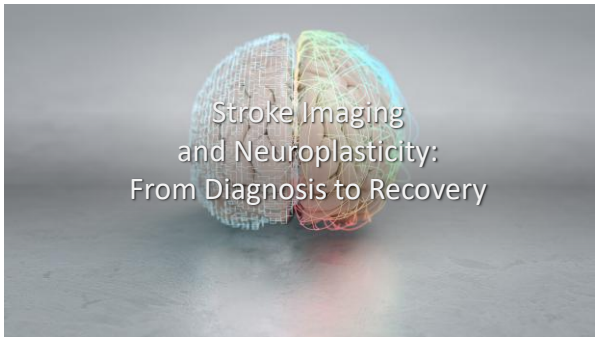


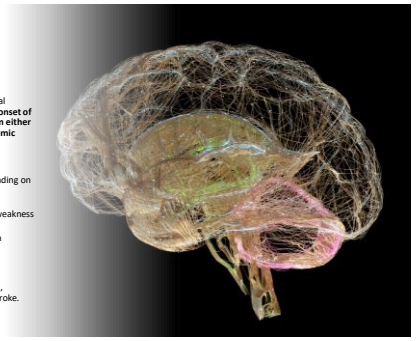
1

STROKE

Stroke is a cerebrovascular medical emergency define as the **sudden onset of neurological deficit resulting from either disruption of cerebral flow (ischemic stroke) or intracranial bleeding (hemorrhagic stroke).**

Clinical manifestations vary depending on the location and extent of brain involvement. It may include:

- **hemiparesis or hemiplegia** (weakness or paralysis on one side),
- **aphasia or dysarthria** (speech difficulties),
- **visual disturbances,**
- **ataxia** (loss of coordination),
- and sudden **severe headache,** particularly in hemorrhagic stroke.



4

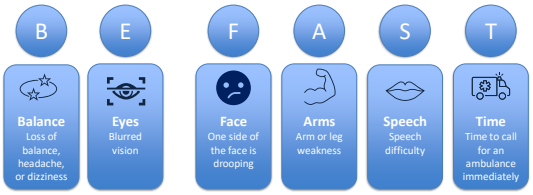
Timeliness

Timely diagnosis and treatment are critical

- "time is brain"
- Swift evaluation and management minimizes brain damage and improves outcomes

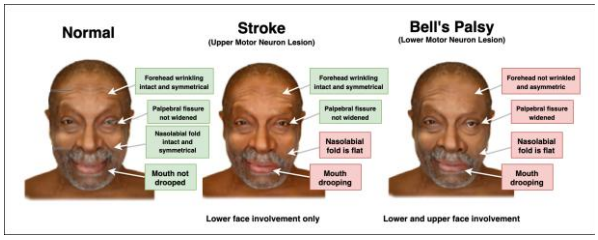
5

SPOT A STROKE

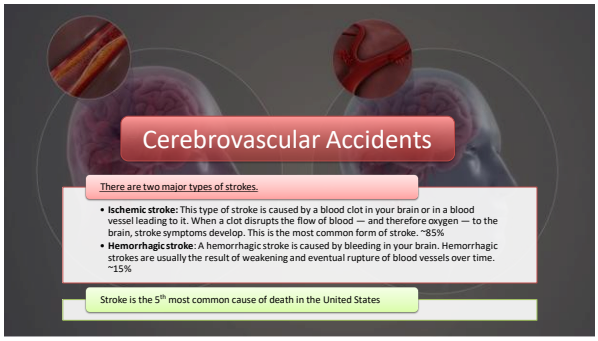


6

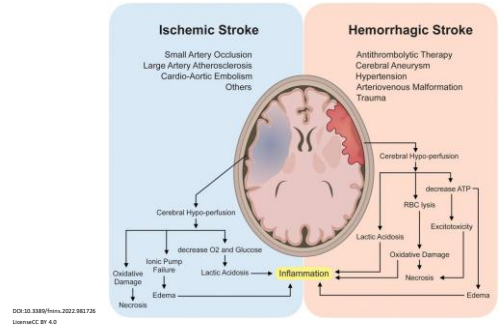
Stroke Mimicker



7



8



DOI:10.3389/fnins.2022.981726

9

Etiology of Ischemic Strokes

Thrombus (blood clot)

- Atherosclerosis
- Arterial dissection
- Fibromuscular dysplasia (condition that causes the medium-sized arteries in the body to narrow and grow larger)
- Inflammatory conditions

Embolic event

- Originating from atherosclerotic plaque such as the internal carotid artery or the heart

