ECHOCOLORDOPPLER LESSONS

CARDIOEMBOLIC OR ATEROTHROMBOTIC STROKE:
how to decide which is the most likely cause?

Franco Accorsi
CLASSIFICATION OF THE ISCHEMIC STROKE SUBTYPE

**ISCHEMIC STROKE SUBTYPE CLASSIFICATION**

4 main categories of ischemic stroke:

i. atherothrombotic
ii. cardioembolic
iii. small vessel disease
iv. other causes

**ISCHEMIC STROKE SUBTYPE CLASSIFICATION:**

1. the classification should identify the most likely etiology(ies)

2. to identify the most likely causative subtype for each patient it is imperative to integrate:
   a. diagnostic test results and
   b. clinical stroke features
CLASSIFICATION OF THE ISCHEMIC STROKE SUBTYPE

ISCHEMIC STROKE CLASSIFICATION: LIMITS!

1. Types of etiologic classification: causative subtypes
   (for instance: TOAST)
   - causative subtypes frequently are assigned based on a presumed
     mechanism of stroke, rather than on direct demonstration of the cause by a
     gold standard
   - there is loss of information
     is subject to an important bias!

2. Types of etiologic classification: phenotypic subtypes
   (for instance: ASCO)
   - subtypes typically are determined according to the potential for each
     underlying etiology to cause stroke
   - there are no tradeoffs among positive test findings, so there is no loss of
     information
     a patient can be categorized into more than one etiologic subtype!
THE CLASSIFICATION OF THE ISCHEMIC STROKE SUBTYPE SHOULD BE BASED ON:

A. clinic

B. diagnostic tests:
   i. blood tests
   ii. TC/MR
   iii. electrocardiogram, TEE, TTE, TCD bubble test
   iv. US/NR assessment of extracranial/intracranial arteries
THE CLASSIFICATION OF THE ISCHEMIC STROKE SUBTYPE SHOULD BE BASED ON:

A. clinic

B. diagnostic tests:
   i. blood tests
   ii. TC/MR
   iii. electrocardiogram, TEE, TTE, TCD bubble test
   iv. US/NR assessment of extracranial/intracranial arteries
CHARACTERISTIC CLINICAL FEATURES OF CARDIOEMBOLIC /ATHEROSCLEROTIC STROKE

There are no absolute criteria for the diagnosis of cardioembolic/atherosclerotic cerebral infarction, although the following is required:

1) compatible clinical picture
2) exclusion/recognition of an emboligenic heart disease
3) exclusion/recognition of carotid and/or cerebral atherosclerosis
CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: CLINIC

LARGE-ARTERY Atherosclerosis:
CHARACTERISTIC CLINICAL FEATURES

- clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction.
- hypertension, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia and age were significantly associated with atherothrombotic infarction.
- a history of intermittent claudication, TIAs in the same vascular territory, a carotid bruit, or diminished pulses helps support the clinical diagnosis.
CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: CLINIC

CARDIOEMBOLISM:

CHARACTERISTIC CLINICAL FEATURES

- clinical findings are similar to those described for large-artery atherosclerosis
- atrial fibrillation, recognition of an emboligenic heart disease, sudden onset and rapid regression of symptoms are independently associated with CE stroke
- evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke
- onset of symptoms after a Valsalva-provoking activity (coughing, bending, etc.) suggesting paradoxical embolism
CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: CLINIC

CARDIOEMBOLIC CEREBRAL INFARCTION

is the most severe ischaemic stroke subtype, with:

1. high in-hospital mortality rate (6–27%)
2. a substantial number of patients with neurological dysfunction at the time of hospital discharge
3. the risk of early embolic recurrence varies between 1 and 10%


Histopathological specimen showing a hemorrhagic cerebral infarction of a cardioembolic origin with signs of ventricular displacement and brain herniation in the territory of the middle cerebral artery.

CHARACTERISTIC CLINICAL FEATURES OF CARDIOEMBOLIC STROKE

1. sudden onset to maximal deficit and altered consciousness

1. sudden (< 5 min) onset to maximal deficit (47–74% of cases) and decreased level of consciousness at onset (19–31% of cases).

2. altered consciousness is a predictive factor of cardioembolic cerebral infarction (odds ratio of 3.2 as compared with atherothrombotic infarction).

3. sudden onset of neurological deficit occurs:
   1. in 79.7% of cases of cardioembolic cerebral infarction
   2. in 38% of lacunar infarcts
   3. in 46% of thrombotic infarctions

Caplan LR. Brain embolism, revisited. Neurology 1993;
CHARACTERISTIC CLINICAL FEATURES OF CARdioEMBOLIC STROKE

2. rapid regression of symptoms

1. the cardioembolic cerebral infarction shows a rapid regression of symptoms (spectacular shrinking deficit syndrome) in 4.7–12% of cases

2. the recognition of this syndrome may be important for a clinical suspicion of cardioembolism.

