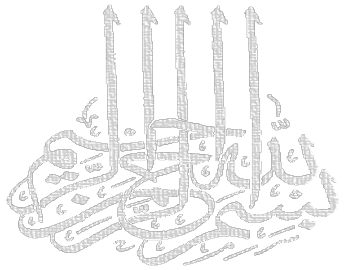
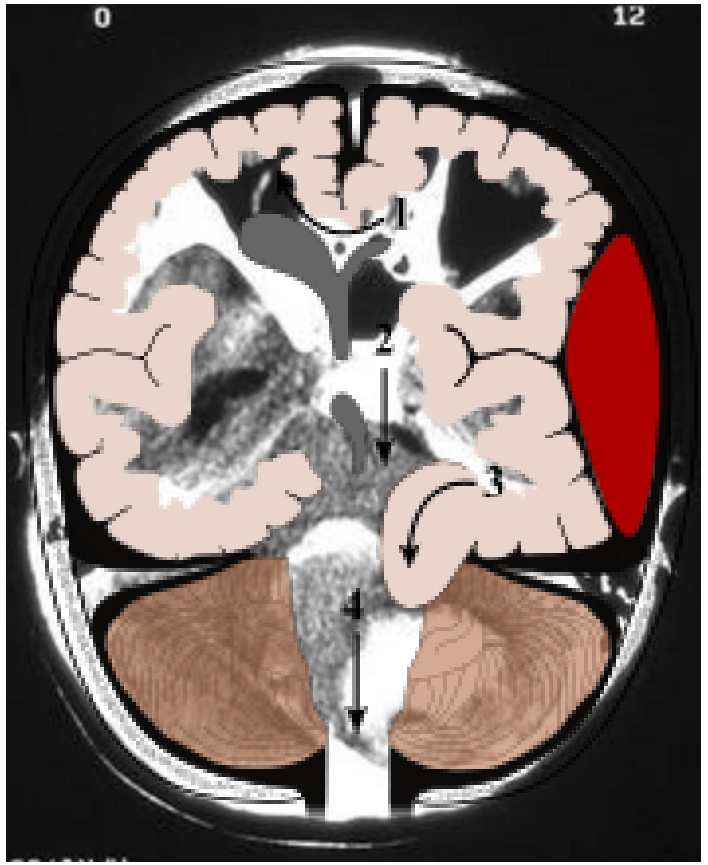


Organ Dysfunction

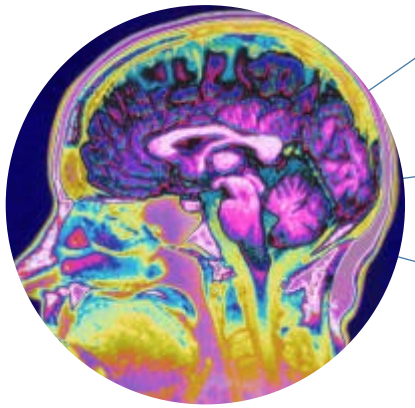
in the Potential Brain-Dead Organ Donor

Sequence of Events in Brain Death

- Rostral – caudal progression of ischemia
  - Medulla oblongata
    - Autonomic storm to maintain CPP
    - Elevated levels of catecholamines
  - Spinal cord
    - Sympathetic deactivation
      - Bradycardia
    - Loss of vasodilatory tone
      - Ischemia / reperfusion
      - Diffuse endothelial injury
      - Hypotension
  - Herniation



Physiologic Changes Associated with Severe Brain Injury and Brain Death



Autonomic (sympathetic) storm

- Cushing's triad
- Catecholamine surge
  - Increased systemic vascular resistance
  - Severe hypertension
  - Stunned myocardium
  - Cardiac arrhythmias
  - Neurogenic pulmonary edema

Loss of sympathetic tone

- Hypotension
- Hypothermia

Disruption of pituitary axis

- Decreased T3, Arg-VP, cortisol and insulin
- Anaerobic metabolism
- Endothelial activation
- Cytokines, immune, etc.

Potential Injuries to Transplanted Organ

Before Brain Death:

Multi trauma

Tissue damage

Hemorrhage/hypotension

Aspiration

Asphyxia

Mechanical ventilation

Hospital acquired infections

Surgery

Adverse drug effects

After Brain Death:

Hemodynamic collapse

End-organ ischemia

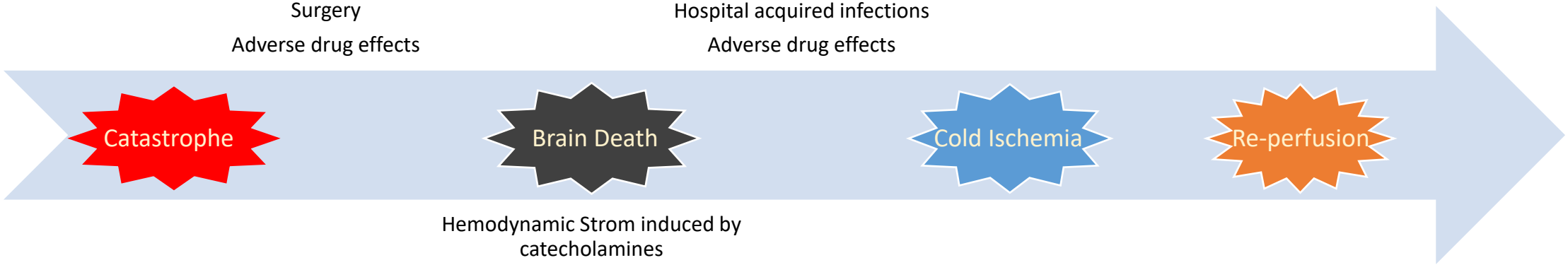
Metabolic/hormonal changes

Fluid/electrolytes disturbance

Mechanical ventilation

Hospital acquired infections

Adverse drug effects



Hemodynamic Strom induced by catecholamines

Severe hypertension causing endothelial shear stress

Peripheral vasoconstricton causing end-organ ischemia

Loss of Hypothalamic Control

Unphysiological State of the Brain Death: Organ Dysfunction

Cardiovascular dysfunction
Respiratory dysfunction
Endocrine dysfunction
Hyperglycemia
Electrolyte disturbances
Coagulopathy
Inflammatory response

Incidence of Common Physiological Derangements in Brain-dead Donors

Derangment	Cause	Approximate incidence
Hypothermia	Hypothalamic damage; reduced metabolic rate; vasodilation and heat loss	Invariable if not prevented
Hypotension	Vasoplegia; hypovolemia; reduced coronary blood flow; myocardial dysfunction	81%–97%
Diabetes insipidus	Posterior pituitary damage	46%–78%
Disseminated intravascular coagulation	Tissue factor release; coagulopathy	29%–55%
Arrhythmias	‘Catecholamine storm’; myocardial damage; reduced coronary blood flow	25%–32%
Pulmonary edema	Acute blood volume diversion; capillary damage	13%–18%

Complications of brain death: frequency and impact on organ retrieval.

