Nikolaus A. Haas

Endocrine Aspects of Cardiac Intensive Care
- Thyroid Dysfunction -

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Northrhine-Westphalia

Universitätsklinik der
Ruhr-Universität Bochum
children – thyroid hormones – bypass surgery

Questions:

- has cardiac surgery impact on thyroid function?

1. If so – is this relevant?

2. What are the effects?

3. What can we do – has been done...

4. Can we recommend a form of treatment?
Normal actions of thyroid hormones...

- T3 is 5 x more potent
- T4 is 100 x more blood conc
- 80% T3 produced from T4
  - mainly in the liver

- T3 actions ↑ contractility
- improved diastolic relaxation
- ↑ heart rate and automaticity
- ↓ afterload - PVR & SVR
- ↑ coronary blood flow

- increases O2 consumption
- protein synthesis
- CHO, lipid & vit metabolism

“optimal drug”
Stress reaction, Sepsis, SIRS, cardiopulmonary bypass, etc. ->

- impact on thyroid hormones
- absence of primary thyroid disease

Non thyroidal illness or Sick euthyroid syndrome - SES
Sick euthyroid syndrome - SES

**SES type 1:** Decrease in total T3
decrease in fT3
TSH low
normal T4

**SES type 2:**
decrease in total T3
decrease in fT3
decrease in total T4
decrease in fT4
low TSH

**low T3 syndrome**

**low T4 syndrome**
Sick euthyroid syndrome - SES

Inflammatory cytokines ++++ → SES ++++

Endotoxin
Steroids
Hypoxia
Cytokines
Sepsis
Etc.

Liver
5’ deionidase (Se)

T4
-------------------→ T3
-------------------→ reverse T3

TSH-response to low T3 → impaired
TSH response tom TRH → impaired

Thyroid-hormone binding activity → impaired
Thyroid binding globulin levels → decreased

T3- synthesis in the liver

5’- mono-iodinase activity → decreased

Impaired de-iodination

Increase rT3 production
Cytokines – T3

McMahon 2003; Thyroid 13:301-304
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Rothwell et al.</td>
<td>TSH levels predict outcome in critical illness</td>
</tr>
<tr>
<td>1993</td>
<td>Jarek et al.</td>
<td>TSH, T3, T4 predict outcome for ICU patients</td>
</tr>
<tr>
<td>1995</td>
<td>Rothwell &amp; Lawler</td>
<td>APACHE II plus endocrine parameters better than APACHE II</td>
</tr>
<tr>
<td>1996</td>
<td>Koh et al.</td>
<td>Thyroid and Adrenal function in ICU patients</td>
</tr>
<tr>
<td>2001</td>
<td>Parle et al.</td>
<td>Thyroid hormone strong predictor of mortality</td>
</tr>
<tr>
<td>2003</td>
<td>Iervasi et al.</td>
<td>Low T3-syndrome – predictor of death</td>
</tr>
<tr>
<td>2005</td>
<td>Chinga-Alayo et al.</td>
<td>Thyroid hormone levels improve prediction of mortality in ICU patients</td>
</tr>
</tbody>
</table>

573 adult cardiac patients
Thyroid hormone profiles
1 year follow-up
Cumulative cardiac death

Low- T3- syndrome
Strong predictor of death
Hazard ratio 0,395, p=0,0003
Low fT3 in NYHA III- IV
Higher fT3 in NYHA I- II

Iervasi 2003; Circulation 107:708-713
Thyroid hormone levels improve prediction of mortality in ICU patients

113 patients
3 hospitals
Prospective
T3 and other hormones...

Optimized logistic regression model
APACHE plus
TSH plus
fT3

Chinga-Alayo 2005; Int Care Med 31:1356-61
## Sick euthyroid syndrome – children ?

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Description</th>
<th>SES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Zucker et al.</td>
<td>Critically ill pediatric patients</td>
<td>SES +</td>
</tr>
<tr>
<td>1986</td>
<td>Uzel et al.</td>
<td>Paediatric infections</td>
<td>SES +</td>
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<tr>
<td>1991</td>
<td>Tahirovic et al.</td>
<td>Hepatitis</td>
<td>SES +</td>
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<tr>
<td>1991</td>
<td>Tahirovic et al.</td>
<td>Diabetic ketoacidosis</td>
<td>SES +</td>
</tr>
<tr>
<td>1994</td>
<td>Anand et al.</td>
<td>PICU patients</td>
<td>SES +</td>
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<tr>
<td>1998</td>
<td>Szychowska et al.</td>
<td>Paediatric meningitis</td>
<td>SES +</td>
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<tr>
<td>2001</td>
<td>Mohn et al.</td>
<td>Hodgkin disease</td>
<td>SES +</td>
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<tr>
<td>2004</td>
<td>Matsumoto et al.</td>
<td>Paed. Bone marrow transplant</td>
<td>SES +</td>
</tr>
<tr>
<td>2004</td>
<td>Yildizdas et al</td>
<td>Sepsis</td>
<td>SES +</td>
</tr>
<tr>
<td>2005</td>
<td>denBrinker et al.</td>
<td>Meningococceal disease</td>
<td>SES +</td>
</tr>
<tr>
<td>1985</td>
<td>Franklin et al.</td>
<td>Sick Neonates</td>
<td>SES +</td>
</tr>
<tr>
<td>1990</td>
<td>Fisher</td>
<td>prematures and sick neonates</td>
<td>SES +</td>
</tr>
<tr>
<td>1994</td>
<td>Van den Berghe et al.</td>
<td>Dopamine infusion -&gt; partial hypopituitarism</td>
<td>SES +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aggravates SES</td>
<td></td>
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</tbody>
</table>
Sick euthyroid syndrome – cardiac surgery?

Cardiopulmonary bypass

- SIRS
  leucocyte count ++
  leucocyte activation
  oxidative stress
  release of cytokines
  [IL6, IL8, TNF alpha, etc...]

hypothermia
Low cardiac output
hypoperfusion
steroids ?
filtration ? MUF

dopamine use

SES
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Study Description</th>
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<tbody>
<tr>
<td>1989</td>
<td>Allen et al.</td>
<td>SES after CBP correlated to severity of illness</td>
</tr>
<tr>
<td>1993</td>
<td>Belgorosky et al.</td>
<td>SES for some days after CBP</td>
</tr>
<tr>
<td>1994</td>
<td>Mainwarning et al.</td>
<td>Neonates at risk for SES</td>
</tr>
<tr>
<td>1994</td>
<td>Mainwarning et al.</td>
<td>Fontan patients</td>
</tr>
<tr>
<td>1995</td>
<td>Murzi et al.</td>
<td>Prolonged decrease in thyroid hormones</td>
</tr>
<tr>
<td>1996</td>
<td>Saatvedt, Lindberg</td>
<td>Correlation SES and IL6</td>
</tr>
<tr>
<td>1997</td>
<td>Bettendorf et al.</td>
<td>Transient hypothyroidism SES-2, correlation to morbidity, neonates at risk</td>
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<td>1998</td>
<td>Saatvedt et al.</td>
<td>SES after CBP</td>
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<tr>
<td>2002</td>
<td>Bartkowsky et al.</td>
<td>SES after CBP</td>
</tr>
<tr>
<td>2003</td>
<td>McMahon et al.</td>
<td>SES linked to IL-6 levels</td>
</tr>
<tr>
<td>2004</td>
<td>Lynch et al.</td>
<td>Thyroid binding globulin decreased</td>
</tr>
<tr>
<td>2005</td>
<td>Plumpton, Haas</td>
<td>Neonates and infants at risk, correlation to morbidity, correlation to bypass</td>
</tr>
</tbody>
</table>
Effect of bypass on fT3- levels

Plumpton 2005; Int Care Med. 31:581-587

Klinik für Angeborene Herzfehler

Herz- und Diabeteszentrum
Nordrhein-Westfalen
Universitätsklinik der Ruhr-Universität Bochum
effect of fT3 levels on ventilation

Plumpton 2005; Int Care Med. 31:581-587
TSH-recovery and ventilation

Plumpton 2005; Int Care Med. 31:581-587
Thyroid And Catecholamine support

Figure 1
FT₄ levels over time – comparison between groups.

Dagan 2006; Pediatric Anesthesia 16:538-542
Sick euthyroid syndrome - other factors?