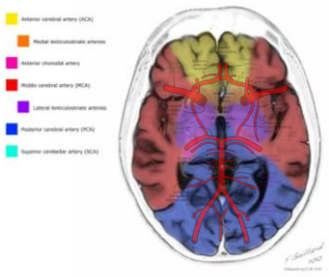
10

Cerebral Vascular Territories

Sudden focal neurological deficit whereby the exact clinical **features depend on the specific vascular territory involved.**

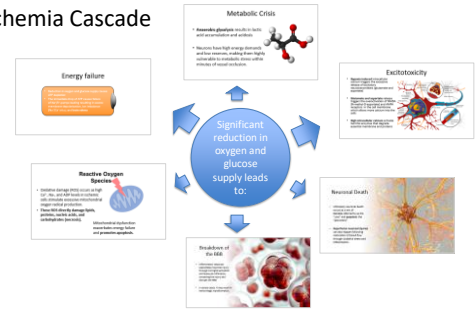
Territorial infarcts typically occur in regions supplied by major cerebral arteries and affect both the **cortex** and **subcortical white matter**. **Most common causes are atherothrombosis and cardioembolism.**

The **Middle Cerebral Artery (MCA) is the most common affected artery in ischemic stroke** which corresponds to motor and sensory functions on the contralateral side of infarct involvement.



11

Ischemia Cascade



12

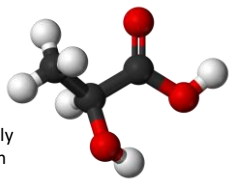
Energy failure

- Reduction in oxygen and glucose supply causes ATP depletion
- The immediate drop of ATP causes failure of Na^+/K^+-pumps leading resulting in severe membrane depolarization, ion imbalance (Na^+/Ca^+ influx), and **brain edema**

13

Metabolic Crisis

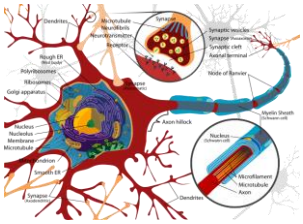
- **Anaerobic glycolysis** results in lactic acid accumulation and acidosis
- Neurons have high energy demands and low reserves, making them highly vulnerable to metabolic stress within minutes of vessel occlusion.



14

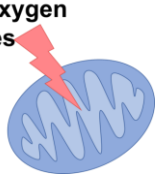
Excitotoxicity

- **Hypoxia induced** intracellular calcium triggers the excessive release of excitatory neurotransmitters (glutamate and aspartate)
- **Glutamate and aspartate** release triggers the overactivation of NMDA (N-methyl-D-aspartate) and AMPA receptors in the cell membrane which allows more calcium into the cells
- **High intracellular calcium** activate harmful enzymes that degrade essential membrane and proteins



15

Reactive Oxygen Species



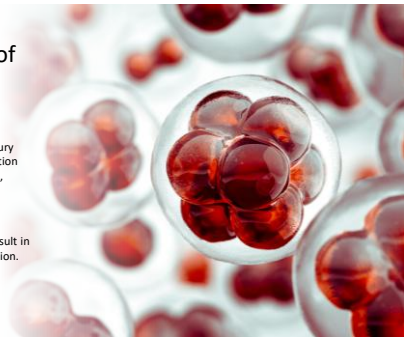
- Oxidative damage (ROS) occurs as high Ca^{2+}, Na-, and ADP levels in ischemic cells stimulate excessive mitochondrial oxygen radical production.
- **These ROS directly damage lipids, proteins, nucleic acids, and carbohydrates (necrosis).**

Mitochondrial dysfunction exacerbates energy failure and **promotes apoptosis**.

16

Breakdown of the BBB

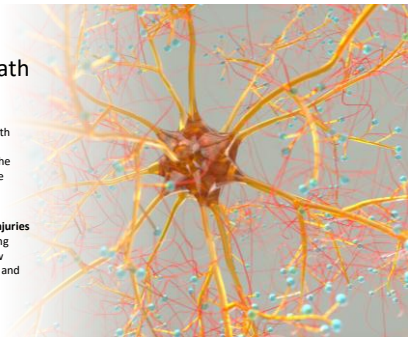
- Inflammatory response exacerbates neuronal injury through microglial activation and leukocyte infiltration, worsening the injury and disrupts the BBB.
- In severe cases, it may result in hemorrhagic transformation.



