Endocrine Disease and the Heart

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Topics to be covered

- Pituitary axis
- Acromegaly (GH)
- Cushing’s (ACTH, cortisol)
- Conn’s syndrome (hyper-aldosteronism)
- Addison’s disease (hypo-aldosteronism)
- Hyperparathyroidism (Ca^{2+})
- Hypocalcemia
- Pheochromocytoma
- Hyperthyroidism
- Hypothyroidism
- Amiodarone effects on thyroid function
Hypothalamic hormones regulate anterior pituitary trophic hormones that, in turn, determine target gland secretion. Peripheral hormones feed back to regulate hypothalamic and pituitary hormones.
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Acromegaly

- Approximately 900 new cases in the US each year
- Excessive production of Human Growth Hormone (hGH) which subsequently increases levels of Insulin-like growth factor type 1 (IGF-1)
- hGH also has target receptors on heart, muscle, liver, kidney and fat cells
Features of acromegaly/gigantism. A 22-year-old man with gigantism due to excess growth hormone is shown to the left of his identical twin. The increased height and prognathism (A) and enlarged hand (B) and foot (C) of the affected twin are apparent. Their clinical features began to diverge at the age of approximately 13 years.
Cardiac changes in Acromegaly

- Increased cardiac mass
- Increased cardiac output/index
- Increased stroke volume/index
- Left ventricular hypertrophy

- Hypertension, Diabetes, Hyperlipidemia are common in patients with acromegaly
Diagnosis and Treatment of Acromegaly

- Serum growth hormone >5ng/dL and serum IGF-1 >300μIU/mL measured 1 hour after 100g oral glucose load
- MRI of pituitary usually shows macroadenoma (>10mm)
- Transsphenoid resection of the pituitary is treatment of choice (in most patients)
- Octreotide can be used to lower hGH
- Pegvisomant (hGH receptor antagonist) can be used in octreotide resistant patients (normalizes IGF-1 levels)
- ACE inhibitors can paradoxically elevate blood pressure
- Treatment of Acromegaly can improve hypertension

Braunwald's Heart Disease, 8th ed.
ACTH

- Anterior pituitary produces proteins including ACTH
- ACTH binds to target cells in adrenal gland
- ACTH regulates cortisol secretion from zona fasciculata and zona reticularis of the adrenal gland
The hypothalamic-pituitary-adrenal axis. The main sites for feedback control by plasma cortisol are the pituitary gland (1) and the hypothalamic corticotropin-releasing center (2). Feedback control by plasma cortisol also occurs at the locus coeruleus/sympathetic system (3) and may involve higher nerve centers (4) as well. There may also be a short feedback loop involving inhibition of corticotropin-releasing hormone (CRH) by adrenocorticotropic hormone (ACTH) (5). Hypothalamic neurotransmitters influence CRH release; serotonergic and cholinergic systems stimulate the secretion of CRH and ACTH; -adrenergic agonists and -aminobutyric acid (GABA) probably inhibit CRH release. The opioid peptides -endorphin and enkephalin inhibit, and vasopressin and angiotensin II augment, the secretion of CRH and ACTH. -LPT, -lipotropin; POMC, pro-opiomelanocortin; LC, locus coeruleus; NE, norepinephrine.
Cushing’s Disease
Excess ACTH and Cortisol

- Cushing’s Disease
  - Excess ACTH production from pituitary
  - Results in excess cortisol secretion from adrenal zona fasciculata

- Cushing syndrome
  - Excess cortisol secretion from adrenal tumor
  - Ectopic ACTH can also be produced by carcinoid tumors, lung and thyroid tumors
Excess Cortisol and the Heart

- Accelerated Atherosclerosis
- Also Cerebral and peripheral vascular disease
- Mainly due to hypertension and hyperlipidemia
- Carney complex
  - Cushing syndrome
  - Cardiac myxoma
  - Variety of pigmented dermal lesions (not café-au-lait)
  - Monogenic autosomal dominant trait on chromosome 17q2
Diagnosis of Cushing’s Disease/Syndrome