3. this rapid improvement of an initially severe neurological deficit may be due to distal migration of the embolus followed by recanalization of the occluded vessel.

Bechich J et al. Regresión espectacular del déficit hemisférico neurológico. Neurología 1997;
Hart RG. Cardiogenic embolism to the brain. Lancet 1992
CHARACTERISTIC CLINICAL FEATURES OF CARDIOEMBOLIC STROKE

3. other clinical features

1. in cardioembolism: a) cardiac arrhythmia is frequent; b) a systemic embolism is possible; c) the onset of symptoms after a Valsalva maneuver (coughing, bending, etc.) suggests paradoxical embolism.

2. cardioembolism is a very rare cause of lacunar infarction.

3. visual-field abnormalities, neglect, and aphasia are more common in cardioembolic than in non-cardioembolic stroke.

Caplan LR. Clinical diagnosis of brain embolism. Cerebrovasc Dis 1995; 
Cacciatore A et al. Lacunar infarction as an embolic complication of cardiac and arch angiography. Stroke 1991; 
Lodder J et al. Are hypertension or cardiac embolism likely causes of lacunar infarction? Stroke 1990
<table>
<thead>
<tr>
<th>CLINICAL FEATURES THAT SUPPORT ATHEROSCLEROTIC STROKE</th>
<th>CLINICAL FEATURES THAT SUPPORT CARDIOEMBOLIC STROKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction</td>
<td>1. clinical findings are similar to those described for large-artery atherosclerosis (but, more often: severe stroke, disability and death)</td>
</tr>
<tr>
<td>2. lacunar clinical presentation (e.g., pure motor hemiparesis or ataxic hemiparesis) is frequent in ATS stroke</td>
<td>2. cardiac embolism is a very rare cause of lacunar infarction</td>
</tr>
<tr>
<td>3. TIAs in the same vascular territory, a carotid bruit, diminished pulses support a clinical diagnosis of ATS stroke</td>
<td>3. previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of CE stroke</td>
</tr>
<tr>
<td>4. hypertension, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia are significantly associated with ATS stroke</td>
<td>4. atrial fibrillation, recognition of an emboligenic heart disease are independently associated with CE stroke</td>
</tr>
<tr>
<td>5. sudden onset of neurological deficit are less frequent in ATS infarctions</td>
<td>5. sudden onset of neurological deficit and the rapid regression of symptoms are important for a clinical suspicion of the CE origin of stroke</td>
</tr>
<tr>
<td>6. altered consciousness is a predictive factor of CE cerebral infarction</td>
<td>7. the onset of symptoms after a Valsalva-provoking activity (coughing, bending, etc.) suggesting paradoxical embolism.</td>
</tr>
</tbody>
</table>
THE CLASSIFICATION OF THE ISCHEMIC STROKE SUBTYPE SHOULD BE BASED ON:

A. clinic

B. diagnostic tests:
   i. blood tests
   ii. TC/MR
   iii. electrocardiogram, TEE, TTE, TCD bubble test
   iv. US/NR assessment of extracranial/intracranial arteries
**CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE:**

**BLOOD TESTS**

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>General Features</th>
<th>Ischemic Stroke Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>Vasoactive peptide hormone</td>
<td>↑ BNP in acute phase</td>
</tr>
<tr>
<td></td>
<td>Natriuretic, diuretic, and vasodilator activity</td>
<td>↑ BNP predicts poststroke mortality</td>
</tr>
<tr>
<td>DD</td>
<td>Products of degradation of fibrin</td>
<td>↑ DD in acute, subacute, and chronic phases</td>
</tr>
<tr>
<td></td>
<td>Marker of hemostatic imbalance</td>
<td>↑ DD in cardioembotic stroke</td>
</tr>
<tr>
<td>S100b</td>
<td>Calcium-binding protein</td>
<td>↑ S100b in acute phase</td>
</tr>
<tr>
<td></td>
<td>Synthesized in astroglial cells</td>
<td>S100b associated with clinical deficit, infarct volume, and functional disability</td>
</tr>
<tr>
<td></td>
<td>Marker of brain damage</td>
<td>No studies</td>
</tr>
<tr>
<td>RAGE</td>
<td>Transmembrane receptor</td>
<td>Immunoglobulin superfamily</td>
</tr>
<tr>
<td></td>
<td>Expressed by endothelial cells, mononuclear cells, and neurons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overexpressed at sites of vascular damage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sRAGE have antithromogenic effects</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>Pentraxin</td>
<td>↑ CRP in acute phase</td>
</tr>
<tr>
<td></td>
<td>Acute-phase protein; participates in the systemic response to inflammation</td>
<td>Predictor of risk of cerebrovascular events</td>
</tr>
<tr>
<td></td>
<td>Hepatic and extrahepatic synthesis</td>
<td>Prognostic value after stroke</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Proteolytic enzyme</td>
<td>↑ MMP-9 in acute phase</td>
</tr>
<tr>
<td></td>
<td>Involved in tissue remodeling</td>
<td>MMP-9 associated with hemorrhagic transformation</td>
</tr>
<tr>
<td></td>
<td>Important role in neuroinflammation</td>
<td>Correlated with infarct size and clinical deficit</td>
</tr>
<tr>
<td></td>
<td>Synthesized by neurons (α1 isoform)</td>
<td>No studies</td>
</tr>
<tr>
<td>Chimerin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretagoin</td>
<td>Calcium-binding protein</td>
<td>↑ Secretagoin in acute phase</td>
</tr>
<tr>
<td>Neurotrophin-3</td>
<td>Nonprotein kinase C (GAP family)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Expressed in neuroendocrine cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marker of neuronal death</td>
<td></td>
</tr>
<tr>
<td>Caspase-3</td>
<td>Cysteine protease</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Executioner</em> in apoptosis</td>
<td></td>
</tr>
<tr>
<td>Neurotrophin-3</td>
<td>&quot;Neuronal survival factor&quot; (neurotrophin family of growth factors)</td>
<td>Endogenous neurotrophin-3 enhances neuronal injury during acute stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Neurotrophin-3 synthesis has neuroprotective role</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activation of caspase-3 in permanent and transient brain ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caspase activation after ischemia-induced brain damage</td>
</tr>
</tbody>
</table>

