Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Thyroid and Brain Natriuretic Peptide Response in Children Undergoing Cardiac Surgery for Congenital Heart Disease

– Age-Related Variations and Prognostic Value –

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Background: Interest in hormonal response after pediatric cardiac surgery is growing, but many aspects remain unclear. The aim of this study was to test age-related variations and prognostic values of thyroid hormones, and brain natriuretic peptide (BNP) levels before and after surgery.

Methods and Results: A total of 162 children undergoing cardiac surgery were divided into 3 age groups (group 1, n=57 neonates; group 2, n=58 infants; group 3, n=47 toddlers). Free thyroid hormones (fT3 and fT4), thyrotropin (thyroid-stimulating hormone [TSH]) and BNP were measured preoperatively, daily postoperatively in the intensive care unit and after 15 days. The primary outcome was time to extubation (TTE; variable used as time to event by survival analysis). The hormonal response differed among age groups. In older children the TSH nadir occurred at 6–12 h after surgery (0.42 mIU/L, P<0.001), with a progressive recovery thereafter, while in neonates the TSH nadir occurred later, at 36–60 h (0.14 mIU/L, P<0.001), followed by a much slower recovery. In neonates, BNP also dropped after surgery (from 2,899 to 824.0 ng/L, P<0.001) while increased in older children (from 71.00 to 527.00 ng/L, P<0.001). On multivariate analysis independent predictors of TTE were fT3 nadir in all age groups, together with TSH nadir and Aristotle score in neonates, and body surface area and BNP peak in older children.

Conclusions: BNP and thyroid response after pediatric cardiac surgery differs widely according to age. Beside Aristotle score, combined measurement of fT3 and TSH are the strongest predictors of TTE, especially in neonates. (*Circ J* 2013; **77:** 188–197)

Key Words: Brain natriuretic peptide; Cardiac surgery; Children; Thyroid

Cardiac surgery with or without cardiopulmonary bypass (CPB) induces a marked and persistent depression of circulating thyroid hormones during the postoperative period both in adults and in children.[1–9]

Postoperative thyroid hormone levels are proposed as low-cost, adjunctive prognostic markers in children undergoing cardiac surgery for congenital heart disease (CHD).[2,4,5,10,11] In particular, the degree of hypothyroxinemia reached after surgery is related to important clinical endpoints in pediatric cardiac surgery including the duration of mechanical ventilation,[3,4,6] intensive care treatment[3,10] and the degree of inotropic support.[4,5]

The growing interest in thyroidal response after cardiac surgery is even more justified by the potentially dangerous effects of a hypothyroid-like condition with decreased heart rate, cardiac output, and increased systemic vascular resistance.[2]

Preoperative and postoperative brain natriuretic peptide (BNP) or NT-pro-BNP values are also useful markers of postoperative outcome in children with CHD.[12–18] Higher BNP values are associated with the duration of mechanical ventilation, intensive care unit (ICU) stay, the need for inotropic support and low cardiac output syndrome[12–18] and composite endpoint.[12]

Many aspects of thyroid and BNP response after pediatric cardiac surgery still remain undefined. In particular, the effect

Received June 28, 2012; revised manuscript received July 26, 2012; accepted August 22, 2012; released online September 27, 2012 Time for primary review: 20 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-12-0834

Table 1. Patients Characteristics

	Neonates (n=57)	Infants (n=58)	Toddlers-children (n=47)	Total (n=162)
A. Baseline characteristics				
Age	7 days (5–11.5 days)	4.5 months (2–7 months)	3 years (2–7 years)	4 months (0–18.5 months)
Male	34 (59.6)	28 (48.3)	25 (53.2)	87 (53.7)
Weight (kg)	3.1 (2.8–3.4)†	5.4 (4.1–6.7)§	15 (9.7–27)‡	4.94 (3.2–9.5)*
Height (cm)	50 (50–51)†	62 (55–68)§	98 (79–124)‡	60 (50–77.5)*
BSA (m^2)	4.8 (4.8–4.8)†	5.3 (5.0–5.5)§	6.4 (5.8–7.1)‡	5.19 (4.8–5.8)*
Cavo-pulmonary connection	0 (0)	0 (0)	6 (14)	6 (3.9)
Biventricular volume overload	0 (0)	1 (1.8)	0 (0)	1 (0.6)
LV pressure overload	10 (17.9)	4 (7.1)	3 (7)	17 (11)
LV volume overload	4 (7.1)	30 (53.6)	8 (18.6)	42 (27.1)
Palliated univentricular heart	0 (0)	1 (1.8)	3 (7)	4 (2.6)
RV pressure overload	0 (0)	10 (17.9)	9 (20.9)	19 (12.3)
RV volume overload	3 (5.4)	1 (1.8)	12 (27.9)	16 (10.3)
Transposition of the great arteries	24 (42.9)	4 (7.1)	1 (2.3)	29 (18.7)
Univentricular heart	15 (26.8)	5 (8.9)	1 (2.3)	21 (13.5)
BNP (ng/L)	2,899 (1,203–5,697)†	99 (44–197)§	42 (24–84)‡	139 (44–1,996)*
TSH (mIU/L)	2.4 (0.8–3.9)	2.9 (2.2–4.3)	2.4 (1.5–3.4)	2.5 (1.6–3.9)
fT3 (pg/ml)	2.7 (2.0–3.2)†	3.20 (2.7–3.8)	3.3 (2.7–3.8)‡	3.1 (2.5–3.6)*
fT4 (pg/ml)	13.3 (11.9–15.1)†	11.9 (11.0–13.0)	11.4 (10.2–12.9)‡	12.2 (10.9–13.6)*
CPB time (min)	145 (134–172.8)†	116 (85–151.5)	110 (72–152)‡	128 (96.5–160)*
Cross-clamp (min)	61.5 (27.8–94.5)	59 (21–74)	53 (21–95.5)	58 (23.8–89.8)
Aristotle ABC classification				
Category I: 1.5–5.9	0 (0)	3 (5.2)	13 (27.7)	16 (9.9)
Category II: 6–7.9	12 (21.1)	30 (51.7)	8 (17.0)	50 (30.9)
Category III: 8–9.9	9 (15.8)	21 (36.2)	25 (53.2)	55 (34.0)
Category IV: 10–15	36 (63.2)	4 (6.9)	1 (2.1)	41 (25.3)*
B. Post-surgery details				
TTE (h)	132 (46.5–200)†	19 (12–36)§	8 (5–12)‡	21.5 (10–112.5)*
Hours in ICU	178 (108–300)†	60 (36–108)§	36 (12–50.5)‡	66 (36–159)*
Inotropic time (h)	132 (36–204)†	36 (10–83)	18 (10–36)‡	36 (12–108)*
Dopamine	45 (78.8)	37 (64.5)	28 (58.8)	110 (67.9)
Major complications	14 (24.6)	2 (3.4)	3 (6.4)	19 (11.7)#
Complication type	LCO, n=9; Death, n=7	LCO, n=1; Tamponed, n=1	Redo, n=1	LCO, n=10; Redo, n=1; Death, n=7; Tamponed, n=1

