Nikolaus A. Haas

Endocrine Aspects of Cardiac Intensive Care - Thyroid Dysfunction -

Heart and Diabetes Centre
Northrhine-Westphalia

Universitätsklinik der
Ruhr-Universität Bochum

Herz- und Diabeteszentrum
Nordrhein-Westfalen
Universitätsklinik der Ruhr-Universität Bochum

Klinik für Angeborene Herzfehler

? 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

"optimal drug"

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

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

low T3 syndrome

SES type 2:

decrease in total T3
decerase in fT3
decrease in total T4
decerease in fT4
low TSH

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

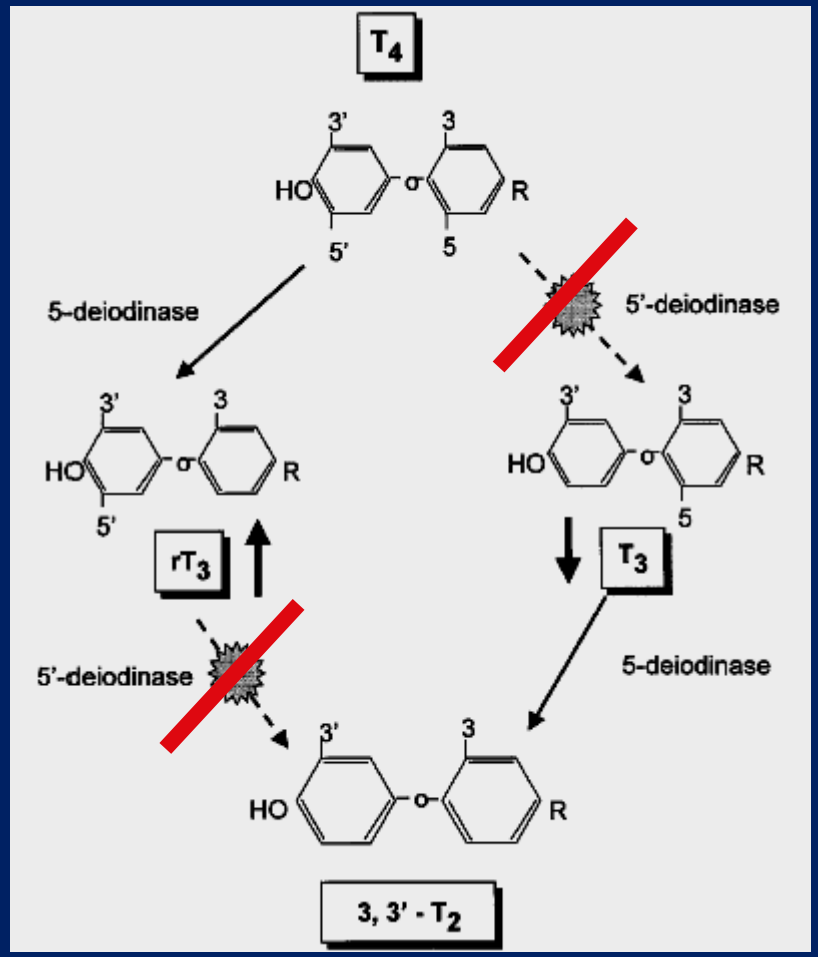
Berger et al. Int Care Med. 1996;22:575-581, Kelly Altern Med Rev 2000;5:306-333
Papanicolaou Rev Endocr Metab Dis 2000;1:43-48, Peeters J Clin Endocrinol Metab 2003;88:3202-11