Several biomarkers have been recently related to cardiac disorders or thrombotic diseases.

*Joan Montaner et al. Etiologic Diagnosis of Ischemic Stroke Subtypes With Plasma Biomarkers. Stroke. 2008*
BIO-MARKERS IN ACUTE ISCHEMIC STROKE PATIENTS

- biomarkers, to date, lack sensitivity or specificity to be of clinical use in stroke


BIO-MARKERS IN ACUTE ISCHEMIC STROKE PATIENTS

- B-type natriuretic peptide and D-dimer are strongly associated with CE stroke and functional outcome
ETIOLOGIC DIAGNOSIS OF ISCHEMIC STROKE SUBTYPES WITH PLASMA BIOMARKERS

- 707 ischemic stroke pts included
- blood samples to test selected biomarkers: C-reactive protein, D-dimer, soluble receptor for advanced glycation end products, matrix metalloproteinase, S-100b, brain natriuretic peptide (BNP), neurotrophin, caspase, chimerin, and secretagogin.

  independent predictors of CE stroke were:
  i. AF and other embolic cardiopathies
  ii. total anterior circulation infarction
  iii. BNP >76 pg/mL; and D-dimer >0.96 g/mL.

CONCLUSIONS

Using a combination of biomarkers may be a feasible strategy to improve the diagnosis of CE stroke in the acute phase

VALUE OF THE USE OF BRAIN NATRIURETIC PEPTIDE (BNP) IN ACUTE ISCHEMIC STROKE PATIENTS

1) BNP is strongly associated with CE stroke and functional outcome at 6 months after ischemic stroke.

2) elevated plasma BNP levels can be a potential marker of the presence of left atrial sources of emboli in ischemic stroke pts.

3) BNP has been shown to be an independent predictor of the mortality and myocardial infarction in stroke pts.

4) the cut-off values of BNP are different in several studies and need further validation


Di Angelantonio E et al. Determinants of plasma levels of brain natriuretic peptide after acute ischemic stroke or TIA. J Neurol Sci. 2007;

VALUE OF THE USE OF PLASMA D-DIMER IN ACUTE ISCHEMIC STROKE PATIENTS

1) high-level plasma D-dimer of acute period strongly indicates an unfavorable clinical outcome

2) pts with CE has the highest level of plasma D-dimer (with the most serious neurological deficit and the worst outcome among the five subtypes)

3) CE strokes can be distinguished from other stroke etiologies by measuring plasma D-dimer levels very early


1. At present there is no biologic marker offering precise information about stroke etiology.

2. Elevated plasma BNP/D-dimer levels can be a potential marker of the presence of left atrial sources of emboli in ischemic stroke pts.

3. BNP/D-dimer are strongly associated with CE stroke and functional outcome.

4. The cut-off values of BNP/D-dimer need further validation.
THE CLASSIFICATION OF THE ISCHEMIC STROKE SUBTYPE SHOULD BE BASED ON:

A. clinic

B. diagnostic tests:
   i. blood tests
   ii. TC/MR
   iii. electrocardiogram, TEE, TTE, TCD bubble test
   iv. US/NR assessment of extracranial/intracranial arteries
CARDIOEMBOLIC / ATHEROSCLEROTIC STROKE:

CT / MR

CE / ATHEROSCLEROTIC STROKE:

NEURORADIOLOGY

presence of territorial infarct:

a. cortical
b. cerebellar
c. of the trunk
d. subcortical \( \geq 1.5 \) cm.
Brain imaging findings that support:
1. large-artery atherosclerotic stroke
2. CE stroke
1. BRAIN IMAGING FINDINGS THAT SUPPORT LARGE-ARTERY ATHEROSCLEROTIC STROKE