Data given as median (25^{th}–75^{th} percentiles) or n (%). *P<0.05 Kruskall-Wallis test or chi-square test; †P<0.05 post-hoc test neonates vs. infants; ‡P<0.05 post-hoc test for neonates vs. toddlers-children; §P<0.05 post-hoc test for infants vs. toddlers-children; #P<0.05 Fisher test. Congenital heart diseases were divided into main groups according to the hemodynamics (19): biventricular volume overload group (atrio-ventricular defects); LV pressure overload group (including aortic stenosis and aortic coarctation); LV volume overload group (ventricular septal defects, significant patent arterial duct, truncus arteriosus); RV pressure overload group (tetralogy of Fallot, pulmonary stenosis); RV volume overload group (atrial septal defect, anomalous pulmonary venous drainage).
BNP, brain natriuretic peptide; BSA, body surface area; CPB, cardiopulmonary bypass; fT3, free triiodothyronine; fT4, free thyroxine; ICU, intensive care unit; LCO, low cardiac output syndrome; LV, left ventricular; Redo, reoperation; RV, right ventricular; TSH, thyroid-stimulating hormone; TTE, time to extubation.

of cardiac disease/repair and age-related differences have not been thoroughly investigated.[2,3,5,10,12,13–17] Also, most studies have included relatively small numbers of neonates[4,6,13,14] or none at all.[7,14,17,19]

Neonates clearly represent a separate group due to the higher operative risk (as determined by Aristotle score)[20–22] and to the different response to the cardiac disease/surgical stress. Maturational variation of endocrine function, mainly occurring within the first month of life, may have an additional influence on post-surgical hormonal response.[19]

Starting from these considerations, in the first step of the study we tested the hypothesis that a different hormonal response may be related to prognosis according to age; as a second step, we tested if different responses were related to age per se, to the age-associated complexity of disease and surgical procedure, or to both.

Methods

Patients

We prospectively evaluated 162 consecutive children (median age, 4 months; 25^{th}–75^{th} percentiles, 0–18.5 months; 87 boys, 75 girls) undergoing surgery for correction/palliation of CHD at the Paediatric Cardiac Surgery Department, Heart Hospital,

Table 2. Correlation Coefficients

	Neonates (n=57)	Infants-Toddlers-Children (n=105)	Total (n=162)
TSH nadir vs. TTE	–0.51†	0.02	–0.30†
Hours in ICU	–0.38‡	–0.08	–0.32†
Inotropic time	–0.45‡	–0.12	–0.41†
CPB time	–0.57†	0.11	–0.22‡
Aristotle score	–0.40‡	–0.13	–0.40†
BNP before surgery	–0.14	0.09	–0.24‡
BNP before surgery vs. TTE	0.19	0.27‡	0.56†
Hours in ICU	0.28‡	0.18	0.50†
Inotropic time	0.26	0.01	0.40†
Aristotle score	0.37‡	–0.02	0.42†
BNP peak vs. TTE	0.27‡	0.45†	0.65†
Hours in ICU	0.29‡	0.54†	0.68†
Inotropic time	0.42†	0.46†	0.64†
CPB time	0.14	0.33‡	0.29†
fT3 nadir	–0.32‡	0.04	–0.10
BNP before surgery vs. BNP peak	0.41†	0.38†	0.67†
TSH before surgery vs. TSH nadir	0.38‡	0.36†	0.38†
fT3 before surgery vs. fT3 nadir	0.46‡	0.54†	0.41†
fT4 before surgery vs. fT4 nadir	0.42‡	0.29‡	0.44†
BNP before surgery vs. fT3 before surgery	–0.36‡	–0.26‡	–0.41†
BNP after surgery vs. TSH after surgery	0.05	–0.14‡	–0.04
fT3 after surgery	–0.20‡	–0.01	–0.06
EF after surgery	0.02	–0.58‡	–0.21‡
CVP after surgery	0.32‡	–0.07	0.14‡
Lactate after surgery	0.40‡	0.07	0.38‡

Peak and nadir values are limited to the intubation period. †P<0.001; ‡P<0.05.
CVP, central venous pressure; EF, ejection fraction. Other abbreviations as in Table 1.

Fondazione G. Monasterio, Massa, Italy from June 2009 to January 2011. Serum samples from 12 newborns aged 4–7 days, 11 neonates aged 7–30 days, 10 children aged 1 month–1 year, and 12 children aged >1 year represented the control group for thyroid hormones. Reference intervals previously reported by us, however, were utilized for BNP.[19]

Children previously palliated (including shunts, pulmonary artery bending, Norwood stage 1 procedure, cavo-pulmonary palliation) were included while patients who had a previous correction were excluded. Patients with known thyroid disease, under treatment with thyroid hormones/anti-thyroid drugs or medications that could interfere with thyroid metabolism, were also excluded.

