formation. Macrophages accumulate in CA walls and express proinflammatory genes promoting CA progression, but the molecular mechanisms of monocyte/macrophage recruitment into CA walls remain to be elucidated.

Methods—Monocyte chemoattractant protein-1 (MCP-1) expression in experimentally induced CAs was assessed by immunohistochemistry and Western blotting. The role of MCP-1 in CA formation was examined by MCP-$1^{-/-}$ mice and a plasmid DNA encoding a dominant negative mutant of MCP-1 (7ND). MCP-1 expression in human CAs was examined by immunohistochemistry.

Results—MCP-1 expression was upregulated in aneurysmal walls at the early stage of CA formation. MCP-$1^{-/-}$ mice exhibited a significant decrease of CA formation and macrophage accumulation with decreased expression of matrix metalloproteinase-2, -9, and inducible nitric oxide synthase. Immunohistochemistry for the DNA binding form of nuclear factor-kappa B showed nuclear factor-kappa B activation in MCP-1-expressing cells. Blockade of MCP-1 activity by 7ND resulted in the inhibition of CA progression in rats. In human CAs, MCP-1 was also expressed in CA walls.

Conclusions—These data suggest that MCP-1 plays a crucial role in CA formation as a major chemoattractant for monocyte/macrophage. MCP-1 expression in CA walls is induced through nuclear factor-kappa B activation. MCP-1 may be a novel therapeutic target of medical treatment preventing CA progression. (***Stroke***. **2009;40:942-951.**)

ROLE OF ANTI-INFLAMMATORY DRUGS

Aspirin as a Promising Agent for Decreasing Incidence of Cerebral Aneurysm Rupture

David M. Hasan, MD; Kelly B. Mahaney, MD; Robert D. Brown, Jr, MD, MPH; Irene Meissner, MD; David G. Piepgras, MD; John Huston, MD; Ana W. Capuano, MPS, MS; James C. Torner, PhD; for the International Study of Unruptured Intracranial Aneurysms Investigators

Background and Purpose—Chronic inflammation is postulated as an important phenomenon in intracranial aneurysm wall pathophysiology. This study was conducted to determine if aspirin use impacts the occurrence of intracranial aneurysm rupture.

Methods—Subjects enrolled in the International Study of Unruptured Intracranial Aneurysms (ISUIA) were selected from the prospective untreated cohort (n=1691) in a nested case–control study. Cases were subjects who subsequently had a proven aneurysmal subarachnoid hemorrhage during a 5-year follow-up period. Four control subjects were matched to each case by site and size of aneurysm (58 cases, 213 control subjects). Frequency of aspirin use was determined at baseline interview. Aspirin frequency groups were analyzed for risk of aneurysmal hemorrhage. Bivariable and multivariable analyses were performed using conditional logistic regression.

Results—A trend of a protective effect for risk of unruptured intracranial aneurysm rupture was observed. Patients who used aspirin 3× weekly to daily had an OR for hemorrhage of 0.40 (95% CI, 0.18–0.87); reference group, no use of aspirin), patients in the "< once a month" group had an OR of 0.80 (95% CI, 0.31–2.05), and patients in the "> once a month to 2×/week" group had an OR of 0.87 (95% CI, 0.27–2.81; $P=0.025$). In multivariable risk factor analyses, patients who used aspirin 3 times weekly to daily had a significantly lower odds of hemorrhage (adjusted OR, 0.27; 95% CI, 0.11–0.67; $P=0.03$) compared with those who never take aspirin.

Conclusions—Frequent aspirin use may confer a protective effect for risk of intracranial aneurysm rupture. Future investigation in animal models and clinical studies is needed. **(*Stroke*. 2011;42:3156-3162.)**

STATIN'S ROLE IN INHIBITION OF INFLAMMATION

HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE INHIBITORS (STATINS)

Simvastatin Suppresses the Progression of Experimentally Induced Cerebral Aneurysms in Rats

Tomohiro Aoki, MD; Hiroharu Kataoka, MD, PhD; Ryota Ishibashi, MD; Kazuhiko Nozaki, MD, PhD; Nobuo Hashimoto, MD, PhD

Background and Purpose—The pathophysiology of cerebral aneurysms (CAs) is linked to chronic inflammation and degradation of extracellular matrix in vascular walls. Because statins have protective effects on various vascular diseases independent of their lipid-lowering effects, we investigated the effect of simvastatin on CA progression.

Methods—CAs were induced in Sprague-Dawley rats with or without oral administration of simvastatin. The size and media thickness of CAs was evaluated 3 months after aneurysm induction. Expression of macrophage chemoattractant protein-1, vascular cell adhesion molecule-1, endothelial nitric oxide synthase, interleukin-1β, inducible nitric oxide synthase, matrix metalloproteinase-2, and matrix metalloproteinase-9 in aneurysmal walls was examined by reverse transcriptase–polymerase chain reaction and immunohistochemistry. To examine whether simvastatin has a suppressive effect on preexisting CAs, simvastatin administration started at 1 month after aneurysm induction.

Results—Rats treated with simvastatin exhibited a significant increase in media thickness and a significant reduction in aneurysmal size compared with control rats. Treatment with simvastatin resulted in reduced expression of macrophage chemoattractant protein-1 and vascular cell adhesion molecule-1, increased expression of endothelial nitric oxide synthase, and reduced the number of macrophage infiltration. In quantitative polymerase chain reaction and immunohistochemistry, simvastatin significantly inhibited upregulated expression of interleukin-1β, inducible nitric oxide synthase, matrix metalloproteinase-2, and matrix metalloproteinase-9 associated with CA progression. Gelatin zymography revealed decreased activity of matrix metalloproteinase-2 and matrix metalloproteinase-9 in aneurysmal walls by simvastatin treatment. Simvastatin also effectively inhibited aneurysm enlargement and thinning of the media of preexisting CAs.

Conclusions—Treatment with simvastatin suppresses the development of CAs by inhibiting inflammatory reactions in aneurysmal walls. Simvastatin also has a preventive effect on the progression of preexisting CAs. Simvastatin is a promising candidate of a novel medical treatment for the prevention of CA progression. (***Stroke***. **2008;39:1276-1285.**)

PROPOSED NON-INVASIVE TARGETED TREATMENT

- Transfection of 7ND (dominant negative DNA of MCP-1) into skeletal muscle for anti-MCP-1 gene therapy . May prevent aneurysm growth and rupture.

- Anti-inflammatory drug, e.g., Aspirin (Corticosteroids?)
  - Inhibiting of MMP-2 and MMP-9
  - Inhibition of TNF-α
  - Reduction of NF κB
  - Antiplatelet effect?

- Statins
  - Reduced expression o MCP-1 and VCAM-1
  - Increased expression of eNOS
  - Reduced infiltration of Macrophages

SUMMARY

- Understanding Epigenetics may be critical in CV disease including brain aneurysms
- Carotid atherosclerotic disease and brain aneurysms may be linked
- NF κB plays a role in cellular response to stress, to cytokines, lipid deposition and immune response
- miRNA important regulatory molecule involved in dysregulation of NF κB
- Drugs targeted at inhibition of MCP-1, VCAM-1, iNOS, MMP-2 and MMP-2
- Flow diverter may serve as an excellent endovascular bypass to repair CV diseased segments

II. NEURODEGENERATIVE DISORDERS

Parkinson's

Tay Sachs

ALS

Huntington’s

ORIGINAL RESEARCH

Frameless multimodal image guidance of localized convection-enhanced delivery of therapeutics in the brain

- ✓ Developments in genetics and virology have resulted in new therapeutic agents (viral vectors, antibodies, and immunotoxins) for neurodegenerative disorders (Huntington's, Tay-Sachs, Parkinson's).
- ✓ Because of their macromolecular size, these drugs cannot be given systemically.
- ✓ Convection enhanced delivery (CED): Drugs are forced directly into the anatomy of interest through a needle/cannula (localized and small volume).
- ✓ Objective: accurate placement of microcannula using multimodal image-guidance by machine calibration

