

How to Evaluate Patients with Cryptogenic Stroke

Jeffrey Saver, MD
Professor of Neurology
Director, UCLA Stroke Center

How to Evaluate Patients with Cryptogenic Stroke

Disclosure

Scientific Consultant, Unpaid Trialist:
AGA

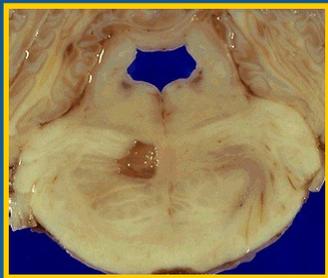
Causes of Stroke

Ischemic Stroke (83%)

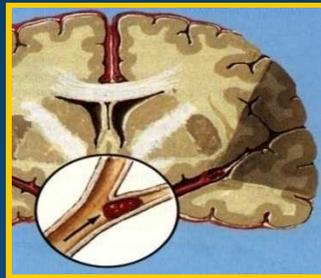
Atherothrombotic
Cerebrovascular
Disease (28%)



Lacunar - small
vessel dz (24%)



Cardioembolic
(28%)

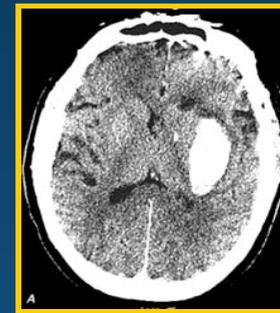


Other (vasculitiis,
dissection, hyper-
coagulable, etc (10%))

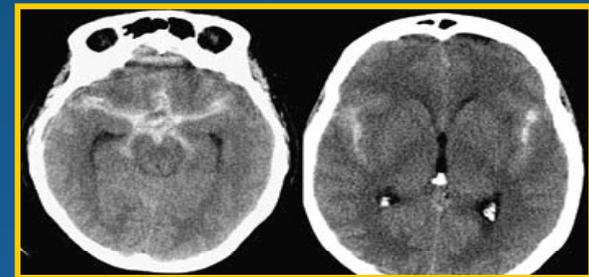
Cryptogenic (10%)

Hemorrhagic Stroke (17%)

Intracerebral
Hemorrhage (70%)