According to the literature,[3] we first defined 3 age groups: group 1 (neonates, ie, <1 month), n=57, median age 7 days (25^{th}–75^{th} percentiles, 5.0–11.5 days); group 2 (infants, ie, 1–12 months), n=58, median age 4.5 months (2–7 months); group 3 (children, ie, >12 months–18 years), n=47, median age 3 years (2–7 years).

Among the neonatal group no intervention were performed within the first 3 days of life and for some additional analysis we defined 2 further age groups: group 1, 4–7 days of life (n=26); and group 2, 8–30 days of life (n=31).

Congenital heart defects in patients undergoing cardiac surgery were thereafter divided into 4 major classes of severity according to the Aristotle ABC classification,[20–22] as indicated by latest observations for Single-Center experiences.[21]

Baseline clinical and biochemical characteristics, including arterial blood gases and arterial lactate collected using a fully automated assay (ABL 700 series Radiometer Copenhagen), are reported in Table 1A.

Notably, distribution according to Aristotle ABC score significantly differed between age group (P<0.001); Aristotle ABC IV (corresponding to more severe disease) was almost totally constituted by neonates, while in the first category there were almost only older children.

Written consent was obtained for all patients and the protocol was approved by the Local Review Board.

Free Thyroid Hormones, Thyroid-Stimulating Hormone and BNP Sampling

According to standardized procedures,[23,24] blood samples for thyroid-stimulating hormone (TSH; mlU/L), free-triiodothyronine (fT3; pg/ml), free-thyroxine (fT4; pg/ml) and BNP (ng/L) were drawn preoperatively, daily after surgery during ICU stay and at 15 days after surgery. Hormones were measured only on blood samples taken for necessity of treatment (at 07.30 a.m.) and no additional samples were drawn. Serum TSH, fT3 and fT4 were measured by Architect Abbott Laboratories (Abbott Park, IL, USA).

Plasma BNP was measured using the fully automated Access platform (Triage BNP reagents, Access Immunoassay Systems, REF 98200; Beckman Coulter, Fullerton, CA, USA). The analytical characteristics and performance of the Access Immunoassay method used in this study for measurement of BNP were previously evaluated in our laboratory.[24]

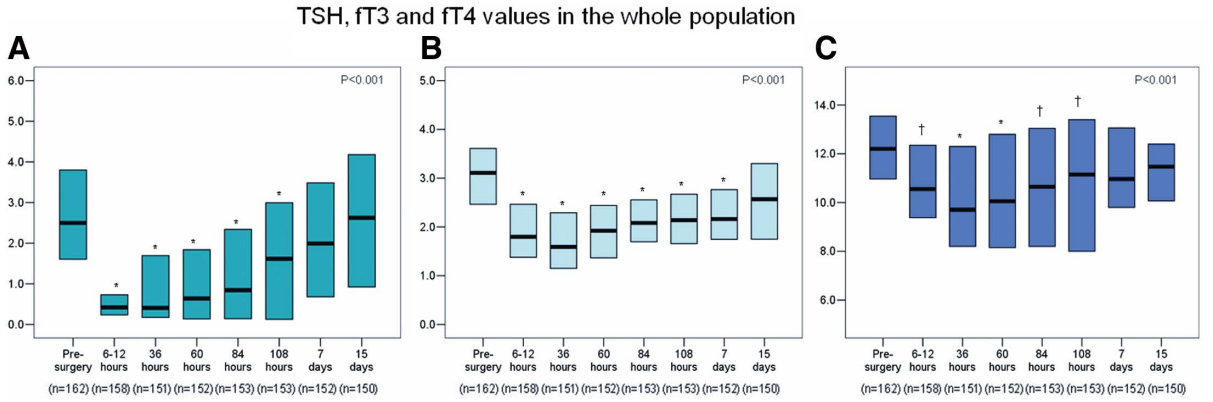

Figure 1. Time course of (**A**) thyroid-stimulating hormone (TSH), (**B**) free triiodothyronine (fT3) and (**C**) free thyroxine (fT4) circulating levels in the whole patient group. Bold horizontal line, median; box, interquartile range. *P<0.001 and †P<0.05 for differences with pre-surgery levels. Units are mIU/L for TSH and pg/ml for fT3 and fT4.

Surgical and Clinical Management

Preoperative anesthesia management, intraoperative bypass strategy, and subsequent ICU management followed standard institutional practice.

Non-iodinated topical antiseptics were used for every patient. A standard technique was used to institute CPB (roller pump, disposable membrane oxygenator and arterial filter) and involved bicaval drainage and ascending aorta perfusion.

Different myocardial protection (anterograde cold crystalloid cardioplegia or with cold blood cardioplegia) and degrees of body temperature were used (ranging from 35° to 19°C) depending on the surgical strategy. Dexamethasone prophylaxis was routinely performed in all patients at the same dose (1 mg/kg body weight i.v. bolus).

In the postoperative period, hemodynamic management was conducted using epinephrine ($0.005–0.15\,\mu g \cdot kg^{-1} \cdot min^{-1}$), milrinone ($0.5–0.75\,\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine ($5–20\,\mu g \cdot kg^{-1} \cdot min^{-1}$), and noradrenaline ($0.05–0.5\,\mu g \cdot kg^{-1} \cdot min^{-1}$). Data on dopamine therapy are given in **Table 2**. Intravascular volume expansion was conducted according to the attending physician and consisted of 20% human albumin or fresh frozen plasma. Diuretics usually consisted of furosemide ($1–10\,mg \cdot kg^{-1} \cdot day^{-1}$).