- (unique) cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI
Brain imaging findings that support:

1. large-artery atherosclerotic stroke
2. CE stroke
2. BRAIN IMAGING FINDINGS THAT SUPPORT CE STROKE

a) brain imaging findings are similar to those described for large-artery atherosclerosis.

b) evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism

c) hemorrhagic transformation of infarction (more frequent in CE stroke)

CE AND HEMORRHAGIC TRANSFORMATION OF AN ISCHEMIC STROKE

1. the hemorrhagic transformation of an ischemic stroke and early recanalization are suggestive of a CE stroke

2. the hemorrhagic transformation occurs at least in 71% of CE stroke

3. about 95% of hemorrhagic strokes are caused by CE

Ferro J. (J Neurol 2003); Weir NU. (Postgrad Med J, 2008); Murtag B. (Curr. Ather Rep, 2006)
**CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: CT/MR**

<table>
<thead>
<tr>
<th>CT/MR FINDINGS THAT SUPPORT LA ATS STROKE INCLUDE:</th>
<th>CT/MR FINDINGS THAT SUPPORT CE STROKE INCLUDE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts &gt; than 1.5 cm in diameter</td>
<td>▪ brain imaging findings are similar to those described for large-artery atherosclerosis</td>
</tr>
<tr>
<td>▪ unique (more often) ischemic area</td>
<td>▪ simultaneous or sequential infarctions in differential arterial territories</td>
</tr>
<tr>
<td></td>
<td>▪ hemorrhagic transformation of infarction (more frequent in CE stroke)</td>
</tr>
</tbody>
</table>
THE CLASSIFICATION OF THE ISCHEMIC STROKE SUBTYPE SHOULD BE BASED ON:

A. clinic

B. diagnostic tests:
   i. blood tests
   ii. TC/MR
   iii. electrocardiogram, TEE, TTE, TCD bubble test
   iv. US/NR assessment of extracranial/intracranial arteries
Embolicism from the heart to the brain results from one of three mechanisms:

1. blood stasis and thrombus formation in an enlarged left cardiac chamber
2. release of material from an abnormal valvular surface
3. abnormal passage from the venous to the arterial circulation (PFO)

Cardiac emboli are often large and hence especially likely to cause severe stroke, disability and death
**TOAST CLASSIFICATION. STROKE 1993**

**HIGH-RISK SOURCES OF CARDIOEMBOLISM**

- mechanical prosthetic valve
- mitral stenosis with atrial fibrillation
- atrial fibrillation (other than lone atrial fibrillation)
- left atrial/atrial appendage thrombus
- sick sinus syndrome
- recent myocardial infarction (<4 weeks)
- left ventricular thrombus
- dilated cardiomyopathy/akinetie left ventricular segment
- atrial myxoma, infective endocarditis

**MEDIUM-RISK SOURCES OF CARDIOEMBOLISM**

- mitral valve prolapse
- mitral annulus calcification/mitral stenosis without atrial fibrillation
- left atrial turbulence (smoke)
- atrial septal aneurysm/patent foramen ovale
- atrial flutter, lone atrial fibrillation
- bioprosthetic cardiac valve
- nonbacterial thrombotic endocarditis
- congestive heart failure/hypokinetie left ventricular segment
- myocardial infarction (>4 weeks, <6 months)
CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: 

**ECG**

CARDIOEMBOLIC VERSUS AHEROTHROMBOLIC STROKE screening for emboligenic arrhythmias

- atrial fibrillation is independently associated with cardioembolic stroke
- non-valvular atrial fibrillation remains the commonest cause of cardioembolic stroke

paroxysmal atrial fibrillation may remain underdiagnosed after stroke
CARDIOEMBOLIC VERSUS AHEROTHROMBOLIC STROKE screening for emboligenic arrhythmias (paroxysmal atrial fibrillation)

1. ECG
2. 24-hour Holter ECG (may not be sufficient for diagnosing PAF)
3. 7-day ambulatory ECG monitoring increases detection rate of PAF
149 consecutive pts with an acute stroke or TIA were systematically screened for embolicogenic arrhythmias

- AF was detected in 22 pts.
- standard ECG identified AF in 2.7% of the cases at admission (4/149 pts) and in 4.1% of remaining pts within 5 days (6/145).
- Holter disclosed AF in 5% of pts with a normal standard ECG (7/139 pts)
- 7-day ECG monitoring using an event-loop recording detected AF in 5.7% of pts with a normal standard ECG and normal Holter (5/88 pts).

Jabaudon, MD et al. Usefulness of Ambulatory 7-Day ECG Monitoring for the Detection of Atrial Fibrillation and Flutter After Acute Stroke and Transient Ischemic Attack. Stroke 2004
TRANSTHORACIC ECHOCARDIOGRAM

- can disclose structural cardiopathies (dilated cardiomyopathies, mitral stenosis and other structural ventricular diseases and intraventricular thrombus, vegetations or tumors)
- enables measurement of the left atrial size and left ventricular systolic function.