IMJ Bom et al., J Neurointerv Surg. 2013 Jan 1;5(1):69-72

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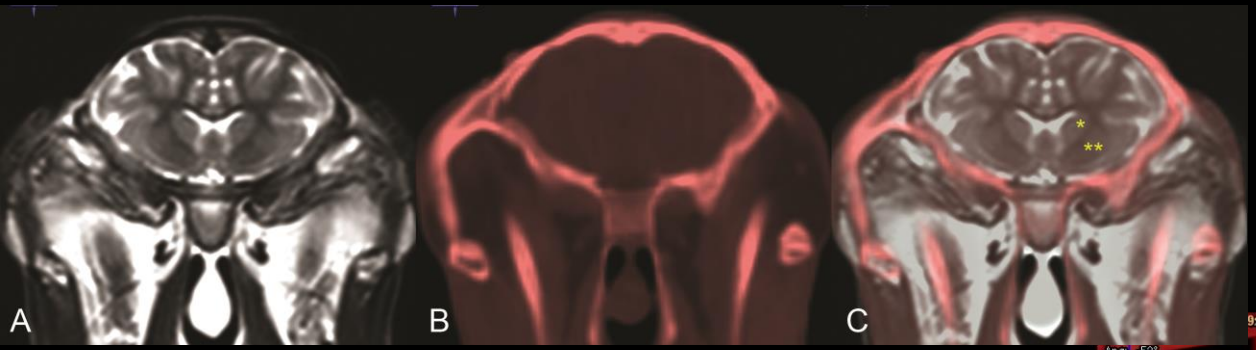
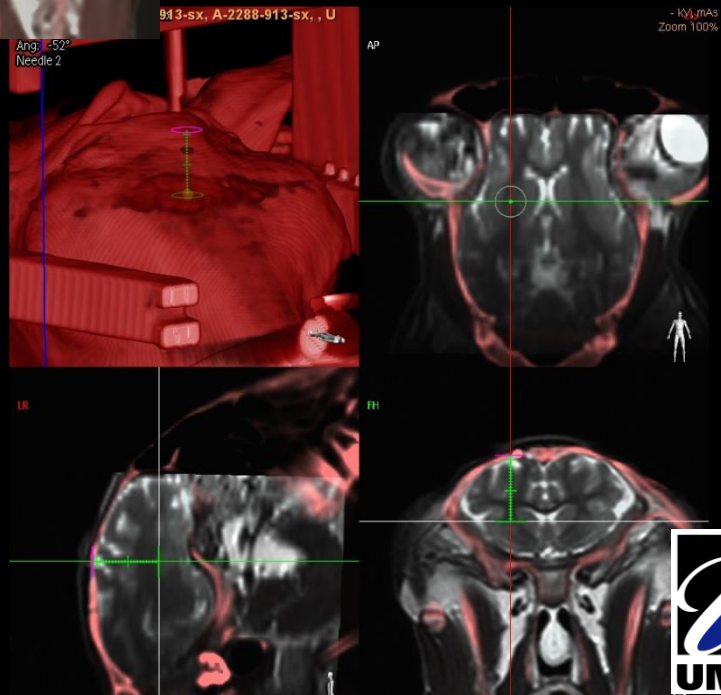
Delivery of Therapeutics for Neurodegenerative Disease

Multi-Modal Image-Guidance of Localized Drug Delivery in Huntington's Disease





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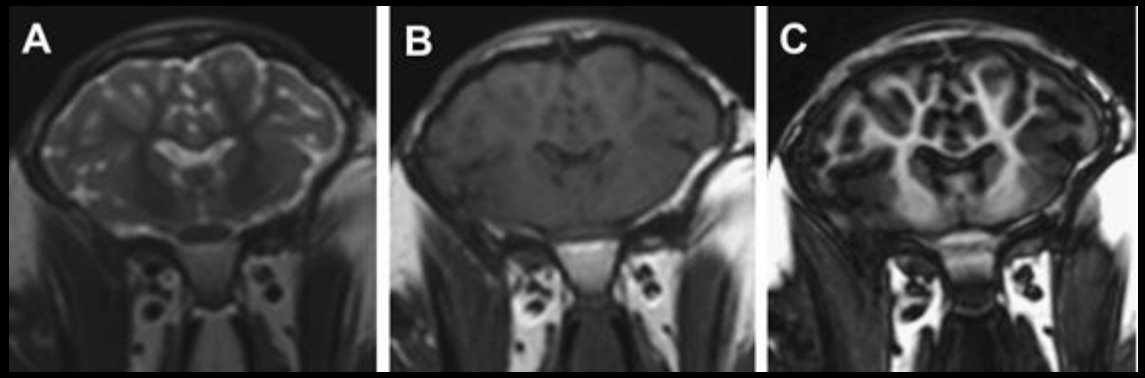
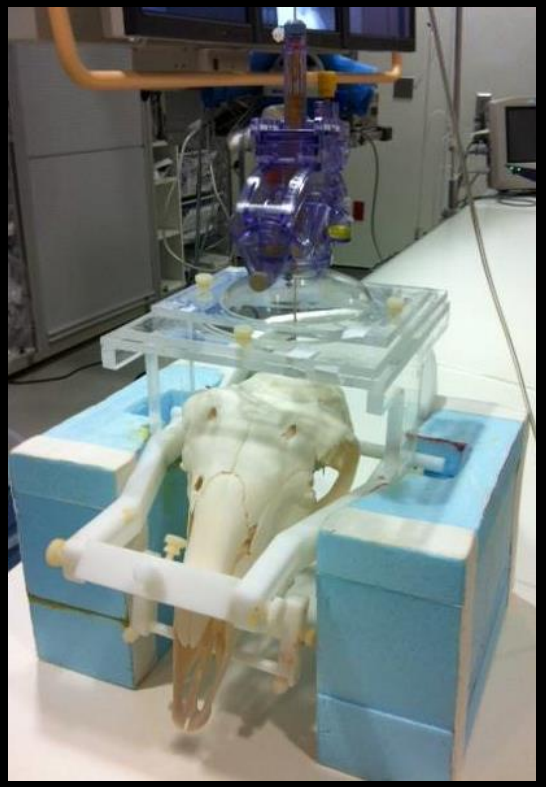
Materials & Methods

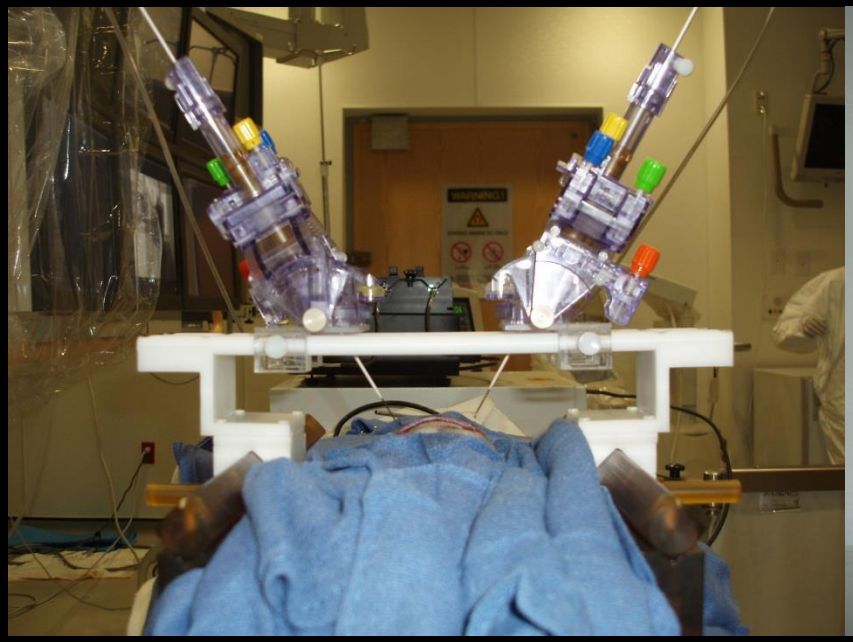
- ✓ Pre-clinical trail to test safety and efficacy of adeno-associated viral vector (AAV) delivery of shRNAmir for knockdown mutant Huntington in brain of sheep.
- ✓ Prior to CED surgery, MR imaging (T2w-TSE, T1w-TSE, and MPRAGE) was performed for surgery planning.
- ✓ Non-invasive frame to hold and manipulate cannula was mounted onto the skull.