Complication	Incidence (%)
Intravenous vasopressor requirement	97.1
Coagulopathy	55.1
thrombocytopenia	53.6
Diabetes insipidus	46.4
Cardiac ischemia	30.4
lactic acidosis	24.6
Renal failure in per cent	20.3
Acute respiratory distress syndrome	13

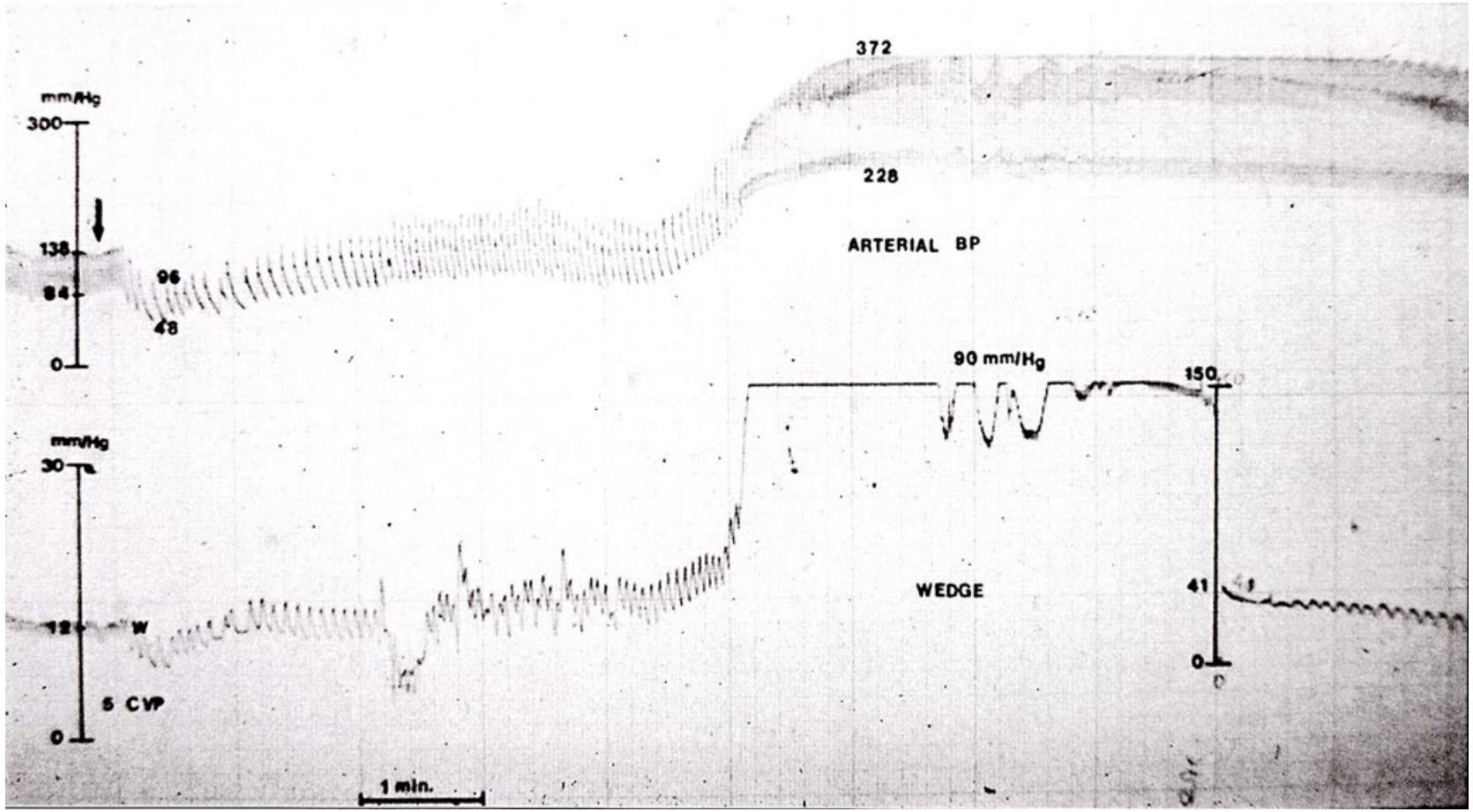
Sixty-nine organ donors

Am Surg. 2006 May;72(5):377-81.

Cardiac Dysfunction

- Cushing's effect:
  - Hypertension, bradycardia, and irregular respiration
- Catecholamine surge (catecholamine storm)
  - Intense vasoconstriction, raised systemic vascular resistance, and tachycardia
  - Severe hypertension
  - Central redistribution of blood volume, increased afterload, and visceral ischemia.
  - Stunned myocardium
  - Coronary vasoconstriction
  - Cardiac arrhythmias
  - Myocardial injury occurs in 20–25% of DBD hearts
    - Echocardiographic evidence of myocardial dysfunction is seen in 40%:
      - Impaired LV contractility/hypokinesis
    - Subendothelial ischemia
    - Focal myocardial necrosis
    - Endothelial injury

Autonomic Storm



Cardiac dysfunction following brain death after severe pediatric traumatic brain injury: A preliminary study of 32 children

Early Echocardiogram Findings In Final Sample Of Severe Pediatric Traumatic Brain Injury Without Brain Death (*N*=22) And TBI With Brain Death (*N*=10)

	All Severe TBI (*N* = 32) (%)	Severe TBI without brain death (*N* = 22) (%)	Severe TBI with brain death (*N* = 10) (%)	*P* (0.025 = significant)
LVEF				
Low (LVEF <50%)	5 (15.6)	1 (4.5)	4 (40)	0.024
Normal (LVEF ≥50%)	27 (84.4)	21 (95.5)	6 (60)	
RWMA grade				
Normal	25 (78.1)	19 (86.4)	6 (60)	0.165
Abnormal	7 (21.9)	3 (13.6)	4 (40)	
Mild hypokinesis	3 (9.4)	2 (9.1)	1 (10)	
Severe hypokinesis	3 (9.4)	1 (4.5)	2 (20)	
Akinesis	1 (3.1)	0	1 (10)	
Dyskinesis	0	0	0	

TBI = Traumatic brain injury, LVEF = Left ventricular ejection fraction, RWMA = Regional wall motion abnormalities

Krishnamoorthy, V. Int J Crit Illn Inj Sci. 2015 Apr-Jun; 5(2): 103–107.