68 patients with ischemic stroke at low-risk for CE

In 28 out of 68 pts TEE found an abnormal lesion not been detected by TTE:

1) 23 diffuse (>5mm) atherosclerotic atheromas in the aortic arch
2) 5 patent PFO lesions
3) 3 left atrial thrombi
4) 1 ventricular septal defect (VSD)
5) 1 atrial septal defect (ASD)
6) (6 patients had more than 1 finding)

CONCLUSIONS:

In half of the patients TEE (but not TTE) found a significant lesion that changed our policy of management. None of these lesions were detected by TTE.

It seems that TEE is mandatory in the evaluation of patients with acute ischemic stroke.

CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: TTE-TEE

**TEE is superior to TTE for identification of a cardiac embolic source in patients with TIA or stroke**

**TABLE 1. Potential Cardiac Sources of Embolism in 231 TIA or Stroke Patients Assessed by TTE or TEE**

<table>
<thead>
<tr>
<th>Potential Cardiac Source</th>
<th>TTE</th>
<th>TEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA cavity thrombus</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>LA appendage thrombus</td>
<td>1 (1%)</td>
<td>38 (16%)</td>
</tr>
<tr>
<td>LV thrombus</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Aortic thrombus</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy (LVEF&lt;35%)</td>
<td>5 (2%)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve stenosis</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Minor risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>4 (2%)</td>
<td></td>
</tr>
<tr>
<td>Mitral annular calcification</td>
<td>4 (2%)</td>
<td></td>
</tr>
<tr>
<td>Calcified aortic stenosis</td>
<td>8 (3%)</td>
<td></td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>3 (1%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Spontaneous echo contrast</td>
<td>2 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td>5 (2%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>LV aneurysm</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>False tendon</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aortic plaques</td>
<td>1 (1%)</td>
<td>69 (30%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

TEE ability to more sensitively detect atrial septal aneurysm, PFO and aortic atheroma

- in patients with normal TTE, a cardiac source of embolism was detected by TEE in ≈40% of patients, independent of age.
- more than 1 of 8 patients of any age with normal TTE revealed a major cardiac risk factor on TEE, in whom anticoagulation is warranted.

Sebastiaan F.T.M. de Bruijn et. Al. Transesophageal Echocardiography Is Superior to Transthoracic Echocardiography in Management of Patients of Any Age With Transient Ischemic Attack or Stroke. Stroke 2006
TRANSESOPHAGEAL ECHOCARDIOGRAM

- is able to study the aortic arch and ascending aorta, left atrium and left atrial appendages, intra-arterial septum, pulmonary veins and valve vegetations
- is more likely to be helpful in young patients with stroke, stroke of unknown cause and in patients with nonlacunar stroke.

CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: TEE

WHEN SHOULD TEE BE PERFORMED?

- when there is a need to assess the right and left atrial cavities;
- when searching for an atrial septal aneurysm;
- when there is a need to assess the thoracic aorta;
- at times, in addition to TEE, a cardiac CT or MRI can help search for a cardiac pathology.

*P. Amarenco. Classification of Stroke Subtypes. Cerebrovasc Dis 2009*
TRANSESOPHAGEAL ECHOCARDIOGRAPHY AND AORTIC ARCH ATHEROMATOSIS

- ulcerated aortic plaques were observed in 17 (61%) of 28 pts with cerebral infarction of unknown aetiology as compared with 34 (22%) of 155 pts in whom a cerebral infarction-attributable aetiology was found.

- the main emboligenic risk criteria for atheromatous plaques of the aortic arch include plaque thickness ≥ 4 mm and the presence of mobile components

PATENT FORAMEN OVALE

- a PFO is present in approximately 25% of the general population, and can be found in up to 40% of younger pts with otherwise cryptogenic stroke.
- there is a higher risk of stroke with PFO, especially when combined with atrial septal aneurysm.
- in a meta-analysis of case control studies that examined the relative frequency of PFO, atrial septal aneurysm, or both, in all pts with ischaemic stroke, cryptogenic stroke and known stroke cause, PFO and atrial septal aneurysm were significantly associated with ischaemic stroke in pts <55 years.

CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE:

TCD MICROBUBBLE

TRANSCRANIAL DOPPLER (TCD)
AND PARADOXICAL EMBOLISM

- TCD is a first-line non-invasive diagnosis of right-to-left shunt caused by a PFO by detecting bubble signs in the middle cerebral arterial territory after the injection of agitated saline in the antecubital vein.
TCD AND PFO

RECOMMENDATIONS TO STANDARDIZE THE EXAMINATION PROCEDURE

1. The patient should be prepared with an 18-gauge needle inserted into the cubital vein and should be in the supine position.

2. Insonation of at least one middle cerebral artery (MCA) using TCD is performed.

3. The contrast agent is prepared using 9 ml isotonic saline solution and 1 ml air mixed with a three-way stopcock by exchange of saline/air mixture between the syringes and injected as a bolus.