**Dopamine**

Healthy subjects - directly inhibits pituitary function
- reduction of prolactin, FSH, LH, growth hormone, etc.
- sustained suppressed TSH release
- impaired response of TSH to TRH

ICU patients - aggravated effect on TSH suppression
- children at special risk
- SES-2 in meningococcal disease
- neonates suffer general hypopituitarism

Dopamine induces SES

Goldsmith 1979; J Histochem Cytochem 27:1205-1207
Kaptein 1980; J Clin Endocrinol Metab 51:488-491
Leebaw 1978; J Clin Endocrinol Metab 47:480-487
Kaptein 1980; J Clin Endocrinol Metab 51:387-393
Vanden Berghe 1996; Crit Care Med 24:1580-90
Vanden Berghe 1994; Crit Care Med 22:1747-1753
denBrinker 2005, Int Care Med 31: 970-976
Sick euthyroid syndrome - other factors?

Iodinated antiseptics

Percutaneous absorption of iodine

- especially in infants and neonates
- dose dependent effect (redo-sternotomy)
- hypothyroidism (Wolff-Chiakoff effect)
- delayed sternal closure
- prematures at special risk

Markou 2001; Thyroid 11:501-510
Pyati 1977; J Pediatr 91:825-828
Chabrolle 1978; Arch Dis Child 53:495-498
Linder 1997; Arch Dis Child Fet Neonat Ed 77:F239-40
Brogan 1997; Crit Care Med 25:1583-1587
Sick euthyroid syndrome - other factors?

Amiodarone

- Highly effective antiarrhythmic drug
- widely used for common postoperative arrhythmias (i.e. JET)
- High content of molecular Iodine
- Directly affects thyroid function (up to 24%)
  - hypothyroidism
  - hyperthyroidism
- Structurally similar to thyroid hormones
- Competitive inhibition of 5´ mono-deiodinase (T4-T3-conversion)

SES ++++

Plumpton 2005; Cardiol Young 15:13-18
Martino 2001; Endocrin Rev 22:240-254
Costigan 1986, Pediatrics 77:703-708
Celiker 1997; Turk J Pediatr 39:219-225
Guccione 1990; J Am Coll Cardiol 15:1118-1124
Intermediate summary - cardiopulmonary bypass and sick euthyroid syndrome

<table>
<thead>
<tr>
<th>Cardiopulmonary bypass</th>
<th>induces SIRS</th>
</tr>
</thead>
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<tr>
<td></td>
<td>induces SES</td>
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<tr>
<td></td>
<td>SIRS correlates to SES</td>
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</tbody>
</table>

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<thead>
<tr>
<th>SES</th>
<th>impact on outcome</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>impact on morbidity</td>
</tr>
</tbody>
</table>

| SES detected? | yes in all children after cardiac surgery |

<table>
<thead>
<tr>
<th>Children at risk:</th>
<th>infants and neonates</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>long bypass times</td>
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</table>

| Other factors     | dopamine               |
|                   | amiodarone             |
|                   | iodinated antiseptics  |

-> Treatment?
Sick euthyroid syndrome - treatment

Effects of T3-treatment in adults:

Smaller series:

- improved haemodynamics
- reduced systemic resistance
- increased cardiac output
- positive inotropy without increase in oxygen consumption

-- low T3 – increased rate of atrial fibrillation

Sabatino 2002; J Endocrinol 175:577-586
Dillmann 2002; Thyroid 12:447-452
Sick euthyroid syndrome - treatment in adults

low T3
T3 supplementation

-> increased rate of atrial fibrillation (CABG)

-> reduced rate of atrial fibrillation (CABG)


T3-supplementation
- lower inotropic requirement
- less diuretics
- improved CO
- improved stroke volume
- reduced SVR and PVR
- improved survival

T3- treatment beneficial

Novitzky 1996; Cardiology 87:509-515
Sirlak 2004; Eur J Cardiothorac Surg 26:720-726
## Sick euthyroid syndrome - treatment in children