Electrocardiographs Findings in Brain Death; Description and Presumed Mechanism

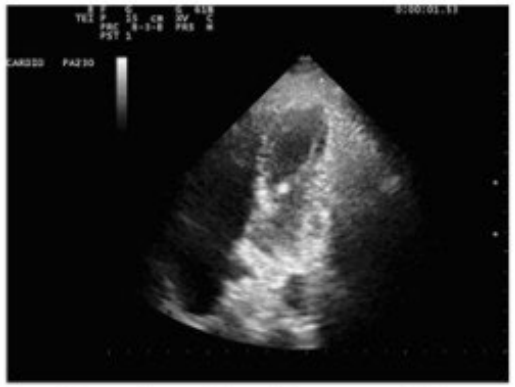
Table 2—*Electrocardiographic Findings in 28 Cases of Brain Death

ECG findings	No of cases
Broadening of the terminal part of the QRS complex (J wave)	24
Prolonged QT interval	21
ST depression, negative T waves	16
ST elevation	5
Flat T waves	9
Giant T waves	1
Prolonged PR interval	2
Broad and notched P waves	1
Arrhythmia	1
Normal tracing	1

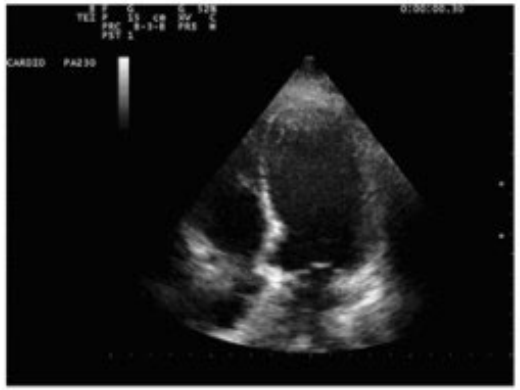
Drory, Y. CHEST,67: 4, APRIL,1975

Serial Four Chamber Cineloops Of A Potential Heart Donor With Hemodynamic Instability

A – LV function before brain death



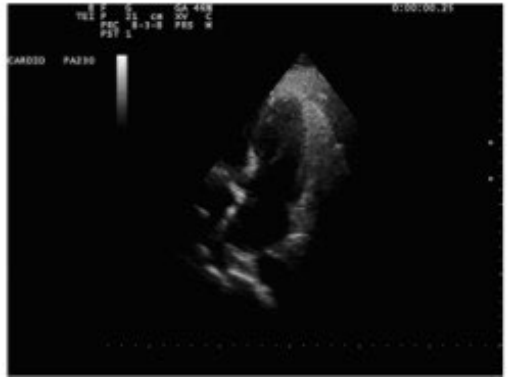
B – LV dysfunction at brain death



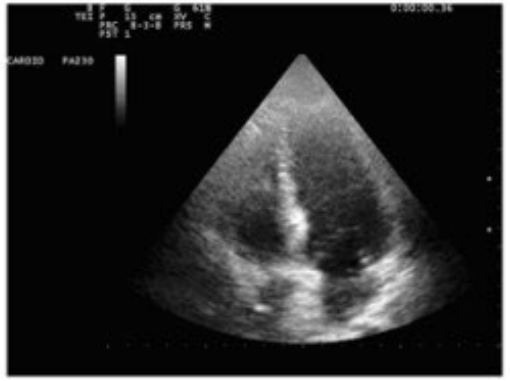
Normal LV function before brain death

Takotsubo-like LV dysfunction immediately after subarachnoid hemorrhage and brain death: echocardiographically detected left ventricular systolic dysfunction excludes this heart from transplant according to standard criteria

C – One day after Hormonal T.



D – Two days after Hormonal T.