Echocardiograms were performed at every hormonal blood sample interval, ejection fraction was derived according to current guidelines.[25]

Outcome Measures

Time to extubation (TTE) was the primary outcome. Secondary endpoints included the length of ICU stay and the inotropic support time. Adverse events were recorded up to 30 days after cardiac surgery.[11]

Statistical Analysis

Data are expressed as median ($25^{th}–75^{th}$ percentiles) for continuous variables and number of subjects (percentage) for categorical variables. Comparison between age groups was performed using Fisher test, non-parametric Mann-Whitney U-test or Kruskall-Wallis test followed by Mann-Whitney U-test with Bonferroni correction for post-hoc comparisons. Spearman rho was used to analyze the relations between pre-surgery and post-surgery variables. Correlations between variables across the whole post-surgery period were assessed using cross-correlation coefficient. Thyroid hormones and BNP over time were evaluated with mixed-effects regression models to properly account for correlation among repeated measures and missing values. TTE was the primary outcome and extubation events were considered until 15 days after surgery. Patients remaining on the ventilator were censored at death or at 15 days. Kaplan-Meier method and log-rank test were used to compare TTE across groups. Cox proportional hazard models were used to identify variables affecting TTE within age groups.

Modeling extubation in terms of time to event, the hazard ratio (HR) should be interpreted as an indicator of chance of extubation, with HR <1 indicating low probability of extubation (negative outcome) and HR >1 suggesting higher chance of extubation (positive outcome).

Variables with P<0.1 on univariate analysis were considered for multivariate models. Proportional hazard assumption was checked using the Schoenfeld test and no significant departures from this assumption were observed.

Harrell's C index was used to evaluate discrimination ability of single variables used in univariate analysis as well as multivariate models. Logarithmic transformation was used when appropriate and indicated. A 2-tailed P<0.05 was considered statistically significant. SPSS version 13.0 (SPSS, Chicago, IL, USA) and R 2.11.1 were used for analysis.

Results

Clinical Data

The post-surgical data showed that neonates had greater disease complexity (**Table 2**). Neonates clearly differed from older children in that they had a more complicated postoperative period characterized by a longer median TTE (P<0.001), ICU stay (P<0.001), inotropic support (P<0.001) and higher incidence of adverse events (P=0.001).

Considering Aristotle ABC score II and III, which included 36.8% of neonates and 80% of older children, although not reaching statistical significance (P=0.055; likely because of the low number of events), major complications were more frequently observed in neonates than in older children (19% vs. 6%, respectively). In contrast, no significant differences in outcome were found among neonates in Aristotle ABC score

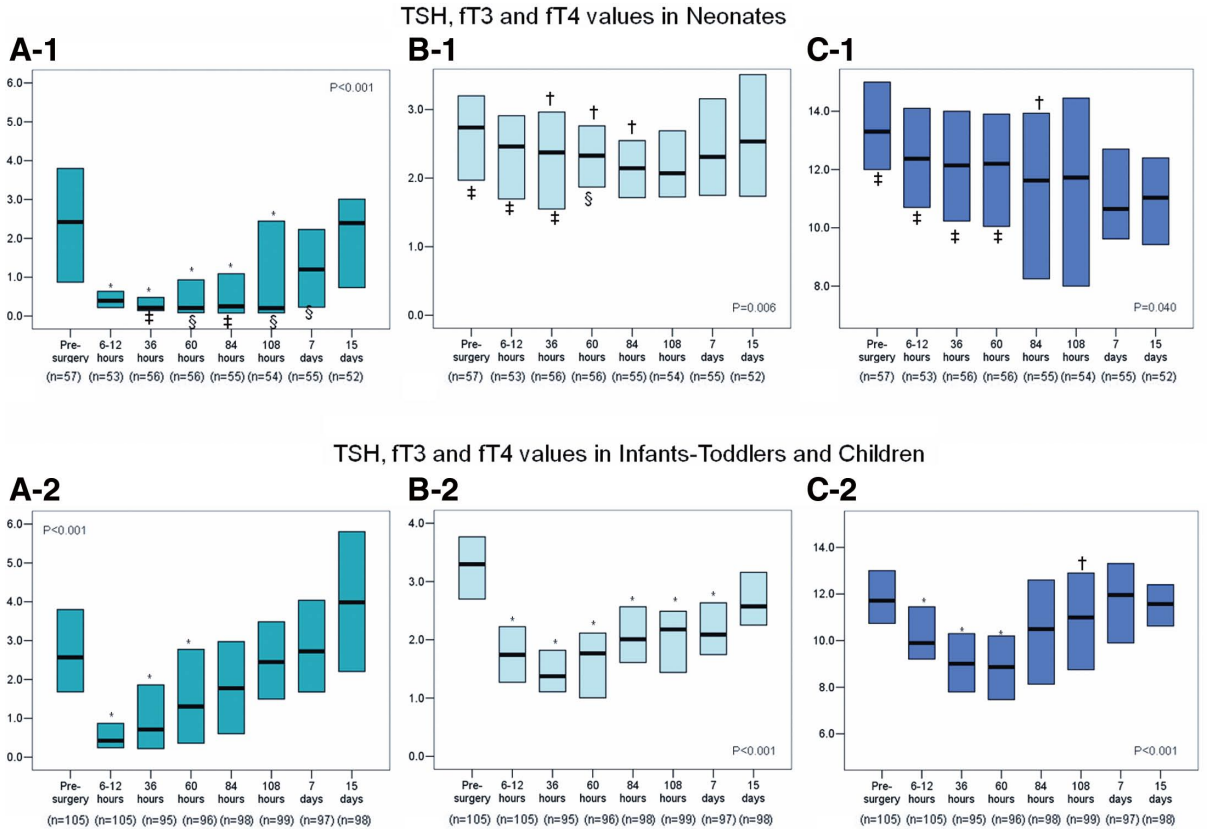

Figure 2. Time course of (**A**) thyroid-stimulating hormone (TSH), (**B**) free triiodothyronine (fT3) and (**C**) free thyroxine (fT4) circulating levels according to age. Bold horizontal line, median; box, interquartile range. *P<0.001 and †P<0.05 for differences with pre-surgery levels. ‡P<0.001 and §P<0.05 for differences between neonates and infants-toddlers and children at each time point. Units are mIU/L for TSH and pg/ml for fT3 and fT4.