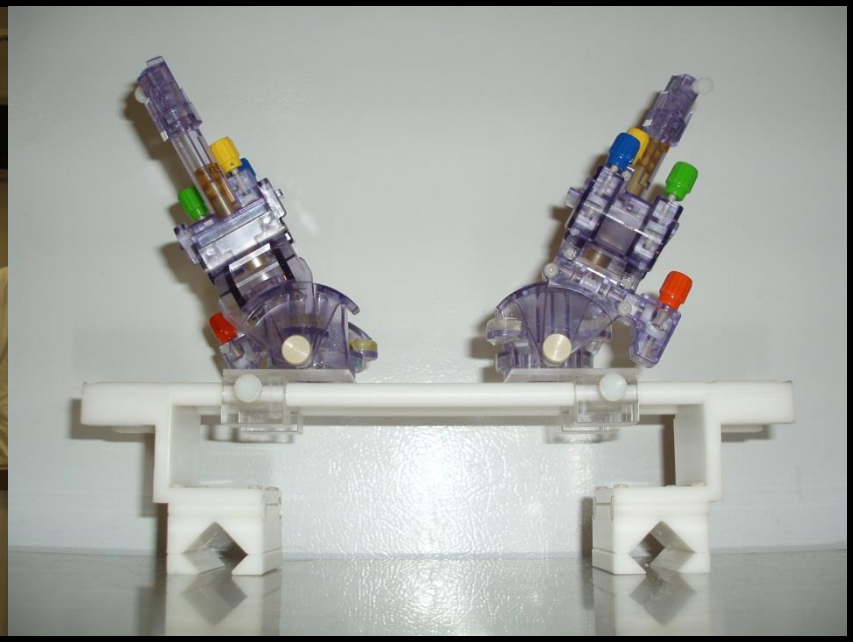




Materials & Methods

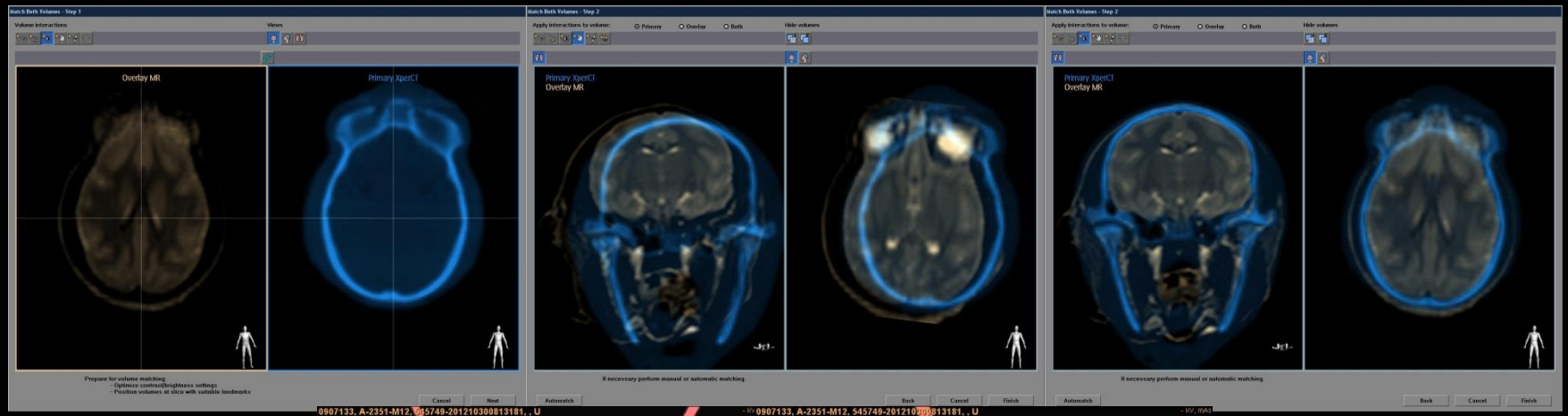
- ✓ Pre-clinical trail to test safety and efficacy of rAAV-mediated gene therapy for treatment of Tay-Sachs disease in non-human primates.
- ✓ Prior to CED surgery, MR imaging (T2w-TSE, T1w-TSE, and MPRAGE) was performed for surgery planning.
- ✓ Non-invasive frame to hold and manipulate cannula was mounted onto the skull.

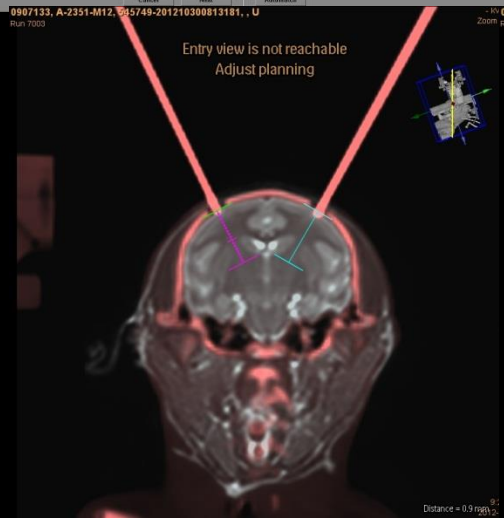


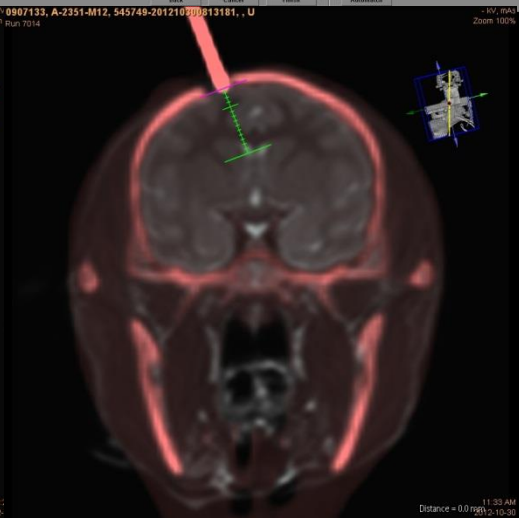


Materials & Methods

- ✓ Incisions and burr holes were created for bilateral thalamic injections and unilateral ventricle injection.
- ✓ CBCT data was acquired and registered with MRI data.
- ✓ Cannula placement was planned on registered CBCT and MRI data.