17

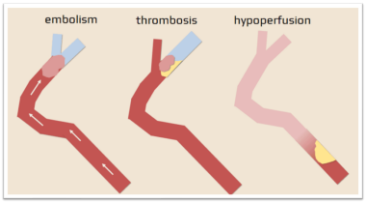
Neuronal Death

- Ultimately neuronal death occurs as a mix of **necrosis** referred to as the "core" and **apoptosis** the "penumbra"
- **Reperfusion neuronal injuries** can also happen following restoration of blood flow through oxidative stress and inflammation

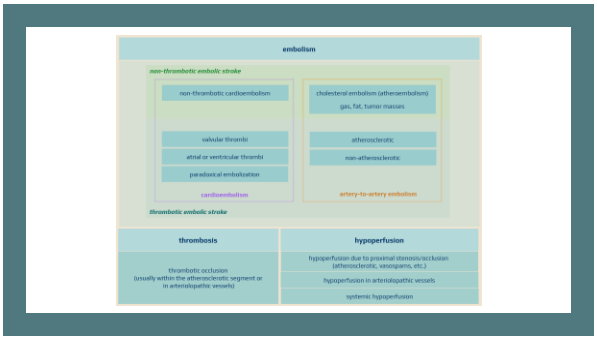


18

Pathophysiologic Classification



19



20

TOAST

Etiological Classification

- **Large-artery atherosclerosis** → significant stenosis (>50%) or occlusion due to atherosclerosis. Common mechanism is thromboembolism or atheroma embolization (cholesterol).
- **Cardioembolism** → accounts for 20-45% of all ischemic strokes. Thromboembolism from the left atrium or ventricle. Often indistinguishable from large artery atherosclerosis origin.
- **Small-vessel occlusion** (lacunar) → small vessels of the brainstem or subcortical
- **Stroke of other determined etiology** → vasculitides, hematologic disorders, dissections, FMD
- **Stroke of undetermined etiology** → undetermined due to insufficient diagnostic criteria, have >2 potential causes of stroke

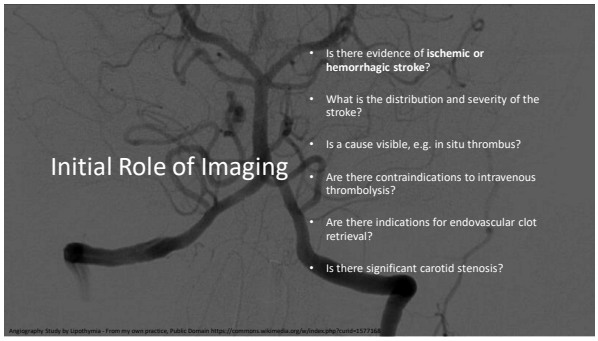
(TOAST = Trial of ORG 10172 in Acute Stroke Treatment)

21

Imaging in Stroke: The Toolbox

- **Computed Tomography (CT)**
  - First-line for hemorrhage exclusion, fast and widely available
- **CTA/MRA**
  - Evaluates vessel occlusion and anatomy
  - Angiography is the gold standard for vascular intervention planning
- **CT Perfusion**
  - Assesses ischemic core and salvageable penumbra
- **MRI**
  - Best for early ischemia, tissue characterization

22



23

CT and MRI: Complementary Tools

CT: Fast, detects hemorrhage and large infarcts

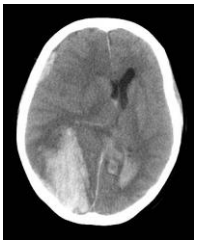
- Nonenhanced CT is essential in the decision-making process by helping **rule out intracranial hemorrhage** and large well-established infarct
- Core infarct volume is measured to **determine intracranial hemorrhage risk and likelihood of thrombolytic treatment benefit**

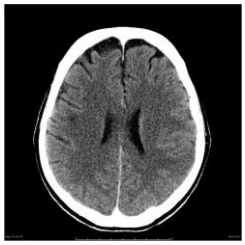
MRI: Sensitive to early ischemic changes

- Diffusion weighted imaging (DWI) measures diffusion of water molecules within tissue. DWI **detects cytotoxic edema** within minutes.
- Fluid attenuation inversion recover (FLAIR) **helps determine stroke** age. This helps with "wake up" strokes.