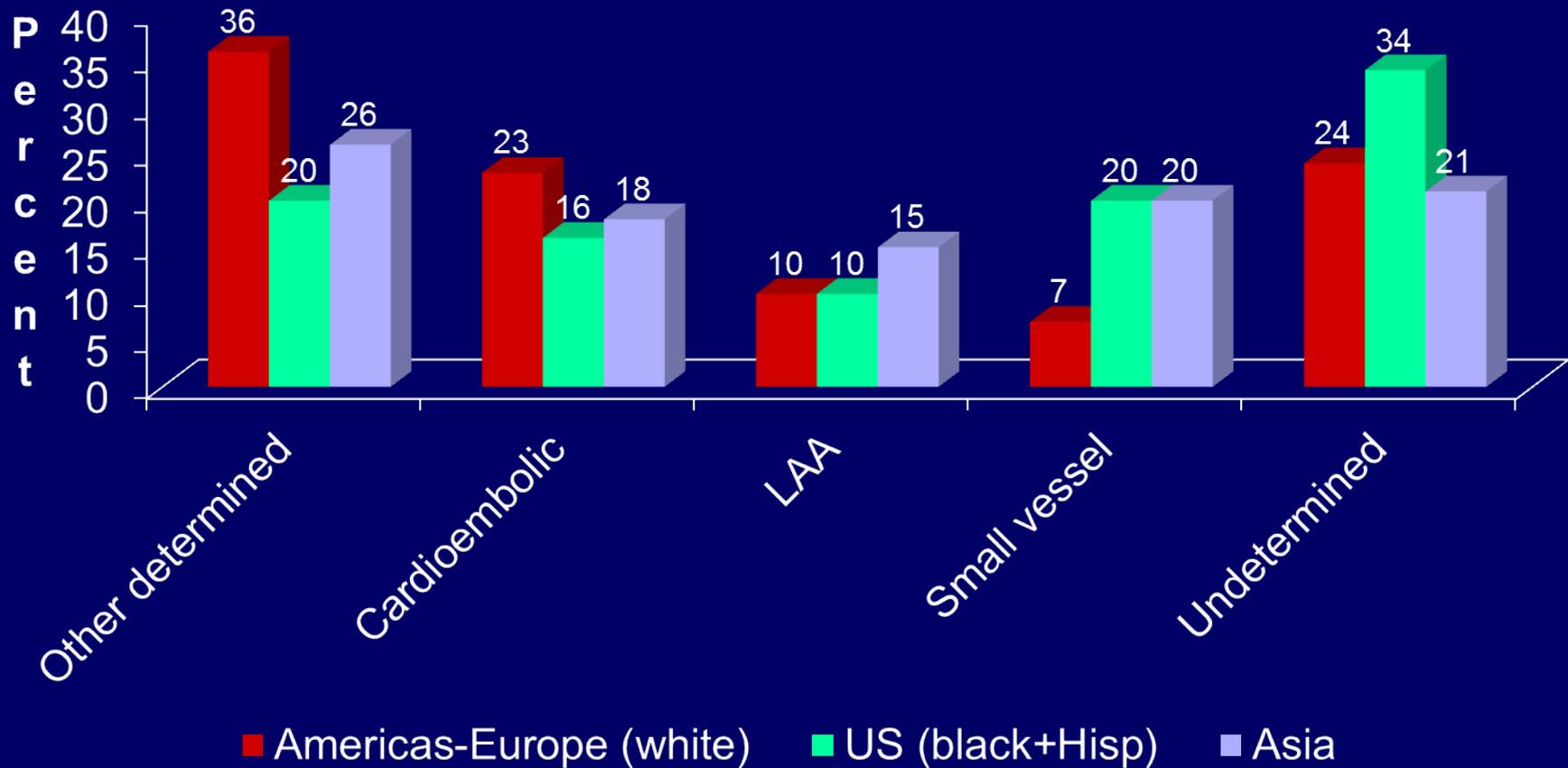


Subarachnoid
Hemorrhage (30%)



More Diverse and Cryptogenic Causes of Ischemic Stroke in Young Adults (Ages 18-45)

(14 series, 2923 patients)



Is the Stroke Really Cryptogenic?

History

Historical Fact	Clinical Import
Neck trauma or manipulation	Carotid or vertebral artery dissection
Migraine	Migrainous infarction, CADASIL
IV drug use	Endocarditis, HIV, vasculities, paradoxical emboli, vasospasm
Dental procedure, systemic bacterial infection	Endocarditis, septic emboli, coagulopathy
Plane travel, Valsalva at onset	Paradoxical embolism
Bruisability	Coagulopathies, cryoglobulinemia
Family history of early MI, ischemic stroke	Genetic accelerated atherosclerosis
Pregnancy and peripartum	Coagulopathies, eclampsia
Sickle cell disease	Secondary moyamoya
Coital onset	Aneurysm, AVM, paradoxical embolus

Physical Examination

Physical Finding	Clinical Import
Asymmetric arm pressures	Coarctation of aorta, aortic dissection, Takayasu disease
Skin: needle tracts	IV drug abuse, HIV infection
Skin: livedo reticularis	Sneddon syndrome, APLA, SLE
Skin: xanthoma, xanthlasma	Hyperlipidemia
Adenopathy	HIV, sarcoid, Tangier disease
Heart murmur	Endocarditis, ventral septal defect, myxoma
Vessels: diminished pulses	Premature atherosclerosis, coarctation of aorta, aortic dissection, Takayasu disease
Vessels: bruit	Premature atherosclerosis, fibromuscular dysplasia, arterial dissection
Extremities: venous thrombosis	Hypercoagulable state

Laboratory Evaluation: Standard

- Chem panel
- CBC and platelets
- INR/PTT
- Troponin
- RPR
- Pregnancy test
- Urine tox screen
- ECG
- CXR
- Pulse oximetry