T3- synthesis in the liver

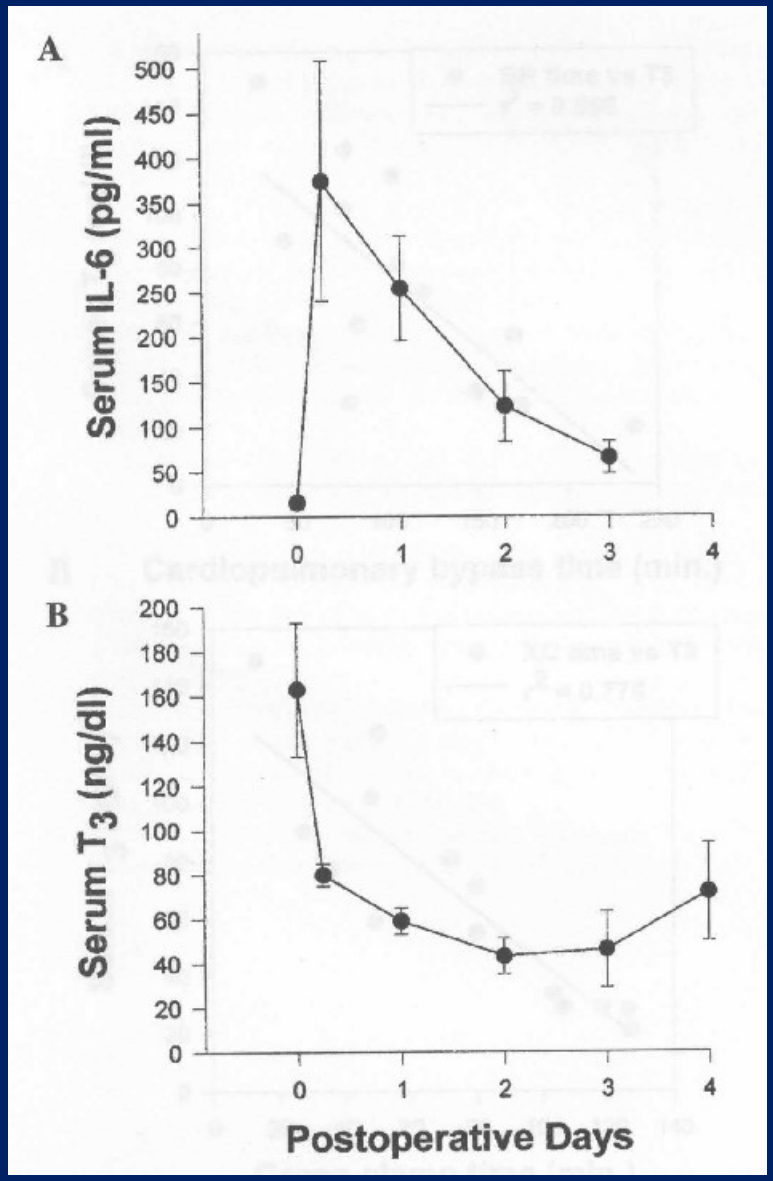
5'- mono- iodinase activity
→ decreased

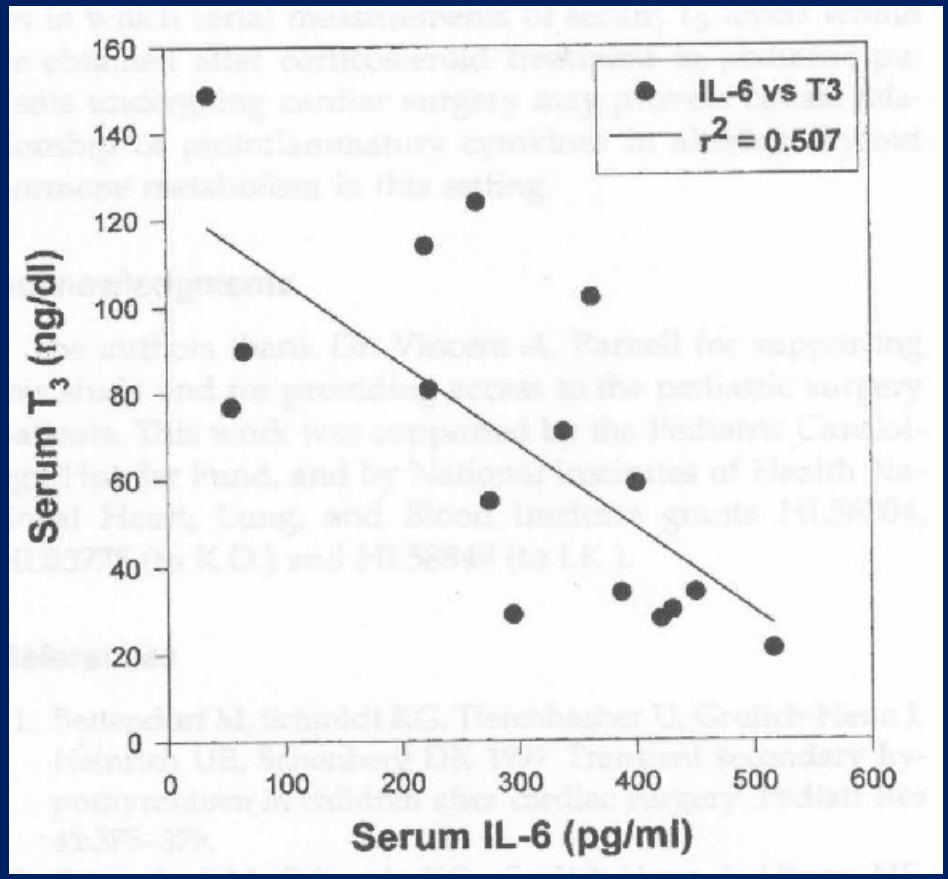
Impaired de- iodination

increase rT3 production



Cytokines – T3



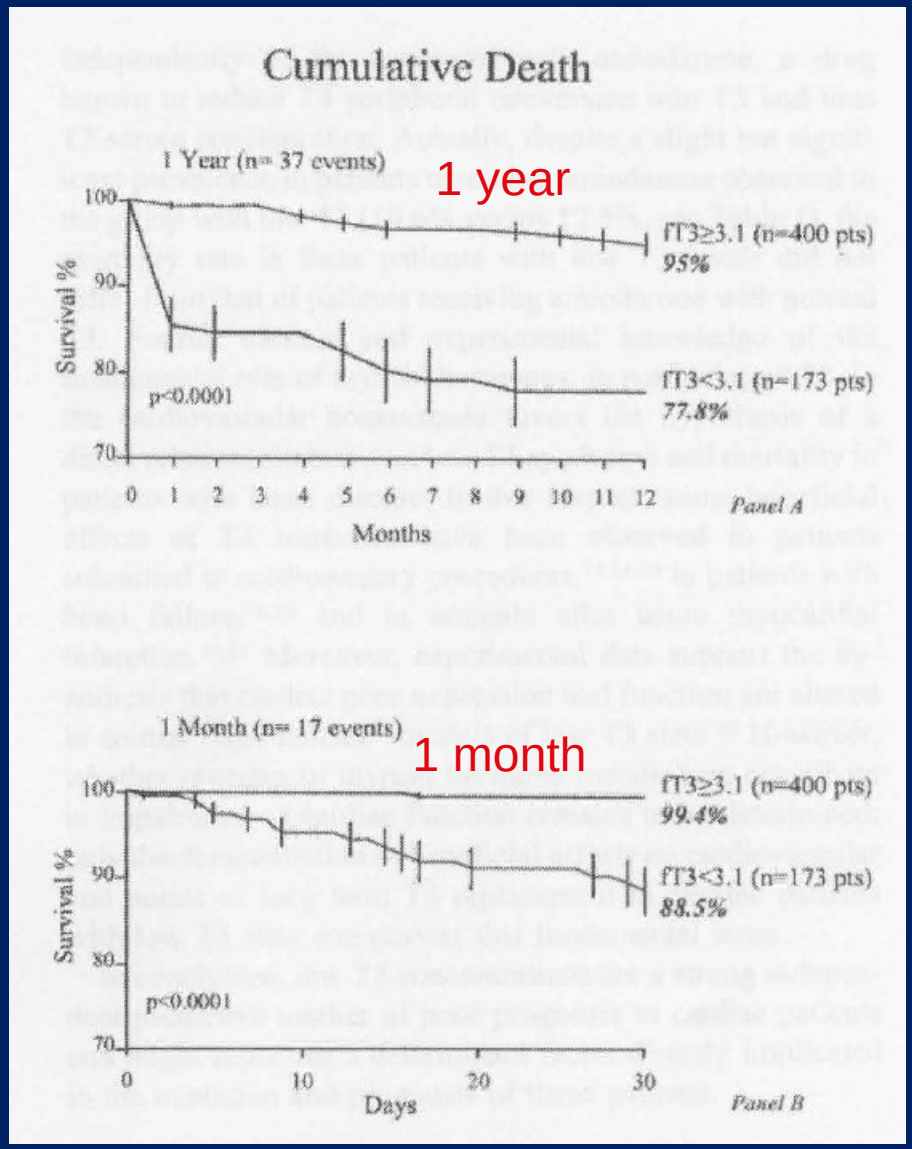


McMahon 2003; Thyroid 13:301- 304

Sick euthyroid syndrome – prognosis ?

1993	Rothwell et al.	TSH levels predict outcome in critical illness
1993	Jarek et al.	TSH, T3, T4 predict outcome for ICU patients
1995	Rothwell&Lawler	APACHE II plus endocrine parameters better than APACHE II
1996	Koh et al.	Thyroid and Adrenal function in ICU patients
2001	Parle et al.	Thyroid hormone strong predictor of mortality
2003	Iervasi et al.	Low T3-sysndrome – predictor of death
2005	Chinga-Alayo et al.	Thyroid hormone levels improve prediction of mortality in ICU patients

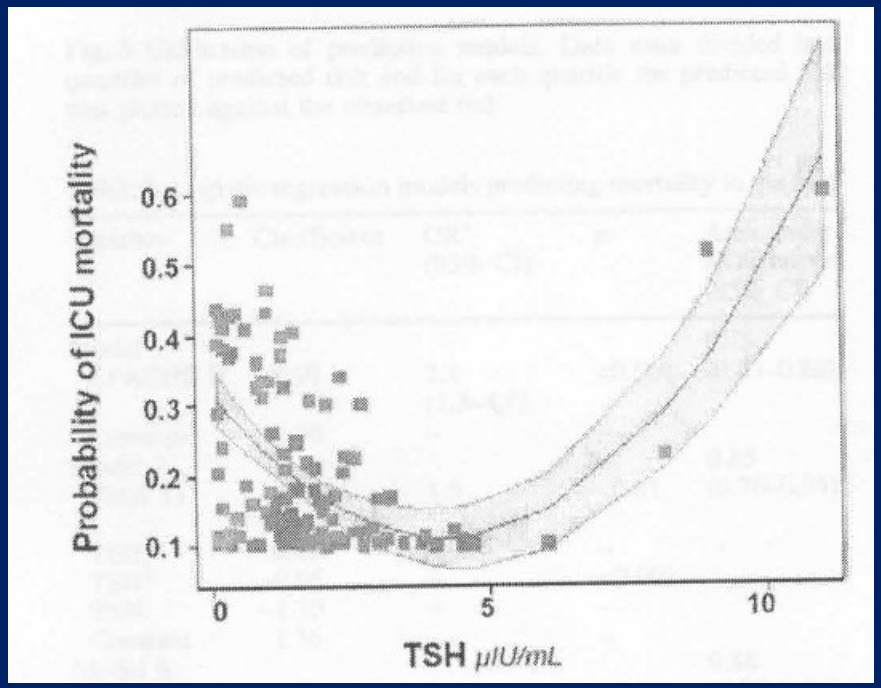
Rothwell 1995; Crit Care Med 23:78-83, Jarek 1993; Crit Care Med 21:543-550
Koh 1996; Ann AcadMed Singap 25:808-815, Chinga-Alayo 2005;Int Care Med 31:1356-61
Iervasi 2003;Circulation 107:708-13, Parle 2001; Lancet:358:861-865