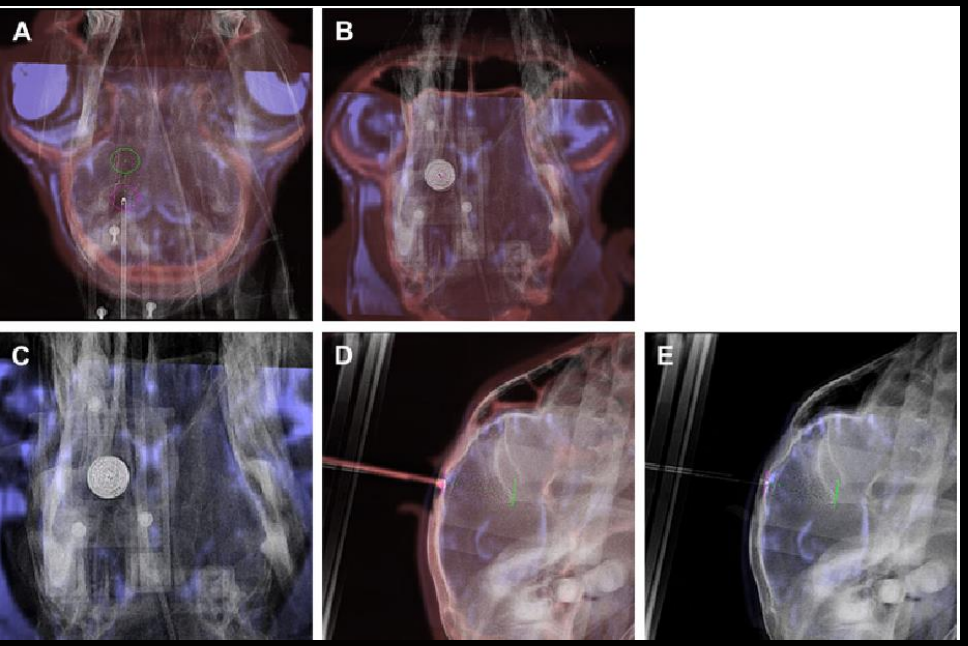




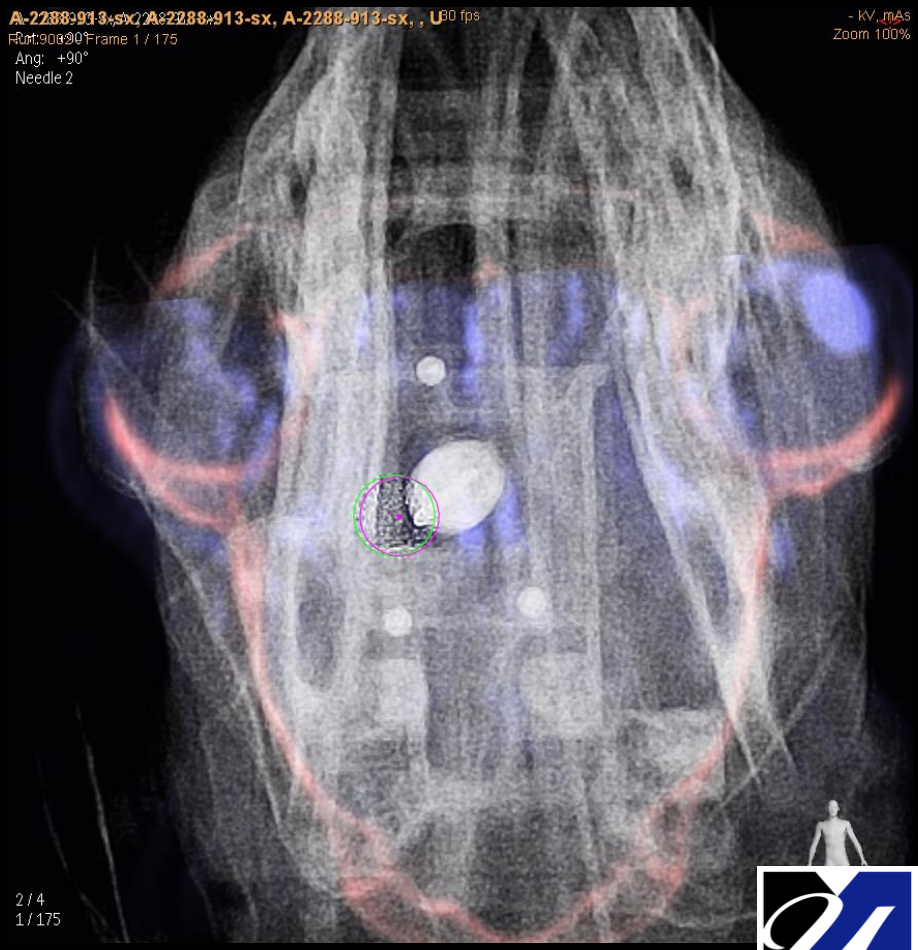
NEW ENGLAND CENTER FOR STROKE RESEARCH

Delivery of Therapeutics for Neurodegenerative Disease

Real-Time Imaging Feedback During Cannula Placement



van der Bom et al. JNIS, 2013



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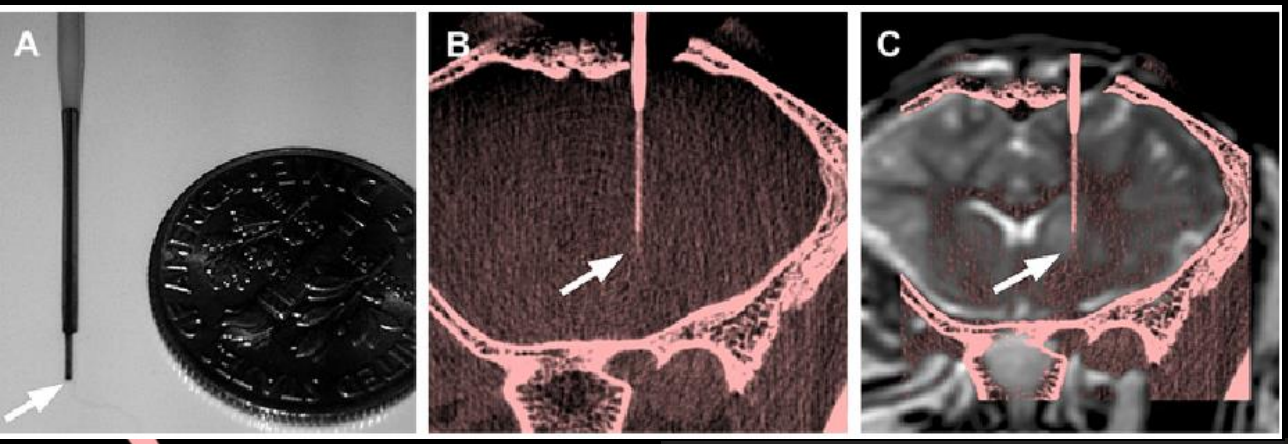
NEW ENGLAND CENTER FOR STROKE RESEARCH

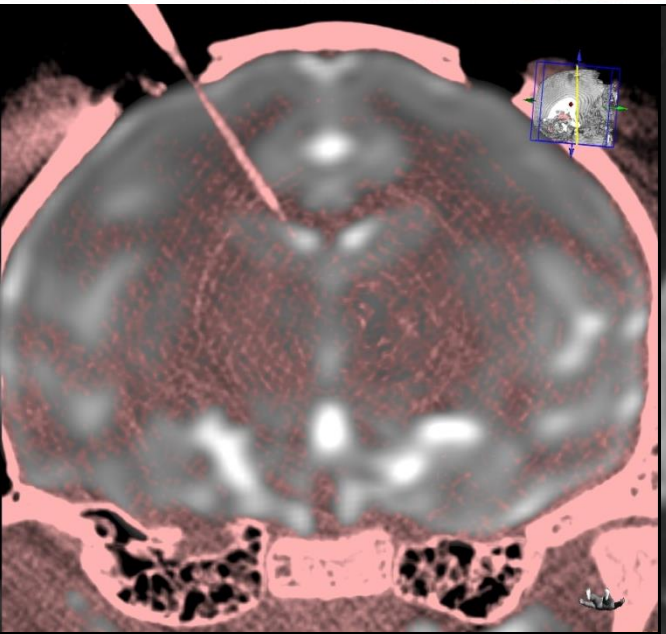
Delivery of Therapeutics for Neurodegenerative Disease

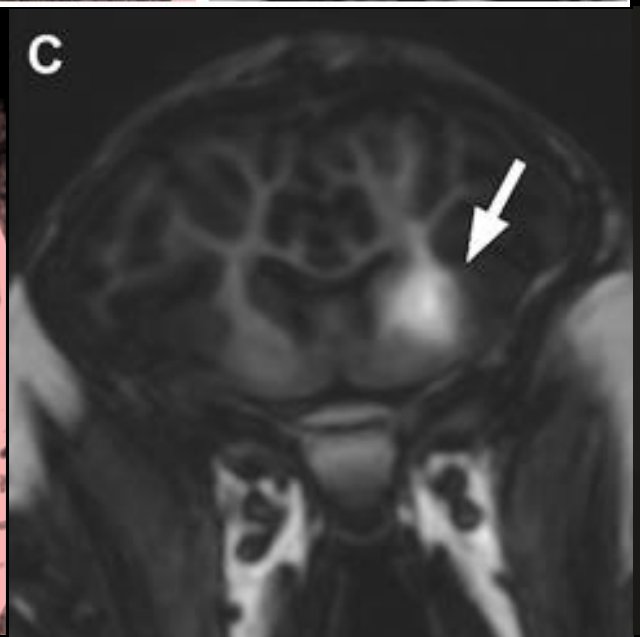
High-Resolution Cone Beam CT (CBCT) Enables Visual Confirmation

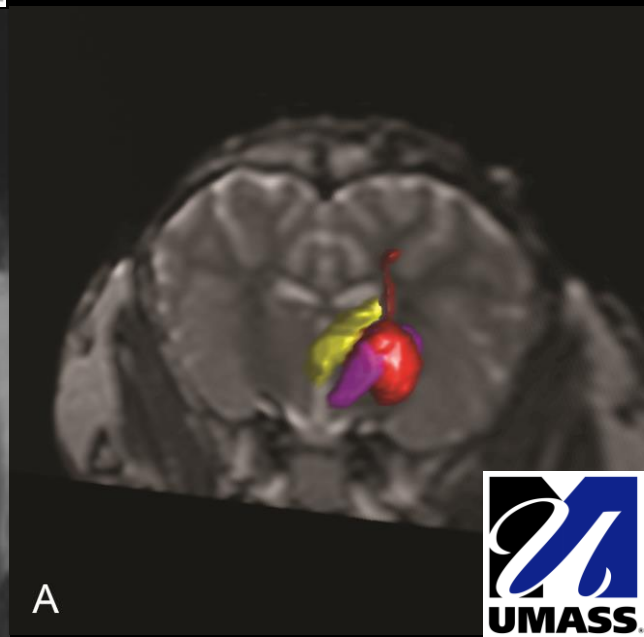


Huntington's Disease

- ✓ Microcannula tip (300 µm) position was confirmed with CBCT registered with MRI