Laboratory Tests: Hypercoagulable State Initial Screening

Arterial

- Antiphospholipid antibodies
 - Anticardiolipin Ab, DRVVT, anti-beta 2-glycoprotein 1 Ab
- Homocysteine (fasting)

Venous (and paradoxical arterial)

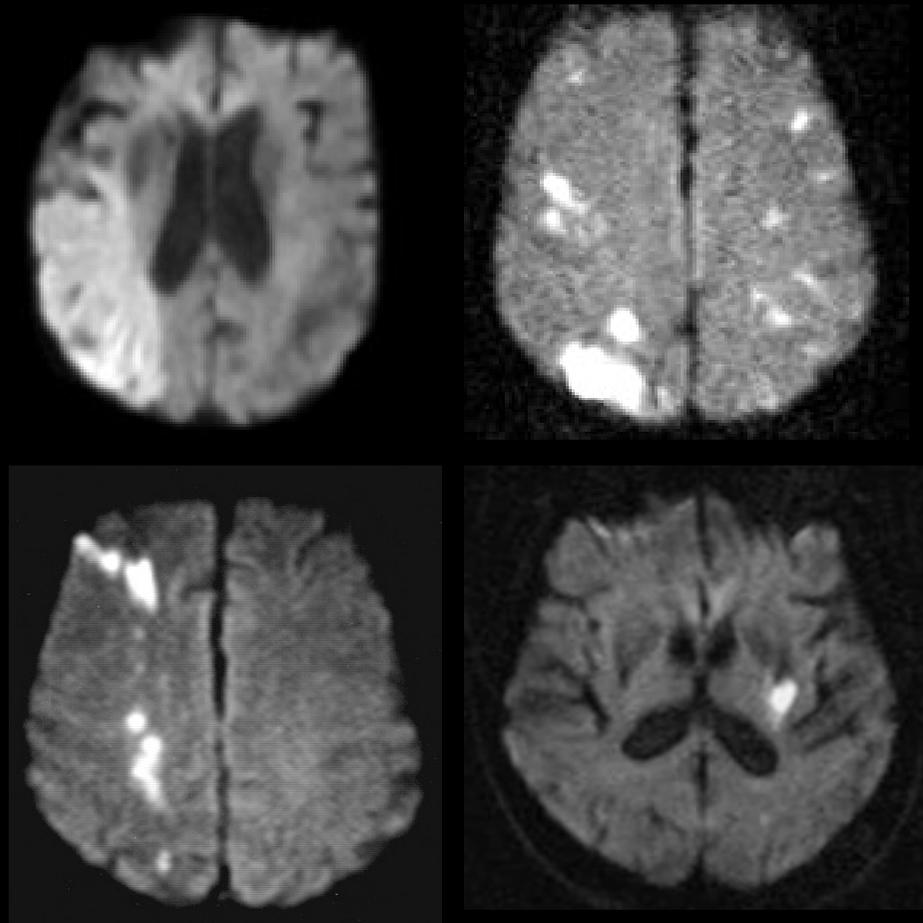
- Activated protein C resistance
- Prothrombin gene mutation
- Protein C, protein S, antithrombin III
- Factor VIII level
- Antiphospholipid antibodies
- Homocysteine (fasting)

Laboratory Tests: Vasculitis

- Initial Screening
 - » Sedimentation rate, C-reactive protein
 - » Antinuclear antibody, rheumatoid factor, ANCA
 - » Serum immune electrophoresis
- Detailed (partial)
 - » dsDNA, RNP, SCL 70, ACE, anti-Ro, anti-LA
 - » C3/Cr, CH-50
 - » Lumbar puncture

Brain Parenchyma Imaging

- Ischemic stroke topography
 - » Territorial
 - » Multi-territorial (proximal embolism or multifocal arteriopathy)
 - » Borderzone
 - » Small vessel



Aortocervicocerebral Vessel Imaging

- Locations
 - » Aorta
 - » Origin of great vessels
 - » ICA origin
 - » Distal cervical ICA
 - Dissection, FMD
 - » Intracranial
- Modality
 - » CTA (CTV)
 - » MRA (MRV)
 - » TCD embolus detection
 - » Catheter angiography
 - Abnormalities seen in up to 75% of young stroke patients
 - Highest yield when performed in first hours after stroke onset
 - Visualizes medium and small vessels