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

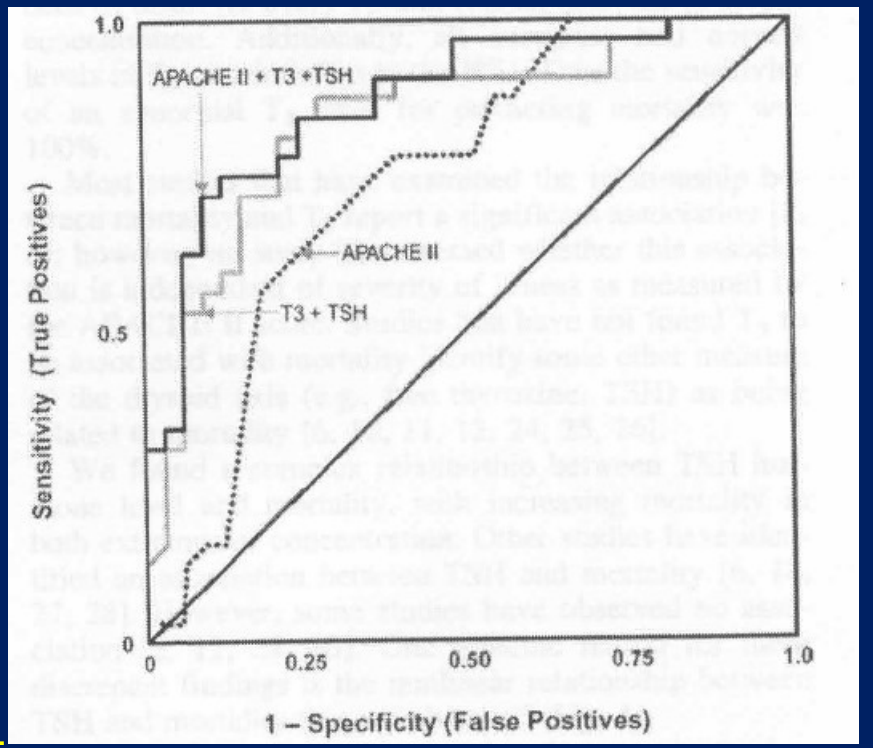
Low-T3-syndrome
Strong predictor of death
Hazard ratio 0,395, p=0,0003
Low fT3 in NYHA III-IV
Higher fT3 in NYHA I-II

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 ?

1985	Zucker et al.	Critically ill pediatric patients	SES +
1986	Uzel et al.	Paediatric infections	SES +
1991	Tahirovic et al.	Hepatitis	SES +
1991	Tahirovic et al.	Diabetic ketoacidosis	SES +
1994	Anand et al.	PICU patients	SES +
1998	Szychowska et al.	Paediatric meningitis	SES +
2001	Mohn et al.	Hodgkin disease	SES +
2004	Matsumoto et al.	Paed. Bone marrow transplant	SES +
2004	Yildizdas et al	Sepsis	SES +
2005	denBrinker et al.	Meningococceal disease	SES +
1985	Franklin et al.	Sick Neonates	SES +
1990	Fisher	prematures and sick neonates	SES +
1994	Van den Berghe et al.	Dopamine infusion -> partial hypopituitarism aggravates SES	

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

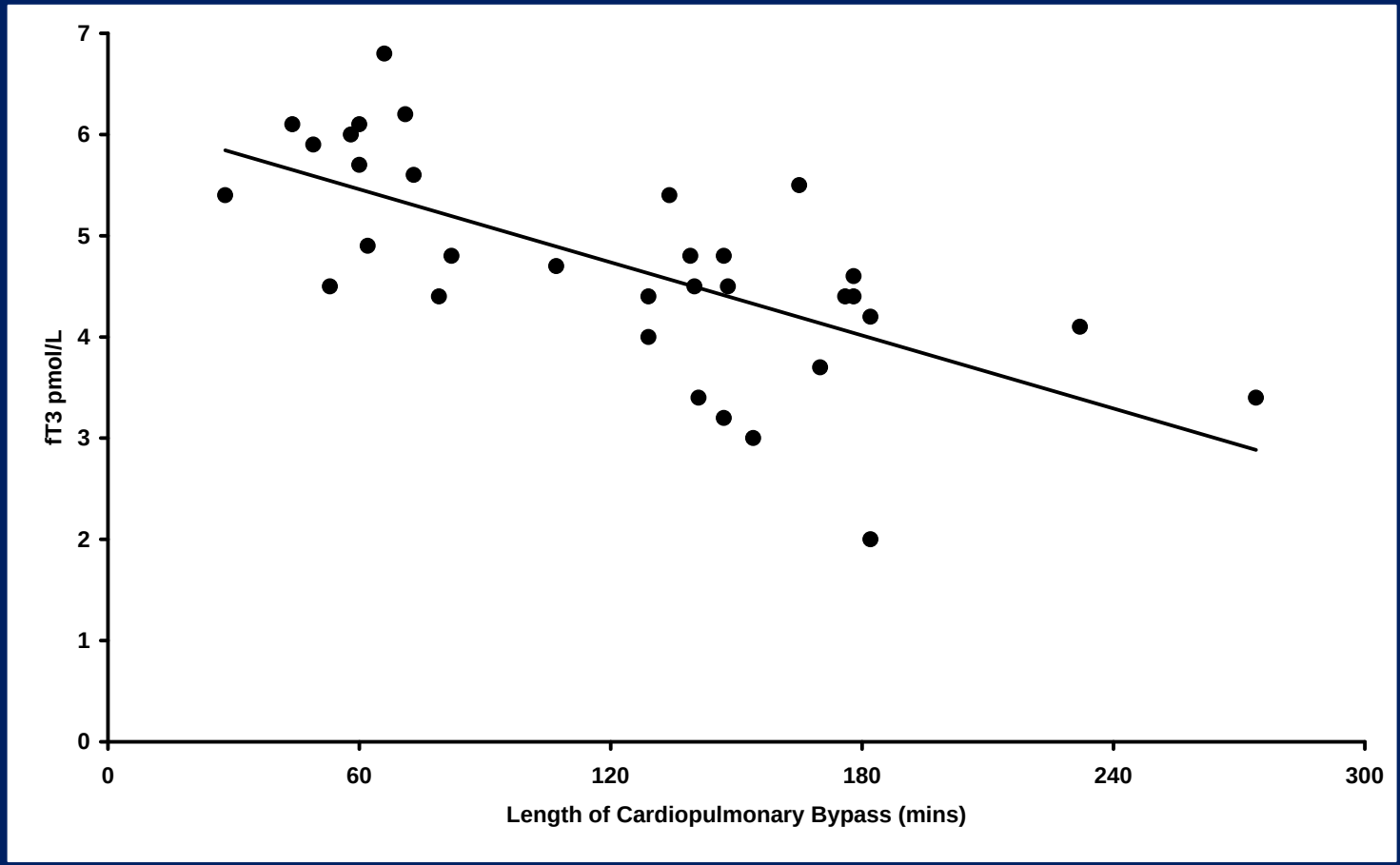
SES

Sick euthyroid syndrome – paediatric cardiac surgery ?

