Brain-Heart Crosstalk

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• The heart’s effects on the brain
  – Cardiac source embolic stroke
• The heart’s effects on the brain
  – Severe global hypoxic-ischemic injury
    • Near-drowning
    • Asphyxia
    • Cardiac/respiratory arrest
  – Primarily affects the gray matter structures
    • Basal ganglia
    • Thalami
    • Cerebral cortex
    • Cerebellum
    • Hippocampi
• Neurocardiac syndromes
  – Friedreich disease
Friedreich's ataxia

- autosomal recessive inherited disease
- progressive damage to the nervous system
- lead to heart disease and diabetes
- Signs and symptoms
  - Muscle weakness in the arms and legs
  - Loss of coordination
  - Vision impairment
  - Hearing impairment
  - Slurred speech
  - Curvature of the spine (scoliosis)
  - High plantar arches (pes cavus deformity of the foot)
  - Diabetes (about 20% of people with Friedreich's ataxia)
  - Heart disorders (91% of patients)
    - Atrial fibrillation
    - Cardiomegaly (up to dilated cardiomyopathy)
    - Symmetrical hypertrophy
• The brain’s effects on the heart
  – Neurogenic heart disease
Neurogenic Electrocardiographic Changes

- Two major categories
  - Arrhythmias
  - Repolarization changes
    - The ST segment and T wave abnormalities
    - Seen best in the anterolateral or inferolateral leads
    - Life-threatening arrhythmias found in patients with acute neurological disease
    - Increases the vulnerable period during which an extrasystole would be likely to result in ventricular tachycardia and/or ventricular fibrillation
Electrocardiographic Abnormalities

• Causes
  – Subarachnoid hemorrhage
  – Intraparenchymal hemorrhage (hemorrhagic stroke)
  – Massive ischemic stroke causing cerebral edema (e.g. MCA occlusion)
  – Traumatic brain injury
  – Cerebral metastases (rarely)
Electrocardiographic Abnormalities

- Widespread giant T-wave inversions (cerebral T waves).
- QT prolongation.
- ST segment elevation /depression – may mimic myocardial ischemia or pericarditis.
- Increased U wave amplitude.
- Other rhythm disturbances:
  - Sinus tachycardia
  - Junctional rhythms
  - Premature ventricular contractions
  - Atrial fibrillation.
Widespread, giant T-wave inversions and prolonged QT interval
Widespread, giant T-wave inversions and prolonged QT interval
Widespread T-wave inversions with slight ST depression and prolonged QT interval
Widespread ST elevation
Evidences

• The electrocardiographic abnormalities usually improve, often dramatically, with death by brain criteria

• Any circumstance that disconnects the brain from the heart blunts neurocardiac damage
  – Cardiac transplantation
  – Severe autonomic neuropathies caused by amyloidosis or diabetes
  – Stellate ganglionectomy for treatment of the long QT syndrome.
Evidences

• In a series of 100 consecutive stroke patients, 90% showed abnormalities on the ECG.
• This of course does not mean that 90% of stroke patients have neurogenic ECG changes.
• Many ECG abnormalities in stroke patients represent concomitant atherosclerotic coronary disease.
• Nonetheless, a significant number of stroke patients have real neurogenic ECG changes.
Evidences

- Ivan Pavlov and Hans Selye, a student of Pavlov
- 1958
- Electrolyte–steroid–cardiopathy with necroses (ESCN)
- Conditioning steroid with 2--methyl-9—fluorocortisol
- The factors that led to ESCN in steroid-sensitized animals
  - Certain electrolytes (eg, NaH2PO4)
  - Various hormones (eg, vasopressin, adrenaline, insulin, thyroxine)
  - Certain vitamins (eg, dihydrotachysterol)
  - Cardiac glycosides
  - Surgical interventions (eg, cardiac reperfusion after ischemia)
  - Psychic or nervous stimuli (eg, restraint, fright)
  \(\rightarrow\) Developing cardiac lesions
- The cardiac lesions could not be prevented by adrenalectomy
  \(\rightarrow\) direct neural connection to the heart rather than by a blood-born route
The phenomenology of the various types of myocardial cell death

- Coagulation necrosis
- Colliquiative myocytolysis
- Coagulative myocytolysis
Coagulation necrosis

- The fundamental lesion of infarction
- The cell loses its capacity to contract
- Dies in an atonic state
- No myofibrillar damage
Colliquative myocytolysis

