Neuro-Cardiology:
The Cerebral-Cardiac Connection

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What's around the brain?

Anatomy B-01

- Meninges = protective triple layer cover
  - Dura mater = outer layer: protection
  - Arachnoid = middle layer: absorption, circulation
  - Pia mater = inner layer: vascular
- Cerebral spinal fluid circulates within middle layer
  - Serous fluid circulates
What's around the heart?

Anatomy C-01

- Pericardium – a double serous membrane
  - Visceral pericardium
  - Next to heart
  - Parietal pericardium
  - Outside layer
- Serous fluid fills the space between the layers of pericardium

What is the common issue

- The serous space communicates with the visceral surface (arachnoid and endocardium)
- In an inflammation, injury or hemorrhage
  - Compression and loss of circulation
  - Tamponade
  - ↑ ICP, herniation
- Profound irritants in pericardial or subarachnoid space
What’s the brain blood flow?

Blood Supply of Brain

• Arises from aortic arch
• 2 common carotid arteries
  • (extracranial)
    • give rise to external & internal carotid
• 2 vertebral arteries

Overview of cerebral circulation

Arterial supply

CAROTID SYSTEM 70%
VERTEBROBASILAR SYSTEM 30%
Middle Cerebral Artery

- Most common stroke syndrome.
- **contralateral weakness**
  - face, arm, and hand more than legs
- **contralateral sensory loss**
  - face, arm, and hand more than legs
  - visual field cut
  - damage to optic radiations

Middle Cerebral Artery

- Aphasia: language disturbances
  - more likely with L. Hemi. Damage
  - especially men
  - Broca’s: production
  - Wernicke’s: comprehension
Middle Cerebral Artery

- Impaired spatial perception
  - more likely after R. Hemi. damage
  - spatial neglect
  - dressing apraxia
  - constructional apraxia
  - topographagnosia

Anterior Cerebral Artery

- Motor disturbance contra lateral distal leg
- urinary incontinence
- speech disturbance (may be more of a motor problem)
- apraxia of arm (sympathetic apraxia) if anterior corpus callosum is affected
- If bilateral may cause apathy, motor inertia, and muteness

Posterior Cerebral Artery

- Visual disturbances
  - contralateral homonymous hemianopsia
    - (central vision is often spared)
  - L. Hemi: lesions alexia
    - (with or without agraphia)
  - Bilateral lesions: cortical blindness
    - patients unaware they cannot see
    - (Anton’s syndrome)
- Memory impairment if temporal lobe is affected
Posterior Cerebral Artery

- Proximal occlusion
  - contralateral hemisensory loss,
  - spontaneous pain and dysesthesia if thalamus affected
    - (thalamic pain syndrome)
  - contralateral severe proximal chorea
    - (hemiballism)

Collateral Circulation

- Effectiveness depends on vessel size
- Effectiveness depends upon speed of occlusion
  - Atherosclerosis
- Circle of Willis: vessels are often narrow and cannot adapt for sudden onset of blockage

Circle Of Willis

- Internal carotid artery
- Middle cerebral artery
- Basilar artery
- Circle of Willis
- Bottom view of brain
Venous drainage at a glance

- Superior sagittal sinus
- Inferior sagittal sinus
- Straight sinus
- Transverse sinus
- Cavernous sinus
- Sigmoid sinuses
- Internal jugular vein

Dural venous sinuses

- Superior sagittal sinus
- Inferior sagittal sinus
- Straight sinus
- Transverse sinus
- Cavernous sinus
- Sigmoid sinuses
Physiological consideration of cerebral circulation

- Ever active brain with little metabolic reserve
- Brain 2% of body weight; receives 1/5th of cardiac output and consumes 20% of oxygen
- Blood flow 750 ml/min
- CBF can increase 4-fold
- Gray matter BF 6X greater than white matter BF
- Circulation time from ICA to internal jugular vein 7 seconds
- Blood flow to CNS - delivers O₂, glucose, nutrients - removes CO₂, lactic acid, metabolites

Regulation of cerebral circulation

- Constant total cerebral blood flow is maintained under varying conditions
  - ABP particularly mean
    - (heart and vascular)
  - Venous pressure
    - Dural, thoracic, U and right atrium
  - Intracranial pressure
  - Blood viscosity
- Degree of active constriction or dilation of cerebral vessels (+/- CO₂, LA)

If The Human Brain Were So Simple That We Could Understand It... We Would Be So Simple That We Couldn't
What's the heart's blood flow?