- Increased 24 hour urinary free cortisol
- ACTH measurement
- MRI localization
Treatment of Excess ACTH

- Cushing’s Disease
  - Transsphenoidal hypophysectomy

- Cushing’s Syndrome
  - Removal of one or both adrenal glands
    - Must replace cortisol and fludrocortisone to prevent adrenal crisis
  - Ketoconazole inhibits adrenal enzymes and can be used in inoperable patients
Histologic section through a normal adult adrenal gland showing the progression, outside in, of the zona glomerulosa, zona fasciculata, and zona reticularis.

Schematic diagram of the structure of the human adrenal cortex, depicting the outer zona glomerulosa and inner zona fasciculata and zona reticularis.
Aldosterone

- Produced by zona glomerulosa
- Aldosterone release stimulated by angiotensin II binding to angiotensin II type 1 receptors
- Aldosterone effect is protein synthesis
- Augments development of left ventricular hypertrophy
The interrelationship of the volume and potassium feedback loops on aldosterone secretion. Integration of signals from each loop determines the level of aldosterone secretion.
Hyperaldosteronism

- **Conn syndrome**
  - Benign adrenal adenoma produces excess aldosterone
  - Diagnosed by low renin:aldosterone ratio
  - Treatment by surgical resection

- Sodium retention

- Hypertension

- Loss of Magnesium and Potassium

- Increased systemic vascular resistance

- Left ventricular hypertrophy beyond degree expected from hypertension alone

Braunwald's Heart Disease, 8th ed.
Addison’s Disease (JFK)

Diagnosed with Addison’s disease at age 30
Addison’s Disease
Hypoaldosteronism

- Primary adrenal insufficiency
  - Loss of bilateral adrenal function due to
    - Autoimmune
    - Hemorrhage
    - Malignancy

- Secondary adrenal insufficiency
  - Due to lack of ACTH from pituitary
  - Usually aldosterone levels are ok (glucocorticoids low)
Signs of Addison’s Disease

- Noncardiac signs
  - Pigmentation
  - Abdominal pain
  - Nausea and vomiting
  - Weight loss

- Addisonian Crisis
  - Hypovolemia
  - Hypotension
  - Hyperkalemia
  - Sodium wasting
Cardiac Manifestations of Addison’s Disease

- Peaked T waves on EKG (hyperkalemia)
- Small cardiac dimensions
- Cardiac atrophy seen in extreme cases
Diagnosis of Addison’s Disease

- **Clinical setting**
  - Acute adrenal insufficiency can occur in patients with acute stress, infection or trauma
  - Adrenal hemorrhage can occur with severe infection or diffuse intravascular coagulation
  - Secondary adrenal insufficiency usually chronic
    - Acute changes can occur with pituitary inflammation or hemorrhage
  - Withdrawal after long-term steroid use can cause acute crisis

- **Laboratory studies**
  - AM cortisol less than 8mg/dL
  - 30 minute cortisol level after 0.25mg IV cosyntropin less than 20mg/dL
Treatment of Addison’s Disease

- Addisonian crisis
  - Hydrocortisone 100mg IV every 8 hours for 24 hours
  - Taper dose for subsequent 72-96 hours
  - Large volume of normal saline with 5% dextrose
  - Identify and treat precipitating cause

- Chronic treatment
  - Corticosteroid and mineralocorticoid
  - Fludrocortisone 0.1mg daily
Hyperparathyroidism

- Typically solitary parathyroid adenoma
- Increases serum calcium
- Hypercalcemia
  - Enhanced cardiac contractility
  - EKG changes
    - Short QT
    - Short PR
    - Flat T wave
  - Chronically calcium deposits in myocardial interstitium, valve annulus and cups
  - Increased blood pressure (although PTH is a vasodilator)
Hypocalcemia
Short PR interval
Short QT interval
Diagnosis and Treatment Hyperparathyroidism