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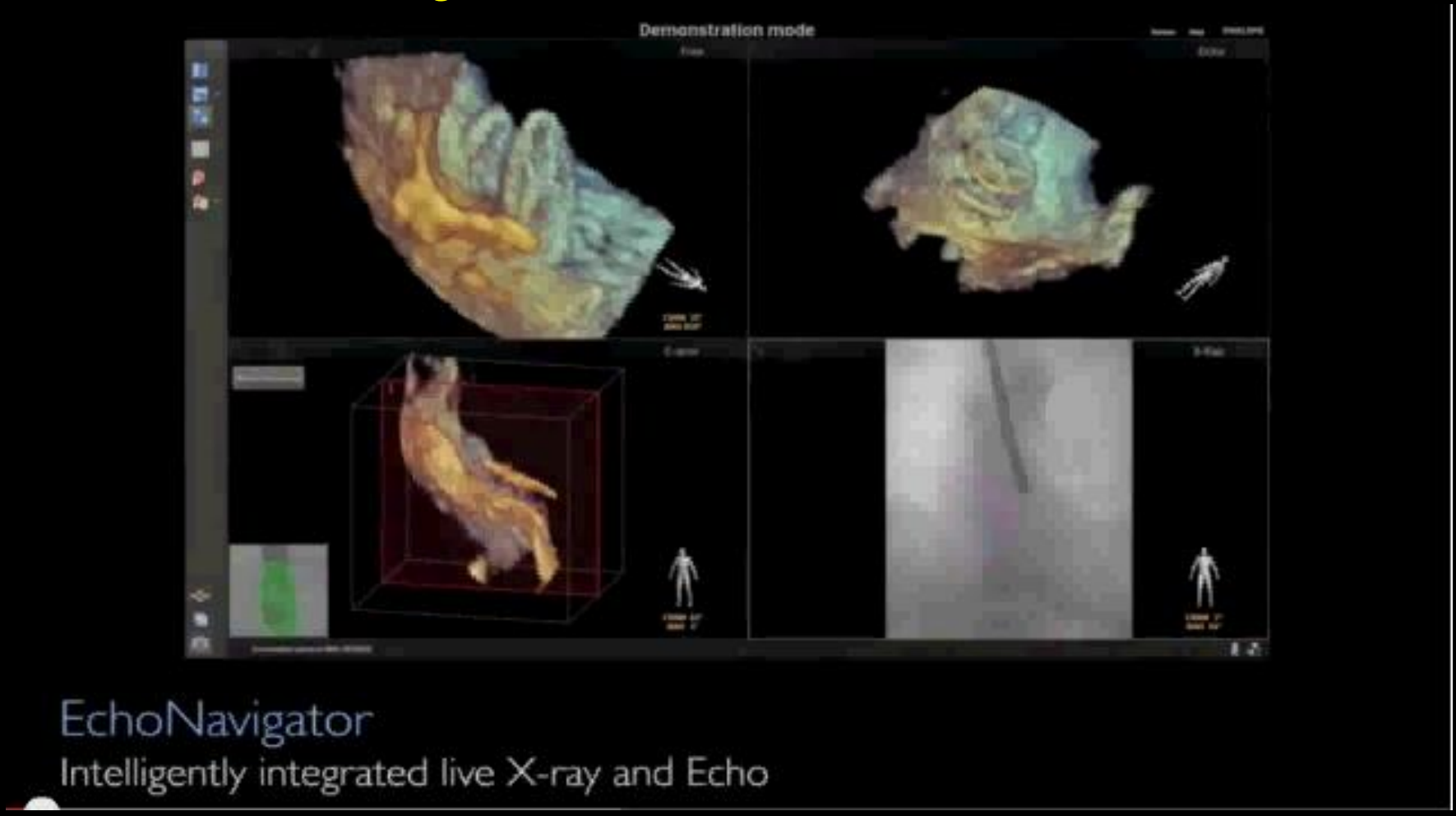
PERCUTANEOUS TRANSCATHETER AORTIC VALVE REPLACEMENT

Multi-Modal Image-Guidance



Courtesy of Philips Healthcare

BRAIN TUMORS

- Astrocytomas account for 80% of all malignant brain tumors
- 18,500 new cases of malignant primary CNS tumors in USA in 2005
- 43,800 new cases of both malignant and non-malignant primary CNS tumors in 2005
- Primary brain tumors account for 2% only of all cancers however
- 5-year survival rate 30% for anaplastic astrocytoma and
- 5-year survival rate 3.3% for gliobastoma
- 12,820 deaths associated with CNS tumors in 2006

MINIMALLY-INVASIVE TUMOR THERAPY

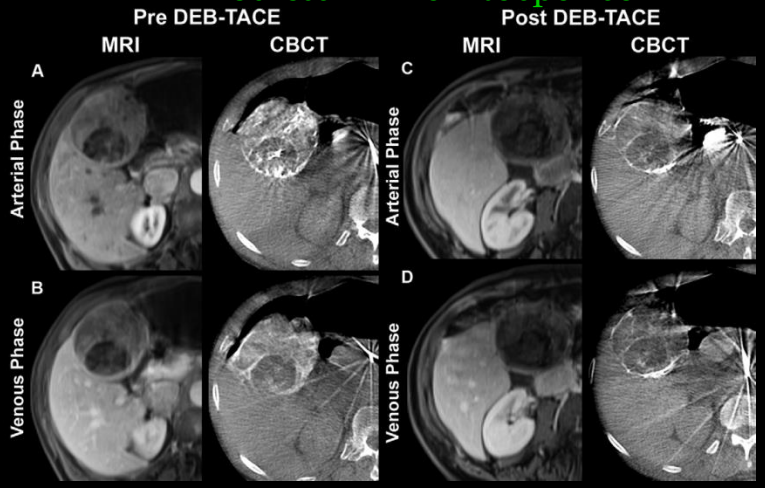
New England Center For Stroke Research

Intravascular:

Automatic Feeder Detection using Contrast-Enhanced CBCT for Ultraselective Chemoembolization

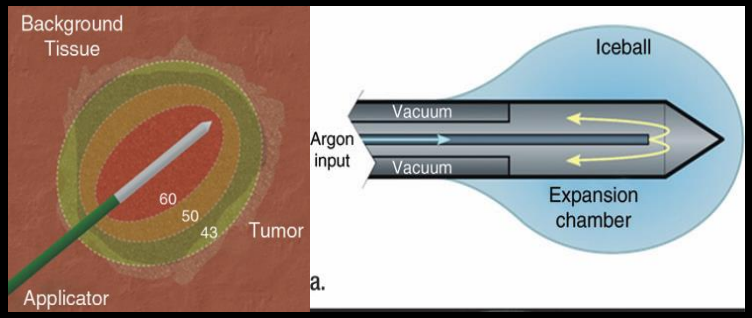
Miyayama et al, JVIR, 2012

Dual-Phase CBCT Immediate pre- and post TACE Predicts Tumor Response



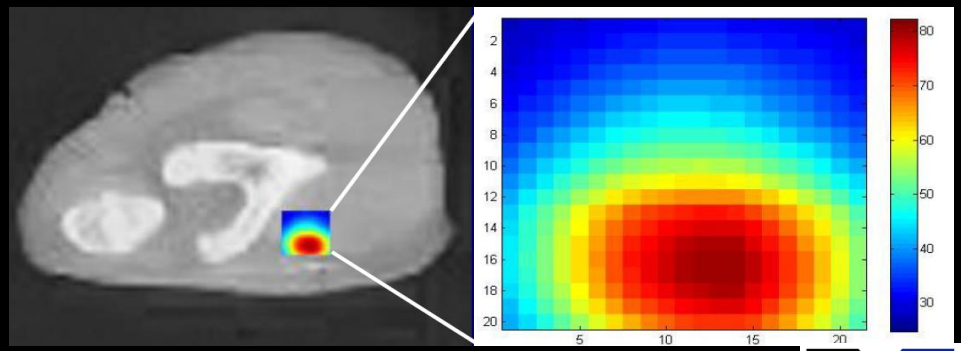
Loffroy et al, Radiology, 2013

Percutaneous:



Ahmed et al, Radiology, 2008

CBCT-based Thermometry



Abi-Jaoudeh et al, RSNA, 2012

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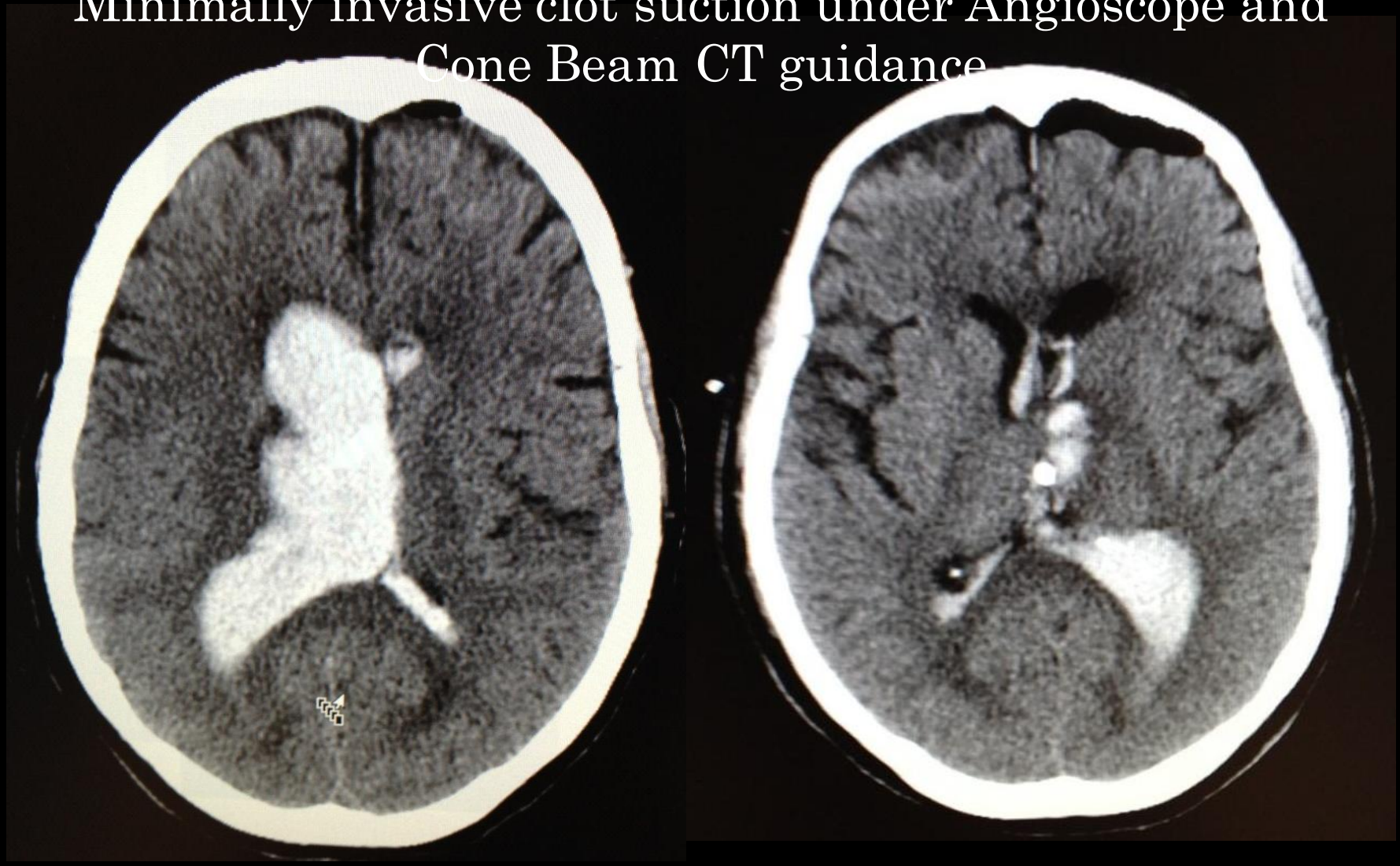
SIEMENS

Apollo Penumbra Aspiration catheter and Ultrasound Minimally invasive clot suction under Angioscope and Cone Beam CT guidance



With courtesy of Dr. Sam Hoh and Dr. Zauner, Santa Barbara, CA

Patient radiation doses is a major issue in Interventional Neuroradiology

Appearance of radiation-induced skin injury approximately 18 to 21 months following multiple coronary angiography and angioplasty procedures – evidence of progressive tissue necrosis (Source: www.fda.gov/cdrh/rsnaii)

Karolinska Institutet


PERRUQUERIA
KUMAR
OFERTA
CORTE DE PELO
5€

Equipment

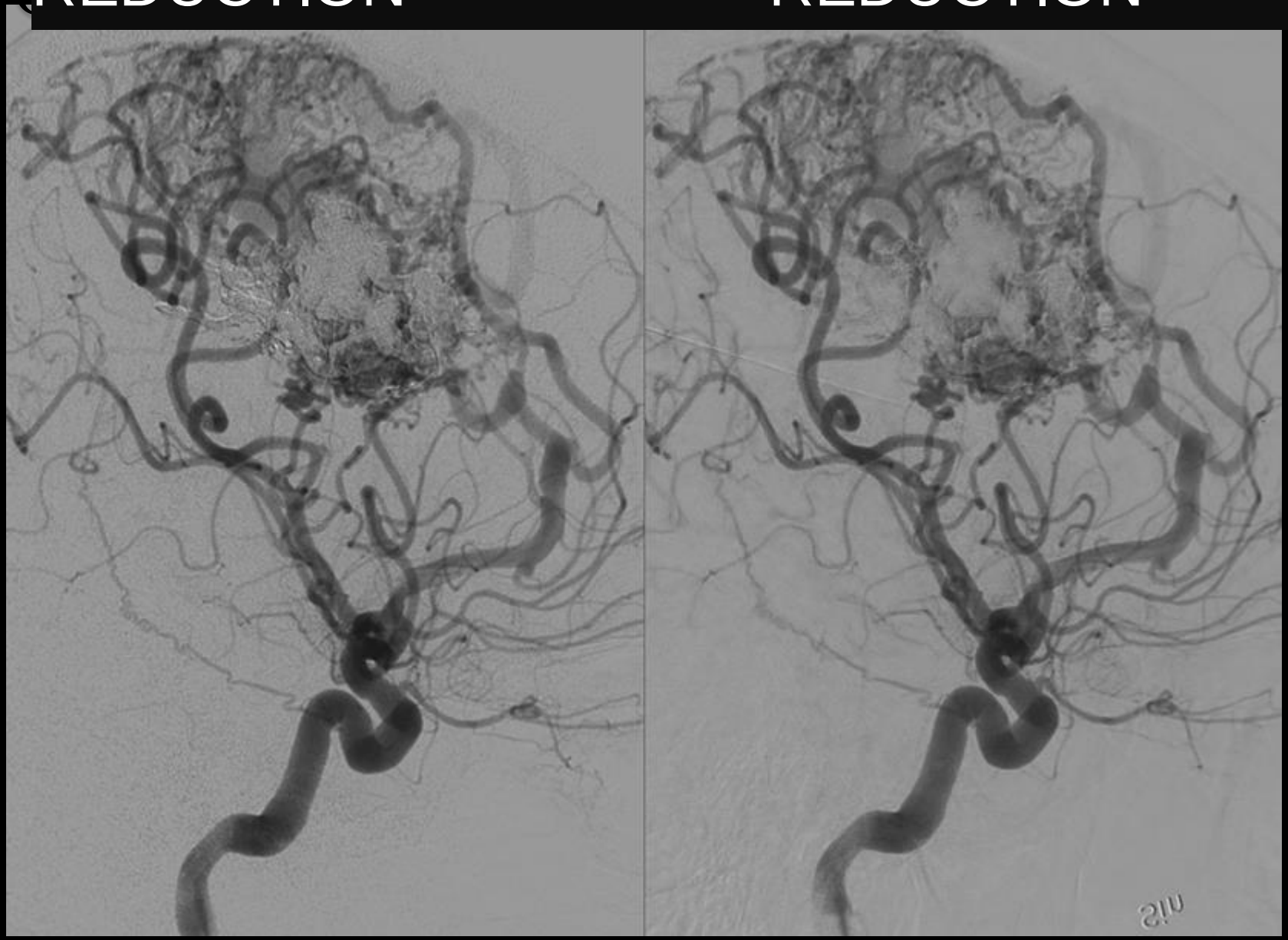
- Biplane Philips Allura Xper FD20/20
  (Allura Clarity, just received FDA approval)

- DoseReductionSystem
  - Increased tube filtration
  - Automatic mask alignment
  - **New reconstruction algorithm**
  - Noise reduction

Söderman et al. Radiology 2013 (June 4, 2013 published on line before pint)