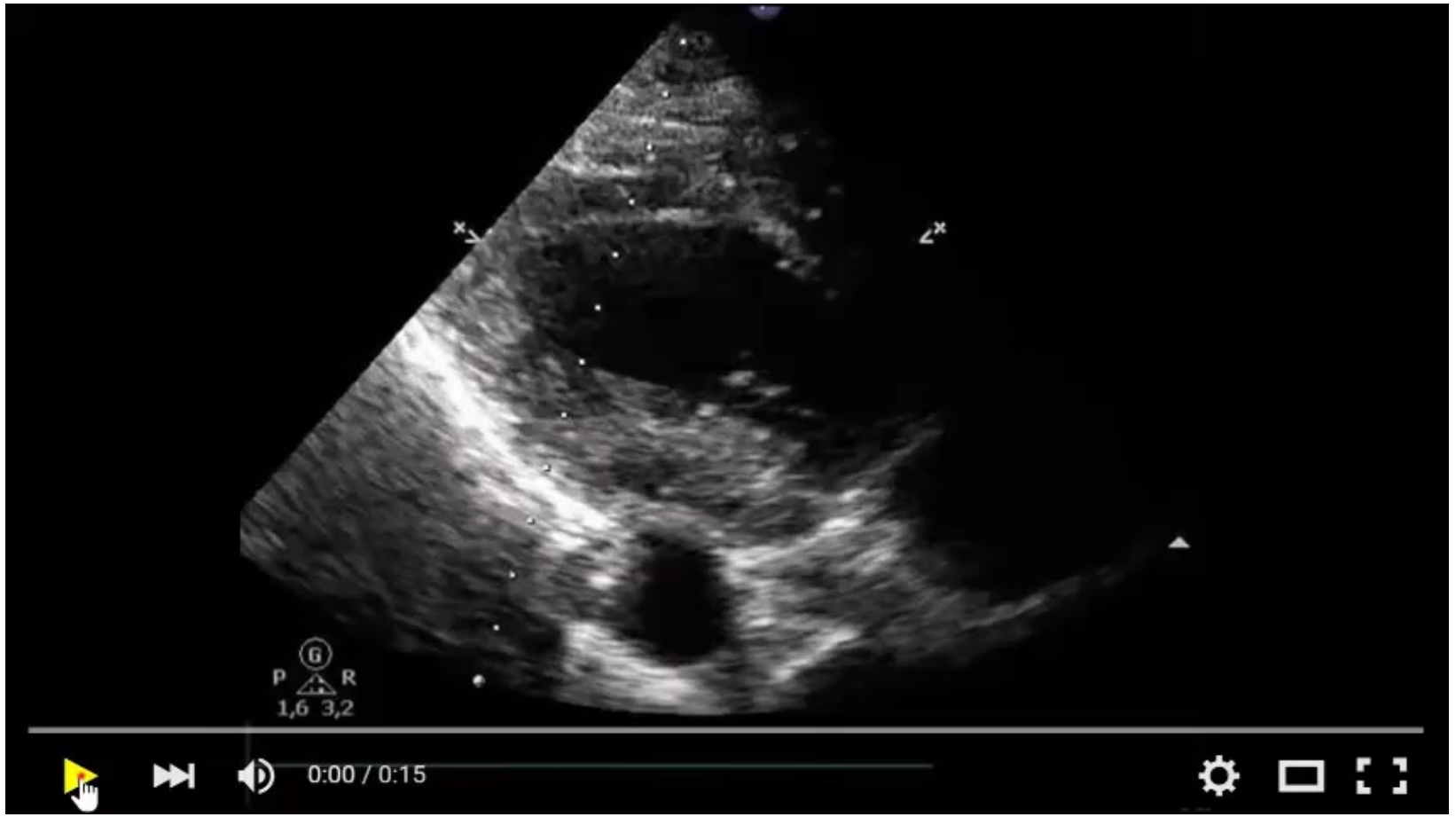


Reduction of end-systolic volume and improved systolic thickening. One day after early and aggressive hormonal treatment, including triiodothyronine, vasopressin, insulin and methylprednisolone with improvement of heart function

Two days after hormonal treatment the heart definitively normalized, was retrieved and was successfully transplanted. An additional movie file shows this in more detail

Casartelli, M. Et al. Cardiovasc Ultrasound. 2012; 10: 25.

Balloon Cardiomyopathy: Takotsubo



Cardiovasc Ultrasound. 2012; 10: 25.

Hypotension in the Potential Organ Donor

Hypovolemia	Cardiac Dysfunction	Vasodilatation

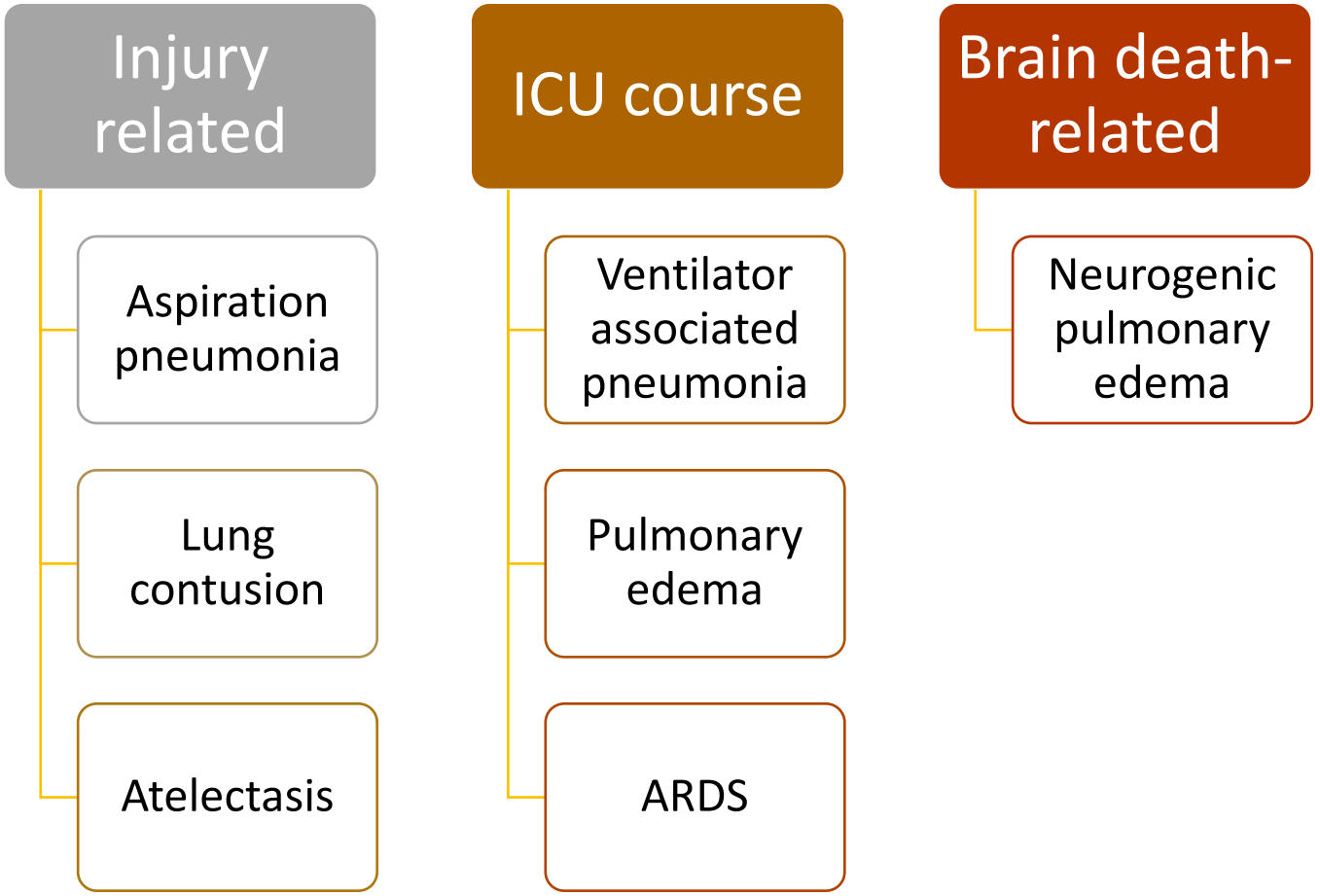
• **Absolute**
  • Initial Injury
  • Inadequate resuscitation
  • Third spacing
  • ICP Treatment Dehydration
  • Mannitol
  • Hyperglycemia-induced and osmotic diuresis
  • Diabetes insipidus
  • Hypothermia “cold” diuresis
• **Relative**
  • Vasodilatation
  • Loss of vasomotor tone and pooling
  • Rewarming of hypothermia
	• **Pre-existing disease**
	• **Initial injury:**
	  • Myocardial contusion
	  • Pericardial tamponade
	  • Myocardial ischemia/infarct
	• Brain-death process:
	  • Catecholamine-ca process
	  • Ischemia-reperfusion injury
	• **Metabolic depression:**
	  • Acidosis
	  • Hypothermia
	  • Hypophosphatemia
	  • Hypocalcemia
	  • Endocrinopathy of brain death
	• **Volume overload-CHF**
	• **Arrhythmias**
	  • Catecholamine
	  • Ischemia
	  • Hypokalemia/hypomagnesemia
		• Spinal shock
		• Catecholamine depletion
		• Loss of vasomotor control and autoregulation
		• Relative adrenal insufficiency of trauma/critical illness
		• Endocrinopathy of brain death
		• Acquired sepsis

Wood KE and McCartney J. *Transplantion Rev* 2007; 21:204-218

Cardiac Arrhythmias

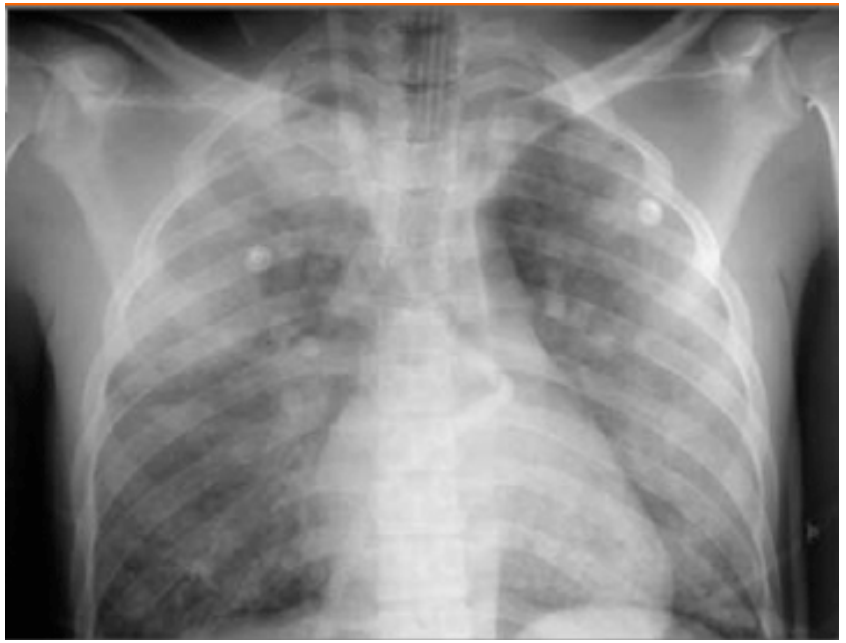
- Etiology:
  - Catecholamine storm
  - Myocardial injury
- Atrial tachycardia
- Ventricular arrhythmias

Respiratory Dysfunction



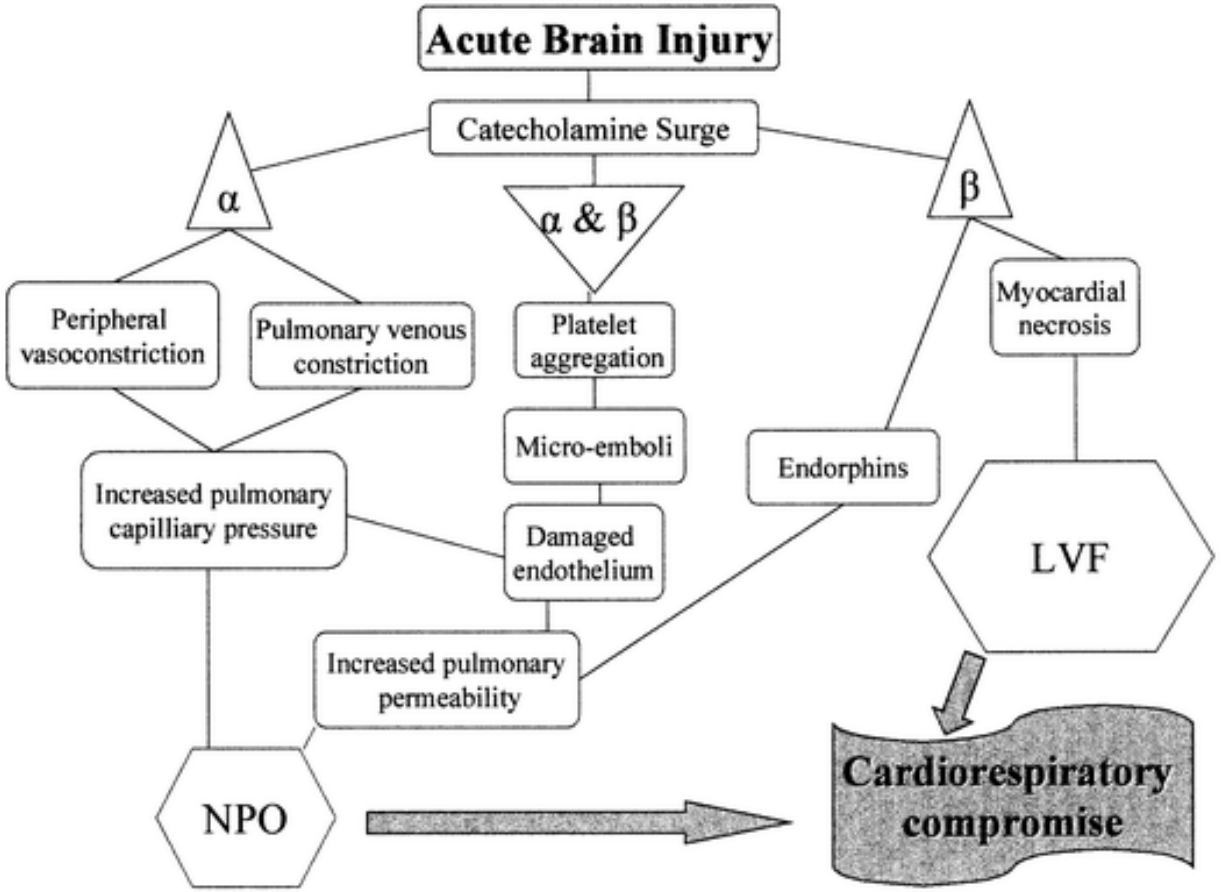
Neurogenic Pulmonary Edema

- The lungs are highly susceptible to injury resulting from the rapid changes that occur during the catecholamine storm
- Left-sided heart pressures exceed pulmonary pressure, temporarily halting pulmonary blood flow
- The exposed lung tissue is severely injured, resulting in interstitial edema and alveolar hemorrhage, a state commonly referred to as neurogenic pulmonary edema

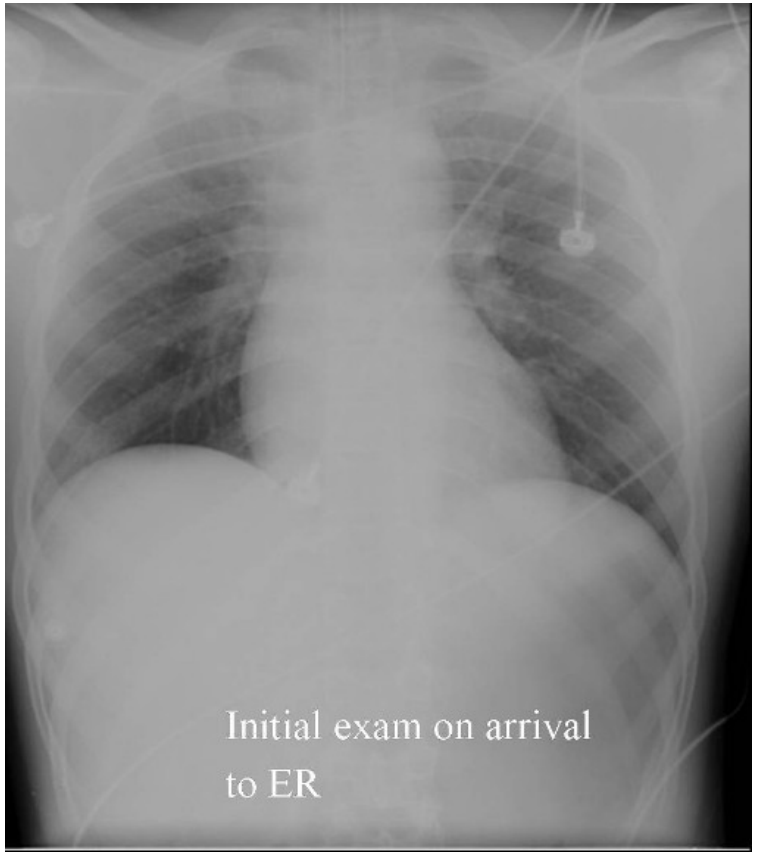


Neurogenic Pulmonary Edema: Blast Theory

- Massive sympathetic discharge
- Systemic arterial hypertension, peripheral vasoconstriction, increased pulmonary arterial pressure and pulmonary mircovascular vasoconstriction
- Pulmonary congestion with development of pulmonary edema
- Endothelial damage



Neurogenic Pulmonary Edema



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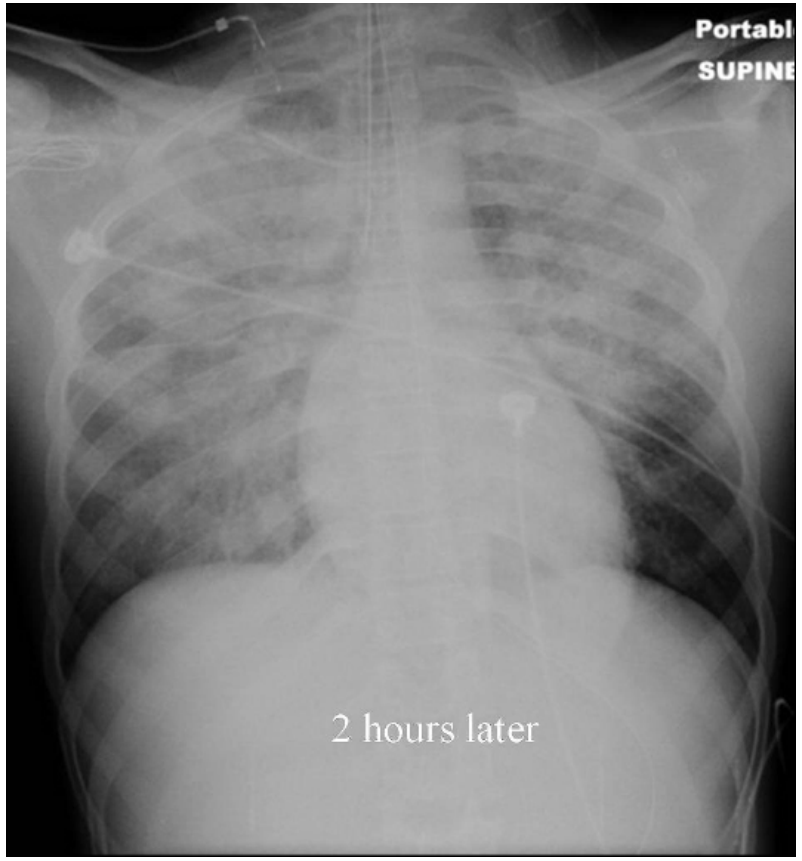

Acta Anaesthesiol Scand 2009; 53: 425–435
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2008.01879.x

Systemic inflammation in the brain-dead organ donor

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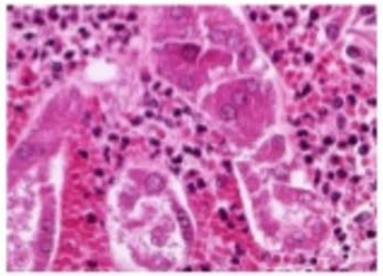
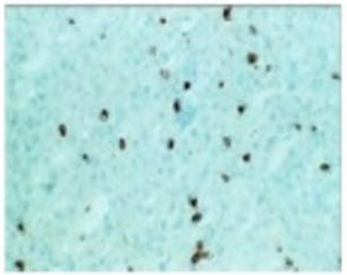
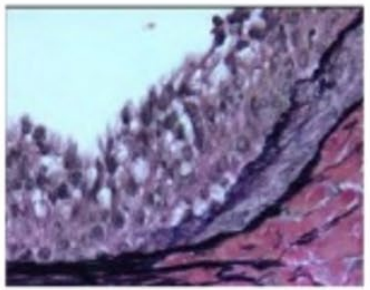
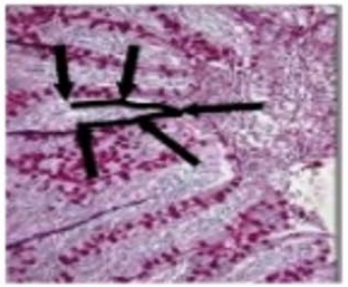
Brain death itself impairs organ function in the potential donor, thereby limiting the number of suitable organs for transplantation. In addition, graft survival of kidneys obtained from brain-dead (BD) donors is inferior to that of kidneys obtained from living donors. Experimental studies confirm an inferior graft survival for the heart, liver and lungs from BD compared with living donors.

The mechanism underlying the deteriorating effect of brain death on the organs has not yet been fully established. We know that brain death triggers massive circulatory, hormonal and metabolic changes. Moreover, the past 10 years have produced evidence that brain death is associated with a systemic inflammatory response. However, it remains uncertain whether the inflammation is induced by brain death itself or by events before and after becoming BD.

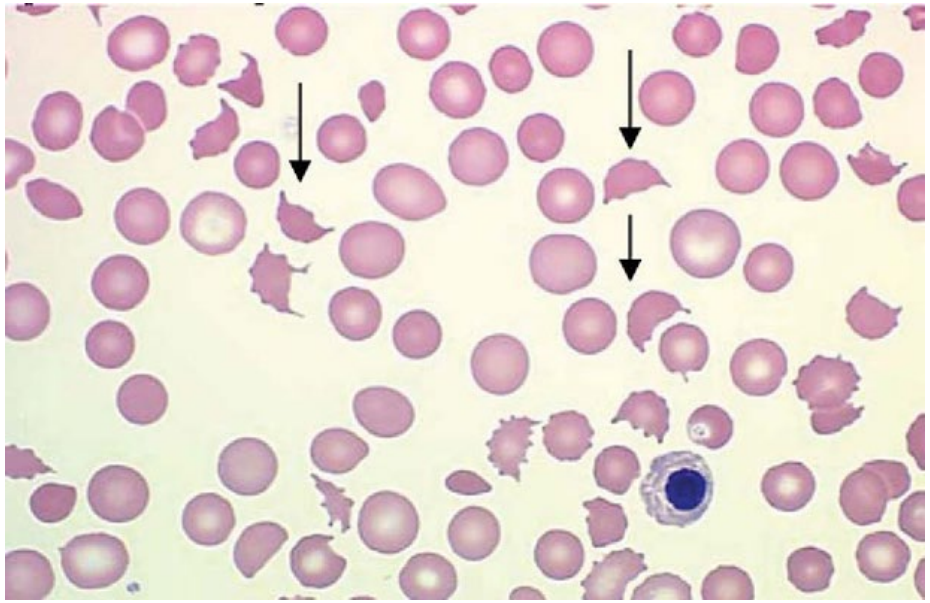
The purpose of this study is to discuss the risk factors associated with brain death in general and the inflammatory response in the organs in particular. Special attention will be paid to the heart, lung, liver and kidney and evidence will be presented from clinical and experimental studies.

Accepted for publication 17 November 2008

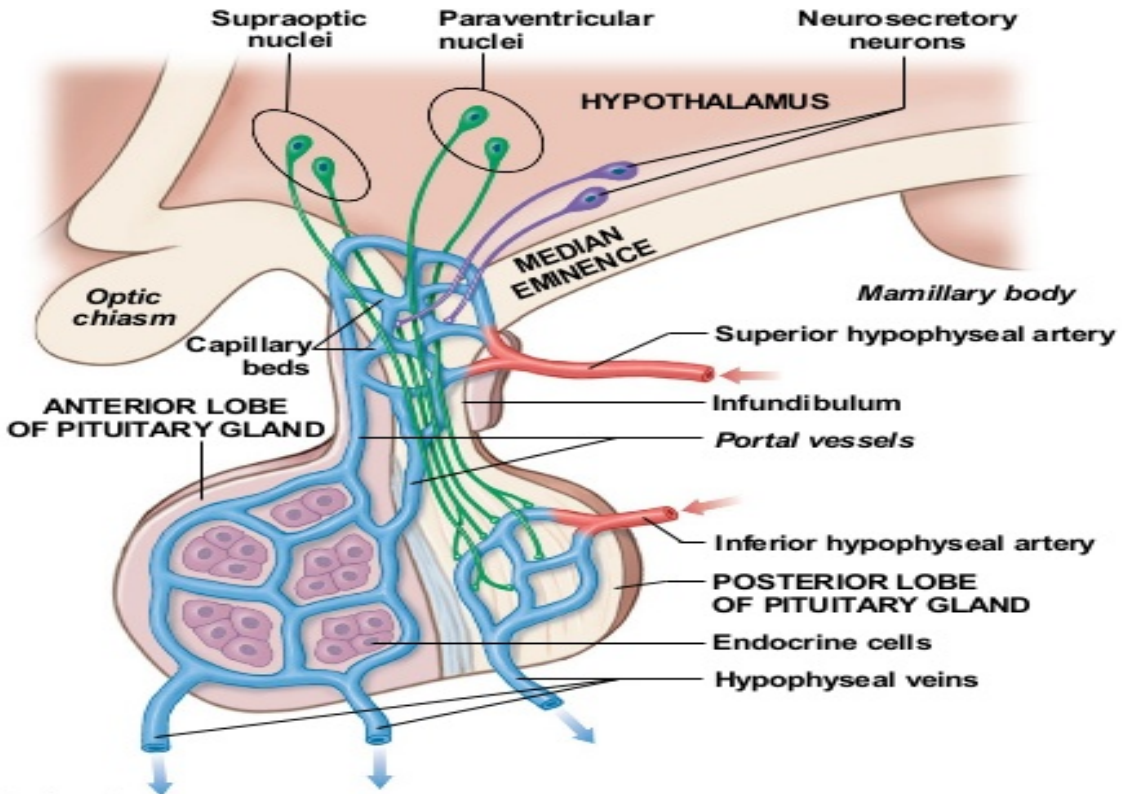
Release of Plasminogen Activator → DIC

- Results from the passage of necrotic brain tissue into the circulation
- Leads to coagulopathy and sometimes progresses further to DIC
- DIC may persist despite factor replacement requiring early organ recovery
- (Also affected by hypothermia, release of catecholamines & hemodilution as a result of fluid resuscitation)



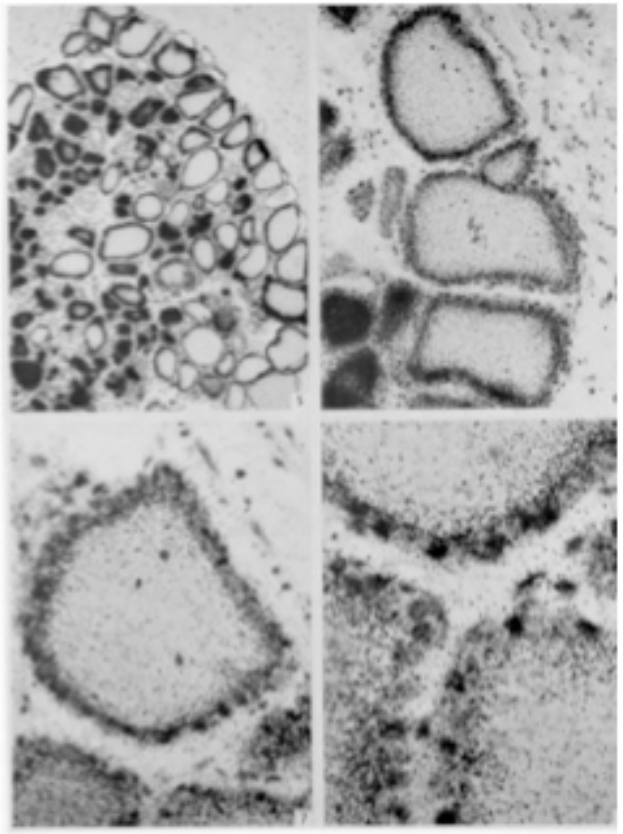
Hypothalamic – Pituitary Axis

- Hypothalamus
  - Located at base of brain
  - Superior hypophyseal artery blood supply
- Pituitary
  - Anterior (adenohypophysis)
    - Portal venous system from HTM
    - Release of ACTH, GH, LH, FSH, TSH
  - Posterior (neurohypophysis)
    - Inferior hypophyseal artery blood supply
    - Neuronal connections from HTM SO and PV nuclei
    - Release of vasopressin and oxytocin



Effects of Thyroid Hormones on Heart

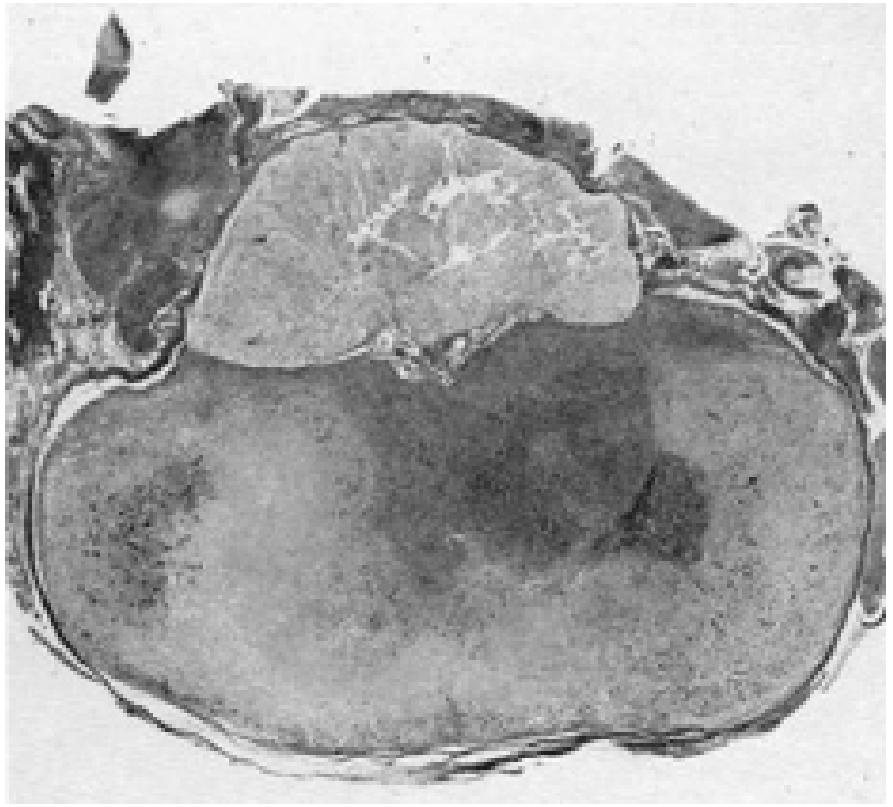
- Increase in cardiac output
  - Chronotropy via beta-adrenergic receptor upregulation
  - Vasodilatation
    - Non-shivering thermogenesis
    - Direct vasodilatory effects on smooth muscle
  - Increased blood volume
    - Stimulate production of erythropoeitin
    - Activation of RAA axis
  - Increase myocardial contractility via increased Ca++



Neuroendocrine Dysfunction

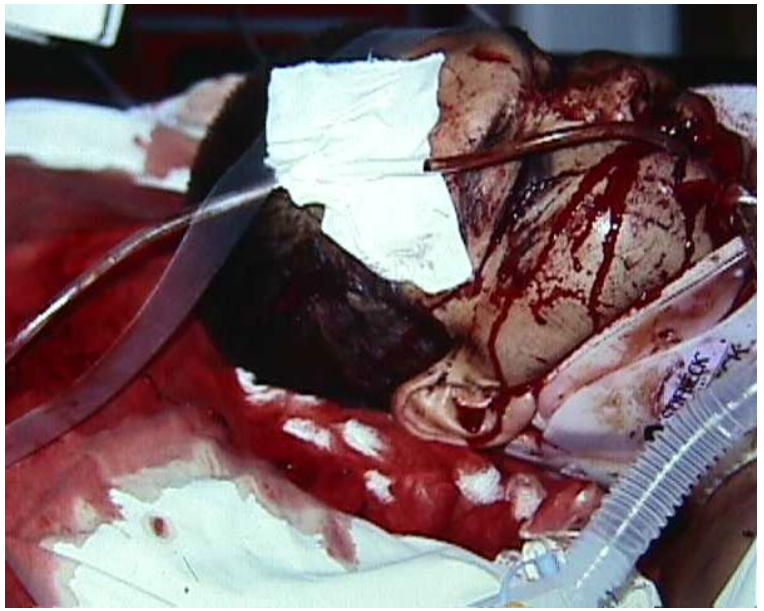
- 40% of patients with acute brain injuries
- Autopsy studies: evidence of pituitary hemorrhage or necrosis in 80% of patients following TBI
  - Diffuse brain injury
  - Hemorrhage
  - Herniation
- May develop subacutely

  after TBI

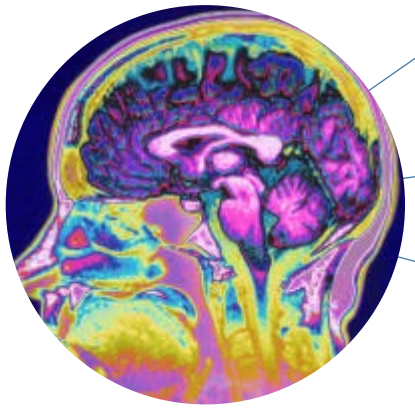


Disruption of Pituitary Axis

- Hypothyroidism
- Diabetes insipidus
- Decreased cortisol
- Decreased insulin and hyperglycemia
- Endothelial activation
- Diffuse vascular regulatory impairment
- Diffuse metabolic cellular injury and Anaerobic metabolism
- Progressive deterioration of organ function



Summary



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  - Neurogenic pulmonary edema

Loss of sympathetic tone

- Hypotension
- Hypothermia

Disruption of pituitary axis

- Hypothyroidism
- DI
- Hyperglycemia
- Anaerobic metabolism
- Endothelial activation