24

Hemorrhagic vs Ischemic Stroke

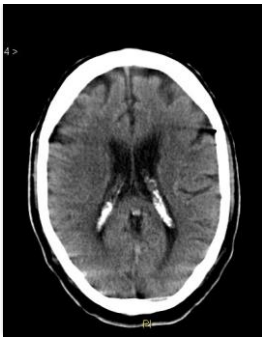




25

Computed Tomography

- A plain CT scan of the head is recommended within 20 minutes of patient presentation to exclude hemorrhage.
- In stroke centers or facilities equipped for emergency care, vascular imaging should be considered to evaluate eligibility for endovascular intervention.
- CT angiography helps identify proximal large vessel occlusions in patients with acute MCA or intracranial internal carotid artery (ICA) syndromes, aiding in the decision of whether to transfer a patient to a comprehensive stroke center accredited to perform endovascular thrombectomy.



26

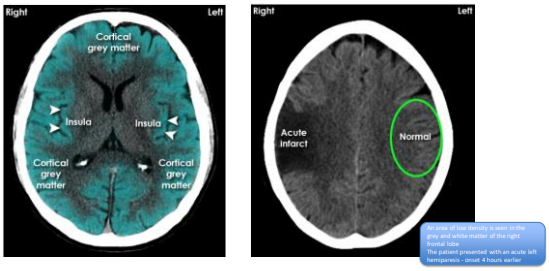
Computed Tomography Investigations

- **Non-contrasted CT** head – 1st imaging choice
  - exclude hemorrhage or other cause
  - may show hyperdense vessel or evidence of infarction
- **CT angiography**
  - used to identify the occluded artery
  - may identify the cause of the ischemic stroke, e.g. carotid stenosis, dissection, intracranial atherosclerotic disease
- **CT perfusion**
  - used in some centers to identify infarcted brain ("core") and brain tissue at risk of infarcting ("penumbra")

A complete CT protocol of all three takes approximately 8 minutes and helps guide recanalization planning. Faster than MRI.

27

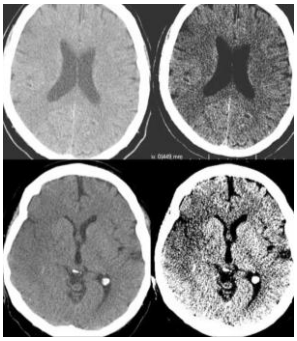
Non-contrasted CT



28

Non-contrasted CT

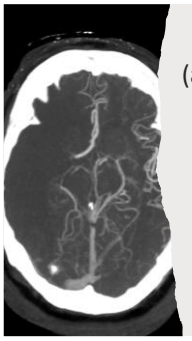
- **Primary function is to rule out bleeding**, for which CT is high sensitive, and to identify other causes of neurological deficits such as tumor or trauma.
- Occurrence and extent of ischemic changes depend on duration of ischemia, location and extent of occlusion, and status of collateral circulation.
- **Early parenchymal changes occur within the first three hours**, indicating ongoing tissue ischemia.
- **Hypodensity develops as a result of cytotoxic edema** (1% water increase = 2.5 HU decrease).

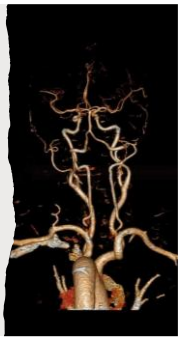


29

CTA (angiography study)

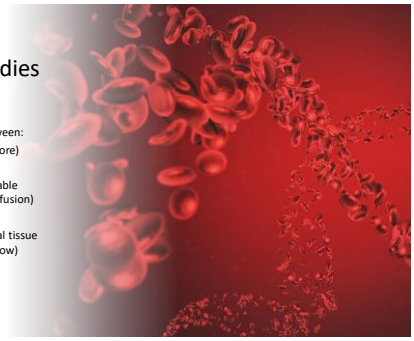
- Fast – app. 5 minutes
- Use iodinated contrast agent
- Assesses both extra- and intracranial arteries for occlusion due to atherosclerotic plaques, dissection, or thrombus
- Scoring of intracranial artery occlusion:
  - Clot Burden Score (anterior circulation)
  - BATMAN score (posterior circulation)
- Image Left: The R internal carotid artery and middle cerebral artery are completely occluded.
- Image Right: digital subtraction software creates a 3-D model





30

Perfusion Studies



Can help differentiate between:

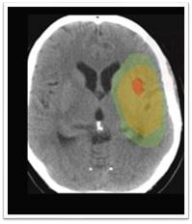
- **irreversible ischemia** (core)
- **ischemic penumbra** (viable tissue with reduced perfusion)
- **benign oligemia** (normal tissue with decreased blood flow)

31

Ischemic Penumbra

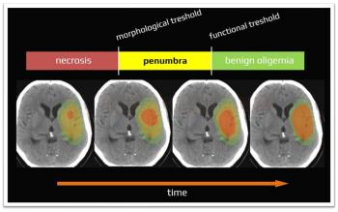
During an acute ischemic stroke, brain tissue that depends solely on one artery for blood supply undergoes infarction, forming the infarct core. Surrounding this core is the ischemic penumbra, an area of brain tissue that retains partial blood flow through collateral circulation. However, as swelling from the infarct increases, the penumbra gradually shrinks, and the infarct core expands.