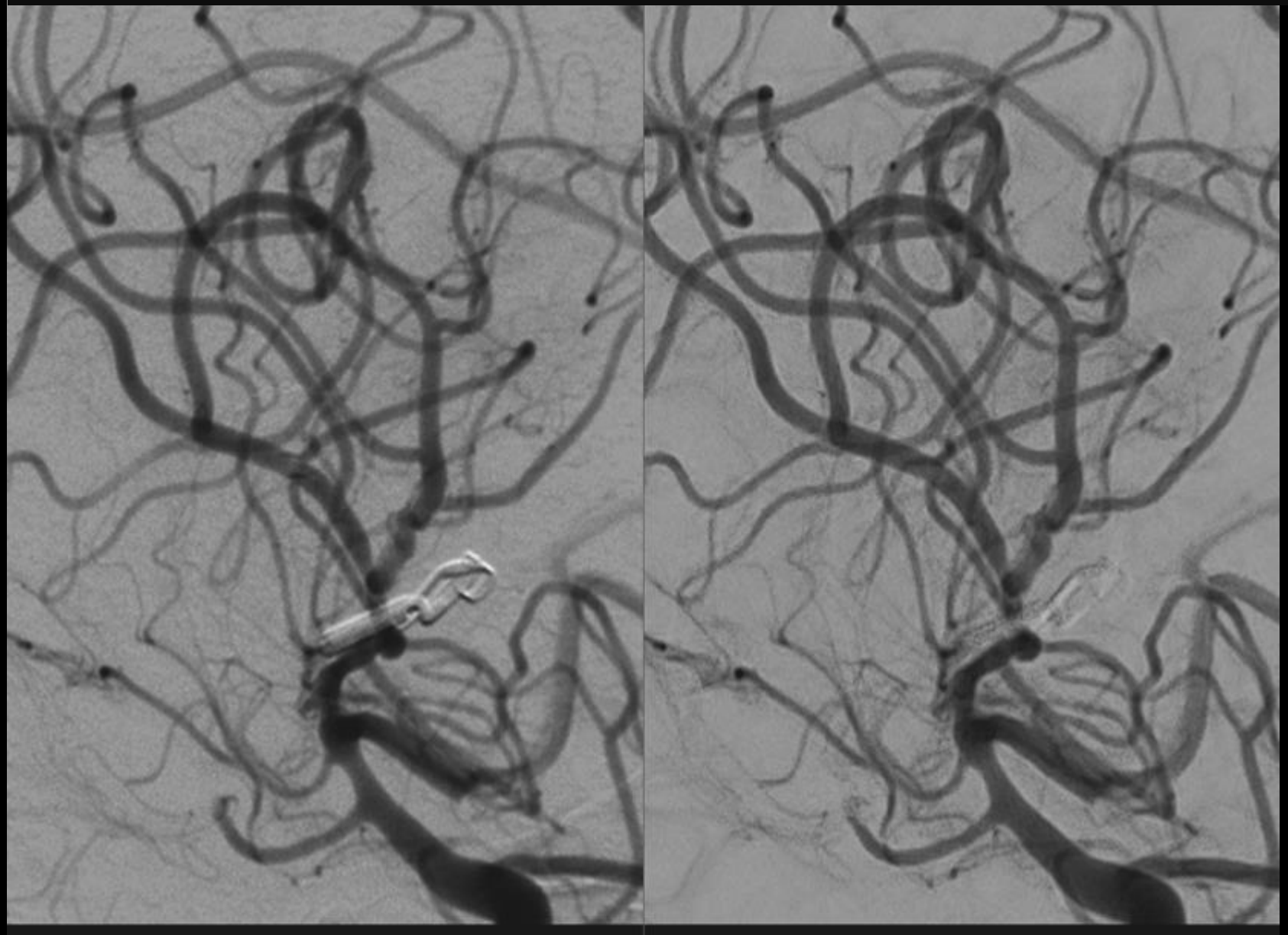
WITHOUT DOSE REDUCTION

WITH DOSE REDUCTION



WITHOUT DOSE REDUCTION

WITH DOSE REDUCTION



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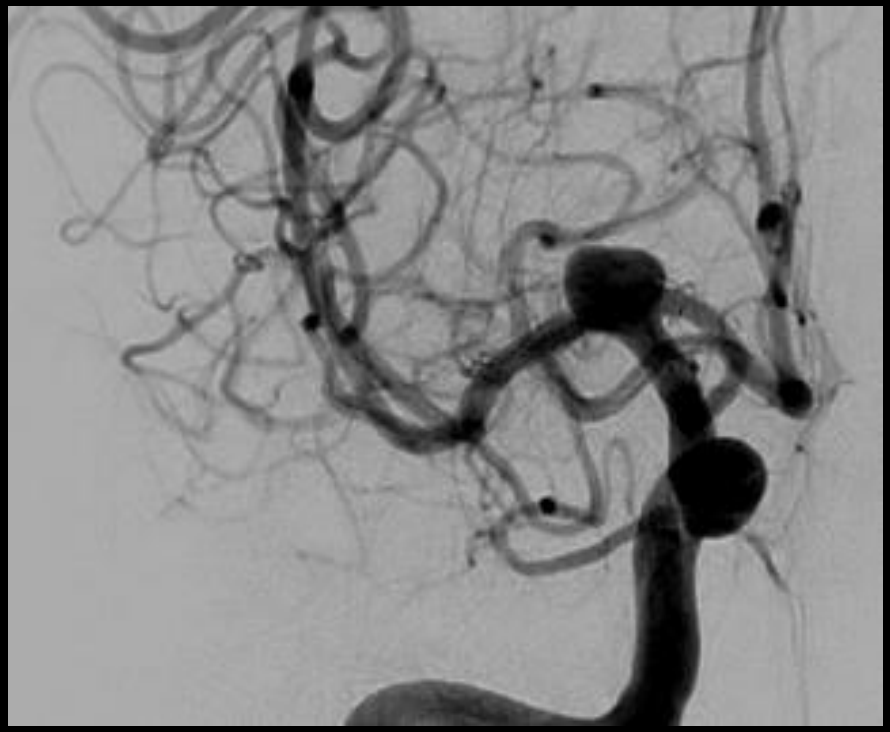
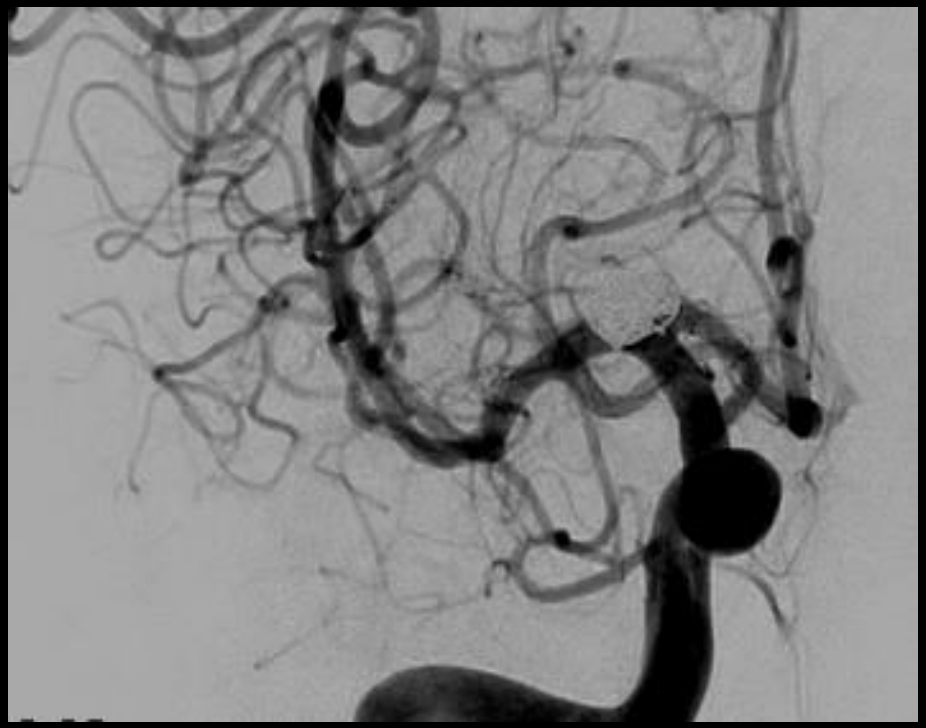
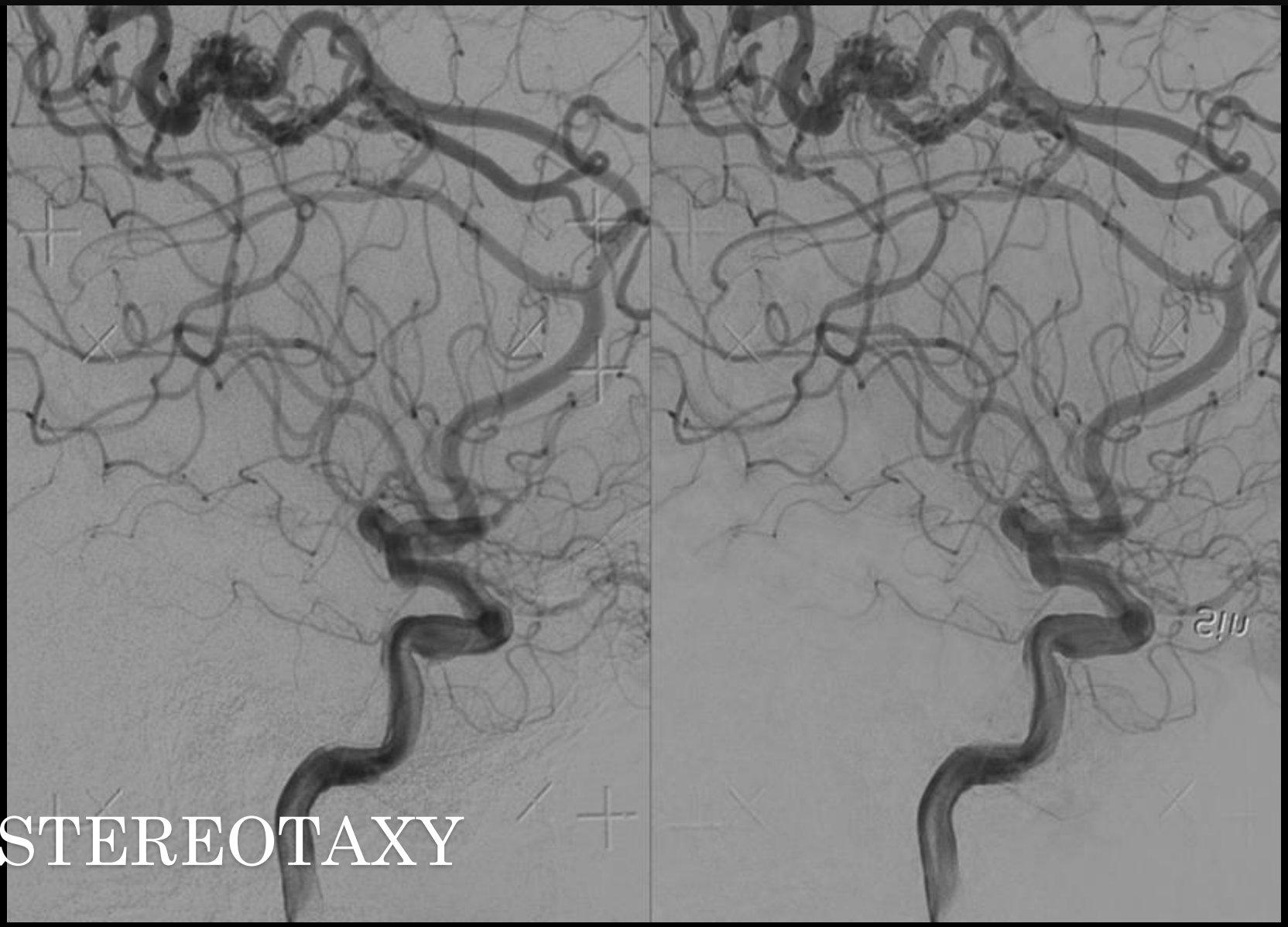


WITH DOSE REDUCTION



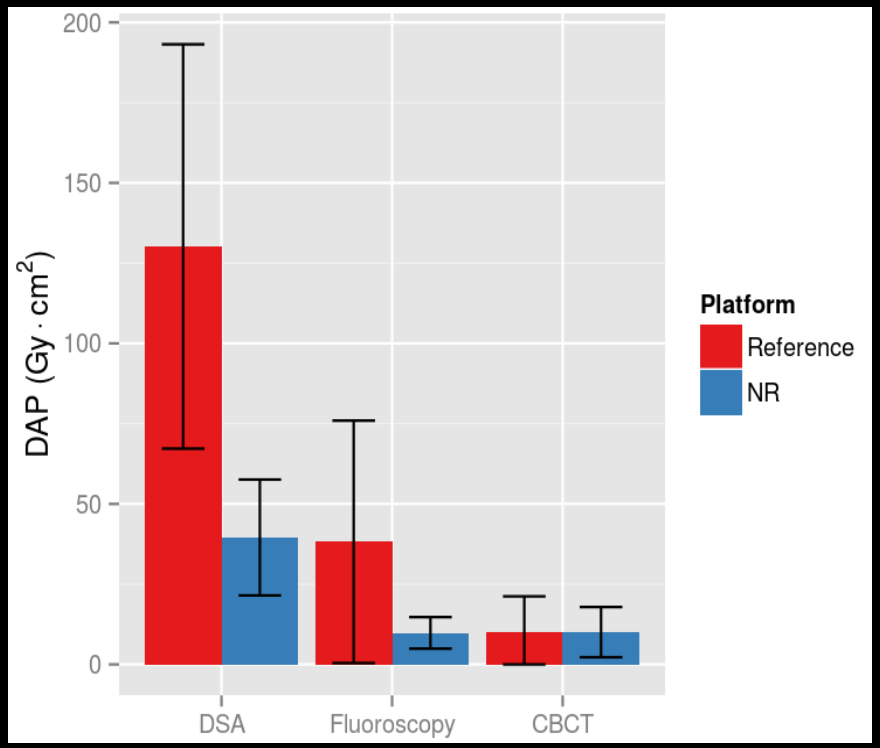
WITHOUT DOSE REDUCTION

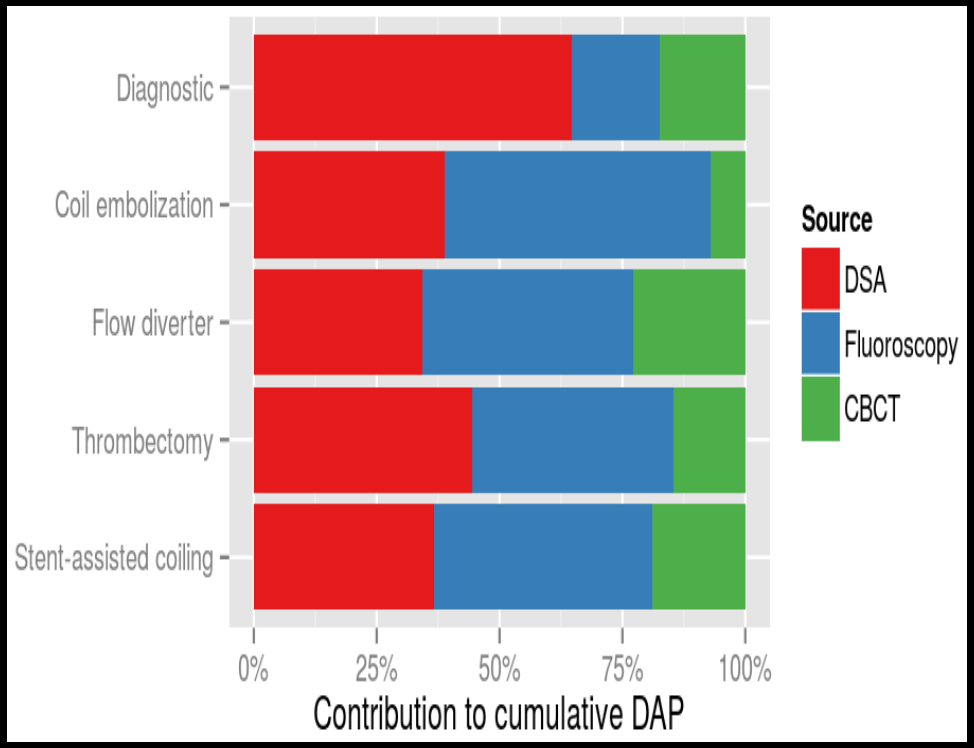
WITH DOSE REDUCTION



STEREOTAXY

NOISE REDUCTION (NR) PROGRAM
CUMULATIVE DAP (DOSE AREA PRODUCT)





DoseReductionSystem allows up to a 75% radiation dose reduction with equal or improved image quality when compared to standard DSA

NEW ENGLAND CENTER FOR STROKE RESEARCH

That's probably how you will be doing…..

From "Startrack"

UMASS