II–III vs. Aristotle ABC score IV (19% and 27.8%, respectively, P=0.460; **Table 1B**).

Thyroid Response According to Age

Overall TSH dropped below the preoperative level after surgery (P<0.001), reached a nadir at 36 h and started recovery by 60 h, reaching baseline by 7 days (P=1.00). A similar time course was observed for fT4 and fT3, with the latter having a slower and delayed recovery up to 7 days after surgery (P<0.001; **Figure 1**).

Thyroid response in neonates differed substantially from the other age groups, while patterns in infants and children were nearly identical (data not shown). Accordingly, we combined results from infants and children and analyzed them as a single group.

Preoperatively, neonates had lower fT3 (P<0.001) but higher fT4 than older children (P<0.001), while TSH did not differ between the 2 groups (P=0.139; **Figure 2**). When neonates were divided into 2 groups (4–7 days of life and 8–30 days of life), TSH, fT3 and fT4 (median, 2.79 μU/ml, 2.51 pg/ml and 14.2 pg/ml vs. 2.30 μIU/ml, 2.92 pg/ml and 12.7 pg/ml, respectively) did not differ significantly and were comparable to controls (2.92 μIU/ml, 2.38 pg/ml and 14.1 pg/ml, respectively). Based on this finding, all neonates surgically treated before 1 month of life were considered as a single group. No differences were also observed among pre-surgery TSH, fT4 and fT3 as measured in older children and in controls (data not shown).

Postoperatively neonates had a prolonged impairment in TSH secretion, with TSH reaching the nadir at 36 h (P<0.001) and remaining depressed up to 108 h. The subsequent recovery was slow and completed only at 15 days (P=1.00).

In contrast, TSH in older children reached a nadir earlier (at 6–12 h), with a prompt and progressive recovery starting at the second postoperative day, and completed at 84 h (P=0.151).

In accordance with the TSH time course, fT4 and fT3 also dropped postoperatively.

fT4 and fT3 decreased relatively less in neonates than in older children. Thyroid hormones were lower preoperatively in neonates but postoperatively were higher than in older children up to 60 h after surgery (P=0.003 for fT3 and P<0.001 for fT4; **Figure 2**). fT3 reached a nadir later in neonates than in older children (ie, at 84 h vs. 36 h, respectively; P=0.002).

No differences were found in TSH, fT3 and fT4 levels in relation to dopamine treatment (P=0.397, P=0.055 and P=0.105, respectively), possibly because drug-induced differences may have been masked by the severity of the cardiac disease/repair and age.

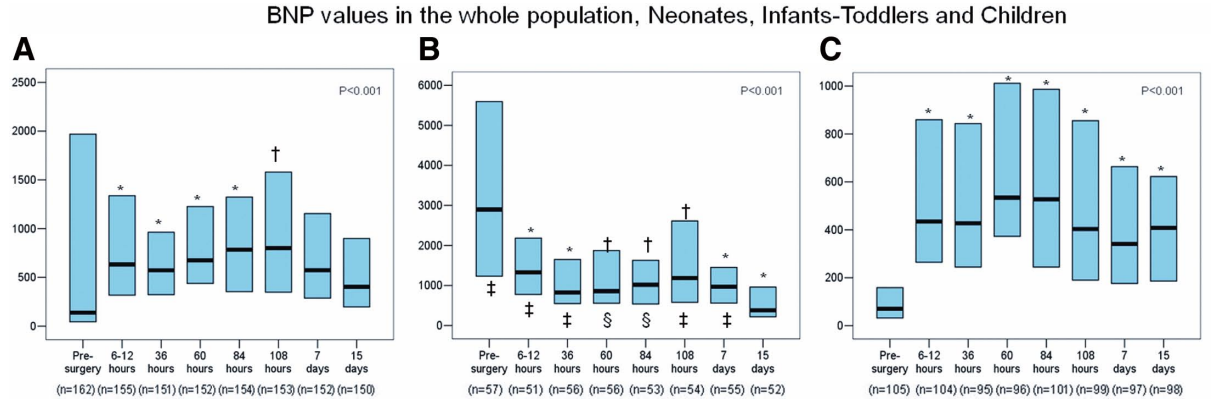

Figure 3. Time course of brain natriuretic peptide (BNP; ng/L) circulating levels in (**A**) the whole group, (**B**) neonates and (**C**) infants-toddlers and children. Bold horizontal line, median; box, interquartile range. *P<0.001 and †P<0.05 for differences with pre-surgery levels. ‡P<0.001 and §P<0.05 for differences between neonates and infants-toddlers and children at each time point.