Studies.....?

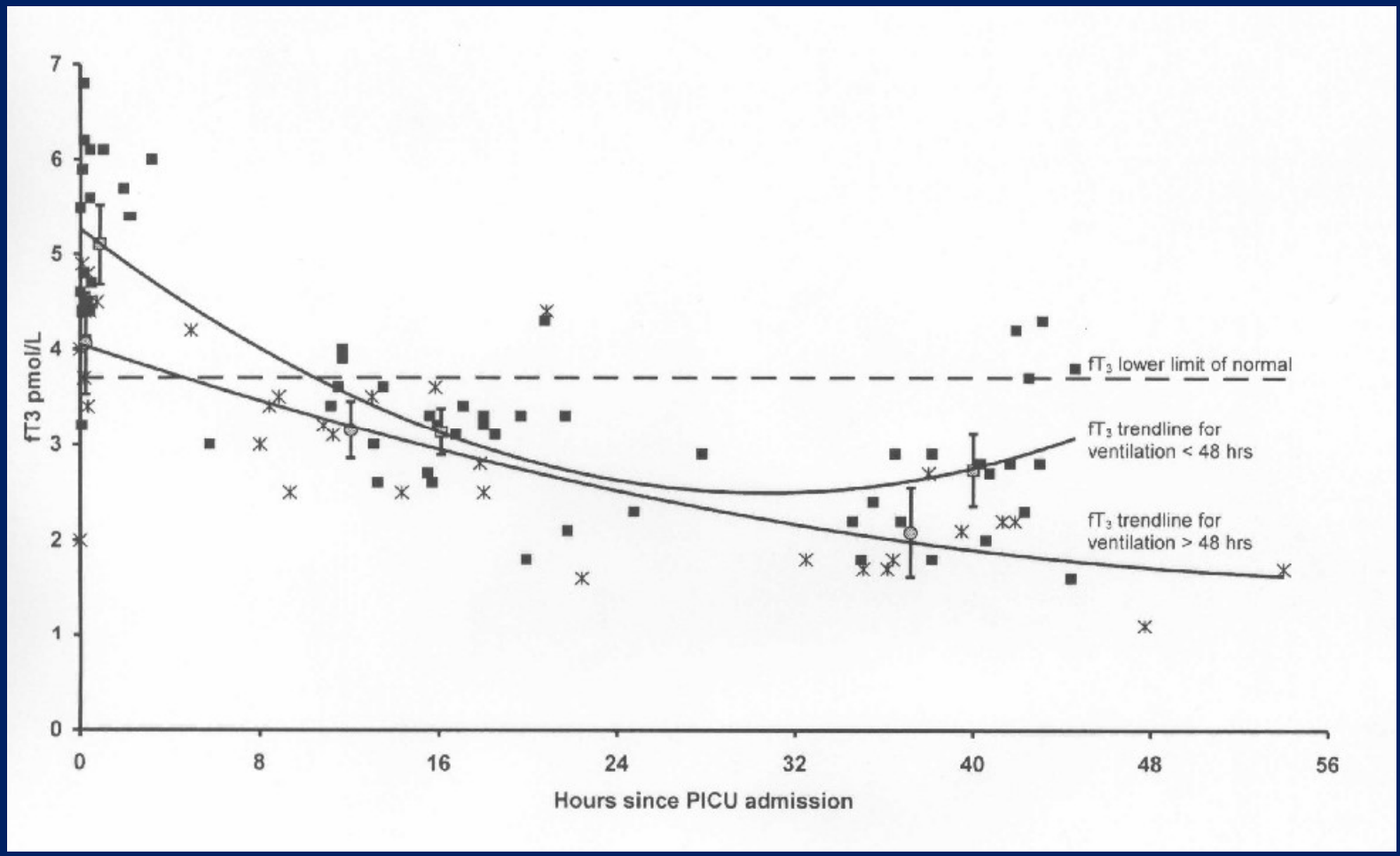
1989	Allen et al.	SES after CBP correltes to severity of illness
1993	Belgorosky et al.	SES for some days after CBP
1994	Mainwarning et al.	Neonates at risk for SES
1994	Mainwarning et al.	Fontan patients
1995	Murzi et al.	Prolonged decrease in thyroid hormones
1996	Saatvedt, Lindberg	correlation SES 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