<table>
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<tr>
<th>Category</th>
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<tbody>
<tr>
<td><strong>Rescue therapy</strong></td>
<td>- children with failed conventional treatment</td>
</tr>
<tr>
<td></td>
<td>- 5/7 survived</td>
</tr>
<tr>
<td></td>
<td>- continuous improvement of haemodynamics 48-96 hrs</td>
</tr>
<tr>
<td></td>
<td>(Carrel 2002; Eur J Heart Fail 4:577-582)</td>
</tr>
<tr>
<td><strong>Vasodilatation</strong></td>
<td>- after T3 in children after bypass surgery</td>
</tr>
<tr>
<td></td>
<td>(Bialowski 1998; Cardiol Young 8:139-140)</td>
</tr>
<tr>
<td><strong>T3 supplementation</strong></td>
<td>- Decreased SVR &gt; 25%</td>
</tr>
<tr>
<td></td>
<td>- increased CO &gt; 20%</td>
</tr>
<tr>
<td></td>
<td>- resolves metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>- positive impact on JET</td>
</tr>
<tr>
<td></td>
<td>(Chowdhury 1999; J Cardiol 84:1107-1109)</td>
</tr>
<tr>
<td><strong>Low T3 levels</strong></td>
<td>- increased inotropic requirements (neonates)</td>
</tr>
<tr>
<td></td>
<td>(Chowdhury 2001; J Thorac Cardiovasc Surg 122:1023-1025)</td>
</tr>
<tr>
<td><strong>T3-treatment</strong></td>
<td>- prevents low-T3 status</td>
</tr>
<tr>
<td></td>
<td>- elevates heart rate</td>
</tr>
<tr>
<td></td>
<td>- improves CO, reduces SVR</td>
</tr>
<tr>
<td></td>
<td>(Portman 2000; J Thorac Cardiovasc Surg 120:604-608)</td>
</tr>
</tbody>
</table>
75 patients
28 randomized 14/14
Administration is safe
Increased T3 levels
Mixed ven Sats + 17%
Less inotropic score

Randomised Study  
$n = 40 \ (20/\ 20)$

Change in echo parameters of cardiac function over time

**Figure 3:** Postoperative changes of cardiac index (% change from postoperative baseline) after first infusion of study drug. Box plots represent 10th, 25th, 50th, 75th and 90th percentiles.

Bettendorf 2000, Lancet 356:529-34
Mean overall change in echo parameters of cardiac function all subjects

Bettendorf 2000, Lancet 356:529-34
Improved echo parameters of cardiac function in those with longer CPB

Bettendorf 2000, Lancet 356:529-34
Effect of bypass on fT3- levels

Plumpton 2005; Int Care Med. 31:581-587

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Sick euthyroid syndrome - treatment in children

Mackie et al 2005: RCT
42 Norwood patients or IAA + VSD
T3 supplementation

Results: higher systolic BP
better fluid balance
improved CO
no side effects

Mackie 2005; J Thorac Cardiovasc Surg 130:810-816
Figure 2. Systolic blood pressure (A) was higher in the T₃ group (P < .001) during the early postoperative period, as was mean blood pressure (B) (P = .02). Error bars represent 95% confidence intervals.

Mackie 2005; J Thorac Cardiovasc Surg 130:810-816
Sick euthyroid syndrome - treatment in children

TRICC-trial
- multicenter RCT
- 200 children
- bypass surgery
- T3 supplementation
- safety, efficacy

- enrolment ended June 2007
- results November 2007
SES treatment with intravenous T3 - side effects?

Potentially thyreotoxicosis - not seen yet

6 hrs intravenous T3 in CABG patients - no side effects
Increase in heart rate, CO, lower SVR

Patients with heart failure - no ischemia or arrhythmia

Pre-term infants (< 28 weeks) iv T3 - no cardiovascular side effects
Effect seen for 2 days

Children after brain death - improvement of hemodynamic stability

Severe low CO (paeds and adults) iv T3 - no side effects

Cardiac children - no side effects reported

Doses used:

- **bolus:** 0,5 – 2 – 3,5 µg/kg bw over 1 hr
- **repeat boluses:** 1-2 µg/kg bw
- **i.v. T3 continuous infusion:** 0,06-0,1 – 0,4 – 0,7 µg/kg/hr
- **duration:** 1-5 days
Summary

Children – thyroid hormones – bypass surgery

1. Cardiac surgery induces SES
   - Patients at risks are neonates and
   - Especially long bypass times, DHCA, dopamine, etc.

2. SES – mainly SES-2 has negative impact on outcome

3. Severity of SES correlates to severity of morbidity
   - inotropic requirements
   - haemodynamics (SVR, PVR, heart rate)
   - acidosis
   - urine output
   - LO ventilation
   - LOS

4. T3 supplementation can reduce/treat SES in children

5. T3-treatment without negative side effects

6. T3-therapy has positive effect on morbidity and outcome
Conclusion
Children – thyroid hormones – bypass surgery

Should we treat our children with T3 after cardiac surgery?

Yes

- All children less 1 year of age
- All children with long bypass times
- All children with DHCA
- For about 5-7 days
- those receiving dopamine
- Results TRICC trial pending

Thank you
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Klinik für Angeborene Herzfehler

Parle 2001; Lancet:358:861-865
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