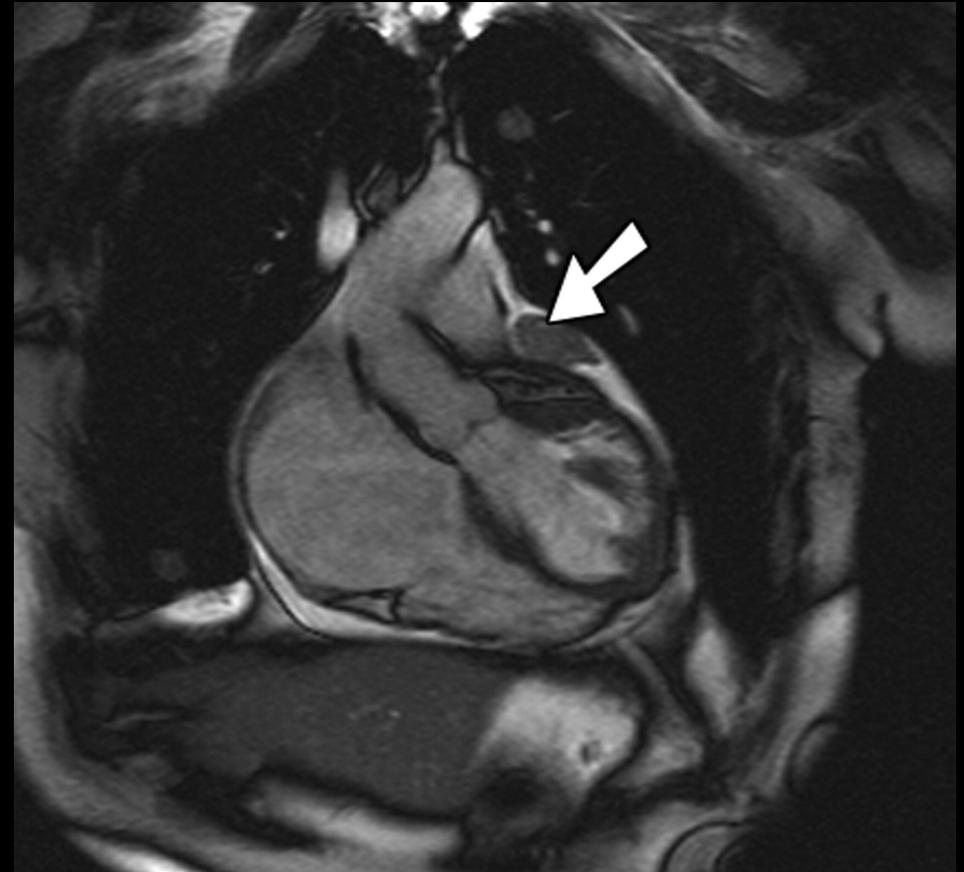


CTA of Cervicocephalic Arterial Tree

© UCLA Stroke Center

Cardiac Evaluation

- Cardiac imaging
 - » Echocardiography
 - TTE - If abnormal cardiac history, physical exam, ECG
 - TEE with contrast – If none of the above, or if TTE unrevealing
 - » Fast gated MRI, CT
- Cardiac rhythm
 - » Cardiac telemetry or Holter monitor x 24 h
 - » Prolonged ambulatory monitor



Atrial appendage thrombus in atrial fibrillation
--Finn JP et al, Radiology 2006;241:338-354

