생각보다 드물지 않은 뇌졸중의 다른 원인

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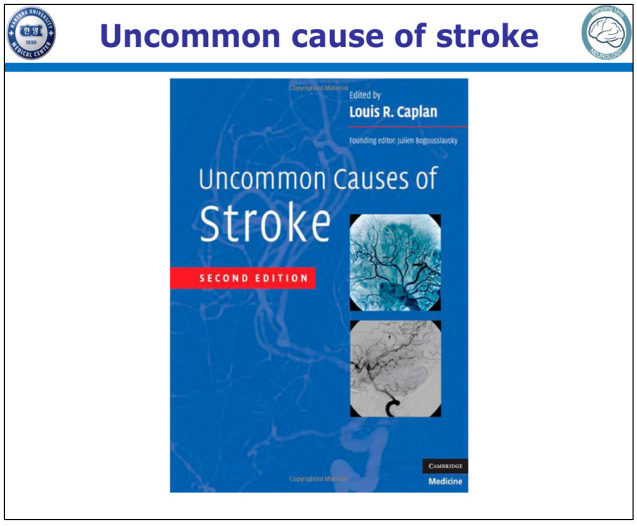

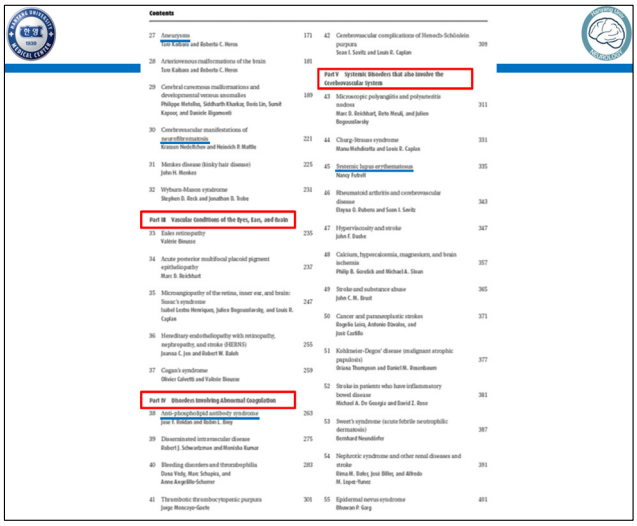

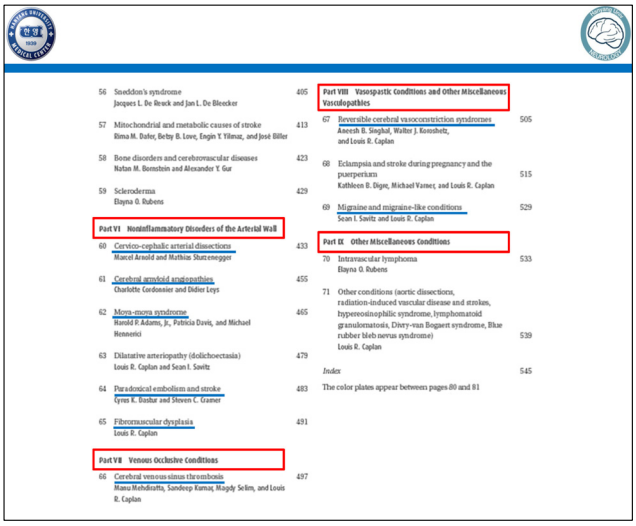

Stroke in Young Adults

VIEWS & REVIEWS

Recognition and management of stroke in young adults and adolescents

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Mitchell S. Elkind, MD, MS, MPhil
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ABSTRACT

Approximately 1.5% of all ischemic strokes (IS) occur in young adults and adolescents. To date, only limited prior public health and research efforts have specifically addressed stroke in the young. Early diagnosis remains challenging because of the lack of awareness and the relative infrequency of stroke compared with stroke mimics. Moreover, the causes of IS in the young are heterogeneous and can be relatively uncommon, resulting in uncertainties about diagnostic evaluation and cause-specific management. Emerging data have raised public health concerns about the increasing prevalence of traditional vascular risk factors in young individuals, and their potential role in increasing the risk of IS, stroke recurrence, and poststroke mortality. These issues make it important to formulate and enact strategies to increase both awareness and access to resources for young stroke patients, their caregivers and families, and health care professionals. The American Academy of Neurology recently convened an expert panel to develop a consensus document concerning the recognition, evaluation, and management of IS in young adults and adolescents. The report of the consensus panel is presented herein. *Neurology*® 2013;81:1-9

Causes and risk factors

Table 3 Selected causes and risk factors for ischemic stroke in young adults and adolescents

A. Frequency of stroke etiology[a]
Large-vessel atherosclerosis (2%-11%)
Small-vessel disease (7%-14%)
Cardiac embolism (20%-47%)
Other determined etiology (20%-34%)
Multiple etiologies (2%-3%)
B. Arterial
1. Cerebral artery dissection
2. Reversible cerebral vasoconstriction syndromes
3. Moyamoya disease
4. Sickle cell disease
5. Transient cerebral arteriopathy of childhood
6. Premature atherosclerosis, lipohyalinosis
7. Radiation-induced arteriopathy
8. Migraine-induced stroke
9. Illicit drug abuse (e.g., cocaine, amphetamines, ecstasy)
10. Infectious arteriopathy (e.g., post-varicella; tuberculous, fungal, or bacterial meningitis; syphilis, HIV)
11. Inflammatory arteriopathy (e.g., Takayasu arteritis, giant cell arteritis, primary angiitis of the CNS, polyarteritis nodosa, Behçet disease, Churg-Strauss syndrome, Kohlmeier-Degos disease)
12. Genetic or inherited arteriopathy (e.g., Fabry disease, fibromuscular dysplasia, dolichoectasia, Susac syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, TREX1 mutation disorders, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), hyperhomocysteinemia, neurofibromatosis type 1)
C. Cardiac
1. Patent foramen ovale
2. Congenital heart disease
3. Infectious and nonbacterial thrombotic endocarditis
4. Rheumatic valvular heart disease
5. Post-cardiac surgery or catheter intervention
6. Arrhythmia (e.g., atrial fibrillation, sick sinus syndrome)
7. Cardiac tumors (e.g., atrial myxoma, papillary fibroelastoma)
8. Recent myocardial infarction
9. Dilative cardiomyopathy
D. Hematologic
1. Heparin-induced thrombocytopenia
2. Hypercoagulable state due to deficiencies of protein S, protein C, or antithrombin; factor V Leiden mutation, prothrombin gene G20210A mutation
3. Acquired hypercoagulable state (e.g., cancer, pregnancy, hormonal contraceptive use, exposure to hormonal treatments such as anabolic steroids and erythropoietin, nephrotic syndrome, antiphospholipid antibody syndrome)
4. Primary hematologic disorders (e.g., polycythemia vera, essential thrombocythemia, paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura, leukemia, lymphoma, multiple myeloma)

[a] Classified according to the Trial of Org 10172 in Acute Stroke Treatment schema.
From *New England Journal of Medicine*, Yager PH, Singhal AB, Nogueira RG, Case records of the Massachusetts General Hospital. Case 31-2012. An 18-year-old man with blurred vision, dysarthria, and ataxia, 367, 1450-1460. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission.