4. In case of little or no detection of microbubbles (MB) in the MCA under basal conditions, the examination will be repeated using the Valsalva maneuver (VM).

5. Contrast agent will be injected 5 s before the start of the VM; the overall VM duration should be 10 s.

1. Injection of a mixture of saline solution (9mL) and air (1 mL) agitated between two 10 mL syringes connected by a 3-way stopcock.

2. ACM rt. US registration: procedure during normal breathing and during a Valsalva maneuver.
A four-level categorization according to the microbubbles (MB) count should be applied:

1. 0 MB (negative result)
2. 1-10 MB
3. >10 MB and no curtain
4. Curtain ('curtain' refers to a shower of MB, where a single bubble cannot be identified)

The results should be documented for basal condition and VM testing separately.

A four-level categorization according to the microbubbles (MB) count should be applied:

1) 0 MB (negative result); 2) 1-10 MB; 3) >10 MB and no curtain; 4) curtain.
CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: TCD MICROBUBBLE

PFO-RELATED STROKE

---

It is essential to quantify the magnitude of RLSH by contrast TCD during the Valsalva maneuver, given that only those with shower and curtain patterns are associated with a higher risk of ischemic stroke in a non selected population.

Serena J. Stroke 1998
STROKE AND PFO

- in PFO diagnosis (TEE/TCD microbubble), for confirming the diagnosis of CE stroke, are useful (for the detection of DVT):
  1. ECD of the veins of the lower limbs
     and, in special cases
  2. angioCT of inferior cava vein and iliac veins
CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE: TCD MICROBUBBLE

CASE REPORT: PARADOXICAL EMBOLISM AFTER SURGERY
US: DVT in iliac and femoral veins
patient 63 year-old woman with recent ankle fracture

1. 17-10 -> ECD: DVT common femoral vein

2. 19-10 (two days later) -> stroke

3. 19-10 -> ECD/TCCD

4. 25-10 ->
   a. TCD: “curtain” (large shunt) and
   b. ECD: DVT extension (iliac vein)
TCD AND PFO

- TEE remains the gold standard for detection of a PFO or an atrial septum defect.
- However, TCD with a contrast agent has been turned out as a potential method to diagnose a RLS in several studies which have been published during the last years, and a RLS other than at the atrial level may be detected only by this method.
- Furthermore, the VM can be applied more comfortably and more reliably during Doppler examination than during TEE.

**CARDIOEMBOLIC/ATHEROSCLEROTIC STROKE:**

**ECG-TTE-TEE-TCD BUBBLE**

<table>
<thead>
<tr>
<th>EC, TEE, TTE, TCD BUBBLE TEST FINDINGS THAT SUPPORT LA ATS STROKE INCLUDE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ no CE sources of high and medium risk (no recognition of an emboligenic heart disease)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EC, TEE, TTE, TCD BUBBLE TEST FINDINGS THAT SUPPORT CE STROKE INCLUDE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ ECG, 24-hour Holter ECG, 7-day ECG (AF and PAF diagnosis)</td>
</tr>
<tr>
<td>▪ TTE/TEE recognition of CE sources of high and medium risk</td>
</tr>
<tr>
<td>▪ TCD/TEE recognition of rt-&gt;lt large shunt in patient with cerebral infarction of unknown aetiology</td>
</tr>
<tr>
<td>▪ TEE recognition of plaque thickness $\geq 4$ mm and mobile components in the aortic arch (pts in whom a cerebral infarction-attributable aetiology is not found)</td>
</tr>
</tbody>
</table>
THE CLASSIFICATION OF THE ISCHEMIC STROKE SUBTYPE SHOULD BE BASED ON:

A. clinic

B. diagnostic tests:
   i. blood tests
   ii. TC/MR
   iii. electrocardiogram, TEE, TTE, TCD bubble test
   iv. US/NR assessment of extracranial/intracranial arteries
CE/ATHEROSCLEROTIC STROKE:
EXTRA/INTRACRANIAL US AND NR ASSESSMENT

LARGE ARTERY PATHOLOGY
- ECD/TCCD are generally sufficient to diagnose a large artery pathology (stenosis/occlusion)
- In special cases are necessary: angioCT/MR (angiography)
1. extra/intracranial pathology characteristic features in atherothrombotic stroke

a) hemodynamic plaque (plaque “at risk”) in an intra or extracranial artery supplying the ischemic field

b) occlusion with imaging evidence of atherosclerosis in an intra or extracranial artery supplying the ischemic field

2. extra/intracranial pathology characteristic features in CE stroke

c) occlusion of the carotid artery by mobile embolus

d) simultaneous or sequential embolism in different arteries
CE/ATHEROSCLEROTIC STROKE: 
EXTRA/INTRACRANIAL US AND NR ASSESSMENT

1. extra/intracranial pathology characteristic features in atherothrombotic stroke
CE/atherosclerotic stroke: extra/intracranial US and NR assessment