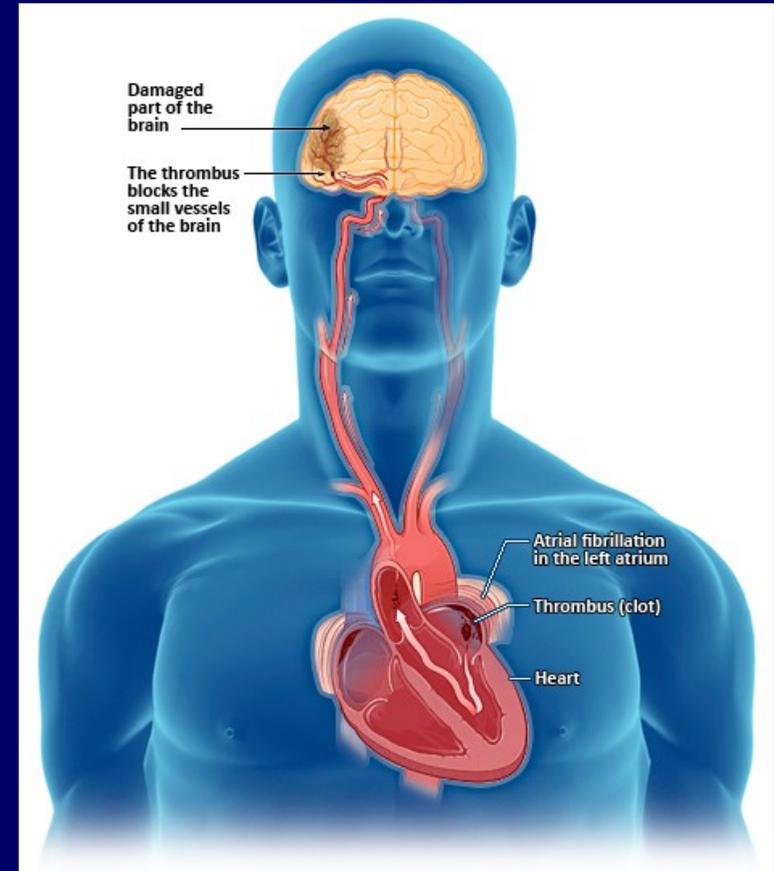
Additional Tests in Select Cases

- Hemoglobin electrophoresis
- HIV, zoster PCR
- Fibrinogen, serum viscosity
- Genetic
 - » Mitochondrial DNA
 - » Notch 3 gene testing (CADASIL)
- Malignancy screen (whole body PET-CT)
- Arterial biopsy
- Brain biopsy
- Perfusion imaging
- Cerebrovascular reserve (MR, CT, PET, SPECT, TCD)

The Most Commonly Missed Cause of Ischemic Stroke Paroxysmal Atrial Fibrillation

- 532 cryptogenic stroke patients in 8 series
 - » Negative 24 hr ECG
 - » Ambulatory monitoring in 7 series (1 implantable loop recorder)
 - » Typically 7-30d
- Paroxysmal AF in 11%

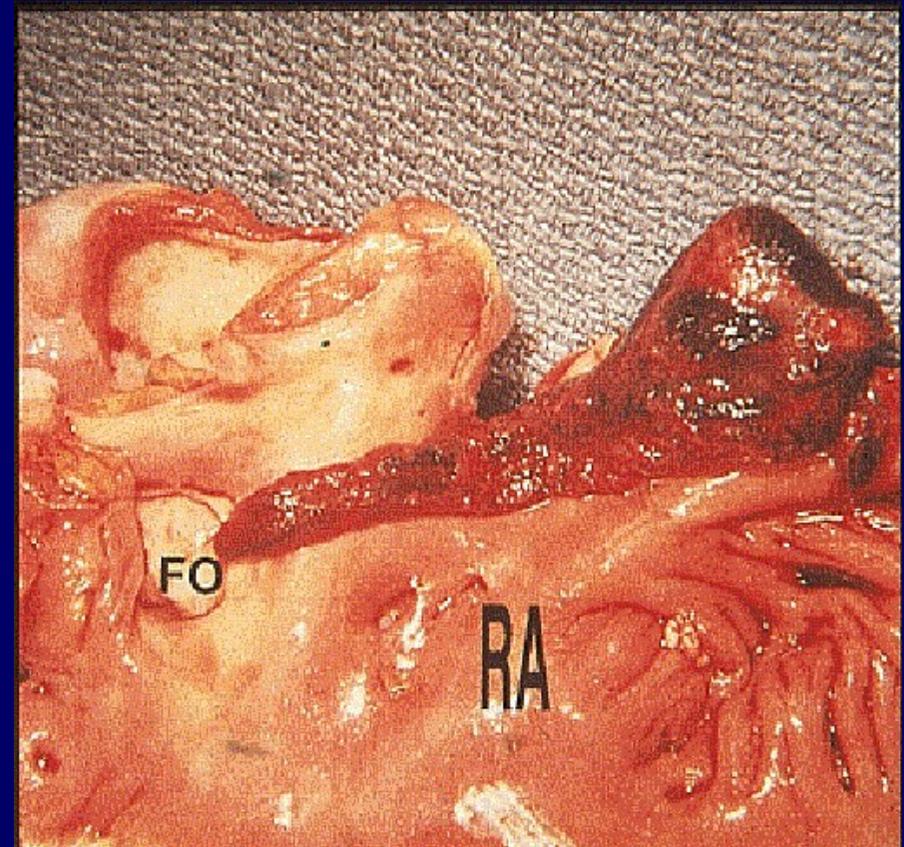
--Prolonged Rhythm Monitoring for the Detection of Occult Paroxysmal Atrial Fibrillation in Ischemic Stroke of Unknown Cause. Seet et al. Circulation 2011