Neurology® 2013;81:1-9

Laboratory tests

Table 4 Laboratory evaluation

Common tests
Complete blood count with differential cell counts
Erythrocyte sedimentation rate
Urinalysis
Prothrombin time (PT with INR), activated partial thromboplastin time
Serum electrolytes, liver and renal function tests
Blood glucose, hemoglobin A1C level
Lipid panel, lipoprotein (a) level, C-reactive protein level
Pregnancy test
Head CT, brain MRI
Cerebral arterial imaging: CT, MR, or digital subtraction angiography of the head and neck, carotid artery Duplex ultrasound, transcranial Doppler ultrasound
Brain perfusion imaging, e.g., CT-perfusion or MR-perfusion (optional)
Transthoracic and/or transesophageal echocardiography
Holter monitoring

Selected tests for specific stroke etiologies
Serum and urine toxicology screen
Lower extremity ultrasound, pelvic CT or MR venography (in patients with PFO)
Advanced brain imaging: axial fat-suppressed T1-weighted MRI, high-resolution (3T) contrast-enhanced T1-weighted MRI, PET scan, MR spectroscopy, transcranial Doppler ultrasound studies for cerebrovascular "reserve"
CSF examination: opening and closing pressure, cell counts, protein and glucose level, oligoclonal bands, cytology, immunoglobulin gene rearrangement analysis, and special tests for viral, fungal, bacterial, and parasitic infections, mitochondrial disease, and rheumatologic diseases
Rheumatologic panel blood tests: antinuclear antibody, antibody to double-stranded DNA, rheumatoid factor, anticardiolipin antibodies, complement levels, cryoglobulin level, neutrophil cytoplasm antibody (cANCA and pANCA), Scl-70 antibody, anti-centromere antibody, anti-Ro (SSA) and anti-La (SSB) cytoplasmic antibodies, serum angiotensin-converting enzyme, anti-proteinase 3
Infectious disease panel tests: varicella-zoster virus, herpes simplex virus, Epstein-Barr virus, HIV, hepatitis B and C viruses, tuberculosis, syphilis, Lyme, and others
Hypercoagulable panel tests: protein C, protein S, and antithrombin levels, prothrombin gene mutation, factor V Leiden mutation, and others
Hematologic panel tests: serum protein electrophoresis, homocysteine level, serum viscosity, Coombs test, bone marrow aspiration biopsy, and others
Ophthalmologic evaluation: fluorescein retinal angiography, Schirmer test
Biopsy: brain/leptomeningeal, skin, temporal artery, sural nerve, muscle, etc.
Genetic tests: for conditions such as CADASIL, RVCL, MTHFR 677C-T pleomorphism, and others

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; cANCA = cytoplasmic antineutrophil cytoplasmic antibodies; INR = international normalized ratio; MR = magnetic resonance; MTHFR = methylenetetrahydrofolate reductase; pANCA = perinuclear antineutrophil cytoplasmic antibodies; PFO = patent foramen ovale; PT = prothrombin time; RVCL = retinal vasculopathy with cerebral leukodystrophy.

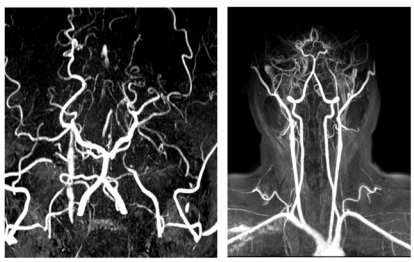
Neurology® 2013;81:1-9

Contents

- Moyamoya disease
- Cerebral venous thrombosis
- Cancer related stroke
- Paradoxical embolism: PFO, Pulmonary AVM
- Reversible cerebral vasoconstriction syndrome

Moyamoya disease

- 8세 여자 아이가 울거나 뜨거운 것을 먹을 때, 달리기를 할 때 갑작스럽게 우측 마비가 발생
- 45세 여자가 갑작스런 좌측 마비가 발생



Moyamoya disease

- Distal ICA, Proximal ACA, MCA steno-occlusion
- Definite moyamoya disease : bilateral
- Probable moyamoya disease : unilateral
- Moyamoya syndrome
  - Atherosclerosis, Autoimmune disease, Meningitis, Tumor, Neurofibromatosis, Rdiation, Down syndrome, Trauma

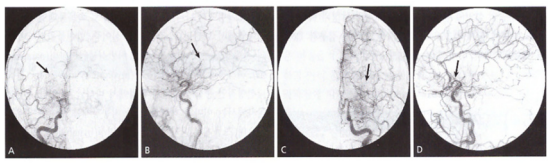


그림 35-1 • **56세 남자 환자의 전형적인 모야모야병 뇌혈관조영 소견.** (A), (B) 오른쪽 속목동맥 원위부의 협착 및 오른쪽 중간대뇌동맥 및 앞대뇌동맥의 폐색과 모야모야혈관(화살표)이 관찰된다. (C), (D) 왼쪽 속목동맥 원위부의 협착 및 왼쪽 중간대뇌동맥의 폐색과 모야모야혈관(화살표)이 관찰된다. (방오영 제공)

Epidemiology

- Prevalence : 3.16/100,000
- Incidence : 0.35/100,000
- Female predominance: 1.8:1
- Two peaks
  - Juvenile form (5~15): symptomatic episodes of ischemia triggered by exercise, crying, coughing, hyperventilation
  - Adult form (30~49): ICH is the presenting event in more than 60 %
- Genetics: Ring finger protein 213 (RNF 213)

Epidemiology

Incidence, Prevalence, and Survival of Moyamoya Disease in Korea

A Nationwide, Population-Based Study

Il Min Ahn; Dong-Hyuk Park, MD, PhD; Hoo Jae Hann, MD, PhD; Kyoung Hoon Kim, MPH, PhD; Hyun Jung Kim, MPH, PhD; Hyeong Sik Ahn, MD, PhD

(*Stroke*. 2014;45:1090-1095.)

Table 1. Incidence and Prevalence of Moyamoya Disease in Korea, 2007 to 2011

	Incident Cases			Prevalent Cases			Incidence* per 10^5/y			Prevalence† per 10^5/y		
Year	T	M	F	T	M	F	T	M	F	T	M	F

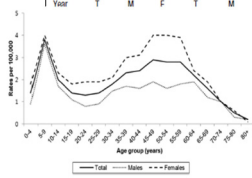


Figure 1. Incidence of moyamoya disease by sex and age in Korea, 2007 to 2011. Vertical axis shows incidence by 10^5; horizontal axis shows age in 5-y increments until the age of 80 y.

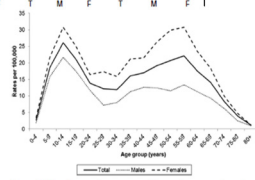


Figure 2. Prevalence of moyamoya disease by sex and age in Korea, 2011. Vertical axis shows prevalence by 10^5; horizontal axis shows age in 5-y increments until the age of 80 y.

Pathology

- Intima : fibrosis, fibrocellular hypertrophy
- Internal elastic lamina : waving, undulation
- Media : thinning

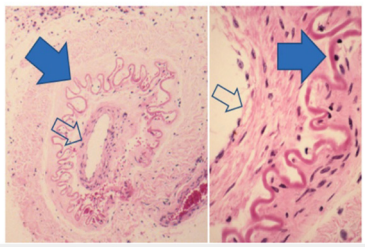


FIGURE 4:

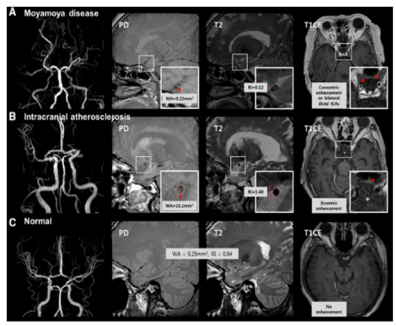
Histological findings on hematoxylin and eosin staining of cross section of a large basal artery in a patient with moyamoya. Note the fibrosis and thickening of the intima and proliferation of smooth muscle cells (open arrows) and in-folding and chronic contraction of the internal elastic lamina (closed arrows), as well as notable absence of inflammatory or atherosclerotic changes. (Courtesy of Dr Seven Rostad, Swedish Neuroscience Institute, Seattle, Washington.)

Diagnosis

- Digital subtraction angiography (DSA), MRA
- High resolution MRI

High-Resolution Magnetic Resonance Wall Imaging Findings of Moyamoya Disease

Sookyung Ryoo, MD; Jihoon Cha, MD; Suk Jae Kim, MD; Jin Wook Choi, MD; Chang-Seok Ki, MD; Keon Ha Kim, MD; Pyoung Jeon, MD; Jong-Soo Kim, MD; Seung-Chyul Hong, MD; Oh Young Bang, MD, PhD



(*Stroke*. 2014;45:2457-2460.)