1. ATS stroke:
   a) hemodynamic plaque (plaque “at risk”) in an intra or extracranial artery supplying the ischemic field

US characteristic features of unstable ICA plaque:
- high degree of luminal stenosis, surface ulceration and plaque rupture, thinning of the fibrous cap
CE/ATHEROSCLEROTIC STROKE: EXTRA/INTRACRANIAL US AND NR ASSESSMENT

1. ATS stroke:
   a) hemodynamic plaque (plaque “at risk”) in an intra or extracranial artery supplying the ischemic field

US characteristic features of intracranial stenosis “at risk”:
- siphon: hemodynamic stenosis with abnormal spectrum and circumscribed velocity changes (PSV = 2.80 m/s -> 0.80 m/s)
CE/ATHEROSCLEROTIC STROKE:
EXTRA/INTRACRANIAL US AND NR ASSESSMENT

1. ATS stroke:
   a) hemodynamic plaque (plaque “at risk”) in an intra or extracranial artery supplying the ischemic field

US characteristic features of intracranial stenosis “at risk”:
- MCA high-grade stenosis with abnormal spectrum and circumscribed high velocity flow (PSV = 3.54 m/s)
CE/ATHEROSCLEROTIC STROKE:
EXTRA/INTRACRANIAL US AND NR ASSESSMENT

2. extra/intracranial pathology characteristic features in CE stroke
2. CE stroke:
c) occlusion of the carotid artery by mobile embolus

**US characteristic features of ICA occlusion mobile embolus:**
- CCA and ICA occlusion (cardiac embolus)
- MCA embolic occlusion
2. CE stroke:
c) occlusion of the carotid artery by mobile embolus: follow up

- ICA occlusion (cardiac embolus)

- control two days later: early ICA recanalisation
2. CE stroke:
c) occlusion of the carotid artery by mobile embolus

- patient ♂, 67 years. Acute phase (28-3): ICA occlusion (cardiac embolus)

- same patient ♂, 67 years. Control two days later (30-3): ICA occlusion with morphological change of the embolus
2. CE stroke:
c) occlusion of the carotid artery by mobile embolus

US/NR images in CE stroke:
a) ICA occlusion (mobile embolus)
b) MCA embolic occlusion
c) temporal ischemic area
CE/ATHEROSCLEROTIC STROKE: EXTRA/INTRACRANIAL US AND NR ASSESSMENT

2. CE stroke:
  d) simultaneous/sequential embolism in different arteries

angiographic characteristic features of CE:
- AA, rt SCA and lt ICA occlusion (simultaneous cardio-embolism)
CE/ATHEROSCLEROTIC STROKE:
EXTRA/INTRACRANIAL US AND NR ASSESSMENT

2. CE stroke:
d) simultaneous/sequential embolism in different arteries

TCD characteristic features of CE:
- TCD monitoring: bilateral MES suggestive of CE stroke
Color Doppler Ultrasound:

In presence of

1. not hemodynamic plaque: ats stroke? CE stroke?
2. extracranial ICA “high resistance flow”: ats stroke? CE stroke?

Pitfalls!
CE/ATHEROSCLEROTIC STROKE: 
EXTRA/INTRACRANIAL US AND NR ASSESSMENT

1. not hemodynamic plaque: ATS stroke? CE stroke?

patient 65 years: acute stroke
- ECD: not hemodynamic plaque --->
  → CE stroke? other?

same patient, but 60 days before (in emergency room for dizziness and vomiting)
- ECD irregular, heterogeneous, not hemodynamic plaque: PSV = 0.59 cm/s.
  → ATS stroke!!
2. ICA “high resistance flow”: ATS stroke? CE stroke? other?

a. extracranial ICA “high resistance flow” (indirect information of intracranial ICA occlusion) and cardiac arrhythmia (atrial fibrillation): indirect information about heart rate/rhythm; b) TCCD/MR/CT: rt MCA occlusion and right infarction

- the ICA “high resistance flow” is a “non-specific sign” (ICA dissection? atherosclerosis/ cardioembolism with obstruction of distal ICA?)
- it is necessary to evaluate the “high resistance flow” in the clinical setting!
  - in this case: AF-> CE stroke
2. ICA “high resistance flow”: ATS stroke? CE stroke? other?

a. extracranial rt ICA “high resistance flow” (indirect information of intracranial ICA occlusion) and bulb plaque in 82 y-old patient; 
b) TCCD/angioCT/CT: rt MCA occlusion and right infarction

▪ the ICA “high resistance flow” is a “non-specific sign” (ICA dissection? atherosclerosis/cardioembolism with obstruction of distal ICA?)