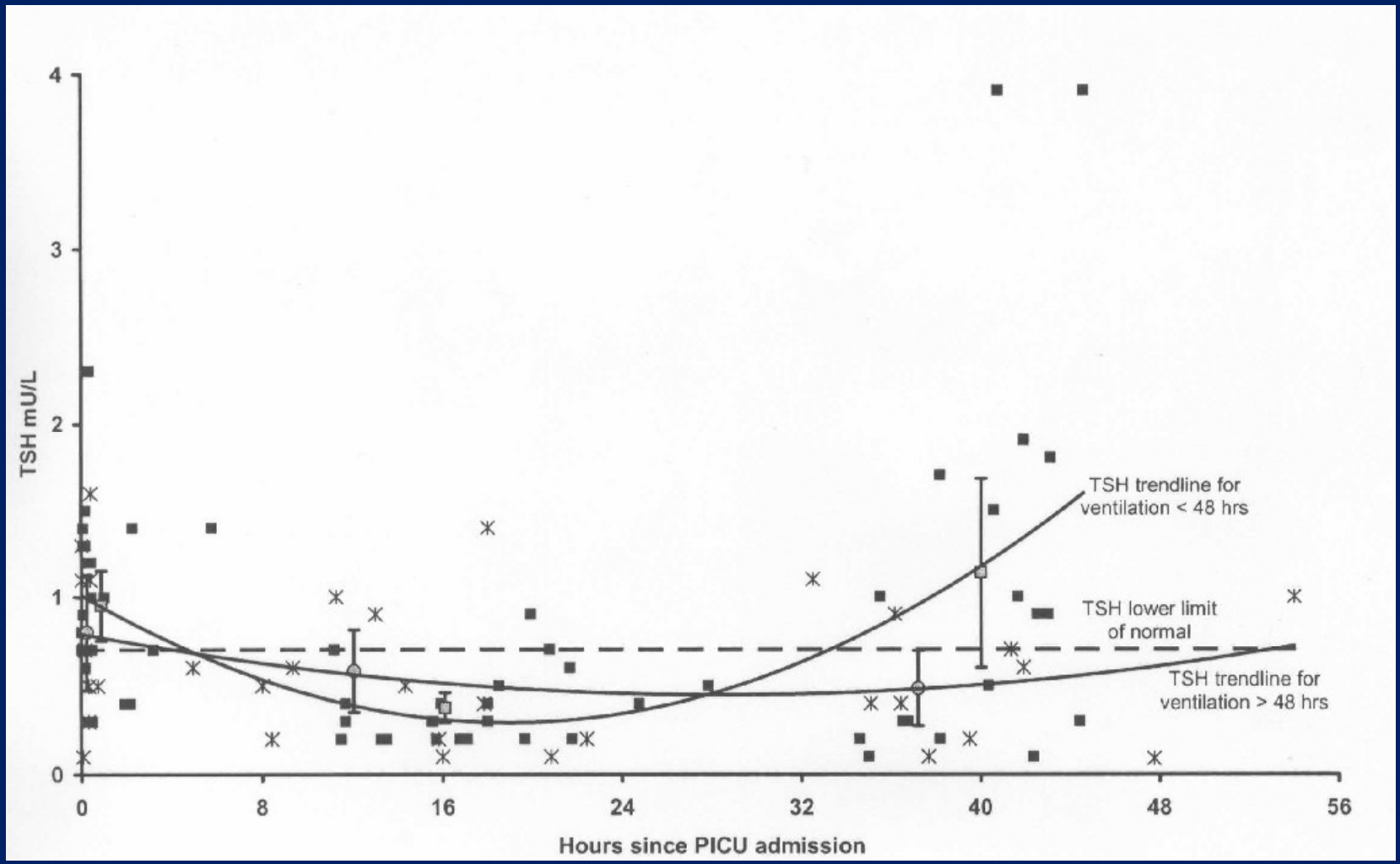
Plumpton 2005; Int Care Med. 31:581-587

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

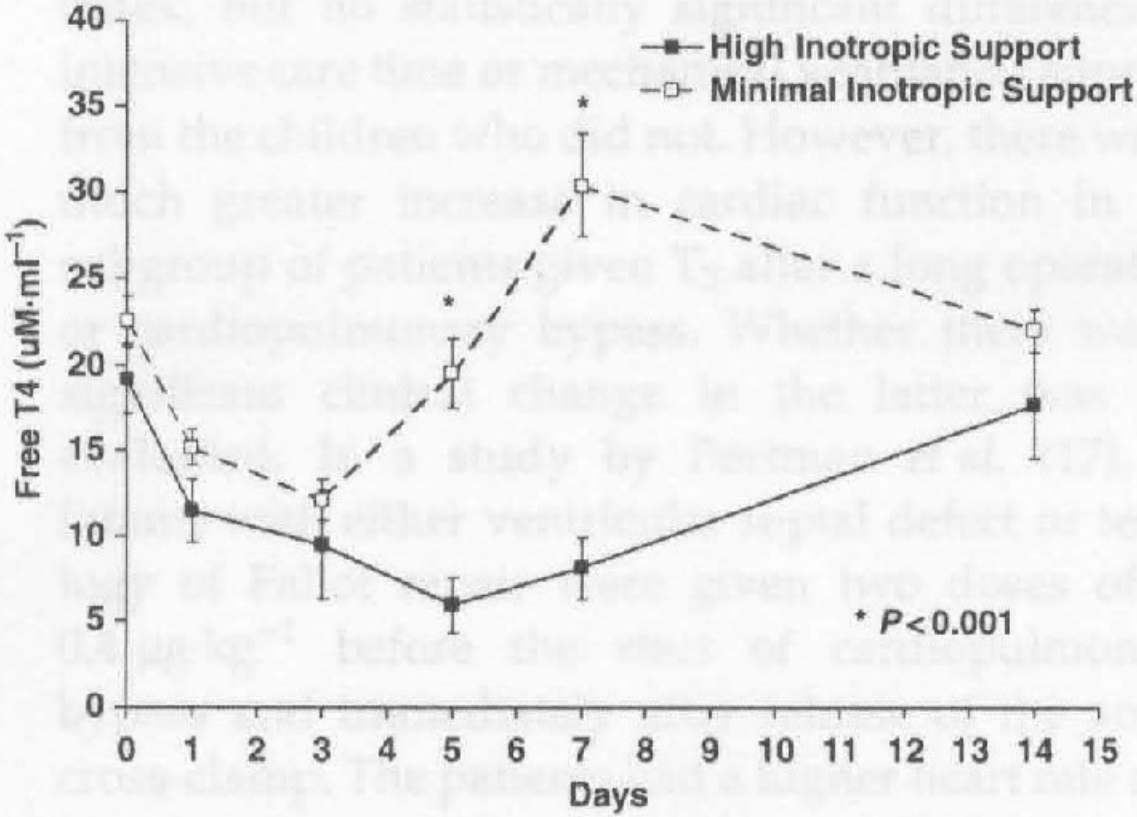


Figure 1
FT_4 levels over time – comparison between groups.

Dagan 2006; Pediatric Anesthesia16:538-542

Sick euthyroid syndrome - other factors ?

Dopamine

Healthy subjects
- directy 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 absorbtion of Iodine

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

SES ++++

Mitchell 1991; Ann Thorac Surg 52:1138-1140
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

Klemperer 1995; J Thorac cardiovasc Surg 109:457-465
Sabatino 2002; J Endocinol 175:577-586
Dillmann 2002; Thyroid 12:447-452

Sick euthyroid syndrome - treatment in adults

low T3 –> increased rate of atrial fibrillation (CABG)
T3 supplementation -> reduced rate of atrial fibrillation (CABG)

Kokkonen 2005; J Cardiothorac Vasc Anaest 19:182- 187
Klemperer 1996; Ann Thorac Surg 61:1323- 1327

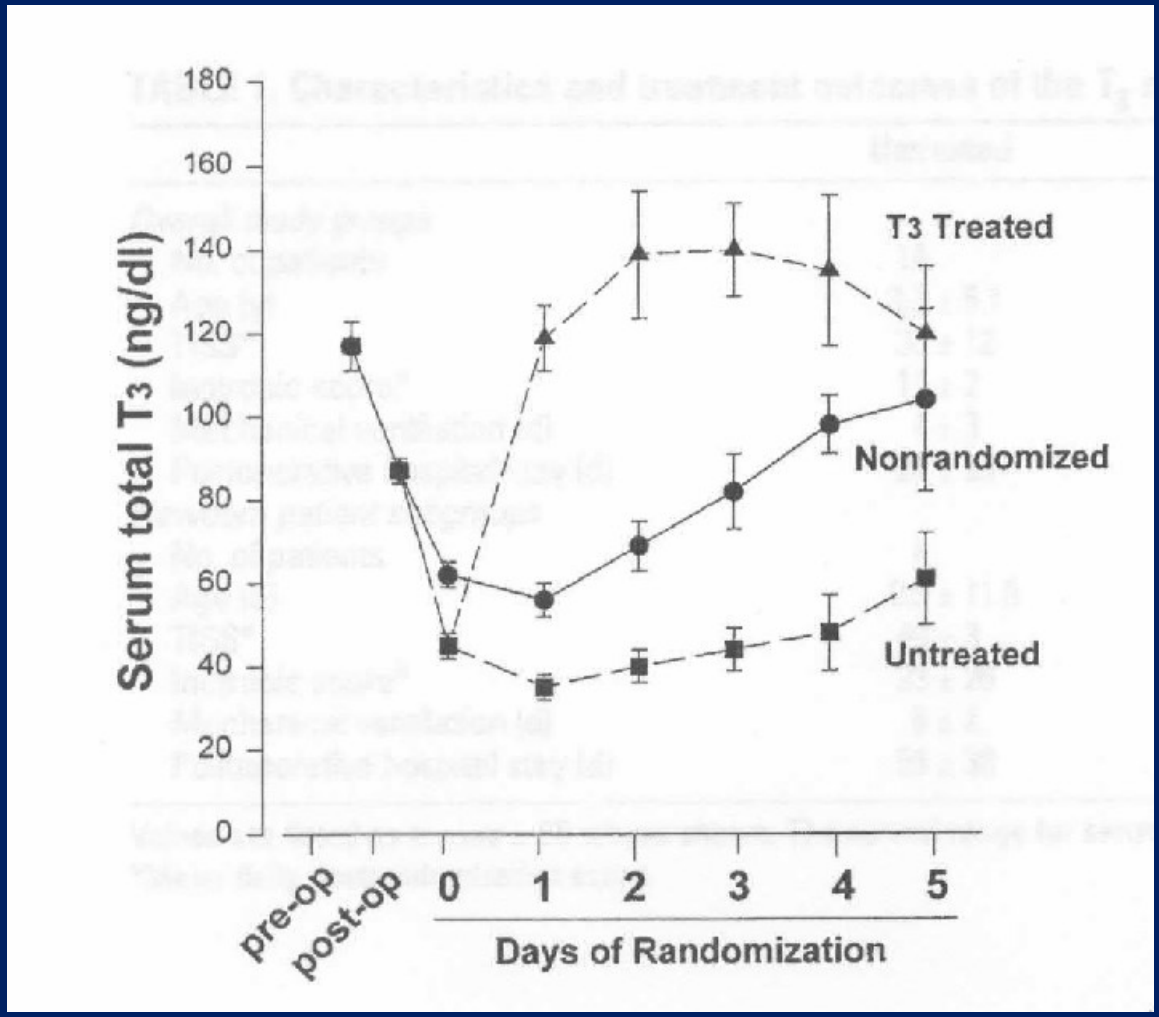
T3-supplementation
- lower inotropic requirement
- less diuretics
- improved CO
- improved stroke volume
- reduced SVR and PVR
- improved survival