Moyamoya grading

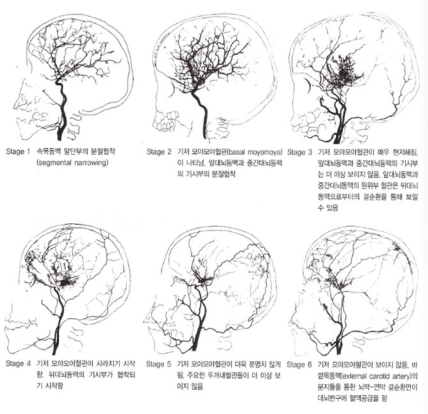


그림 35-2 • Suzuki 단계별 뇌혈관조영 소견

Treatment

- No evidence
- Medical treatment
  - Follow ischemic stroke guideline
  - Antiepileptic drug, Anti-hypertensive drug
  - Antiplatelet agents (especially cilostazole)
- Surgical treatment
  - Replace circulation, increase collateral circulation
  - Useful in juvenile form
  - Direct bypass : STA-MCA anastomosis
  - Indirect bypass : Encephaloduroarteriosynangiosis (EDAS), Encephalomyosynangiosis (EMS), Multiple burr hole surgery, Encephaloduroarteriomyosynangiosis (EDAMS)

Prognosis

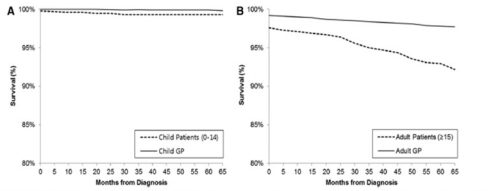


Figure 3. Survival of child (<15; A) and adult patients (≥15; B) with moyamoya disease compared with corresponding general population. Vertical axis represents survival by percentage; horizontal axis represents months after diagnosis. GP indicates general population.

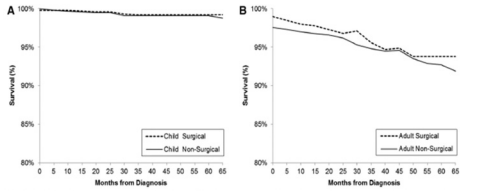


Figure 4. Survival of child (<15; A) and adult patients (≥15; B) with moyamoya disease by surgical and nonsurgical groups. Vertical axis represents survival by percentage; horizontal axis represents months after diagnosis.

(*Stroke*. 2014;45:1090-1095.)

Prognosis

The natural clinical course of hemodynamically stable adult moyamoya disease

Won-Sang Cho, MD,[1] Young Seob Chung, MD, PhD,[1] Jeong Eun Kim, MD, PhD,[1] Jin Pyeong Jeon, MD,[1] Young Je Son, MD,[1] Jae Seung Bang, MD,[1] Hyun-Seung Kang, MD, PhD,[1] Chul-Ho Sohn, MD, PhD,[2] and Chang Wan Oh, MD, PhD[1]

Departments of [1]Neurosurgery and [2]Radiology, Seoul National University College of Medicine, Seoul, Korea

J Neurosurg 2015;122:82-9

TABLE 2. Annual risk of stroke*

Group	Hemorrhagic Stroke	Ischemic Stroke	Overall Stroke
All patients	2.3	2.2	4.5
Hemorrhagic group	4.3	1.4	5.7
Ischemic group	1.2	3.0	4.2
Asymptomatic group	2.5	0.8	3.4

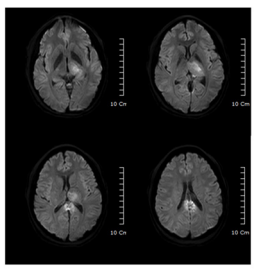
* Values indicate %/person-year.

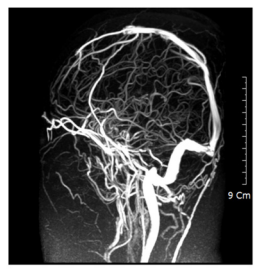
TABLE 3. Significant risk factors for stroke during follow-up on multivariate analysis with Cox proportional hazard method

Event & Risk Factor	HR	95% CI	p Value
Any stroke event			
Familial MMD	2.624	1.276–5.393	0.009
Thyroid disease	2.562	1.158–5.669	0.02
Hemorrhagic event			
Initial symptoms (hemorrhage vs others)	2.527	1.236–5.166	0.011
Familial MMD	3.094	1.238–7.730	0.016
Ischemic event			
Initial symptoms (ischemia vs others)	2.686	1.150–6.272	0.022
Familial MMD	3.108	1.260–7.665	0.014

Cerebral venous thrombosis

- 10년전 Nephrotic syndrome으로 진단 받았으나 최근 제대로 치료받고 있지 않은 여자가 최근 두통과 배뇨 장애로 신장내과에 입원 도중 갑작스런 의식소실과 경련, 사지마비로 신경과에 의뢰됨





Venous anatomy

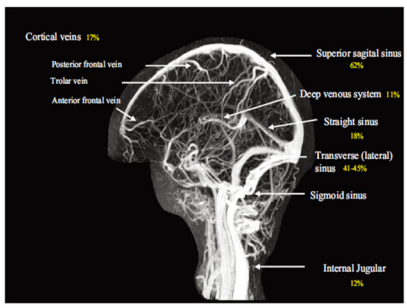


Figure 2. Magnetic resonance venogram showing the cerebral venous system and most frequent (%) location of cerebral venous and sinus thrombosis, as reported in the International Study on Cerebral Venous and Dural Sinuses Thrombosis (n=624).[44]

(*Stroke*. 2011;42:1158-1192.)

Predisposing factors

Table 3. Predisposing Conditions for CVT and Principles in Favor of a Cause-and-Effect Relationship

Condition	Prevalence, %*	Consistency†	Strength of Association†‡ OR (95% CI)	Biological Plausibility†‡	Temporality†‡	Biological Gradient†‡
Prothrombotic conditions	34.1					
Antithrombin III deficiency		Yes[3,11]	NA	Yes	Yes	Yes‡
Protein C deficiency		Yes[3,11]	11.1 (1.9–66.0)	Yes	Yes	Yes‡
Protein S deficiency		Yes[3,11]	12.5 (1.5 to 107.3)	Yes	Yes	Yes‡
Antiphospholipid and anticardiolipin antibodies	5.9	Yes[3,11,47]	8.8 (1.3–57.4)*	Yes	Yes	Yes‡
Resistance to activated protein C and factor V Leiden		Yes[3,31]	3.4 (2.3 to 5.1)	Yes	Yes	Yes‡
Mutation G20210A of factor II		Yes[31]	9.3 (5.9 to 14.7)	Yes	Yes	Yes=‡
Hyperhomocysteinemia	4.5	Yes[3,11,13,32]	4.6 (1.6–12.0)	Yes	Yes	Yes[32]
Pregnancy and puerperium	21	Yes[3,11,18]	NA	Yes	Yes	NA
Oral contraceptives	54.3	Yes[3,11,14,15,23,24,32,48]	5.6 (4.0 – 7.9)*	Yes	Yes	Yes
Drugs						
Androgen, danazol, lithium, vitamin A, IV immunoglobulin, ecstasy	7.5		NA	Yes	Yes	NA
Cancer related	7.4	Yes[3,11]	NA	Yes	Yes	NA
Local compression						
Hypercoagulable						
Antineoplastic drugs (tamoxifen, L-asparaginase)						
Infection	12.3		NA	Yes	Yes	NA
Parameningeal infections (ear, sinus, mouth, face, and neck)		Yes[11,49]				
Mechanical precipitants	4.5	Yes[3,11]	NA	Yes	Yes	NA
Complication of epidural blood patch						
Spontaneous intracranial hypotension						
Lumbar puncture	1.9					
Other hematologic disorders	12	Yes[3,11]	NA	Yes	Yes	NA
Paroxysmal nocturnal hemoglobinuria						
Iron deficiency anemia		Yes	NA	Yes	Yes	NA
Nephrotic syndrome	0.6					
Polycythemia, thrombocythemia	2.8					
Systemic diseases	7.2	Yes[3,11]	NA	Yes	Yes	NA
Systemic lupus erythematosus	1					
Behçet disease	1					
Inflammatory bowel disease	1.6					
Thyroid disease	1.7					
Sarcoidosis	0.2					
Other	1.7					
None identified	12.5		NA	NA	NA	NA

(*Stroke*. 2011;42:1158-1192.)