The ischemic penumbra remains viable for a limited time due to partially preserved collateral blood flow. Timely intervention can salvage this tissue.



32

Ischemic Penumbra – Tissue Thresholds



Functional Threshold - as blood flow decreases, an initial **loss of function occurs while structural integrity remain intact**

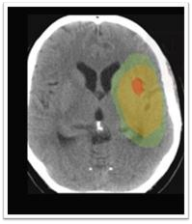
Morphologic Threshold – with a further decrease in cerebral blood flow or prolonged blood flow deficit, irreversible loss of membrane functions and permanent morphologic changes occur

Image: https://www.stroke-manual.com/ischemic-penumbra/#toc-heading-10

33

Cerebral Blood Flow and Volume

- CBF and CBV
- Benign Oligemia
  - Normal or even increased CBV and slightly decreased CBF
- Ischemic Penumbra
  - Reduced CBF < 65% of the healthy side
  - CBV is normal or increased due to collateral flow
- Infarct Core
  - CBF <30% compared to contralateral side
  - CBV <30% compared to contralateral side



34

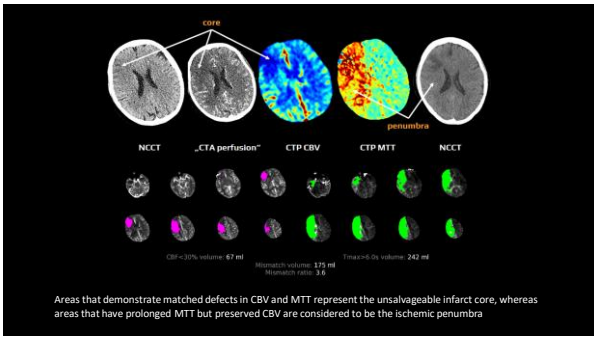
Measuring Blood Flow: Mean Transit Time, Time to Peak, Tmax

MTT represents the duration that blood stays in microcirculation before exiting. **Prolonged MTT indicates delayed perfusion.**

TTP indicates the time it takes for contrast to reach its peak concentration. It cannot differentiate between low flow and delayed flow.

Tmax is utilized in stroke imaging to assess salvageable ischemic brain tissue (penumbra) from irrevocably damaged tissue (core). Penumbra with Tmax ≥ 6s can be rescued with recanalization therapy

35

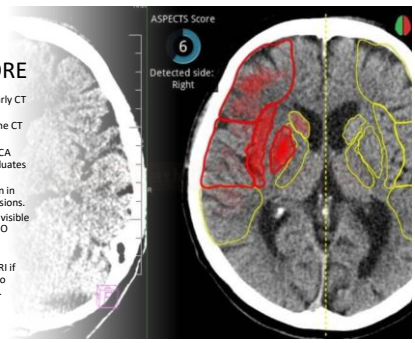


Areas that demonstrate matched defects in CBV and MTT represent the unsalvageable infarct core, whereas areas that have prolonged MTT but preserved CBV are considered to be the ischemic penumbra

36

ASPECT SCORE

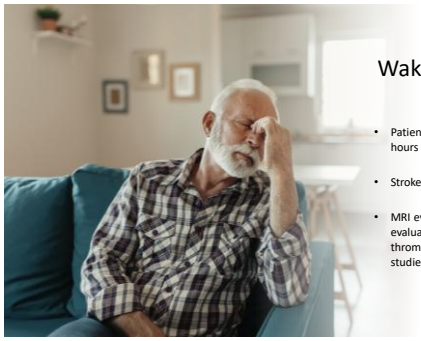
- Alberta Stroke Program Early CT Score
- Can be used with any of the CT exams discussed
- Primarily evaluates the MCA territory (PC-ASPECTS evaluates the posterior circulation).
- Software driven evaluation in guiding management decisions.
- A score of 10 indicates no visible early ischemic changes to O indicating complete MCA infarction.
- Clinical correlation and MRI if available should be used to confirm ongoing ischemia.



37

What if the patient has a stroke while asleep?