• Low-output syndromes
• Edematous vacuolization with dissolution of myofibrils
• No hypercontraction
Coagulative myocytolysis

• The cell dies in a hypercontracted state
• Early myofibrillar damage
• Anomalous irregular cross-band formations
• Reperfusion injury
Common pathology of neurogenic heart disease

• Myofibrillar degeneration
• Coagulative myocytolysis
• Contraction band necrosis
• An easily recognizable form of neurogenic cardiac injury
• Distinct in several major respects from coagulation necrosis
• Myofibrillar degeneration is predominantly subendocardial.
• May involve the cardiac conducting system, which thus predisposes to cardiac arrhythmias.
• This lesion, combined with the propensity of catecholamines to produce arrhythmias even in a normal heart, may well raise the risk of a serious arrhythmia.
• This may be the major immediate mechanism of sudden death in many neurological circumstances, such as subarachnoid hemorrhage, stroke, epilepsy, head trauma, psychological stress, and increased intracranial pressure.
Mechanism of the production of neurogenic heart disease

- Catecholamine
- Stress plus or minus steroids
- Nervous system stimulation
- Reperfusion
Catecholamine infusion

• Systemically administered catecholamines
  – ECG changes reminiscent of widespread ischemia
  – A characteristic pathological picture in the cardiac muscle that is distinct from myocardial infarction.

• Catecholamines
  – Either released directly into the heart by sympathetic nerve terminals
  – Reach the heart through the bloodstream after release from the adrenal medulla
  – May be excitotoxic to myocardial cells
• Patients with pheochromocytoma
  – An identical picture
  – Chronically elevated catecholamines
• Patients with stroke
  – Often elevated systemic catecholamine levels
  – May take in part account for the high incidence of cardiac arrhythmias and ECG changes
Stress Plus or Minus Steroids

• A similar, if not identical, cardiac lesion can be produced with various models of stress.
• cardiac lesions induced by
  – Pretreatment
    • 2--methyl-9--fluorohydrocortisone (fluorocortisol)
    • Dihydrotachysterol (calciferol)
    • Thyroxine
  – Stress
    • Restraint, surgery, bacteremia, vagotomy, and toxins
• Although the administration of exogenous steroids facilitates the production of cardiac lesions, it is clear that stress alone can result in the production of morphologically identical lesions.
• Takotsubo-like cardiomyopathy occurs after an acute psychological stress → an example of a neurocardiac lesion.
• Prevalence
  – About 1.7-2.2% of cases presenting with suspected ACS
  – Women with a mean age of 61-76 yrs
• The onset of stress-induced cardiomyopathy is frequently but not always triggered by
  – An acute medical illness
  – Intense emotional or physical stress
    • Death of relatives
    • Arguments
    • Catastrophic medical diagnoses
    • Devastating financial or gambling losses
    • Natural disasters
• Mayo Clinic diagnostic criteria
  – Transient hypokinesis, akinesia or dyskinesia of the left ventricular mid segments with or without apical involvement. The regional wall motion abnormalities typically extend beyond a single epicardial coronary distribution. A stressful trigger is often, but not always present.
  – Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
  – New EKG abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin.
  – Absence of pheochromocytoma or myocarditis.
Clinical presentation

- Electrocardiographic abnormalities are the most common finding.
  - ST segment elevation: 34-56%, especially in the anterior precordial leads
  - Deep T wave inversion with QT interval prolongation
  - Abnormal Q waves
  - Non-specific abnormalities,
  - In some cases the ECG is normal at presentation
- Cardiac biomarker levels, particularly high-sensitivity troponin assays, are usually elevated. However, the elevations are typically mild, which contrasts with the often severe hemodynamic compromise.
  - Cardiac troponins: elevation in 86%
  - Creatine kinase MB: elevation in 74%
- Left ventriculography or echocardiography usually show the characteristic apical ballooning with akinesis or dyskinesis of the apical one-half to two-thirds of the LV
  - Overall systolic function is reduced
  - Average LVEF: 20-49%
- Transient LVOT obstruction: 16%
  - In some cases, this is accompanied by systolic anterior motion of the mitral valve, similar to that seen in hypertrophic cardiomyopathy
- Reversible perfusion abnormalities in the left ventricular apex
• Stress-induced myocardial lesions may be prevented by sympathetic blockade

• Antiadrenergic agents
  – Ganglionic blockers such as mecamylamine
  – Catecholamine-depleting agents such as reserpine
• If a lethal arrhythmia does not intervene, the process is potentially completely reversible.