Clinical presentation

Clinical presentation	Frequency (%)
Headache	75%
Papilledema	49%
Ataxia	34%
Seizure	37%
Altered consciousness	30%
Speech disturbance	12%
Cranial nerve dysfunction	12%
Cerebellar dysfunction	3%
Nystagmus	2%
Hearing loss	2%

Diagnosis

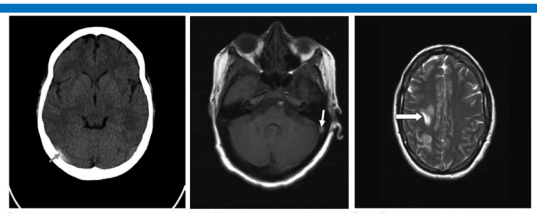


Figure 3. Noncontrast computed tomography head scan showed spontaneous hyperdensity of right transverse sinus.

Figure 5. Flair magnetic resonance image showing hypersensitivity signal at left sigmoid sinus (arrow).

Figure 6. T2-weighted magnetic resonance image showing high-intensity bland venous infarct in frontal lobe.

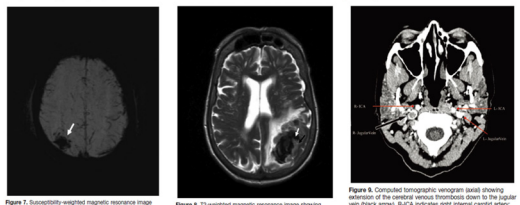


Figure 7. Susceptibility-weighted magnetic resonance image showing hemorrhagic venous infarct in the right parietal lobe.

Figure 8. T2-weighted magnetic resonance image showing mixed hypointensity (white arrow) and isointensity (black arrow) signals representing an acute hemorrhage at left parietal lobe.

Figure 9. Computed tomographic venogram (axial) showing extension of the cerebral venous thrombosis down to the jugular vein (black arrow). R-ICA indicates right internal carotid artery; L-ICA, left internal carotid artery; R, right; and L, left.

(*Stroke*. 2011;42:1158-1192.)

Diagnosis

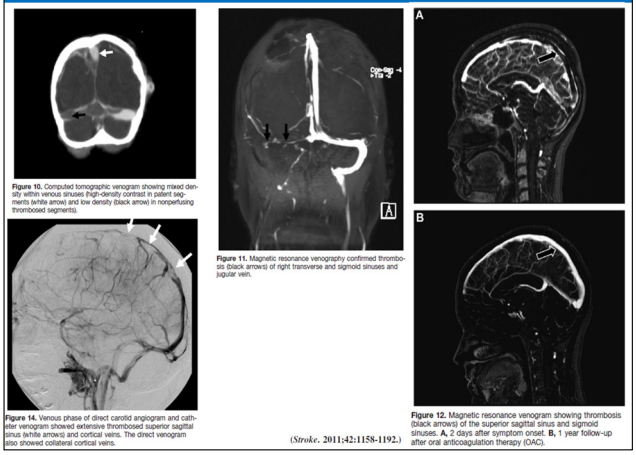


Figure 10. Computed tomographic venogram showing mixed density within venous sinuses (high-density contrast in patent segments (white arrow) and low density (black arrow) in nonperfusing thrombosed segments).

Figure 11. Magnetic resonance venography confirmed thrombosis (black arrows) of right transverse and sigmoid sinuses and jugular vein.

Figure 14. Venous phase of direct carotid angiogram and catheter venogram showed extensive thromboseed superior sagittal sinus (white arrows) and cortical veins. The direct venogram also showed collateral cortical veins.

(*Stroke*. 2011;42:1158-1192.)

Figure 12. Magnetic resonance venogram showing thrombosis (black arrows) of the superior sagittal sinus and sigmoid sinuses. **A,** 2 days after symptom onset. **B,** 1 year follow-up after oral anticoagulation therapy (OAC).

Treatment

Proposed Algorithm for the Management of CVT

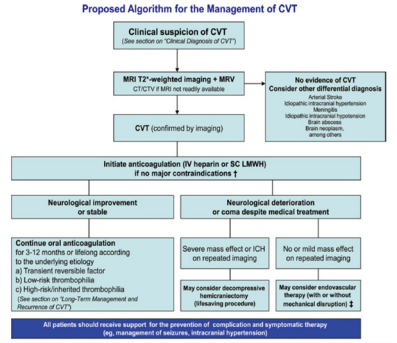
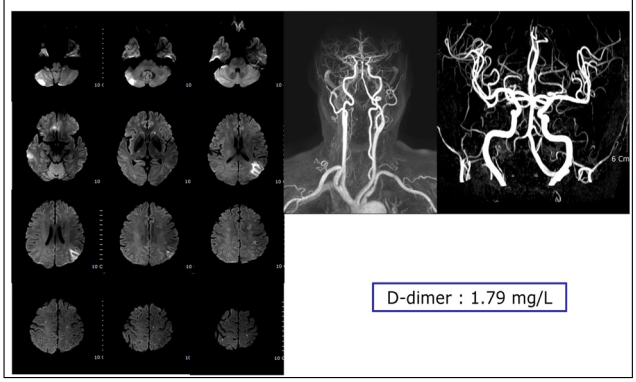


Figure 4. Proposed algorithm for the management of CVT. The CVT writing group recognize the challenges facing primary care, emergency physicians and general neurologists in the diagnosis and management of CVT. The aim of this algorithm is to provide guidance to physicians in the initial management of CVT. Anticoagulation remains the principal therapy and is aimed at preventing thrombus propagation and increasing recanalization. This algorithm is not comprehensive, nor applicable to all clinical scenarios and patient management must be individualized. Limited evidence is available on the benefits of decompressive hemicraniectomy and endovascular therapy for the management of CVT as reflected by the low grade and level of recommendations. Anticipated future advances in imaging techniques, new pharmacological agents and endovascular procedures may provide other therapeutic alternatives to be considered in patients with CVT, and in the future these guidelines will be periodically updated to reflect the changing evidence. CVST indicates cerebral venous and sinus thrombosis; LMWH, low molecular weight heparin; Tx, therapy; ICH, intracerebral hemorrhage; CTV, CT venogram; MRV, MR venogram.
†Intracranial hemorrhage that occurred as the consequence of CVST is not a contraindication for anticoagulation.
‡Endovascular therapy may be considered in patients with absolute contraindications for anticoagulation therapy or failure of initial therapeutic doses of anticoagulant therapy.

(*Stroke*. 2011;42:1158-1192.)

Cancer related stroke

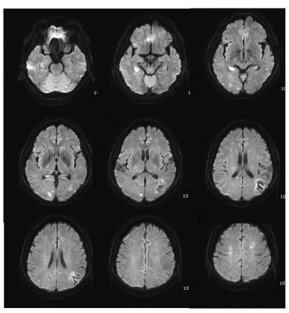
- 69세 여자가 허리통증으로 정형외과 치료 받고 있었으며, 7일전 시작된 단어가 기억나지 않는 증상 발생

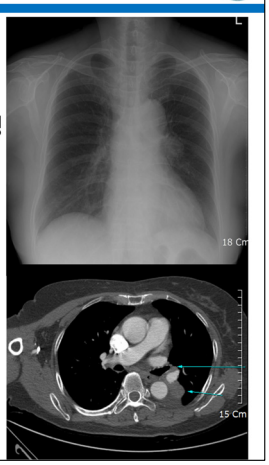


D-dimer : 1.79 mg/L

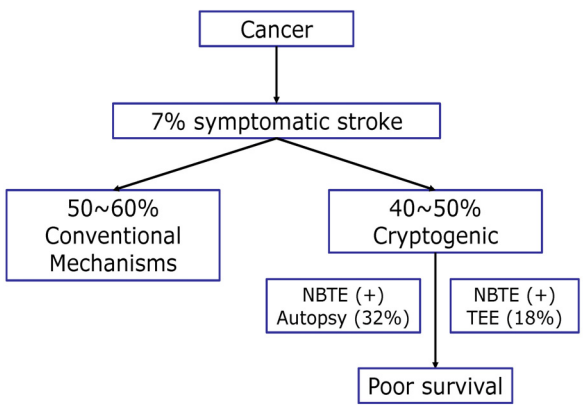
Cancer related stroke

- Hidden malignancy w/u
  - Lung cancer (lower lobe)
- 1개월 후 양쪽 눈의 시력장애 발생





Cancer related stroke



Clinical characteristics

Ischemic Stroke in Cancer Patients With and Without Conventional Mechanisms

A Multicenter Study in Korea (*Stroke*. 2010;41:798-801.)