38

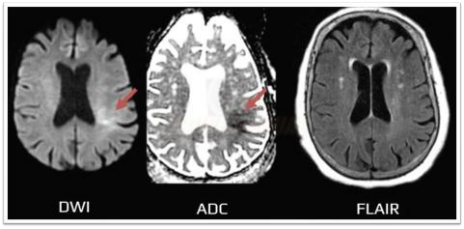


Wake Up Strokes

- Patient last seen well >4.5 hours
- Stroke of unknown onset
- MRI evaluation is useful for evaluation to guide use of IV thrombolysis. DWI and FLAIR studies

39

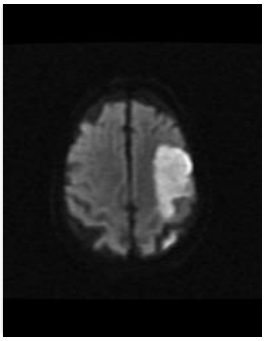
MRI Evaluations



40

DWI

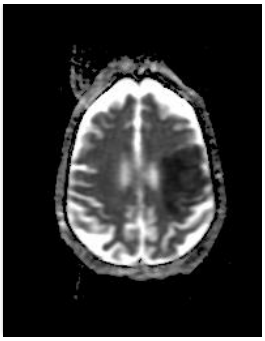
- **Diffusion-weighted imaging** (DWI) is a commonly performed MRI sequence for the evaluation of acute ischemic stroke and is very sensitive in the detection of small and early infarcts.
- DWI **highlights areas where water movement is hindered by cellular membranes** and structures, making it highly sensitive to acute ischemia (stroke).
- Conventional MRI sequences (T1WI, T2WI) may not demonstrate an infarct for 6 hours, and small infarcts may be hard to appreciate on CT for days, especially without the benefit of prior imaging.
- **Increased DWI signal in ischemic brain tissue** is usually observed within a few minutes after arterial occlusion and is primarily due to **cytotoxic edema**.



41

ADC

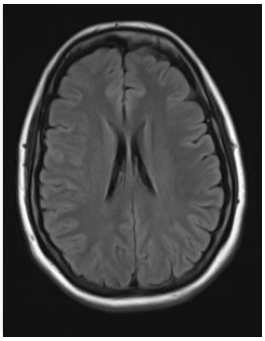
- **Apparent diffusion coefficient** (ADC)
- A measure of the **magnitude of diffusion (of water molecules) within tissue** and is commonly clinically calculated using MRI with diffusion-weighted imaging (DWI).
- The impedance of water molecules diffusion can be **quantitatively assessed** using the apparent diffusion coefficient (ADC) value.



42

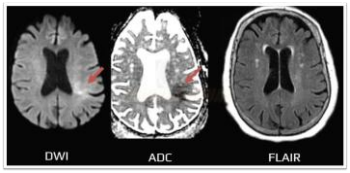
FLAIR

- **Fluid attenuated inversion recovery** (FLAIR) is a special inversion recovery sequence with a long inversion time.
- This **removes signal from the cerebrospinal fluid** in the resulting images.
- Brain tissue on FLAIR images appears similar to T2 weighted images with **grey matter brighter than white matter but CSF is dark instead of bright**.



43

DWI/FLAIR Mismatch



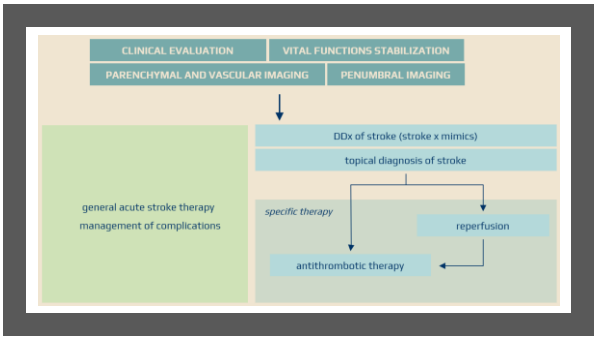
- DWI positive
  - Hyperintense
- ADC
  - Lower value than normal tissue
- Flair negative
- Stroke will likely have occurred within 4.5-6 hours.