Is the Cryptogenic Stroke Actually Due to Paradoxical Embolism Through PFO

Historical Features Suggestive of Causative Relation between PFO and Stroke

- Donor sites
 - » Sedentary prior to onset
 - » Identified DVT source
 - » Absence of traditional risk factors
- Shunt pathway open
 - » Valsalva at onset
 - » Pulmonary hypertension
- Recipient sites
 - » Abrupt onset
 - » No stereotyped prior TIAs/strokes
 - » Sudden cutoff
 - » Superficial vessel



Clinical Features More Frequent in Cryptogenic Stroke Patients with (n=89) than without (n=86) PFO

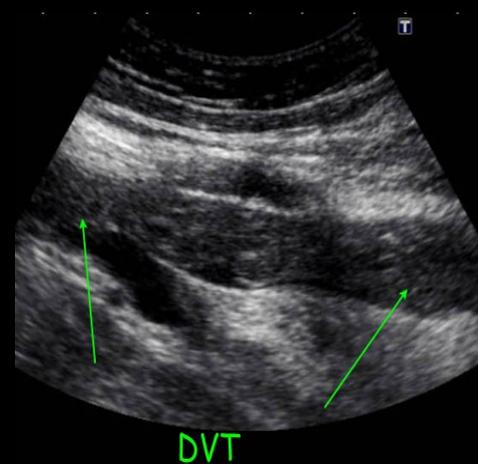
	OR
Long Travel	8.8
H/o DVT or PE	4.4
Valsalva at onset	3.3
Migraine	2.3
Wake-up stroke	4.5



-Ozdemir et al, J Neurol Sci 2008

Search for Venous Source

- Lower extremity
 - » Physical exam
 - Only 30% of PE patients have clinical DVT
 - Much less in PFO
 - » Ultrasound
 - Detects one fourth of thrombi found at venography
 - Miss small thrombi, popliteal only, superficial
 - » Venography
 - Discomfort
 - » Cause or consequence?
- Upper extremity
- Pelvis
 - » MRI/CT