Table. Patient Characteristics and Odds Ratios for Cryptogenic Group

	CSM Group (n=97)	Cryptogenic Group (n=64)	Estimated Odds Ratio for Cryptogenic Group		
			Crude	Adjusted (95% CI)	*P*
Risk factor profiles					
Age	70.0±10.3	63.0±10.6‡	0.967	…	
Male gender	58 (59.8%)	46 (71.9%)	4.760*	…	
Hypertension	59 (60.8%)	20 (31.3%)‡	0.641	…	
Diabetes	26 (26.8%)	8 (12.5%)*	0.430	…	
Smoking	28 (28.9%)	22 (34.4%)	…		
Alcohol	17 (20.7%)	14 (24.6%)	…		
Dyslipidemia	14 (14.6%)	8 (12.5%)	…		
Atrial fibrillation	20 (20.6%)	0 (0%)‡	N/A		
Ischemic heart disease	9 (12.3%)	6 (12.0%)	…		
Distant metastasis	21 (24.4%)	32 (54.2%)‡	1.912	…	
DWI patterns					
Single vascular territory	77 (79.4%)	19 (29.7%)	Reference	Reference	
Multiple vascular territories	20 (20.6%)	45 (70.3%)‡	10.73‡	11.16 (3.74–33.28)	<0.001
Laboratory findings					
D-dimer levels, μg/mL	3.6±10.3	11.5±14.6†			
D-dimer levels of >1.11 μg/mL	29 (39.7%)	45 (81.8%)‡	11.79‡	10.55 (3.29–33.84)	<0.001

*P<0.05; †P<0.01; ‡P<0.001.

Image findings

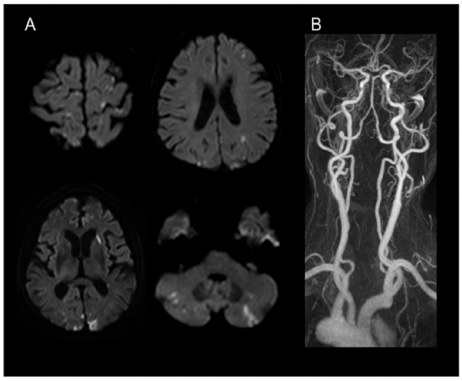


Figure 1. A typical example of cryptogenic stroke with active cancer (cancer-related stroke). The patient was a 55-year-old female, who was diagnosed with metastatic adenocarcinoma of lung one year ago. Neurologic examination revealed motor aphasia, right-central facial paralysis, and right hemiparesis. Initial D-dimer levels were 20.56 μg/mL. Diffusion-weighted MR (A) shows multiple lesions involving multiple vascular territories. MR angiography (B) reveals no significant stenosis or occlusion of the craniocervical arterial vasculature. Comprehensive workup including transesophageal echocardiogram and 24-hour Holter monitoring demonstrated no sources of cardioembolism.
doi:10.1371/journal.pone.0044959.g001

Kim SJ et al. PLOS one 2012

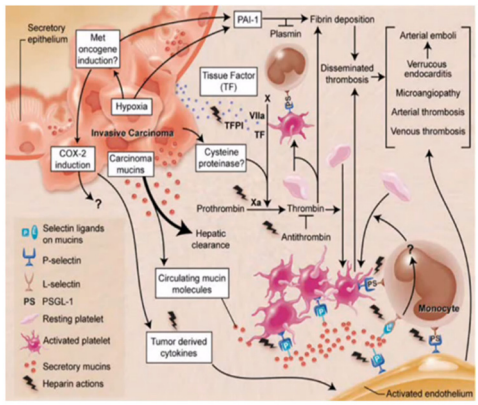
Cancer profiles

Table 1. Baseline characteristics.

	Cancer-related stroke (N=71)	Cryptogenic stroke without active cancer (N=277)	Active lung cancer without stroke (N=33)
Laboratory findings			
D-dimer, μg/mL	10.67 (3.08–25.67)	0.45 (0.29–1.01)‡	0.67 (0.40–1.35)‡
Fibrinogen, mg/dL	337 (213–500)	306 (259–380)	N/A
DWI patterns			
Single vascular territory	17 (23.9%)	229 (82.7%)	N/A
Single lesion	5	143	N/A
Multiple lesions	12	86	N/A
Multiple vascular territories	54 (76.1%)	48 (17.3%)‡	N/A
Cancer profiles			
Time interval between stroke onset and the diagnosis of cancer, months	5 (2–25)	N/A	N/A
Primary cancer type			
Lung	29 (40.8%)	N/A	33 (100%)
Gastrointestinal	11 (15.5%)	N/A	N/A
Hepatobiliary	18 (25.4%)	N/A	N/A
Breast-gynecologic	7 (9.9%)	N/A	N/A
Others	6 (8.5%)	N/A	N/A
Systemic metastasis	47 (66.2%)	N/A	20 (60.6%)
Adenocarcinoma	48 (67.6%)	N/A	26 (78.8%)
Chemotherapy causing coagulopathy	23 (32.4%)	N/A	12 (36.4%)
Cisplatin	23	N/A	12
Methotrexate	0	N/A	0
L-asparaginase	0	N/A	0
Bevacizumab	0	N/A	0

Kim SJ et al. PLOS one 2012

Prothrombotic mechanism



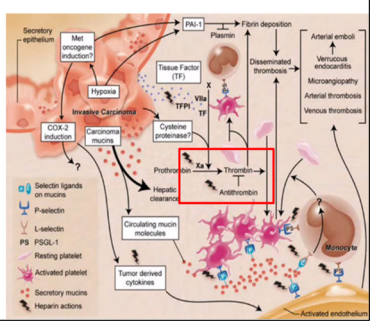
Vark et al. Blood 2007

NBTE

- Nonbacterial thrombotic endocarditis
- Deposition of sterile vegetation on valve leaflets
- "Marantic endocarditis" – wasting away
- Fibrin and platelet deposition
- TEE positive (18%) in cancer stroke
- Murmur: few patients

Treatment

- Anticoagulation
  - Warfarin
  - Low molecular heparin (preferred)
  - Heparin
  - New anticoagulants



Prognosis

Cryptogenic Subtype Predicts Reduced Survival Among Cancer Patients With Ischemic Stroke

Babak B. Navi, MD; Samuel Singer, MD; Alexander E. Merkler, MD; Natalie T. Cheng, MD; Jacqueline B. Stone, MD; Hooman Kamel, MD; Costantino Iadecola, MD; Mitchell S.V. Elkind, MD, MS; Lisa M. DeAngelis, MD

(*Stroke*. 2014;45:2292-2297.)

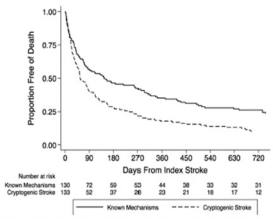


Figure 1. Kaplan–Meier plot of survival free of death, stratified by cryptogenic stroke.

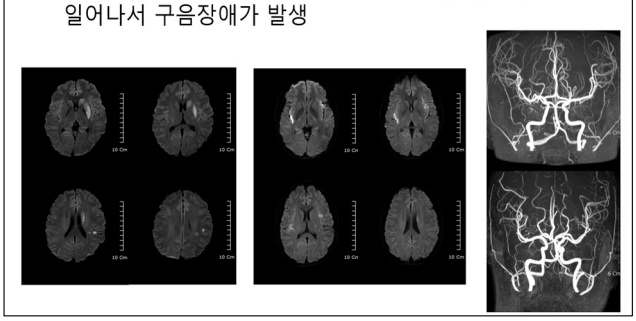
Table 3. Multivariate Cox Hazard Analysis of Prespecified Clinical Factors and Death

	Hazard Ratio (95% CI)	*P* Value
Metastases to other organs	2.55 (1.84–3.53)	<0.01
Cryptogenic stroke	1.64 (1.25–2.14)	<0.01
Adenocarcinoma	1.08 (0.81–1.44)	0.60
Age, y	1.00 (0.99–1.01)	0.42
Modified Rankin Scale score ≤2	0.48 (0.36–0.63)	<0.01

CI indicates confidence interval.