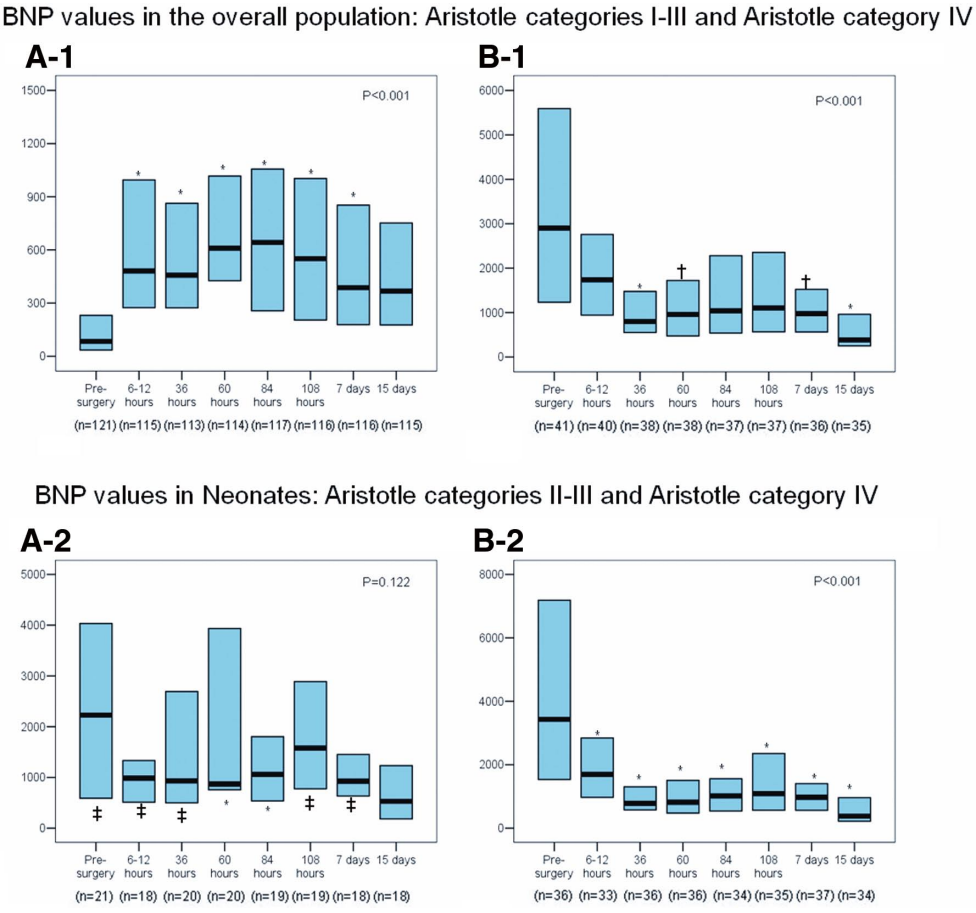

Figure 4. Time course of brain natriuretic peptide (BNP; ng/L) circulating levels in the whole group and in neonates according to disease severity. (**A-1**) Aristotle categories I–III overall; (**B-1**) Aristotle category IV overall; (**A-2**) Aristotle categories II–III in neonates; (**B-2**) Aristotle category IV in neonates. Bold horizontal line, median; box, interquartile range. *P<0.001 and †P<0.05 for differences with pre-surgery levels. ‡P<0.001 and §P<0.05 for differences between neonates and infants-toddlers and children at each time point.

Table 3. Cox Proportional Hazard Regression for Chance of Extubation

	Infants-Toddlers-Children (n=105)			Neonates (n=57)		
	HR (95%CI)	P-value	Harrell's C index (95% CI)	HR (95%CI)	P-value	Harrell's C index (95% CI)
Univariate models						
Female vs. Male	1.03 (0.70–1.52)	0.892	0.49 (0.43–0.55)	0.89 (0.49–1.61)	0.690	0.52 (0.43–0.61)
BSA	1.94 (1.52–2.47)	<0.001	0.71 (0.64–0.77)	1.22 (0.12–12.68)	0.868	0.52 (0.41–0.64)
TSH before surgery	0.83 (0.74–0.94)	0.002	0.61 (0.54–0.69)	1.05 (0.92–1.20)	0.444	0.51 (0.42–0.60)
fT3 before surgery	1.08 (0.87–1.34)	0.486	0.54 (0.46–0.61)	1.21 (0.887–1.64)	0.233	0.55 (0.45–0.65)
fT4 before surgery	0.95 (0.86–1.06)	0.363	0.56 (0.48–0.63)	0.98 (0.90–1.07)	0.690	0.54 (0.44–0.65)
BNP before surgery (log.tranf.)	0.83 (0.70–0.97)	0.023	0.60 (0.53–0.67)	0.89 (0.74–1.08)	0.235	0.58 (0.48–0.68)
TSH nadir	1.07 (0.73–1.56)	0.744	0.50 (0.38–0.61)	1.48 (1.16–1.89)	0.002	0.77 (0.71–0.82)
fT3 nadir	1.90 (1.23–2.94)	0.004	0.67 (0.58–0.76)	2.55 (1.63–4.00)	<0.001	0.69 (0.59–0.79)
fT4 nadir	1.36 (1.11–1.66)	0.003	0.70 (0.62–0.79)	1.30 (1.14–1.49)	<0.001	0.70 (0.62–0.78)
BNP peak (log.tranf.)	0.73 (0.60–0.89)	0.002	0.62 (0.52–0.72)	0.57 (0.38–0.86)	0.007	0.62 (0.51–0.72)
CPB time	0.996 (0.993–0.999)	0.003	0.63 (0.56–0.70)	0.991 (0.986–0.995)	<0.001	0.70 (0.61–0.79)
Cross-clamp	0.997 (0.992–1.00)	0.120	0.58 (0.51–0.65)	0.992 (0.986–0.999)	0.029	0.64 (0.54–0.75)
Aristotle score	0.86 (0.78–0.96)	0.007	0.59 (0.52–0.66)	0.75 (0.64–0.87)	<0.001	0.74 (0.66–0.82)
Multivariate	0.73 (0.64–0.82)			0.79 (0.72–0.87)		
BSA	1.78 (1.06–3.00)	0.029		–	–	
TSH nadir	–	–		1.35 (1.02–1.79)	0.036	
fT3 nadir	2.49 (1.52–4.09)	<0.001		2.61 (1.49–4.58)	0.001	
BNP peak (log.tranf.)	0.75 (0.61–0.92)	0.007		0.71 (0.43–1.18)	0.191	
Aristotle score	0.95 (0.81–1.11)	0.513		0.82 (0.69–0.99)	0.037	

Peak and nadir values are limited to the intubation time.
CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Thyroid Response According to Severity of Cardiac Disease and Type of Repair

When patients were divided according to Aristotle ABC score a disease severity effect emerged for both TSH (P<0.001) and fT3 (P<0.001), while no effect was found for fT4 (P=0.683).

A second analysis was then performed to look at the independent effect of disease severity and age, by excluding ABC I and IV, in which the age effect is clearly dependent on different severity. Disease severity-related difference was no longer significant for fT3 and fT4 (P=0.100 and P=0.613, respectively), and for TSH (P=0.131); age-related difference still remained for both fT3 and fT4 (P=0.049 and P=0.004, respectively), while TSH was borderline significant (P=0.052). When neonates in ABC score II–III were analyzed separately they clearly differed from older children with the corresponding ABC score (P=0.027 for fT3 and P=0.005 for fT4).