44

Treatment

- Focuses on blood flow restoration
- Treatment decisions range from conservative approaches to **IV thrombolysis and/or mechanical revascularization**
- Hinge on **two crucial imaging factors**:
  - timeframe since onset and
  - two primary features observed in imaging
    - parenchymal lesions and arterial blockage locations

45

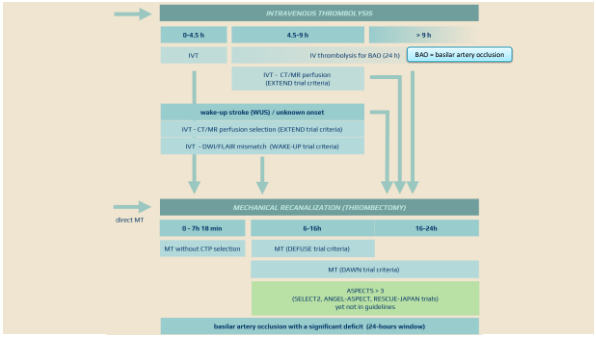


46

Time is Brain

- Penumbral neurons can remain viable for minute to hours after arterial occlusion.
- Early restoration of blood flow to ischemic tissue can rever the damage and improve the outcome.
- **DAWN**: Up to 24h post-onset with perfusion mismatch
- **DEFUSE** 3: 6–16h window using CTP or MRI
- Imaging-based selection for thrombectomy
- Revolutionized stroke eligibility

47



48

Favorable Prognosis Factors

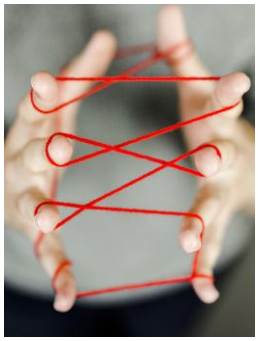
- Early recanalization and reperfusion
- Tissue viability – presence of penumbra
- Lower age, no comorbidities, stroke subtype, and treatment
- No occlusion has better prognosis. Proven occlusion with shorter thrombus have better outcomes.
- Lower stroke severity (quantified by NIHSS protocol)
- Good collateral circulation = better outcome with reperfusion
- Interval from stroke onset to treatment initiation. tPA initiation within 90 minutes has twice as high favorable outcome.
- Extensive early ischemic changes indicate a sever stroke. ASPECT scores ≤ 6 are associated with a worse outcome.

49

Rehabilitation Goals

- Primary goal is to **maximize functional improvement and minimize permanent disability** through targeted interventions.
- **Physical exercise and neurotechnology-aided interventions are the cornerstones of such therapeutic strategy.**
- **These approaches leverage the brain's neuroplasticity**, its capacity to reorganize and adapt, to support the restoration of neurological functions impaired by stroke.
- Despite advances in stroke rehabilitation, **a significant 30% of stroke patients** still do not fully recover limb function, remaining permanently disabled. This persistent challenge underscores the intricate nature of neural recovery, as the spontaneous reorganization that occurs post-stroke is frequently either maladaptive or inadequate for a complete restoration of pre-injury function.

50



Movement Drives Plasticity

- Intensity and specificity matter
- Mirror therapy, constraint-induced movement therapy (CIMT)
- Mental imagery and repetition enhance reorganization
- Movement recruits BDNF…more on this later

51

Task Oriented Training

TOT is a rehabilitation approach based on **motor relearning theory**, emphasizing functional activities and active patient participation to enhance neuroplasticity.

Key components include repetitive practice, active engagement, appropriate training intensity, and task difficulty adjustments to maintain motivation.

TOT integrates training into a specific task environment, providing internal and external feedback to improve motor control.

Clinically, TOT has been shown to enhance upper and lower limb function, balance, and activities of daily living. Common interventions based on TOT include CIMT, mirror therapy (MT), and virtual reality (VR).

52

Neuroplasticity: The Brain's Adaptive Power

- Brain's ability to reorganize and form new connections
- Driven by experience, learning, and injury
- Key to recovery after stroke
- Brain derived neurotrophic factor is key in recovery

53

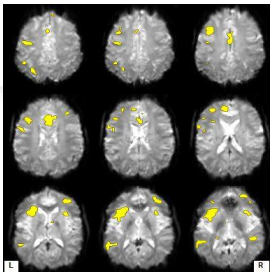
BDNF - Driving Neuroplasticity

- Brain-derived neurotrophic factor (BDNF) plays an **important role in brain plasticity**. It shows a neuroprotective effect under adverse conditions, such as neurotoxicity, cerebral ischemia, and hypoglycemia.
- Several studies have demonstrated the role of BDNF following stroke as a **prognostic biomarker.**
- BDNF is a member of the neurotrophin family that supports the survival of neurons in the nervous system by differentiation and maturation.
- **BDNF stimulates and controls the growth of new neurons** from neural stem cells (neurogenesis).
- Note that alcohol intake suppresses BDNF expression!

54

Functional MRI (fMRI)

- May help predict recovery potential by tracking activation in motor language networks and assists in tailoring therapy to strengthen specific circuits.
- The **activity performed or stimulus received** by the patient is termed a paradigm, and each is designed to elicit a specific cortical response.
- Numerous paradigms have been developed of various complexity. In the clinical setting four paradigms (with modifications according to the clinical situation) suffice for most indications.
  - visual paradigm
  - motor paradigm
  - speech paradigm
  - memory paradigm

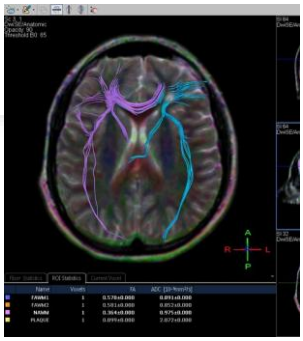


Block design of a language task in a healthy subject. Regions of statistically significant activation during a language task. There is an expected pattern of activation which includes the Broca and Wernicke areas.

55

Diffusion Tensor Imaging (DTI)

- Based on the measurement of motion of water molecules.
- Assesses the extent of white matter disruption in corticospinal tracts and other pathways critical for motor and cognitive functions.
- It is often used to measure the integrity, compactness, and parallelism of myelin sheath. It can sensitively reflect whether the fiber microstructure in white matter is damaged.



Application of Magnetic Resonance DTI Technique in Evaluating the Effect of Postoperative Exercise Rehabilitation. J Healthc Eng. 2022 Mar 21:2022:2385699. doi: 10.1155/2022/2385699.

56

Timing Matters: The Critical Period

- Most recovery occurs in first 3 months
- "Sensitive period" with heightened responsiveness
- Early, task-specific rehab yields best results
- Plasticity continues long term—but slower

57

The Horizon of Stroke Recovery

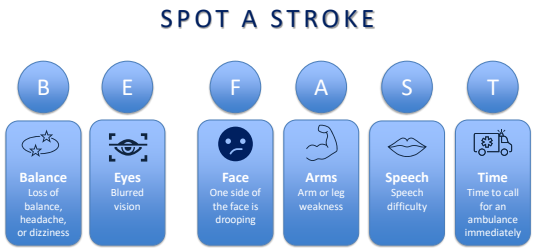
- AI-driven image analysis and prognosis
- Virtual reality and gaming
- Real-time feedback in rehab – robot assisted
- Transcranial magnetic stimulation
- Deep Brain Stimulation
- Prevention of reoccurrence – Lifestyle factors!

58

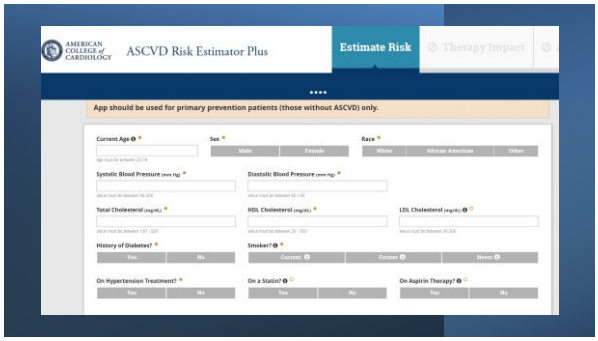
Where do we fit in?

- **Recognition**
- **Prevention**
- **Recovery**

59



60



61

62

Facilitating Motor Recovery

- **Chiropractic + PT Group**
- **Sham Adjustment + PT Group**
- 3 PT sessions/week for each group (app. 40 min/session)
- Chiropractic group was evaluated three times/week
- The primary outcome measures
  - Fugl-Meyer Assessment for motor function for the combined upper and lower limbs, and the primary endpoint was the 4-week assessment
- Secondary outcome measures included:
  - Stroke Specific Quality of Life scale, the Timed Up and Go test, the Modified Rankin Scale, and the five-repetition Sit-to-Stand Test.

The Effects of 4 Weeks of Chiropractic Spinal Adjustments on Motor Function in People with Stroke: A Randomized Controlled Trial. Brain Sci. 2021 May 21;11(6):676

63

Results...

Fifty-five participants completed the 4-week assessment

38 completed the 8-week assessment

This study is the first multi-session study to evaluate the effects of chiropractic spinal adjustments on motor function in stroke survivors. The combination of chiropractic spinal adjustments and physical therapy improved motor function, particularly lower limb motor function, after 4 weeks of care, compared with sham chiropractic spinal adjustments plus physical therapy. The improvements in motor function in the chiropractic group compared with the sham group were no longer significant at the 8-week follow-up. This may have been due to a diminishing effect of the chiropractic care over the 4-week follow-up period with no ongoing care.

64

66