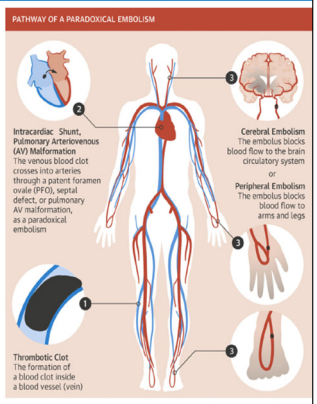
Pardoxical embolism

- 20세 여자가 자고 일어나서 우측 편마비와 감각이상을 발견하였으며, 응급실에 오는 도중 증상은 소실됨
- 36세 여자가 평소 편두통으로 치료받고 있었으며, 자고 일어나서 구음장애가 발생



Paradoxical embolism

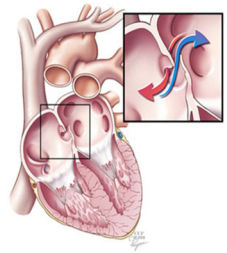
- Thrombotic clot in vein
- Right to left shunt
  - Patent foramen ovale (PFO)
  - Atrial septal defect
  - Pulmonary AVM
- Systemic embolism
  - Ischemic stroke
  - MI
  - GI ischemia
  - Renal ischemia
  - Peripheral artery occlusion



JACC 2014 29;64:403-15

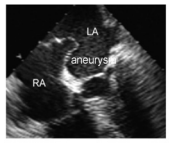
Patent foramen ovale

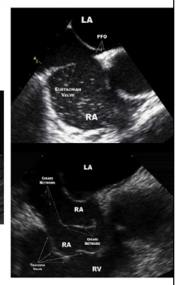
- Congenital, developmental defect
- Incomplete closure of the atrial septum
- Allows shunt between both atrium
- Sources of embolism via PFO
  - Deep vein thrombosis
  - In situ thrombus
- Prevalence
  - First 3 decades : 34%
  - 3-7 decades : 25%
  - Octogenarians : <20%



Right to left shunt in PFO

- Physiologically, a pressure gradient is maintained between the left and the right atrium
- Increased right atrial pressure
  - Valsalva maneuvers (coughing, sneezing, squatting, defecation, micturition)
  - Permanent increase (pulmonary HTN)
- Anatomical variations
  - Eustachian valve
  - Chiari network
  - Atrial septal aneurysm





JACC 2014 29;64:403-15

Right to left shunt in PFO

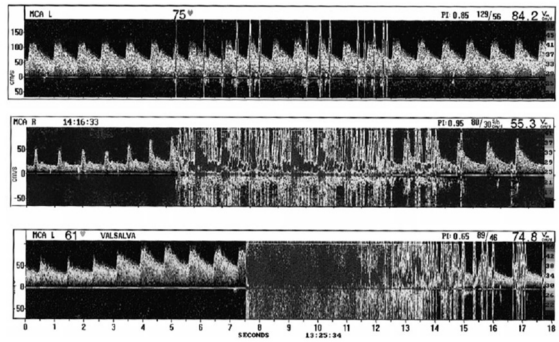


Figure 1. Contrast TCD detected RLSh of >10 signals (upper panel), "shower" (middle panel), and "curtain" (lower panel) patterns in MCA 5 seconds after the end of the Valsalva maneuver.

Stroke 1998;29:1322-1328

Is PFO guilty?

- Incidence in general population : 25%
- Incidence in cryptogenic stroke : 40%

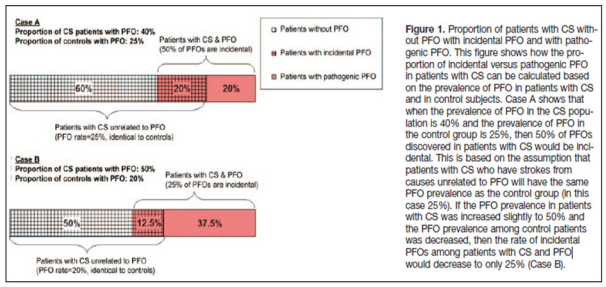


Figure 1. Proportion of patients with CS without PFO with incidental PFO and with pathogenic PFO. This figure shows how the proportion of incidental versus pathogenic PFO in patients with CS can be calculated based on the prevalence of PFO in patients with CS and in control subjects. Case A shows that when the prevalence of PFO in the CS population is 40% and the prevalence of PFO in the control group is 25%, then 50% of PFOs discovered in patients with CS would be incidental. This is based on the assumption that patients with CS who have strokes from causes unrelated to PFO will have the same PFO prevalence as the control group (in this case 25%). If the PFO prevalence in patients with CS was increased slightly to 50% and the PFO prevalence among control patients was decreased, then the rate of incidental PFOs among patients with CS and PFO would decrease to only 25% (Case B).

Stroke 2009;40:2349-2355

Is PFO guilty?

TABLE 1. Prevalence of RLSh by TCD in Patients by Stroke Subtype and in the Study Population

	Patients						
	Stroke of Known Etiology					Study Population	
	Atherosclerotic (n=45)	Cardioembolic (n=39)	Lacunar (n=65)	Other (n=4)	Cryptogenic (n=55)	Total Patients (n=208)	Control Subjects (n=100)
RLSh basal	11 (24.4%)	4 (10.3%)	16 (24.6%)	0 (0)	27 (49.1%)†	58 (27.9%)§	23 (23%)‡
RLSh Valsalva*	11 (25.6%)	6 (15.8%)	21 (32.3%)	0 (0)	30 (56.6%)†	68 (33.5%)§	32 (32%)‡‡
Large RLSh basal	2 (4.4%)	2 (5.1%)	3 (4.6%)	0 (0)	13 (23.6%)†	20 (9.6%)§	8 (8%)‡‡
Large RLSh Valsalva*	2 (4.7%)	4 (10.5%)	10 (15.4%)	0 (0)	24 (45.3%)†	40 (19.7%)§	21 (21%)‡

RLSh basal and RLSh Valsalva include all RLSh detected, independent of the size of RLSh. Large RLSh subgroup contains patients with more than 10 microbubbles (including those with shower and curtain patterns).
*Proportions have been calculated from 203 patients who performed the Valsalva maneuver.
†Cryptogenic vs stroke of known etiology, $P<0.0001$.
‡Control group vs cryptogenic, $P\leq0.001$; ‡‡$P<0.01$.
§Whole group of patients vs control group, $P=$NS.

Cryptogenic의 경우 RL shunt가 많음

Stroke 1998;29:1322-1328

Case-control studies

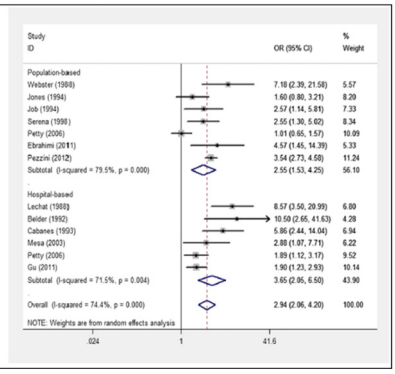


Figure 2. *Meta-analysis of patent foramen ovale and cryptogenic stroke of case–control studies according to population- and hospital-based studies. Abbreviations: CI, confidence interval; OR, odds ratio. (Color version of figure is available online.)*

JSCD 2014 23;5:1207-1215

Cohort studies

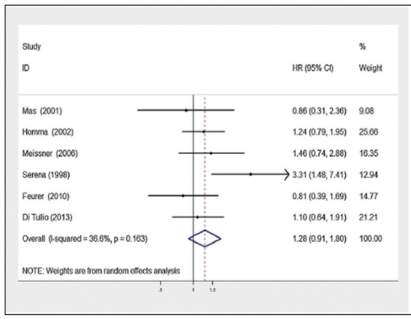


Figure 4. *Meta-analysis of patent foramen ovale and stroke in cohort studies. Abbreviations: CI, confidence interval; HR, hazard ratio. (Color version of figure is available online.)*

JSCD 2014 23;5:1207-1215

Cohort studies

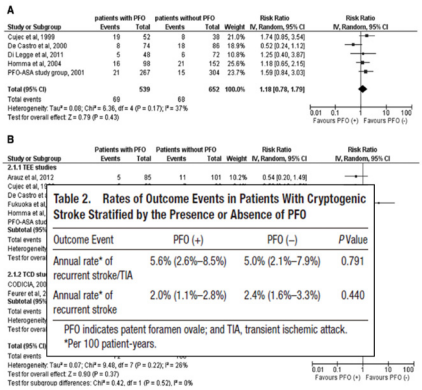


Table 2. Rates of Outcome Events in Patients With Cryptogenic Stroke Stratified by the Presence or Absence of PFO

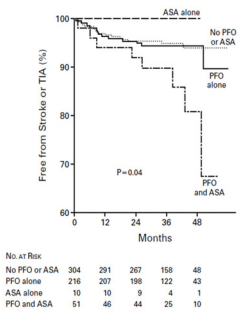
Outcome Event	PFO (+)	PFO (–)	*P* Value
Annual rate* of recurrent stroke/TIA	5.6% (2.6%–8.5%)	5.0% (2.1%–7.9%)	0.791
Annual rate* of recurrent stroke	2.0% (1.1%–2.8%)	2.4% (1.6%–3.3%)	0.440

PFO indicates patent foramen ovale; and TIA, transient ischemic attack.
*Per 100 patient-years.