BNP Response According to Age

Considering the group as a whole, BNP increased after surgery compared to the preoperative value by 6–12 h (P<0.001), reaching a peak at 108 h (P<0.001). A progressive decrease occurred thereafter, with levels similar to that before surgery by 7 days (P=0.098). As previously described for thyroid hormones, BNP showed a different pattern according to age, with marked differences between neonates and older children (Figure 3).

In neonates baseline BNP, which was significantly higher than in older children (P<0.001) and age-matched controls (P<0.001), dropped postoperatively with a nadir at 36 h (P<0.001). In contrast, older children had a significant increase in BNP at the same time, with a peak at 84 h (P<0.001).

The BNP time course also differed markedly among neonates and older children starting from the first day following surgery. After the initial decrease, BNP peaked later in neonates (108 h, P=0.015) and then progressively decreased, with the level at 15 days significantly lower than that preoperatively (P<0.001).

The late BNP peak was not observed in older children, for whom BNP progressively decreased after the initial peak. BNP, however, did not normalize within the period of observation, remaining higher than the preoperative level at both the 7 days (P<0.001) and 15 days (P<0.001).

Baseline BNP was significantly higher in neonates with CHD compared to controls (P<0,001). But when neonates were divided into 2 age groups (4–7 days of life and 8–30 days of life), BNP did not significantly differ (median, 3,575 ng/L; 2,175 ng/L and 5,800 ng/L; median, 2,838 ng/L; 859 ng/L and 5,593 ng/L, respectively). Furthermore when CHD was divided into 2 categories of disease (cyanotic defects and non-cyanotic CHD with significant left-to-right shunt), no significant differences in BNP were observed (median, 2,899 ng/L; 1,231 ng/L and 5,800 ng/L; median, 2,998 ng/L; 1,055 ng/L and 4,916 ng/L, respectively). Based on this finding, as for thyroid hormones, for BNP all neonates surgically treated before 1 month of life were considered as a single group.

BNP Response According to Severity of Cardiac Disease and Type of Repair

As observed for thyroid, BNP response differed according to Aristotle ABC score (P<0.001, Figure 4). When adjusting for age, however, differences in BNP were completely absorbed by age (P<0.001 and P=0.643 for disease severity, respectively). This is well demonstrated for neonates in ABC II and III, who differed from older children in the same ABC score but not from neonates in ABC IV.

Correlations

For the entire cohort, negative correlations (Table 3) were found between TSH nadir and both clinical and outcome parameters, including the Aristotle score (P<0.001), TTE (P<0.001), ICU stay (P<0.001) and inotrope duration (P<0.001). These correlations were particularly strong in neonates. A positive correlation was found between preoperative TSH and fT3 and their nadirs (P<0.001).

Also basal BNP was positively related with both clinical and outcome parameters, including the Aristotle score (P<0.001), TTE (P<0.001), ICU stay (P<0.001) and inotropic support (P<0.001). Post-surgical BNP negatively correlated with fT3 in neonates (P<0.05) and with TSH in older children (P<0.05). Moreover, peak BNP positively correlated with TTE (P<0.001), ICU stay (P<0.001), CPB (P<0.001), and inotropic support (P<0.001), overall and in each age group. Post-surgery BNP also significantly correlated with ejection fraction (P<0.05), central venous pressure (P<0.05) and serum lactate (P<0.05).

Survival Analysis

TTE was significantly longer in neonates (P<0.001 for log-rank test) than in older children. Infants and toddlers-children had similar TTE (Figure 5) so these 2 groups are presented together in Cox models.

In all age groups, univariate Cox models showed a lower probability of extubation for higher Aristotle score, lower fT3 and fT4 nadir and higher BNP peak. In neonates univariate models showed that TTE was also significantly affected by TSH nadir, while in older children major predictors of TTE were body surface area and pre-surgical BNP and TSH.

On multivariate analysis performed for separate groups, in older children fT3 nadir, BNP peak and body surface area remained the only significant predictor affecting TTE.

In neonates fT3 nadir remained a significant predictor of TTE in the multivariate model, together with TSH nadir and Aristotle score. Peak BNP, however, was no longer meaningful when fT3 was entered into the model (Table 3).

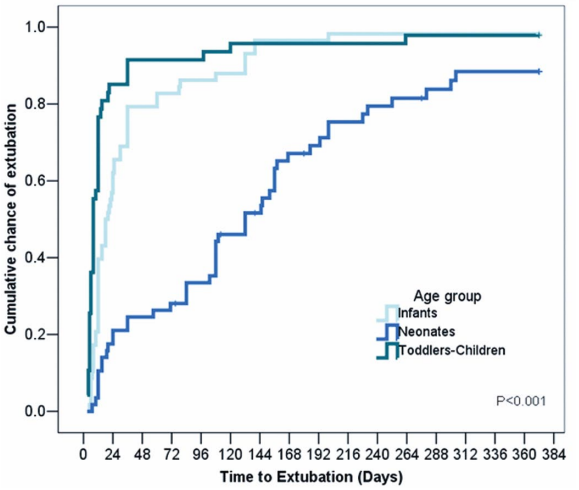

Figure 5. Kaplan-Meier curves for probability of extubation vs. age group (P-value, log-rank test).

Discussion

Our principal objective was to examine the relationships between the principal biomarkers of thyroid hormone status (ie, T4, T3 and TSH) with the cardiac marker BNP according to age and/or severity of cardiac disease in young children undergoing cardiac surgery for correction/palliation of congenital heart defects. Prior studies have clearly outlined disturbances in thyroid hormone homoeostasis[1–11] as well as alterations in BNP,[12–19] which are associated with cardiac surgery in these young patients. With respect to thyroid hormone, Portman et al studied the largest cohort of infants as part of the TRICC clinical trial.[11] Previous investigations, however, did not clearly separate out the very vulnerable neonatal population from the older cohort undergoing lower risk surgery.[11,18] Accordingly, the present study contains the largest defined neonatal cohort, with evaluation of their hormone levels during the perioperative period, to date.

