Nikolaus A. Haas

Endocrine Aspects of Cardiac Intensive Care
- Thyroid Dysfunction -

Heart and Diabetes Centre
Northrhine-Westphalia

Universitätsklinik der
Ruhr-Universität Bochum
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 to 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>Study Details</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>Condition</th>
<th>Reference</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>
</tr>
<tr>
<td>1991</td>
<td>Tahirovic et al.</td>
<td>Hepatitis</td>
<td>SES +</td>
</tr>
<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>
</tr>
<tr>
<td>1998</td>
<td>Szychowska et al.</td>
<td>Paediatric meningitis</td>
<td>SES +</td>
</tr>
<tr>
<td>2001</td>
<td>Mohn et al.</td>
<td>Hodgkin disease</td>
<td>SES +</td>
</tr>
<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 aggravates SES</td>
<td></td>
</tr>
</tbody>
</table>

**Herz- und Diabeteszentrum Nordrhein-Westfalen**

Universitätsklinik, Ruhr-Universität Bochum

**Klinik für Angeborene Herzfehler**
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
Sick euthyroid syndrome – paediatric cardiac surgery?

Studies.....?

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

Plumpton 2005; Int Care Med. 31:581-587
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
FT$_4$ 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 meningococceal 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

**SES +++++**

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

Cardiopulmonary bypass - induces SIRS
- induces SES
- SIRS correlates to SES

SES - impact on outcome
- impact on morbidity

SES detected ? - yes in all children after cardiac surgery

Children at risk: - infants and neonates
- long bypass times

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

Rescue therapy:
- children with failed conventional treatment
- 5/7 survived
- continuous improvement of haemodynamics 48-96 hrs
(Carrel 2002; Eur J Heart Fail 4:577-582)

Vasodilatation
- after T3 in children after bypass surgery
(Bialowski 1998; Cardiol Young 8:139-140)

T3 supplementation
- Decreased SVR > 25%
- increased CO > 20%
- resolves metabolic acidosis
- positive impact on JET
(Chowdhury 1999; J Cardiol 84:1107-1109)

Low T3 levels
- increased inotropic requirements (neonates)
(Chowdhury 2001; J Thorac Cardiovasc Surg 122:1023-1025)

T3-treatment
- prevents low-T3 status
- elevates heart rate
- improves CO, reduces SVR
(Portman 2000; J Thorac Cardiovasc Surg 120:604-608)
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

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 with CPB > 1.8 hr. (Bettendorf 2000, Lancet 356:529-34)
Effect of bypass on fT3- levels

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

Klinik für Angeborene Herzfehler
Sick euthyroid syndrome - treatment in children

Mackie et al 2005: RCT
42 Norwood patients or I AA + 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?**

<table>
<thead>
<tr>
<th>Potentially thyreotoxicosis</th>
<th>- not seen yet</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hrs intravenous T3 in CABG patients</td>
<td>- no side effects increase in heart rate, CO, lower SVR</td>
</tr>
<tr>
<td>Patients with heart failure</td>
<td>- no ischemia or arrhythmia</td>
</tr>
<tr>
<td>Pre-term infants (&lt; 28 weeks) iv T3</td>
<td>- no cardiovascular side effects effect seen for 2 days</td>
</tr>
<tr>
<td>Children after brain death</td>
<td>- improvement of hemodynamic stability</td>
</tr>
<tr>
<td>Severe low CO (paeds and adults) iv T3</td>
<td>- no side effects</td>
</tr>
<tr>
<td>Cardiac children</td>
<td>- no side effects reported</td>
</tr>
</tbody>
</table>

**Doses used:**

| bolus: | 0.5 – 2 – 3.5 µg/kg bw over 1 hr |
| repeat boluses: | 1-2 µg/kg bw |
| 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