Figure 3. Risk of recurrent stroke or transient ischemic attack (A) and risk of recurrent stroke (B) in patients with patent foramen ovale (PFO) compared with patients without PFO. ASA indicates atrial septal aneurysm; CI, confidence interval; TCD, transcranial Doppler; and TEE, transesophageal echocardiography.

Stroke 2014;45:3352-3359

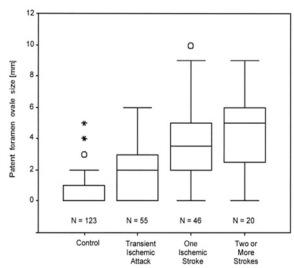
High risk PFO



Atrial septal aneurysm

NEJM 2001;345:1740-6

Eustachian valve



Large PFO

Am J Med 2000;109:456-62

Chiari network

Risk calculation

Table 4 RoPE score calculator

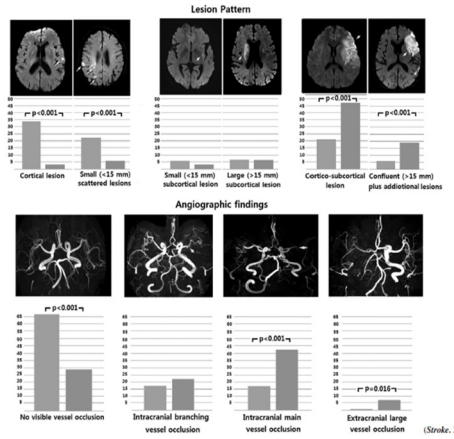
Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, y		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

Abbreviation: RoPE = Risk of Paradoxical Embolism.

	Cryptogenic stroke (n = 3,023)	
RoPE score	No. of patients	Prevalence of patients with a PFO, % (95% CI)*
0–3	613	23 (19–26)
4	511	35 (31–39)
5	516	34 (30–38)
6	482	47 (42–51)
7	434	54 (49–59)
8	287	67 (62–73)
9–10	180	73 (66–79)

Neurology® 2013;81:619-625

Image characteristics



(*Stroke*. 2013;44:3350-3356.)

Medical treatment

Effect of Medical Treatment in Stroke Patients With Patent Foramen Ovale

Patent Foramen Ovale in Cryptogenic Stroke Study

Shunichi Homma, MD; Ralph L. Sacco, MD, MS; Marco R. Di Tullio, MD; Robert R. Sciacca, EngScD; J.P. Mohr, MD; for the PFO in Cryptogenic Stroke Study (PICSS) Investigators*

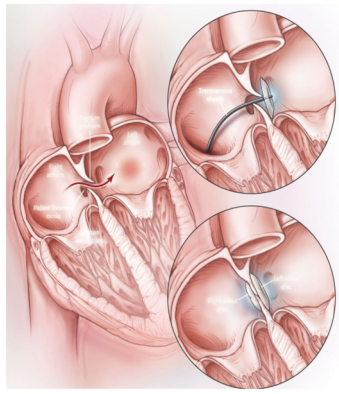
TABLE 3. Two-Year Rates of Recurrent Stroke or Death* in Patients With and Without PFO Assigned to Warfarin or Aspirin

	Warfarin	Aspirin	Hazard Ratio (95% CI)	*P*
Entire PICSS cohort				
With PFO (n=203)	16.5% (n=97)	13.2% (n=106)	1.29 (0.63–2.64)	0.49
No PFO (n=398)	13.4% (n=195)	17.4% (n=203)	0.80 (0.49–1.33)	0.40
Cryptogenic cohort				
With PFO (n=98)	9.5% (n=42)	17.9% (n=56)	0.52 (0.16–1.67)	0.28
No PFO (n=152)	8.3% (n=72)	16.3% (n=80)	0.50 (0.19–1.31)	0.16

*From Kaplan-Meier curves.

(*Circulation*. 2002;105:2625-2631.)

Surgical treatment



Starflex

Amplatzer

Surgical treatment

	CLOSURE (N=909)	RESPECT (N=980)	PC (N=414)
Inclusion	Cryptogenic stroke	Cryptogenic stroke	Cryptogenic stroke, TIA, peripheral embolism
Device	Starflex	Amplatzer	Amplatzer
Medical	Aspirin, Warfarin	Aspirin, Clopidogrel, Aggrenox, Warfarin	Aspirin, Ticlopidine, Clopidogrel, Warfarin
Outcome	2 years TIA/Stroke	8 years Death/Stroke	4 years Death/TIA, Stroke, peripheral embolism
ITT result	Negative	Negative	Negative

Meta-analysis

Potentially Large yet Uncertain Benefits

A Meta-analysis of Patent Foramen Ovale Closure Trials

Georgios D. Kitsios, MD, MS, PhD; David E. Thaler, MD, PhD; David M. Kent, MD, MS

(*Stroke*. 2013;44:2640-2643.)

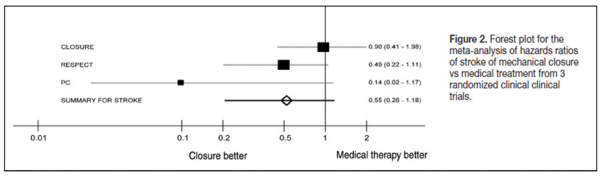


Figure 2. Forest plot for the meta-analysis of hazards ratios of stroke of mechanical closure vs medical treatment from 3 randomized clinical clinical trials.

CLOSURE 제외시 device closure가 좋을 가능성...

Subgroup analysis of RESPECT

Subgroup	Closure Group	Medical-Therapy Group	Hazard Ratio (95% CI)	P Value by Log-Rank Test	P Value for Interaction
	no. of patients/total no. (%)				
Overall	9/499 (1.8)	16/481 (3.3)	0.49 (0.22–1.11)	0.08	
Age					0.52
18–45 yr	4/230 (1.7)	5/210 (2.4)	0.70 (0.19–2.60)	0.59	
46–60 yr	5/262 (1.9)	11/266 (4.1)	0.41 (0.14–1.17)	0.08	
Sex					0.73
Male	5/268 (1.9)	10/268 (3.7)	0.45 (0.15–1.31)	0.13	
Female	4/231 (1.7)	6/213 (2.8)	0.57 (0.16–2.02)	0.38	
Shunt size					0.07
None, trace, or moderate	7/247 (2.8)	6/244 (2.5)	1.03 (0.35–3.08)	0.95	
Substantial	2/247 (0.8)	10/231 (4.3)	0.18 (0.04–0.81)	0.01	
Atrial septal aneurysm					0.10
Present	2/180 (1.1)	9/169 (5.3)	0.19 (0.04–0.87)	0.02	
Absent	7/319 (2.2)	7/312 (2.2)	0.89 (0.31–2.54)	0.83	
Index infarct topography					0.39
Superficial	5/280 (1.8)	12/269 (4.5)	0.37 (0.13–1.04)	0.05	
Small deep	2/57 (3.5)	1/70 (1.4)	1.76 (0.16–19.93)	0.64	
Other	2/157 (1.3)	3/139 (2.2)	0.56 (0.09–3.34)	0.52	
Planned medical regimen					0.20
Anticoagulant	4/132 (3.0)	3/121 (2.5)	1.14 (0.26–5.10)	0.86	
Antiplatelet	5/367 (1.4)	13/359 (3.6)	0.34 (0.12–0.94)	0.03	