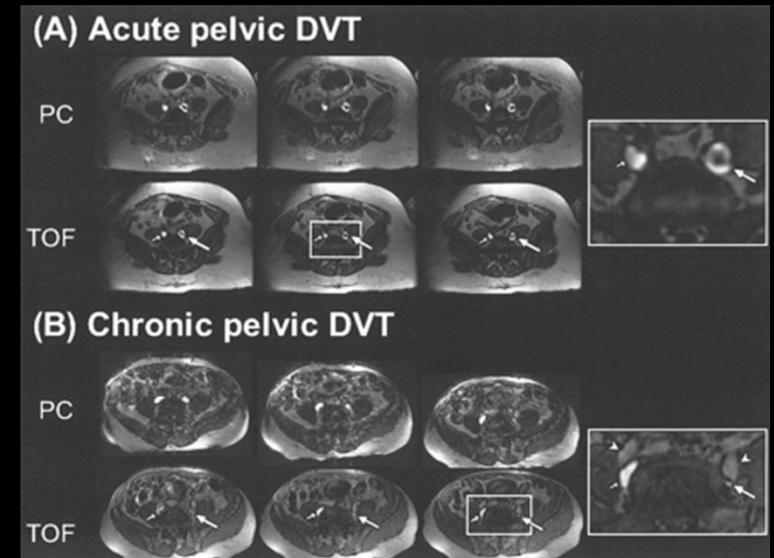


Paradoxical Emboli From Large Veins in Ischemic Stroke (PELVIS) Study

--Cramer et al, Neurology 2004

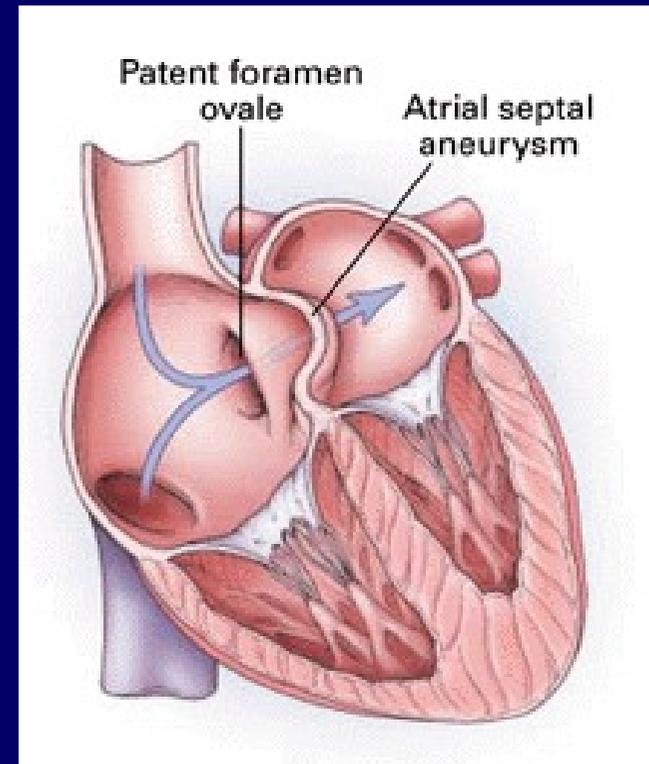
- 5 sites, 95 patients 18-60
- MR venogram within 72h of ischemic stroke

	Determined origin	Cryptogenic	p
N	49	46	
PFO	19%	59%	.0002
Pelvic DVT	4%	20%	.025
PFO + PelvDVT	0%	13%	.029



Atrial Septal Aneurysm Potentiates Risk

- European multicenter prospective cohort
- 581 young cryptogenic ischemic stroke patients
 - » All treated with aspirin
 - » Followed for 4 years
 - » 34% had PFO
 - » Event rates/yr
 - No PFO 1.1%
 - PFO only 0.6%
 - PFO + ASA 3.8%



--Mas et al, NEJM 2001

Potential Predictors of Stroke Risk in PFO

- Size of PFO
 - Cryptogenic stroke patients 2.1 mm
 - Identified cause of stroke patients 0.57 mm
- Microbubble count in LA within 3 cardiac cycles
 - Cryptogenic stroke patients 13.9
 - Identified cause of stroke patients 1.6
- Presence of hypercoagulable state
 - Patients with PFO 75%
 - Patients without PFO 36%

--Homma et al, Stroke 1994

--Cabanès et al, Stroke 1993

--Sacco et al, Heart Dis and Stroke 1993

Can a “high risk” PFO be identified?

- History
 - » Multiple spells
 - » Unprovoked
 - » Hypercoagulable
 - » Migraine?
- Anatomy
 - » Visible defect on echo
 - » Size of defect
 - » Associated features
 - Atrial septal aneurysm
 - Eustachian valve
- Physiology
 - » Shunt at rest
 - » Spontaneous Doppler flow
 - » Many bubbles cross on TEE
 - » Many MCA bubbles on TCD
- Radiology
 - » “Silent” strokes