- **Primary**
  - Increase serum intact PTH
  - Elevated serum calcium
  - Treated by surgical removal of parathyroid adenoma

- **Secondary (malignancy, sarcoidosis)**
  - Increased PTH-related peptide
  - Increased 1,25-dihydroxyvitamin D3
Hypocalcemia

- Can impair cardiac contractility
- Prolonged QT interval on EKG
- Primary hypoparathyroidism
  - due to Surgical resection, DiGeorge syndrome
- Low calcium commonly occurs in renal failure
- High PTH levels
  - Left ventricular hypertrophy
  - Low systemic vascular resistance
Pheochromocytoma

- “Benign” tumor of neuroendocrine chromaffin cells
  - Adrenal medulla
  - Or anywhere else (primarily abdominal)
- Incidence less than 1 in 2000 for patients with diastolic hypertension
- 10% familial
  - More commonly bilateral adrenal or extra-adrenal
- Multiple Endocrine Neoplasia type-2
  - Medullary thyroid carcinoma
  - Hyperparathyroidism
- Releases norepinephrine and epinephrine
  - Dopamine release may indicate malignant transformation
Clinical Features of Pheochromocytoma

- Headache
- Palpitations
- Sweating
- Tremors
- Chest pain
- Weight loss
- Hypertension usually constant
- Orthostatic hypotension may occur in morning
Cardiac Effects of Pheochromocytoma

- Hypertension
- Left ventricular hypertrophy
- Tachycardia induced cardiomyopathy
Diagnosing Pheochromocytoma

- **Screening**
  - 24 hour urine metanephrines
  - Plasma catecholamines

- **Functional**
  - Clonidine will not suppress plasma catecholamines >50%

- **Localizing**
  - CT
  - MRI
  - $^{131}I$ metaiodobenzylguanidine (MIBG)
Treatment of Pheochromocytoma

- $\alpha$ blockade 1-2 weeks before surgery
  - Prazosin
  - Phenoxybenzamine
- Avoid Beta blockers before alpha blockade
  - $\beta_1$ selective (atenolol) preferred
- Phentolamine or nipride used for intraoperative hypertension
- Resection is main treatment
- Metyrosine can be used to decrease catecholamine synthesis in non-operative patients

Braunwald's Heart Disease, 8th ed.
George H. W. Bush

- Developed palpitations while jogging 1991
- Atrial fibrillation with heart rate around 150
- Medically treated
- Ultimately diagnosed with hyperthyroidism due to Grave’s Disease
- Received radioactive iodine ablation

http://www.af.mil/shared/media/photodb/photos/071009-F-2911S-010.jpg
http://www.doctorzebra.com/prez/g41.htm
Schematic representation of thyroid hormone metabolism and the effects of triiodothyronine (T3) on the heart and systemic vasculature. T4 = tetraiodothyronine.
Overview of Thyroid Function

- Thyroid gland produces
  - $T_4 (85\%)$
  - $T_3 (15\%)$
- $T_4$ to $T_3$ conversion in kidney and liver
- $T_3$ mostly responsible for thyroid effects

Braunwald's Heart Disease, 8th ed.
Triiodothyronine (T3) enters the cell and binds to nuclear T3 receptors. The complex then binds to thyroid hormone response elements and regulates transcription of specific genes. Nonnuclear T3 actions on ion channels for sodium (Na+), potassium (K+), and calcium (Ca2+) ions are indicated. AC = adenylyl cyclase; ATPase = adenosine triphosphatase; b-AR = beta adrenergic receptor; cAMP = cyclic adenosine monophosphate; Gs = guanine nucleotide binding protein subunit; Kv = voltage-gated potassium channel; mRNA = messenger RNA; NCX = sodium channel; PLB = phospholamban; TR = T3 receptor protein.
Thyroid Effects on the Heart

- $T_3$ receptors in cardiac myocytes
  - Affects protein synthesis
- Cardiac contractility affected by regulation of calcium cycling through the SERCA-phospholamban system
- Elevated thyroid levels enhance cardiac response to catecholamines
Cardiac Response to T$_3$

**Positively Regulated**
- Alpha-myosin heavy chain
- Sarcoplasmic reticulum Ca$^{2+}$-ATPase
- Na$^+$, K$^+$-ATPase
- Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)
- Atrial and brain natriuretic peptide
- Malic enzyme
- Beta-adrenergic receptor
- Guanine nucleotide–binding protein G$_s$
- Adenine nucleotide transporter 1

**Negatively Regulated**
- Beta-myosin heavy chain
- Phospholamban
- Na$^+$/Ca$^{2+}$ exchanger
- Thyroid hormone receptor alpha1
- Adenylyl cyclase (AC) types V, VI
- Guanine nucleotide–binding protein G$_i$

*Braunwald’s Heart Disease, 8th ed.*
Assessing Thyroid Function

- Thyroid stimulating hormone
  - Decreased in primary hyperthyroidism
  - Increased in primary hypothyroidism

- $T_4$ measurement useful when thyroxine-binding globulin levels are low
  - Nutritional deficiency
  - Hepatic disease

- Antithyroid peroxidase (anti-TPO), antithyroglobulin antibodies useful to diagnose autoimmune thyroid disease
Hemodynamic Effects

- Elevated thyroid levels
  - Decrease systemic vascular resistance
  - Increase heart rate
  - Increase cardiac output
  - Increased blood volume
    - Erythropoiesis mediated by thyroid hormone
    - Increased sodium retention due to lower SVR
Symptoms of Hyperthyroidism

- Palpitations
- Increased heart rate
- Dyspnea
- Exercise intolerance
- Angina
- Pulmonary Hypertension
Atrial Fibrillation and Hyperthyroidism

- Less than 1% of new onset atrial fibrillation is caused by hyperthyroidism
- In patients with hyperthyroidism, 2-20% have atrial fibrillation
Treatment of Hyperthyroid Atrial Fibrillation

- Beta Blockers preferred
- Digoxin can be used
- Anticoagulation based on stroke risk
- Antithyroid medications or radioactive iodine
- Should only try cardioversion when euthyroid state has been restored

Braunwald’s Heart Disease, 8th ed.
“High Output Heart Failure”

- Increased cardiac contractility and output
- Fatigue usually caused due to skeletal muscle weakness
- Increased volume due to renal sodium reabsorption
- Symptoms of right heart failure due to pulmonary hypertension
Tachycardia Induced Cardiomyopathy

- Longstanding hyperthyroidism
- Atrial fibrillation or sinus tachycardia
- Left ventricular dilatation and dysfunction
- Mitral regurgitation
- Control of heart rate can improve cardiac function
Hypothyroidism

- Increased LDL
  - Decreases number of LDL receptors
- Accelerated atherosclerosis?
- Pericardial effusion
  - Decreased lymphatic clearance
  - Improves with thyroid replacement
EKG in Hypothyroidism

- Low voltage
- Bradycardia
- Long QT

Braunwald's Heart Disease, 8th ed.
Treating Patients with Coronary Atherosclerosis and Hypothyroidism

- Is revascularization required before starting thyroid replacement?
- If CAD is stable, start low dose thyroid replacement, titrate slowly every 6-8 weeks
- Patients with risk factors for CAD should be monitored while titrating dose
Screening for Hypothyroidism

- Hypertension
- Hyperlipidemia
- Hypertriglyceridemia
- Coronary atherosclerosis
- Peripheral vascular disease
- Pleural or pericardial effusions
- Myalgias/myositis
Subclinical hypothyroidism

- Mild elevation of TSH
- Cardiac effects
  - Prolonged QT interval
  - Increased risk of heart failure
  - Systolic and diastolic dysfunction
- Vascular effects
  - Increased cholesterol and LDL-c
  - Lower HDL-c
  - Increased peripheral vascular resistance
  - Elevated C-reactive protein
  - Risk of peripheral arterial disease (females)
  - Increased carotid media thickness
Subclinical Hypothyroidism