The major result of the present study is that hormonal response after cardiac surgery differs significantly among age groups, and neonates clearly need to be separated from older children.

Neonatal age is particularly challenging for several reasons, including the severity of cardiac disease treated at that time and the maturational variations occurring within the early weeks of life.

As far as the complexity of cardiac disease is concerned, it is well known that most of the life-threatening congenital heart diseases have a neonatal presentation and that usually neonatal cardiac surgery carries a higher operative risk and a more troublesome postoperative period than surgery performed at older age.[20] This is expressed, in term of hormonal response, preoperatively by higher BNP and lower TSH and postoperatively by a longer and greater severity of disease, as documented by persistently low TSH and fT3 concentrations.

In particular, the present study documents the perioperative differences between neonates with more severe cardiac disease/repair and older infants and children with less severe cardiac disease/repair with regard to thyroid hormone homeostasis. Both cohorts undergo rapid suppression of both TSH and fT3, with the nadirs occurring somewhat later in more compromised patients (ie, mostly neonates) than less compromised patients (ie, mostly older infants). From a pathophysiological perspective, several studies have already showed that inflammatory cytokines, and in particular interleukin-6, are able to inhibit peripheral conversion of fT4 to fT3 after CPB.[1,3,10,11]

Moreover, fT4, although also suppressed in less compromised infants, undergoes only a late and relatively meager drop in more compromised neonates. The discrepancy in the fT4 response, as well as persistent low fT3 even after TSH recovery in more severely ill patients, suggests that disruption in thyroid homeostasis extends beyond inhibition at the pituitary level in relation to the severity of disease.

The different neonatal hormonal response after cardiac surgery, however, cannot be entirely explained by the higher complexity of the cardiac disease and its related surgery; instead, age also plays a role. In fact, when the independent effect of disease severity and age on thyroid response was analyzed, only age remained significant. In particular, neonates had a different hormonal response and a more adverse outcome compared with older children with the same Aristotle ABC score, but hormonal trends (and outcome) were similar regardless of Aristotle score.

The adjunctive relevance of age is even more evident in BNP response, in that differences according to disease severity were completely absorbed by age. Paradoxically, BNP drops after cardiac surgery in neonates while increasing in older in-

fants and children. The postoperative drop of BNP in neonates may reflect an improvement in cardiac hemodynamic as reinforced by the strong correlations, in the neonatal age group, of BNP with parameters of cardiac preload (ie, central venous pressure) and oxygen delivery/utilization (ie, venous lactate). A possible contributor of post-surgical BNP drop in the neonatal age group may be represented by physiological changes of BNP that are much more pronounced in the first days of life but tend to progressively decrease during the first month of life.[26,27] Maturational decrease of BNP, however, is linear while post-surgical neonatal BNP quickly drops. Furthermore, major postnatal variations in BNP generally occur within the first 4 days of life;[27] but in the present study surgical treatment was done only in a negligible number of babies (n=5), in that time period.

Heart disease appears to be better compensated in children, as reflected by the lower preoperative BNP concentration. As previously hypothesized, the increase in BNP may be mainly due to transient post-surgical ventricular dysfunction,[12–18] well expressed by the negative correlation between BNP and ejection fraction. Furthermore, also in agreement with previous recent observations in adult cardiovascular patients,[28] multivariate analysis clearly indicated that fT3 and BNP may provide in older children complementary prognostic information.

In the present study we used a recognized clinical endpoint,[11] TTE, as the primary outcome. Although there is some correlation with TTE and peak BNP, the major finding using a Cox proportional hazards model is confirmation that fT3 nadir after cardiac surgery strongly relates to TTE. Prior studies have suggested using T3 as a prognostic predictor, although this has not been specifically evaluated in a large neonatal cohort.[2–10] The clinical utility of this single parameter, however, is doubtful because it occurs so late in the postoperative period. Nevertheless, fT3 nadir appears to relate to the overall time course for fT3 concentrations. Accordingly, as a flow chart, one may suggest a strategy to serially monitor fT3 in these patients, and alter intervention if it continues to decline. Alternatively, in children aged <5 months supplementation would always be indicated, as suggested by the TRICC trial, because the low T3 may be the source of poor clinical outcome and intervention.[11] The present results may thus open the way for a focused randomized clinical trial on the issue by stratifying patients (and outcomes) also according to age and severity of disease and intervention.

Study Strengths and Limitations

This study has several strengths. First, we used a prospective cohort design and a rigorous protocol to collect specimens. Also follow-up after surgery (15 days) was long enough to clearly define the time course of utilized biomarkers. Second, we enrolled a sufficiently homogeneous cohort of children undergoing cardiac surgery, with the inclusion of a significant number of neonates.

This study, however, does have some important limitations. First, the total number of studied patients was relatively low compared to large trials performed in adults. Studies with a larger number of children are recommended in order to better understand hormonal response for individual CHD. Second, blood samples for research purposes were reduced for ethical reasons only to necessity of treatment and to the period of observation. Consequently, the number of blood determinations is limited, although much higher than that utilized in almost all similar studies reported so far.[4–10,14–18] The difficulty in performing blood samples in children, especially in neonates needs, however, to be further considered when dealing with this age group.

The use of corticosteroids may potentially alter hormonal response but, because dexamethasone was given to all the patients, it is unlikely that the drug's effects could have altered the results.

Conclusion

The pattern of thyroid and BNP response largely differs in pediatric cardiac surgery patients. These differences seem to be mainly related to the higher severity of neonatal disease and to the difficulty of its surgical correction and only partially to age and to incomplete maturation of the hormone systems in neonates.

Disclosures

Authors' conflict of interest disclosure, research founding, employment or leadership: None declared.

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