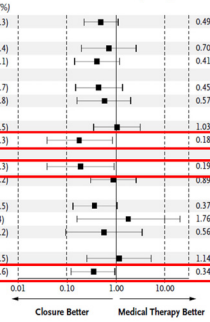
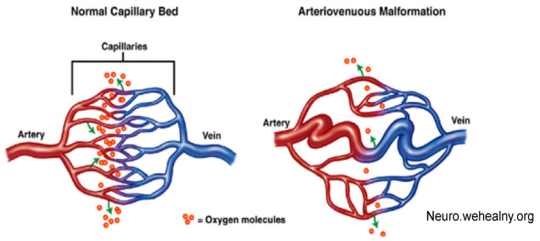


Figure 2. Analysis of the Primary End-Point According to Subgroup, in the Intention-to-Treat Cohort.
Potential heterogeneity of the treatment effect was noted with respect to two baseline characteristics, with a suggestion of greater risk reductions with closure than with medical therapy alone in patients with an atrial septal aneurysm or a substantial shunt size. The percentages are Kaplan–Meier estimates of the event rates.

N Engl J Med 2013;368:1092-100.

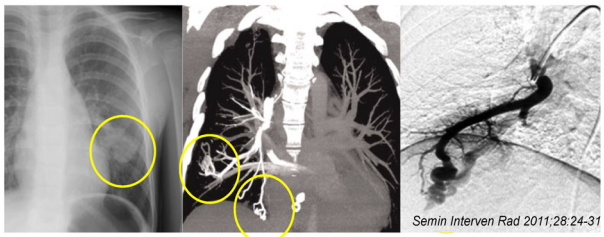
Pulmonary AVM

- Architecture of AVM



- Dilated, tortuous feeding and draining vessels
- A "nidus" or "serpiginous" mass of malformed vss
- Diminished oxygen diffusion

Pulmonary AVM



- Congenital (~90%)
  - Hereditary hemorrhagic telangiectasia
- Acquired (~10%)
- Permanent right to left shunt
  - Hypoxia : Dyspnea, Hypoxemia
  - Paradoxical embolism : Stroke, TIA, Cerebral abscess

Pulmonary AVM

- Delayed microbubble appearance in LA
  - Intracardiac shunt : 11 sec
  - Extracardiac shunt : 14 sec

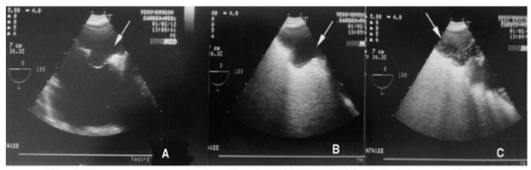


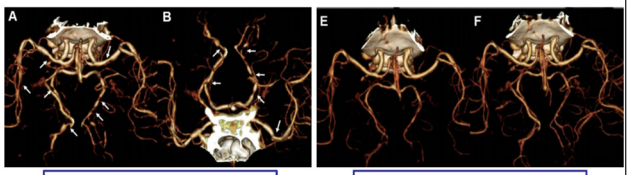
Figure 1 Contrast transesophageal echocardiography (C-TEE). **A**, TEE just before the contrast injection in inferior vena cava; (*arrow*: left atrium). **B**, Contrast echoes in right atrium without atrial shunt; (*arrow*: left atrium). **C**, Delayed appearance of contrast echoes in left atrium (*arrow*).

- Treatment
  - Surgery
  - Embolization

Reversible cerebral vasoconstriction syndrome

- 52세 여자가 1주일 전부터 감기 증상으로 두통이 있었고 약물치료를 받고 있었으며, 금일 오전 두통이 벼락치듯이 심해지고 오심 구토가 동반됨

- 32세 여자가 아이를 낳은 지 6개월 째에 젖을 말리기 위해 Bromocriptine을 복용한 3일 후 벼락치듯 두통이 발생



Headache onset | 3 month later

RCVS - Diagnosis

Table 2. **Summary of Critical Elements for the Diagnosis of Reversible Cerebral Vasoconstriction Syndromes***

Transfemoral angiography or indirect CTA or MRA documenting multifocal segmental cerebral artery vasoconstriction
No evidence for aneurysmal subarachnoid hemorrhage
Normal or near-normal cerebrospinal fluid analysis (protein level < 80 mg%, leukocytes <10 mm^3, normal glucose level)
Severe, acute headaches, with or without additional neurologic signs or symptoms
Reversibility of angiographic abnormalities within 12 weeks after onset. If death occurs before the follow-up studies are completed, autopsy rules out such conditions as vasculitis, intracranial atherosclerosis, and aneurysmal subarachnoid hemorrhage, which can also manifest with headache and stroke

*CTA = computed tomography angiography; MRA = magnetic resonance angiography.

Ann Intern Med. 2007;146:34-44.

Associated conditions

Table 1. **Conditions Associated with Reversible Cerebral Vasoconstriction Syndromes***

Pregnancy and puerperium
Early puerperium, late pregnancy, eclampsia, preeclampsia, and delayed postpartum eclampsia

Exposure to drugs and blood products
Phenylpropanolamine, pseudoephedrine, ergotamine tartrate, methergine, bromocryptine, lisuride, selective serotonin reuptake inhibitors, sumatriptan, isometheptine, cocaine, ecstasy, amphetamine derivatives, marijuana, lysergic acid diethylamide, tacrolimus (FK-506), cyclophosphamide, erythropoetin, intravenous immune globulin, and red blood cell transfusions

Miscellaneous
Hypercalcemia, porphyria, pheochromocytoma, bronchial carcinoid tumor, unruptured saccular cerebral aneurysm, head trauma, spinal subdural hematoma, postcarotid endarterectomy, and neurosurgical procedures

Idiopathic
No identifiable precipitating factor
Associated with headache disorders, such as migraine, primary thunderclap headache, benign exertional headache, benign sexual headache, and primary cough headache

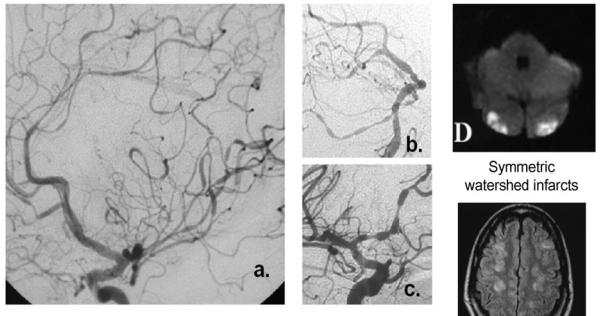
*Adapted from reference 1: Singhal AB, Bernstein RA. Postpartum angiopathy and other cerebral vasoconstriction syndromes. Neurocrit Care. 2005;3:91-7.

Focal neurologic deficits

- Ischemic stroke: 4-54%
- TIAs : <16%
- Cortical SAH : <22%
- ICH : <6%
- SDH : Extremely rare

- Posterior reversible encephalopathy syndrome : 9-14%
- Seizure : 21%

RCVS – typical image



'beading', 'sausage-on-a-string'
Mimics cerebral vasculitis

Symmetric watershed infarcts

Brain edema

Treatment

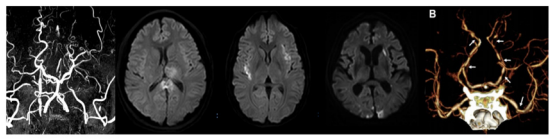
- No evidence
- Often self limited

- Avoid of triggers and withdrawal of secondary causes
- Analgesics
- BP management
- Calcium channel blockers
  - Oral nimodipine 30-60mg every 4 hours
  - Continuous IV nimodipine (0.5-2mg/h)
  - Other CCBs: nicardipine, verapamil

- Steroid are not recommended!!

Take home message

- 뇌졸중의 원인에는 많은 드문 원인들이 있음
- 드물지만 임상에서 만날 가능성이 있는 환자들에 대해서는 알고 있어야 함
- Image pattern을 숙지하고, image에 따른 진단 및 치료방법을 숙지하여야 함



Thank you for your attention