T3- treatment beneficial

Novitzky 1989; J Thorac Cardiovasc Surg 98:972- 977
Novitzky 1996; Cardiology 87:509- 515
Klemperer 1995; N Engl J Med 333:1522- 1527
Vavouranakis 1994; J Cardiovasc Surg 35:383- 389
Sirlak 2004; Eur J Cardiothorac Surg 26:720- 726
Mullis- Jansson 1999; J Thorac Cardiovasc Surg 117:1128- 1134

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

Chowdhury 2001; J Thorac Cardiovasc Surg 122:1023-5

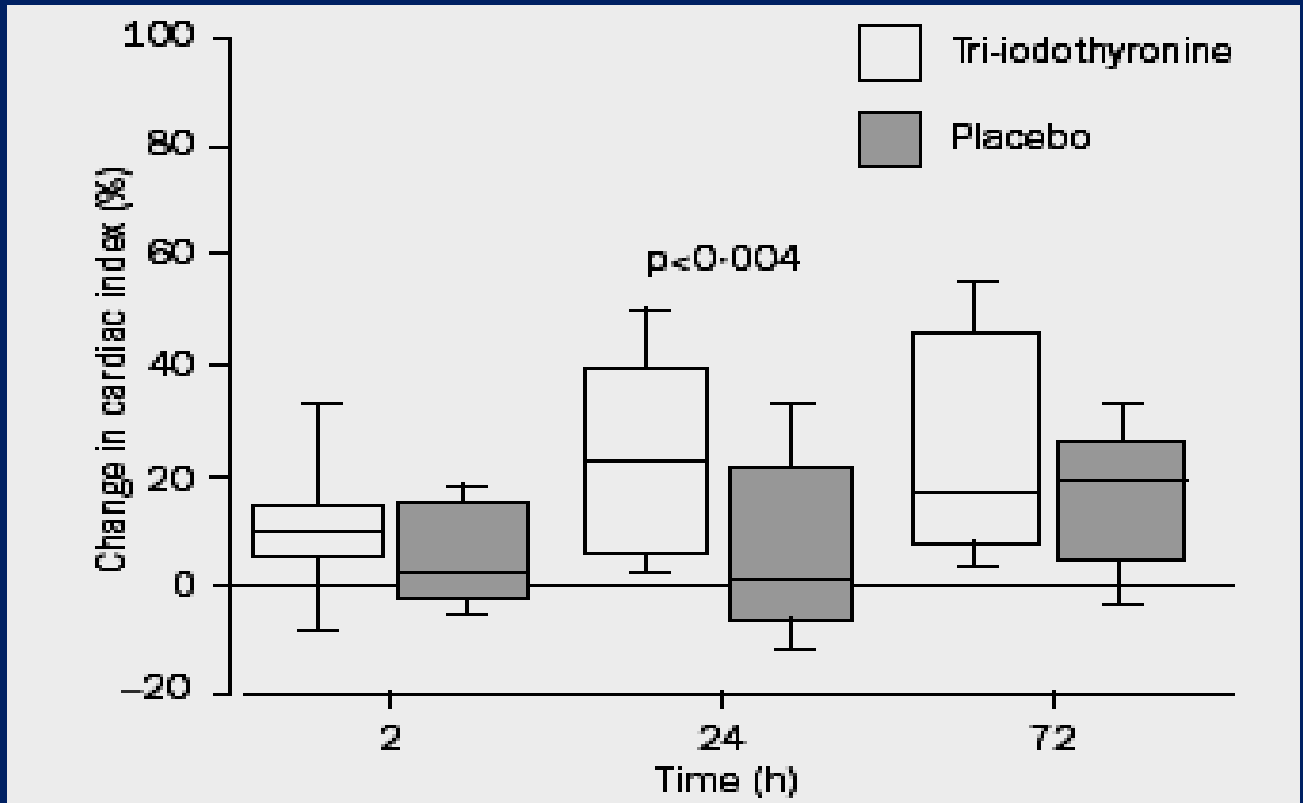
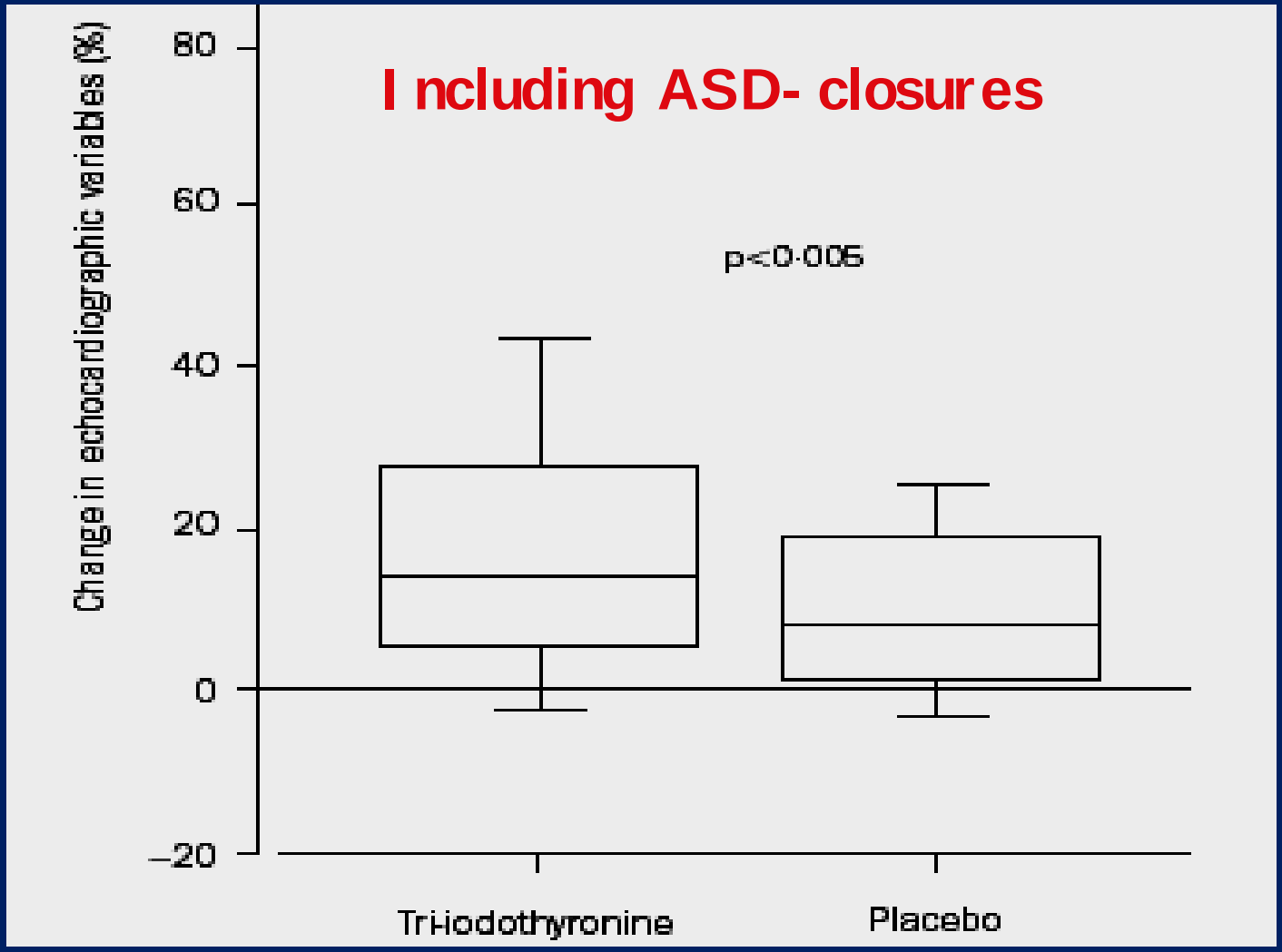