The coronary circulation

- Left Main Coronary Artery (LM)
  - Left Anterior Descending Artery (LAD)
  - Diagonal Branch
  - Septal Perforator
  - Left Circumflex Artery (LCx) or LCx
  - Obtuse Marginal (OM)
  - Ramus Intermedius
- Right Coronary Artery
- Marginal Branch
- Posterior Descending Artery (PDA)

Concept of dominance
The Left Coronary

- LAD
  - Anterior LV
  - High Lateral LV
  - Septum (anterior 2/3)
  - Bundle Branches
- Left Circumflex
  - Low Lateral LV
  - Posterior LV
  - Left Atrium
  - Anterior interventricular muscle of the mitral valve
  - SA Node (40%)
  - AV Node (10%)

The Right Coronary

- RCA
  - Inferior LV
  - Septum (lower 1/3)
  - Right Ventricle (interbranch)
  - Posterior LV (PDA)
  - Posterior LBB
  - Postero medial papillary muscle
  - Right Atrium
  - SA Node (55%)
  - AV Node (90%)
Coronary Blood Flow

- Coronary Blood Flow is directly linked to oxygen demand
- Autoregulation helps to maintain normal coronary blood flow whenever coronary perfusion pressure changes due to changes in aortic pressure

Physiology of Coronary Circulation

- The resting coronary blood flow is about 225 ml/min for 0.7 – 0.8 ml/gm of heart muscle
- 5% of the total cardiac output
- When cardiac work increases:
  - CBF may be increased up to 2 liters/minute, limited by blood volume, stroke volume, and competency of coronary circulation.
- Cardiac metabolism:
  - O2 tension (local hypoxia), CO2, K+, lactic acid, and adenosine are affected with increased cardiac work
- Hypoxia: Direct action on coronary blood vessels
  - Release of chemical substances such as adenosine (from ATP)
  - Coronary vasodilation.

Neural Factors of Flow Control

- Sympathetic nervous system (adrenergic) vasoconstrictor
- Sympathetic acetylcholine (cholinergic) vasodilation in muscle
- Local Metabolites more powerful than sympathetic vasoconstrictors
There is nothing more inspiring than the complexity and beauty of the human heart.
My Patient in ECC

STEMI alert was called after this EKG. After that EKG she was immediately taken for a CT head, which showed catastrophic intracranial hemorrhage.

45 minutes later:

- Missed because sudden, severe headache is not present in 25% of patients
- 1 in 10 with sudden headache, SAH is the cause
- Missed in 20–50% of patients at first presentation

Did you know that many of these patients present with what appears to be primary chest pain??
SAH: What matters?

1. Rapidly identify patients with aneurysmal SAH and secure their aneurysm(s) quickly

2. Lower MAP before securing the aneurysm but not afterwards

3. Detect and manage early complications
   a. Stress cardiomyopathy
   b. Neurogenic pulmonary edema
   c. Cerebral salt wasting
SAH: what matters?

4. Detect vasospasm *early*
   a. Clinical
   b. Electrophysiologic
   c. Sonographic
   d. Radiologic

5. Manage clinical vasospasm aggressively
   a. Augment *pressure and flow*
   b. Angioplasty and IA vasodilators
Critical care issues: rebleeding

- Unsecured aneurysms:
  - 9% - 17% rebleed on day 0, then
  - 1.5%/day for next 13 days (up to 36%/for 2 weeks)
- Antifibrinolytic therapy (e.g., aminocaproic acid)
  - may be useful between presentation and early surgery
- Blood pressure management
  - labetalol, hydralazine, nicardipine
- Analgesia
- Minimal or no sedation to allow examination

Critical care issues: neurogenic pulmonary edema

- Symptomatic pulmonary edema occurs in about 20% of
- SAH patients
  - detectable oxygenation abnormalities occur in 80%
- Potential mechanisms:
  - hypersympathetic state
  - cardiogenic pulmonary edema
  - neurogenic pulmonary edema
- Management

"The heart was made to be broken"

Oscar Wilde
25 years since original description of Takotsubo Syndrome by Hiraku Sato

What is Takotsubo?

- “Broken heart syndrome”
- TC is an acute cardiac syndrome, which presents like ACS
- Transient LV apical ballooning in the absence of coronary artery stenosis
- Often precipitated by acute emotional or physical stress
- Clinical Syndrome
- Pathophysiology hypotheses
- Not acute myocardial infarction

History

- Acute emotional (25% of cases)
- Physical stressor (30% of cases)
- Idiopathic (30% of cases)
Pathophysiology

- The pathophysiology of Takotsubo is poorly understood, hypothesis:

  - Microvascular dysfunction: coronary artery microspasm*
  - Excess plasma catecholamines*
  - Myocardial stunning: Acute sympathetic overactivity
  - *Estrogen deficiency: Increased sensitivity in post-menopausal women

Cannot distinguish between Takotsubo and STEMI at presentation!!!

ECG

At presentation:

ST-elevation in pre-cordial leads
Later that day:

Resolution of ST-elevation Development of T-wave inversion

Primary Takotsubo Classical Clinical P1

Enter PPCI protocol
- Normal Coronary Angiography
  - no culprit coronary disease
  - no coronary intervention
- Apical and usually mid left ventricular wall motion abnormality
- >1 coronary territory
- Preserved basal LV contraction
- Left ventricular dysfunction recovers over days – weeks
  - Myocardial stunning
- Post menopausal women ~90% cases

Why regional effect?
Why regional effect?