- Treatment to normalize TSH has been shown to
  - Improve lipids
  - Lower systemic vascular resistance
  - Improve cardiac contractility
  - Improve diastolic function
Elevated TSH and normal FT4
(in patients not receiving thyroid hormone)

Obtain antithyroid antibody titers

Repeat/confirm TSH and FT4 within 1–3 months

TSH 4.5–10 mIU/L

Presence of antibodies and/or goiter and/or symptoms

Favor treatment with T4

Absence of antibodies, goiter, and symptoms

Repeat evaluation for symptoms, goiter, TSH, and FT4 in 4 months

TSH >10 mIU/L

Favor treatment with T4
Subclinical hyperthyroidism

- Low TSH without overt symptoms
- Increased heart rate
- Increased left ventricular mass and hypertrophy
- Diastolic dysfunction
- Atrial arrhythmias
  - Especially atrial fibrillation
Subclinical Hyperthyroidism

- Increases risk of developing atrial fibrillation
- Overall two times mortality risk compared to euthyroid control
  - Increased cardiovascular mortality
- Treatment? Not well defined
  - Reduce thyroid replacement dose
  - Methimazole
TSH <0.45 mIU/L and normal FT4 and FT3 (in patients not receiving thyroid hormone)

TSH <0.1 mIU/L
- Obtain antithyroid antibodies and repeat/confirm TSH, FT4, and FT3 within 2 weeks
- Establish etiology using, as needed, ultrasonography, antibodies, radiiodine uptake, and scanning
- Treatment based on etiology

TSH 0.1–0.45 mIU/L
- Obtain antithyroid antibodies and repeat/confirm TSH, FT4, and FT3 within 1–3 months (within 2 weeks in the presence of arrhythmia or coronary artery disease)
- Monitor TSH, FT4, and FT3 every 6–12 months (every 3 months in the presence of arrhythmia or coronary artery disease)
Amiodarone

- Antiarrhythmic drug used in variety of settings
  - Atrial fibrillation
  - Ventricular tachycardia
- 30% iodine by weight
- Dronedarone similar in effect without iodine content
Acute Amiodarone Effects

- High iodine content inhibits conversion of $T_4$ to $T_3$
- $T_4$ metabolism is decreased in liver
- Serum $T_4$ increased relative to $T_3$
- TSH remains stable
Amiodarone Induced Hypothyroidism

- Total body iodine content increases
- $T_4$ production in thyroid gland is inhibited
- TSH rises
- Hypothyroidism occurs in 15-20% of patients on chronic amiodarone therapy
- Does not depend on dose
- Can occur at any time during therapy
- Treatment with thyroid replacement
- Consider amiodarone cessation
Amiodarone Induced Hyperthyroidism

- Less common
  - 10% in iodine-poor regions
- Type 1
  - Pre-existing thyroid disease, iodine poor diet
  - Mimics autoimmune thyroid disease
- Type 2
  - Thyroiditis
  - Mediated by cytokines (IL-6)
  - Release of thyroglobulin
- Significant overlap between types
Treatment of Amiodarone Induced Hyperthyroidism

- Iodine-131 not effective (high iodine state)
- Prednisone 20-40mg daily
- Methimazole
- Beta blockers
- Thyroidectomy!
- Amiodarone cessation not helpful

Braunwald’s Heart Disease, 8th ed.
Summary

- Acromegaly (GH)
- Cushing’s (increased ACTH, cortisol)
- Conn’s syndrome (hyper-aldosteronism)
- Addison’s disease (hypo-aldosteronism)
- Hyperparathyroidism (increased Ca^{2+})
- Hypocalcemia
- Pheochromocytoma (norepinephrine, epinephrine)
- Hyperthyroidism
- Hypothyroidism
- Subclinical hypothyroidism and hyperthyroidism
- Amiodarone effects on thyroid function
References