Figure 3: **Postoperative changes of cardiac index (% change from postoperative baseline) after first infusion of study drug**
Box plots represent 10th, 25th, 50th, 75th and 90th percentiles.

Randomised Study
n = 40 (20/20)

Change in echo parameters of cardiac function over time

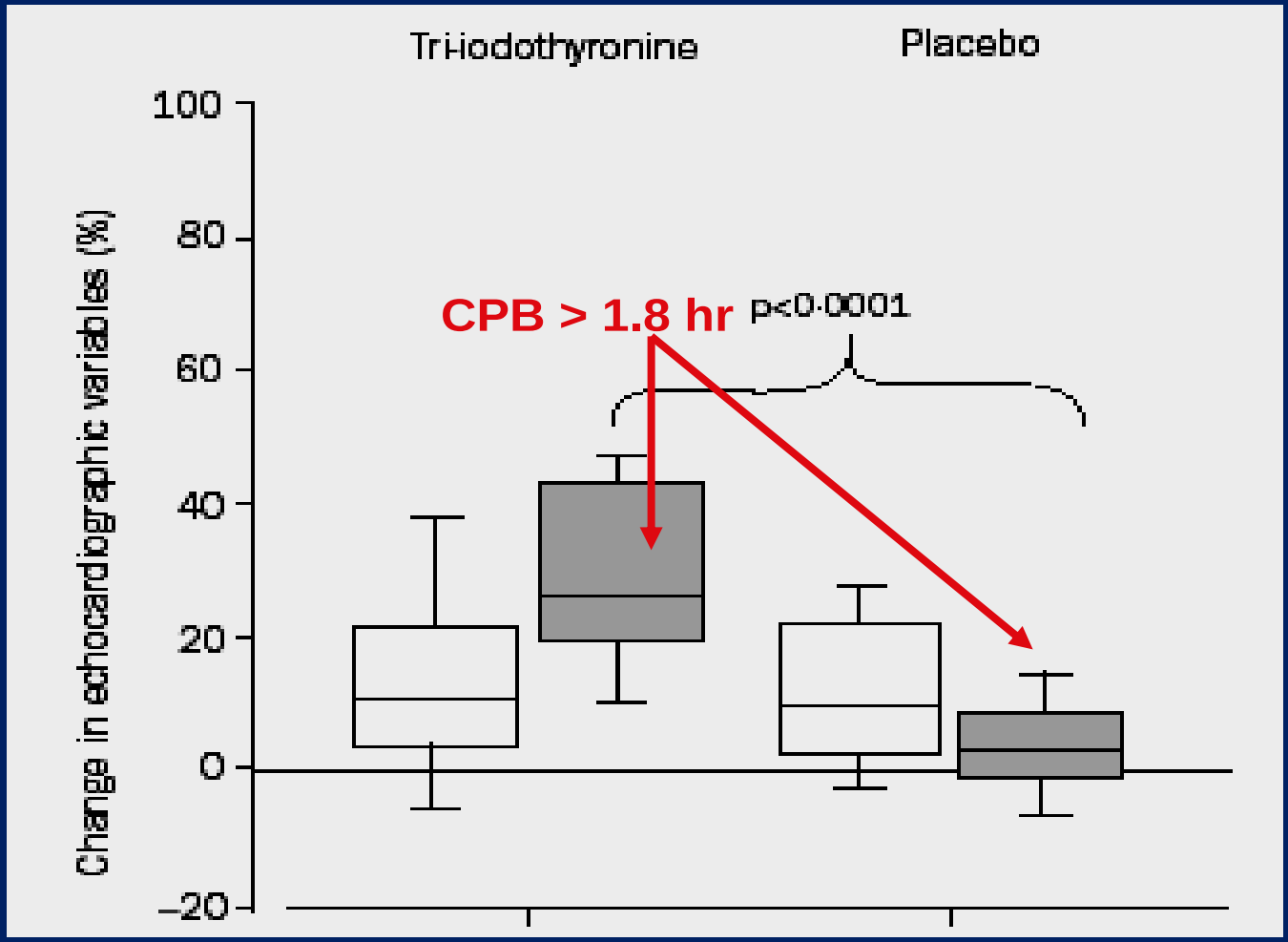
Bettendorf 2000, Lancet 356:529-34



Mean overall change in echo parameters of cardiac function

all subjects

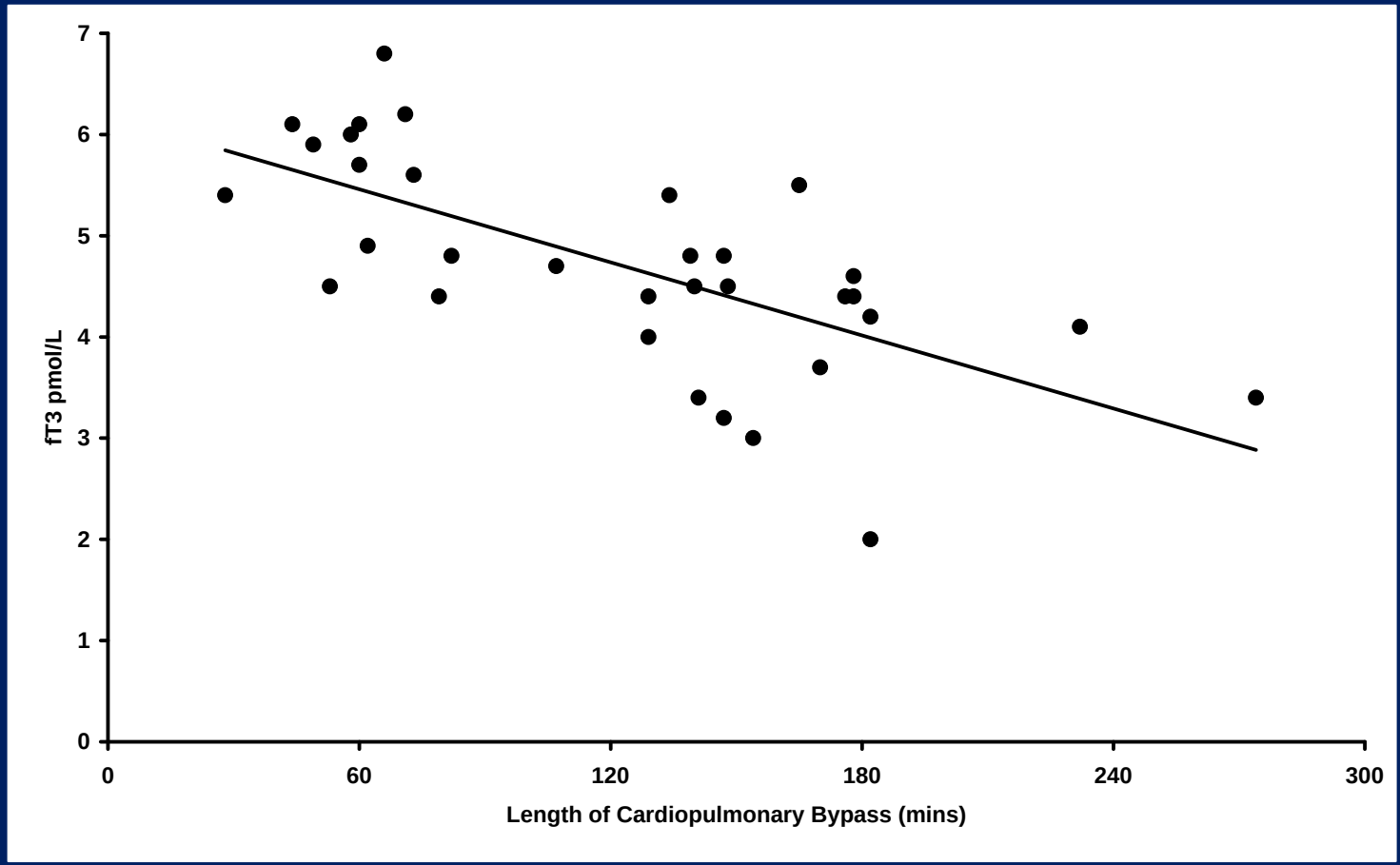
Bettendorf 2000, Lancet 356:529-34