- Typical anatomical variant
- Apical and mid LV suppression with basal sparing?

Takotsubo Syndrome and the Catecholamine Hypothesis

Central Role of Catecholamines

- Supraphysiological serum levels
- Iatrogenic cases
  - Dobutamine
  - Adrenaline
- Pheochromocytoma
- Subarachnoid hemorrhage/head injury
- Myocardial Histopathology
  - Endomyocardial fibrosis from Takotsubo pts
  - Subarachnoid hemorrhage
  - Pheochromocytoma
Adrenaline-Induced Negative Inotropism

- High adrenaline concentrations
- Mediated via the β₂AR switch to the Gᵢ pathway (stimulus trafficking = biased agonism)
- Fully reversible
  - washout during in vitro studies
  - β₂AR dephosphorylation
  - β₂AR internalisation and degradation
- negative inotropism via this mechanism similar to overdose with propranolol

Altered Cortical-Hypothalamic-Pituitary-Adrenal axis response to stress?

- MRI analysis
  - a significant variation of the blood oxygen level dependent signal triggered by the Valsalva maneuver
  - in specific areas of the brain involved in the cortical control of the autonomic system
  - significant differences in the pattern of activation of the insular cortex, amygdala and the right hippocampus

Why?

- Acute Multivessel Coronary Spasm
- Acute Coronary Microvascular Dysfunction
- Acute Endothelial Dysfunction
- Aborted Myocardial Infarction
  - Spontaneous recanalisation
  - "Wrap around LAD"
- Direct Catecholamine-Mediated Myocardial Stunning
**Echocardiography**

Acutely reduced ejection fraction\(^1\)

33 %

(Normal

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**Cardiac enzymes**

- TnI rises in Takotsubo
- In Takotsubo the peak TnI rise is disproportionate to the level of LV dysfunction

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Takotsubo</th>
<th>STEMI</th>
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<tbody>
<tr>
<td>Initial TnI</td>
<td>1.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Peak TnI</td>
<td>4.9</td>
<td>7.3</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>33</td>
<td>25</td>
</tr>
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**Primary Takotsubo Syndrome**

**Classical Clinical Presentation**

- Stressful trigger
- Chest Pain, Dyspnea
- ECG Repolarization changes
  - ST\(\uparrow\), QT\(\uparrow\), T\(\downarrow\)
  - Arrhythmias
- Cardiac Enzyme rise
  - >85% cases troponin +ve
- Acute Heart Failure
  - ~ 20-60% cases
- Serum catecholamines 30x normal
Pathophysiology
What we have to learn?
• How to integrate molecular, cellular and systemic physiology
  – Cardiac
  – Vascular
  – Brain: amygdala
  – Peripheral nerves, adrenal, cognitive responses, and CNS
• Temporal phases
• Spontaneous cases
• Anatomical variants
• Influence of genetics, sex hormones

Pathophysiology
What we have to learn?
• Diagnosis
  – Grey cases
  – Missed cases
• Treatment
  – Severe cases with cardiogenic shock
  – Prevention in recurrent cases
  – Refractory symptoms

Summary Brain Heart Connection
• Complicated systemic biology
  – Not myocardial infarction/plaque rupture
• Cardiac perspective
  – High afterload and intracavity pressure acutely
  – Negative inotropic pathway activation
  – β2AR may play a role in some cases
  – Cardioprotective
  – Metabolic changes
  – Vasospasm  \( \rightarrow \) ischaemia in subset
  – Inflammation
Summary Brain Heart Connection

- Systemic vascular responses
  - Initially high followed by ‘dysregulation’
- Central HPA axis — level of gain.
- Lots still to learn....

Prognosis

- Very good; in the absence of comorbidity
- Systolic dysfunction resolves within days-weeks
- At this time, repeat ECG classically shows resolution of all abnormalities, though T-wave inversion may persist for longer.
- In-hospital mortality is low (1-2%), as is the rate of recurrence
- (10%)¹
- Ventricular thrombosis and heart failure are possible complications
- Long-term prognosis is unknown and future prospective studies are required.

DID YOU INTEND THE PRESENTATION TO BE INCOMPREHENSIBLE, OR DO YOU HAVE SOME SORT OF RARE ‘POWER-POINT’ DISABILITY?
Women > Men

- Females are affected more than men
- 90% of cases involve women
- Majority are post-menopausal
- Mean age 68 yrs

Diagnosing Takotsubo

- New abnormalities
- Absence of obstructive artery disease
- Transient LV apical akinesis/dyskinesis

* Without conditions: head injury/intracranial bleed/myocarditis/hypertrophic cardiomyopathy

Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics