Thyroid Disease and the Heart

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Disclosures

Dr Klein has no conflicts to disclose
In 1786, Caleb Hillier Parry described a woman with goiter and palpitations, whose "each systole shook the whole thorax".

He was the first to suggest "the notion of some connexion (sic) between the malady of the heart and the bronchocoele" (Parry CH, 1815, Crutwell, Bath).
Cardiovascular Symptoms of Hyperthyroidism

- Palpitations
- Atrial Fibrillation
- Exercise Intolerance
- Systolic Hypertension
- Angina
- Peripheral Edema
- Congestive Heart Failure
Cardiovascular Symptoms of Hyperthyroidism

- Palpitations
- Atrial Fibrillation
- Exercise Intolerance
- Systolic Hypertension
- Angina
- Peripheral Edema
- Congestive Heart Failure
Thyroid Hormone and the Cardiovascular System

Thyroid hormone mediated changes may occur via

• Direct effects on the heart
• Effects on the peripheral circulation and then indirectly on the heart
Sites of Action of Thyroid Hormone on the Heart and Cardiovascular System

Klein and Danzi, In: *The Thyroid* 2012
## Cardiovascular Changes With Thyroid Disease

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hyper-</th>
<th>Hypothyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR (dyne•s•cm⁻⁵)</strong></td>
<td>1500-1700</td>
<td>700-1200</td>
<td>2100-2700</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>72-84</td>
<td>88-130</td>
<td>60-80</td>
</tr>
<tr>
<td><strong>% EF</strong></td>
<td>60%</td>
<td>&gt;60%</td>
<td>&lt;60%</td>
</tr>
<tr>
<td><strong>IVRT (msec)</strong></td>
<td>60-80</td>
<td>25-40</td>
<td>&gt;80</td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
<td>5.8</td>
<td>&gt;7.0</td>
<td>&lt;4.5</td>
</tr>
<tr>
<td><strong>(L/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood volume</strong></td>
<td>100</td>
<td>105.5</td>
<td>84.5</td>
</tr>
<tr>
<td><strong>(% normal)</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Cellular Mechanisms of Thyroid Hormone Action on the Heart

Thyroid Hormone Responsive Cardiac Genes

Positive Regulation
- Myosin heavy chain-α
- SR Calcium ATPase (SERCA2)
- β1 Adrenergic receptor
- GTP binding protein Gs
- Na⁺ / K⁺ – ATPase
- Voltage-gated K⁺ channels (Kv 1.5, 4.2, 4.3)

Negative Regulation
- MHC-β
- Phospholamban
- Adenylyl cyclases V, VI
- T₃ Receptor α1
- Na⁺ / Ca²⁺ exchanger (NCX)

# Left Ventricular Diastolic Function in Hyperthyroidism

<table>
<thead>
<tr>
<th></th>
<th>I Untreated Graves</th>
<th>II Beta-Blockade</th>
<th>III Euthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>73</td>
<td>95</td>
<td>81</td>
</tr>
<tr>
<td>Diastolic Filling (ms)</td>
<td>225</td>
<td>173</td>
<td>201</td>
</tr>
<tr>
<td>Diastolic Compliance</td>
<td>156</td>
<td>97</td>
<td>122</td>
</tr>
<tr>
<td>Relaxation Time</td>
<td>58</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- I: Untreated Graves
- II: Beta-Blockade
- III: Euthyroid
Isovolumic Relaxation Times

ISOVOLUMIC RELAXATION TIME (msec)

Control (N = 10)  Hyperthyroid (N = 9)  Propranolol  Euthyroid
Mechanisms of Heart Failure in Patients with Thyrotoxicosis

1) Exacerbation of underlying heart disease

2) Rate related left ventricular dysfunction

3) Right ventricular overload- Pulmonary Hypertension
Treatment of the Thyrotoxic Cardiac Patient

1) Beta-adrenergic Blockade
2) Radioiodine
3) Antithyroid Drugs
4) Calcium Channel Blockers
5) Anticoagulation
Changes in Subclinical Hyperthyroidism

1) Sinus Tachycardia
2) Unexplained Weight Loss
3) Atrial Fibrillation
4) Cardiac Hypertrophy
5) Enhanced Cardiac Contractility
6) Skeletal Muscle Weakness
Incidence of Atrial Fibrillation vs TSH

Sawin et al., 1994
Hypothyroidism and the Heart

- Hypertension
- Elevated Cholesterol
- Long Q-T Syndrome
- Serum CK
- Coagulopathy
- Response to Treatment
### Initial Laboratory Data and Response to Thyroid Hormone Replacement Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>THR Rx</th>
<th>Cholesterol mg/dl</th>
<th>CK U/L</th>
<th>LDH U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Before</td>
<td>322</td>
<td>943</td>
<td>512</td>
<td></td>
</tr>
<tr>
<td></td>
<td>During</td>
<td>157</td>
<td>52</td>
<td>125</td>
</tr>
<tr>
<td>2. Before</td>
<td>265</td>
<td>2650</td>
<td>760</td>
<td></td>
</tr>
<tr>
<td></td>
<td>During</td>
<td>124</td>
<td>67</td>
<td>123</td>
</tr>
<tr>
<td>Reference Range</td>
<td>&lt;200</td>
<td>&lt;90</td>
<td>&lt;220</td>
<td></td>
</tr>
</tbody>
</table>
DIASTOLIC FUNCTION AND THYROID DISEASE

Klein I. In: Braunwald’s Heart Disease. 8th ed., 2007
Cardiovascular Risk Associated with Hypothyroidism

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Response to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>++</td>
</tr>
<tr>
<td>Diastolic hypertension</td>
<td>+</td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunction</td>
<td>++</td>
</tr>
<tr>
<td>Impaired endothelial mediated vasodilatation</td>
<td>++</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>+</td>
</tr>
<tr>
<td>Elevated serum homocysteine</td>
<td>+</td>
</tr>
<tr>
<td>Elevated C-reactive protein</td>
<td>–</td>
</tr>
</tbody>
</table>

Danzi and Klein, *Current Hypertension Reports* 2003
ASCVD and Hypothyroidism

Effect of treatment

1,503 patients

400 (at Risk)

90 Clinical ASCVD

55 Patients with angina before Rx

35 Onset of angina after Rx

ASCVD and Hypothyroidism

Effect of treatment

Patients with angina before Rx

21 (clinically improved)

55

25 (no change)

9 (worse)

ASCVD and Hypothyroidism

Effect of treatment

Onset of angina after Rx

6 (1st month) → 35 → 23 (>1 year)

6 (1st year)

Subclinical Hypothyroidism

- **Definition:**
  - TSH 5–20
  - Normal free $T_4$

- **Synonyms:**
  - Compensated hypothyroidism
  - Decreased thyroid reserve
  - Mild hypothyroidism/mild thyroid failure
## Changes in Cardiovascular Function in Mild Hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypothyroid</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre</td>
<td>Post</td>
<td></td>
</tr>
<tr>
<td>FS (%)</td>
<td>36 +/- 4</td>
<td>36 +/- 4</td>
<td>39 +/- 7</td>
<td></td>
</tr>
<tr>
<td>CO (mL)</td>
<td>5223 +/- 960</td>
<td>5300 +/- 1260</td>
<td>5806 +/- 1760</td>
<td></td>
</tr>
<tr>
<td>SVR (dyn/sec•cm⁻⁵)</td>
<td>1460 +/- 340</td>
<td>1470 +/- 370</td>
<td>1361 +/- 383</td>
<td></td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>84 +/- 8</td>
<td>94 +/- 13</td>
<td>77 +/- 15</td>
<td></td>
</tr>
<tr>
<td>EDRF (%)</td>
<td>503%</td>
<td>358%</td>
<td>446%</td>
<td></td>
</tr>
</tbody>
</table>

Risk of MI and Atherosclerosis


For Myocardial Infarction:
- Euthyroid: 1.0
- Subclinical hypothyroid: 2.3
- Subclinical hypothyroid and antibodies: 3.1

For Aortic Atherosclerosis:
- Euthyroid: 1.0
- Subclinical hypothyroid: 1.7
Carotid intima-media thickness in subclinical hypothyroidism and the response to treatment

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.92±1.05</td>
<td>4.30±0.83</td>
<td>0.018</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.91±0.37</td>
<td>2.41±0.22</td>
<td>0.024</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>11.48±4.70</td>
<td>1.26±3.30</td>
<td>0.015</td>
</tr>
<tr>
<td>Intima-media thickness (mm)</td>
<td>0.67±0.11</td>
<td>0.60±0.10</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Treatment of subclinical hypothyroidism and cardiovascular morbidity and mortality – analysis of the United Kingdom General Practitioner Research Database
S. S. Razvi$^{1,2,*}$, S. H. Pearce$^2$
$^1$Department of Endocrinology, Gateshead Health NHS Foundation Trust, Gateshead, $^2$Institute of Human Genetics, NEWCASTLE UNIVERSITY, Newcastle upon Tyne, United Kingdom

- 2809 females from the General Practitioner Research Data Base in the UK were analyzed with regard to subclinical hypothyroidism and its treatment.
- 50% of the overall population was treated with L-T$_4$.
- When compared to non-treated patients, L-T$_4$ treatment led to a significant decrease in cardiovascular morbidity and mortality.

Conclusion: L-T$_4$ treatment had the beneficial effect to reduce cardiovascular events and all cause mortality in adults with subclinical hypothyroidism.
Thank you for your attention

Questions?