Improved echo parameters of cardiac function in those with longer CPB

Bettendorf 2000, Lancet 356:529- 34

Effect of bypass on fT3-levels



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

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

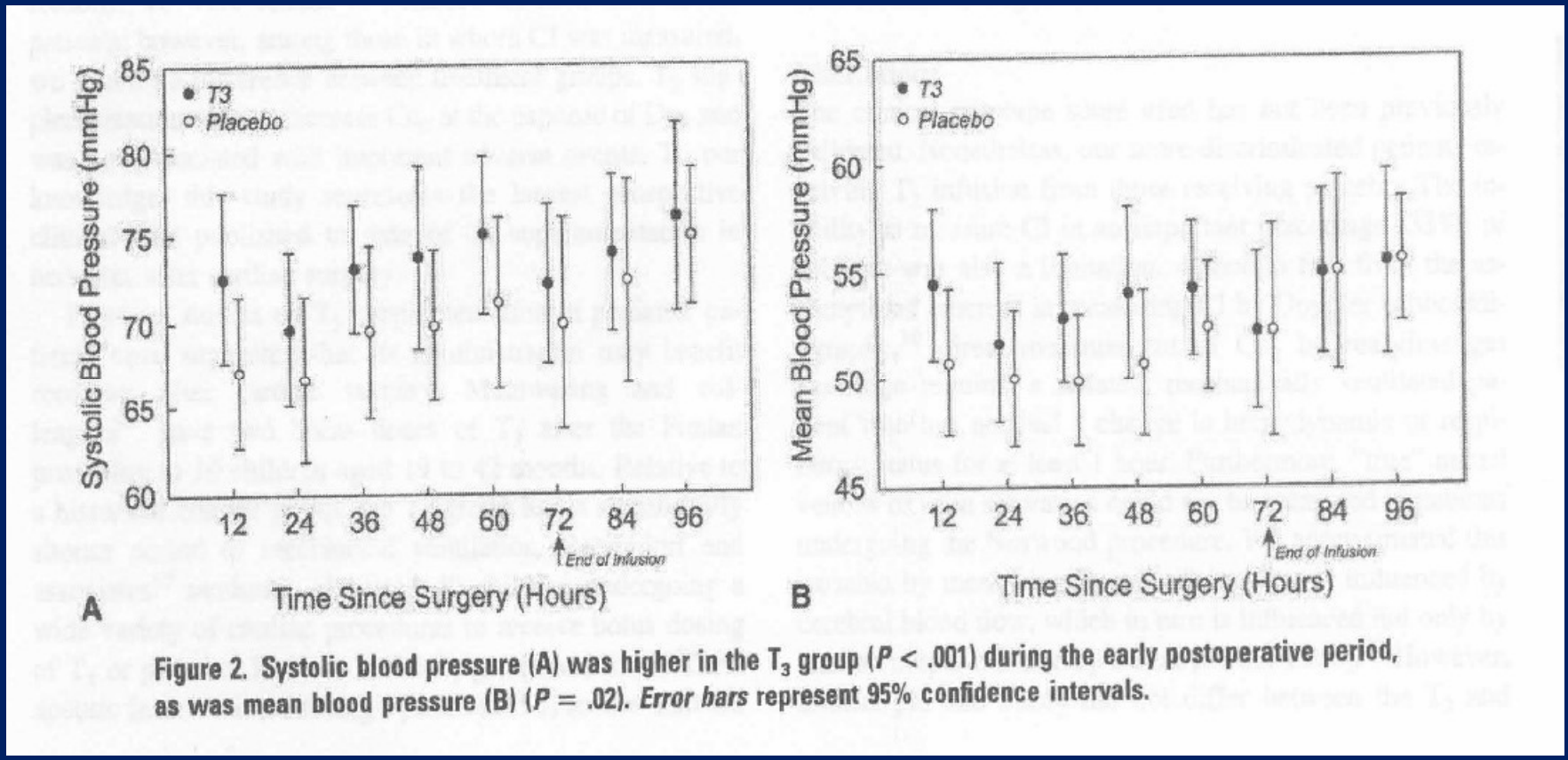


Figure 2. Systolic blood pressure (A) was higher in the T_3 group ($P < .001$) during the early postoperative period, as was mean blood pressure (B) ($P = .02$). *Error bars* represent 95% confidence intervals.

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