▪ it is necessary to evaluate the “high resistance flow” in the clinical setting!
  ▪ in this case: ICA plaque in ats patient-> ATS stroke
2. ICA “high resistance flow”: ATS stroke? CE stroke? other?

a. extracranial rt ICA “high resistance flow” (indirect information of intracranial ICA occlusion) in in 42 y-old woman with rt laterocervical pain
- the ICA “high resistance flow” is a “non-specific sign” (ICA dissection? atherosclerosis/cardioembolism with obstruction of distal ICA?)
- it is necessary to evaluate the “high resistance flow” in the clinical setting! in this case: no ICA plaque in young patient with LC pain -> ICA dissection
CE/ATHEROSCLEROTIC STROKE:
CDU COMPLEMENTARY INDIRECT INFORMATIONS

CDU complementary indirect informations in pts with ischemic event
1. indirect information about heart rate and heart valves
US INDIRECT INFORMATIONS ABOUT HEART VALVES
patient with aortic valve disease

- prolonged systolic acceleration and rounded systolic peak (pulsus tardus)
- characteristic systolic and diastolic contours of the ICA and VA Doppler waveforms
US INDIRECT INFORMATIONS ABOUT HEART RATE AND HEART VALVES

- patient with aortic valve disease and atrial fibrillation
- prolonged systolic acceleration and rounded systolic peak (pulsus tardus)
- characteristic syst. and diastolic contours of the ICA, VA and SCA Doppler waveforms
- in SCA is noted a retrograde flow in diastole (aortic regurgitation)
- cardiac arrhythmia (indirect information about heart rate)
CE/ATHEROSCLEROTIC STROKE: CDU COMPLEMENTARY INDIRECT INFORMATIONS

US INDIRECT INFORMATIONS ABOUT HEART VALVES patient with aortic valve disease

- prolonged syst. acceleration and rounded syst. peak (pulsus tardus)
- characteristic systolic and diastolic contours of the ICA and VA Doppler waveforms
## US/NR Findings That Support LA ATS Stroke Include:

- Hemodynamic plaque in an intra/extracranial artery supplying the ischemic stroke
- Occlusion with imaging evidence of atherosclerosis in an intra/extracranial artery supplying the ischemic stroke
- Not hemodynamic plaque in an intra/extracranial artery supplying the ischemic field with attached luminal thrombus
- Unilateral MES: suggestive of ATS stroke (TCD monitoring)

## US/NR Findings That Support CE Stroke Include:

- Occlusion of the carotid artery by mobile embolus
- Early recanalisation of occluded extra/intracranial vessel
- Simultaneous or sequential embolism in different arteries (extra/intracranial)
- Bilateral MES: suggestive of CE stroke (TCD monitoring)
CE or atherosclerotic stroke: How to decide what is the most likely cause?

Conclusions and suggested algorithmic approach
Cardioembolic or atherosclerotic stroke: How to decide what is the most likely cause?

1. there is no "gold standard" that allows the diagnosis of cardioembolic or atherosclerotic stroke
2. the main criterion of the diagnosis is the presence of a potential source of cardiac or atherosclerotic embolism in the absence of a significant artery or cardiac disease
3. when coexisting heart and artery disease (such as atrial fibrillation and carotid hemodynamic plaque), the etiologic diagnosis of ischemic stroke is difficult
CARDIOEMBOLIC OR AHEROSCLEROTIC STROKE?

1. medical history and physical exam; 2. extra-intracranial vessels imaging; 3. head CT±MRI; 4. ECG; 5. chest Rx

DIAGNOSIS

1. CE stroke?; 2. ATS stroke?
(with exclusion of other cause for the stroke)
CARDIOEMBOLIC OR ATHEROSCLEROTIC STROKE?

1. medical history and physical exam; 2. extra-intracranial vessels imaging; 3. head CT±MRI; 4. ECG; 5. chest Rx

DIAGNOSIS

1. CE stroke?; 2. ATS stroke? (with exclusion of other cause for the stroke)

1. TTE
2. Holter ECG (24 h/7 days)

cardiac source of embolism identified

CARDIOEMBOLIC STROKE
CARDIOEMBOLIC OR ATHEROSCLEROTIC STROKE?

1. medical history and physical exam; 2. extra-intracranial vessels imaging; 3. head CT±MRI; 4. ECG; 5. chest Rx

DIAGNOSIS

1. CE stroke?; 2. ATS stroke? (with exclusion of other cause for the stroke)

CARDIOEMBOLIC OR ATHEROSCLEROTIC STROKE?
CARDOEMBOLIC OR ATHEROSCLEROTIC STROKE?

1. medical history and physical exam; 2. extra-intracranial vessels imaging; 3. head CT±MRI; 4. ECG; 5. chest Rx

DIAGNOSIS

1. CE stroke?; 2. ATS stroke?
(with exclusion of other cause for the stroke)

1. TTE
2. Holter ECG (24 h/7 days)

no cardiac source of embolism identified

1. TEE/TCD bubble test
2. TCD monitoring (bilateral MES)
3. vein ECD/angioCT (IVC, iliac veins)
4. biomarkers (?)

no cardiac source of embolism identified

ATS STROKE
short videos and playlists on echocolor Doppler of the extra-intracranial vessels are available on my youtube channel:
http://www.youtube.com/channel/UCij561sX0bQoEjXlWKnPnKg