• Neurocardiac lesions that are not sufficiently severe and widespread to produce gross heart failure but may predispose to serious cardiac arrhythmias.
Nervous system stimulation

• Nervous system stimulation produces cardiac lesions that are histologically indistinguishable from those described for stress and catecholamine-induced cardiac damage

• Stimulation of the lateral hypothalamus
  – Hypertension
  – ECG changes

• Stimulation of the anterior hypothalamus
  – Bradycardia
  – Can be blocked by vagotomoy
This effect of lateral hypothalamus stimulation on the blood pressure and ECG can be completely prevented by
- Maneuvers that interfere with the action of the sympathetic limb of the autonomic nervous system
  - C2 spinal section
  - Stellate ganglion blockade
- Antiadrenergic drugs such as propranolol
- But not by vagotomy

→ The mechanism of the ECG changes is sympathetic rather than parasympathetic or humoral.
• Unilateral hypothalamic stimulation does not result in histological evidence of myocardial damage by light microscopy.
• Bilateral hypothalamic prolonged stimulation regularly produces myofibrillar degeneration indistinguishable from that produced by catecholamine injections and stress.
• Other sites’ stimulations produce cardiac lesions of this type:
  – Limbic cortex
  – Mesencephalic reticular formation
  – Stellate ganglion
  – Regions known to elicit cardiac reflexes such as the aortic arch.
• These neurogenic cardiac lesions will occur even in an adrenalectomized animal, although they will be somewhat less pronounced.

• High levels of circulating catecholamines exaggerate the EKG findings and myocardial lesions, but high circulating catecholamine levels are not required for the production of pathological changes.
Reperfusion

• Reperfusion injury
• Myofibrillar degeneration
• Is commonly seen in patients who die after a period of time on a left ventricular assist pump or after they undergo extracorporeal circulation.
• Similar lesions are seen in hearts that were reperfused with angioplasty or fibrinolytic therapy
• Calcium deficiency with loss of intracellular calcium during ischemia
• Opening of the receptor operated calcium channels by excessive amounts of locally released norepinephrine during reperfusion
• Sudden calcium influx may be the final common pathway by which the irreversible contractures occur, which leads to myofibrillar degeneration
• The EKG change and the histological lesion
  – Well reflect the effects of large volumes of norepinephrine released into the myocardium from sympathetic nerve terminals
• This locally released norepinephrine
  → Stimulate synthesis of adenosine 3,5-cyclic phosphate
  → Results in the opening of the calcium channel
  → Influx of calcium and efflux of potassium.
• This efflux of potassium could explain the peaked T waves often seen early in neurogenic electrocardiographic changes.
• The actin and myosin filaments interact under the influence of calcium but do not relax unless the calcium channel closes.
• Continuously high levels of norepinephrine in the region
  → Result in failure of the calcium channel to close
  → Leads to cell death
  → Finally to leakage of enzymes out of the myocardial cell.
• Free radicals released as a result of reperfusion after ischemia or by the metabolism of catecholamines to the known toxic metabolite, adrenochrome
  → Contribute to cell membrane destruction
  → Leads to leakage of cardiac enzymes into the blood.
Cardiac toxicity of locally released norepinephrine has various spectrums.

- A brief reversible burst of electrocardiographic abnormalities such as tall T waves
- An irreversible failure of the muscle cell with permanent repolarization abnormalities, or even the occurrence of transmural cardiac necrosis with enzyme (e.g., troponin, creatine kinase) release and Q waves seen on the ECG
Sympathetic Storm

Neurally Released Catecholamines

Adrenal Catecholamines

Exogenous Catecholamines

Cardiac Receptor Operated Calcium Channel

ECG Changes → Sudden Death
Wall Motion Disorders → Takotsubo
Contraction Bands

Free Radical Release

Calcium Entry; Enzyme Leak; Contraction Band Necrosis
Possible therapeutic approaches aimed to prevent neurocardiac damage
Conclusion

• Overactivity of the sympathetic limb of the autonomic nervous system is the common phenomenon that links the major cardiac pathologies seen in neurological catastrophes.

• These profound effects on the heart, especially life-threatening arrhythmias, may contribute in a major way to early mortality rates of many primarily neurological conditions such as subarachnoid hemorrhage, cerebral infarction, status epilepticus, and head trauma.
THANK YOU FOR YOUR ATTENTION :) 

ANY QUESTION ?