The relationship of natriuretic peptides and hemodynamic parameters following heart surgery in infancy

Ph.D. thesis

Tamás Breuer M.D.

Semmelweis University
Doctoral School of Basic Medicine

Supervisor: Prof. Miklós Tóth M.D., Ph.D., D.Sc.
Consulent: Andrea Székely M.D., Ph.D.

Opponents: Prof. Ildikó Horváth M.D., Ph.D., D.Sc.
Barna Babik M.D., Ph.D.

Head of the Examination Committee: Prof. István Karádi M.D., Ph.D., D.Sc.
Members of the Examination Committee: Miklós Szabó M.D., Ph.D.
Ilona Bobek M.D., Ph.D.

Budapest
2010

Introduction

The atrial natriuretic peptide (ANP) and the N-terminal fragment of its prohormone (NT-proANP) are released primarily by the atrial myocytes; brain natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (NT-proBNP) are synthesized both in the atrial and ventricular myocardium due to volume and pressure overload. Recently, a new immunoassay has been developed for a hybrid peptide (referred as NT-proXNP) containing peptide sequences from both NT-proANP and NT-proBNP. This novel assay mimics the physiological signaling pathway since the actions of the different active natriuretic fragments on the target cells are mediated by a single natriuretic peptide receptor. The NT-proXNP assay measures the concentration of the new virtual natriuretic peptide, and thus provides combined information about the plasma levels of NT-proANP and NT-proBNP. In cardiac diseases, the neurohormonal system of the heart is activated. The diagnostic performances of NT-proXNP in adults for coronary artery disease and valvular heart disease are greater than or equal to those of NT-proANP or NT-proBNP, individually.

In the pediatric postoperative intensive care, continuous hemodynamic monitoring is still a problematic issue despite of its clinical importance. Clinical signs of low cardiac output, as cold extremities, tachycardia and decreased urinary output are mostly nonspecific and their assessment depends on the skill and experiences of the practitioner. Recently, transpulmonary thermodilution (TPTD) and pulse contour analysis have become feasible techniques for hemodynamic monitoring in adults due to their safe and less invasive methods and the wide spectrum of the measured parameters. Their applications have been validated in the pediatric intensive care and after pediatric cardiac surgery as well.

Cardiac biomarkers, as creatine kinase-MB (CKMB), troponin and natriuretic peptides, have been used for estimation of cardiac performance and myocardial damage and for prediction of complications after cardiac surgery. In the pediatric population, natriuretic peptide levels are elevated in cardiac dysfunction, congestive heart failure and congenital heart diseases. The role of natriuretic peptides in pediatric cardiac surgery has only been recently investigated and still controversial.

Aims of the study

1. Aim of the study was to examine the perioperative time course of NT-proANP and NT-proBNP in neonates and infants undergoing corrective open heart surgery.

2. We aimed to investigate the clinical applicability of the new virtual natriuretic peptide analyte, NT-proXNP, and its relation to NT-proANP and NT-proBNP levels in children under the age of 1 year.

3. We aimed to examine the perioperative time course of NT-proXNP in neonates and infants undergoing open heart surgery.

4. We aimed to investigate the perioperative changes of the hemodynamic parameters measured by transpulmonary thermodilution and their role in the postoperative evaluation of the circulatory state in neonates and infants undergoing corrective open heart surgery.

5. Our aim was to establish reference values of the invasive hemodynamic parameters in infants after heart surgery in a stable cardiorespiratory state.

6. We aimed to elucidate the relationships between the natriuretic peptide levels, the new virtual natriuretic peptide analyte, NT-proXNP, and the postoperative hemodynamic parameters measured by transpulmonary thermodilution in neonates and infants undergoing corrective heart surgery.

7. We aimed to investigate the associations of the invasive hemodynamic parameters and the clinical and laboratory values obtained routinely in our department for the evaluation of the circulatory state after pediatric cardiac surgery.

8. We aimed to analyze the possible diagnostic and prognostic role of the natriuretic peptide levels following heart surgery in infancy.

Methods

After obtaining approval of the Institutional Ethic Committee of the Gottsegen György Hungarian Institute of Cardiology and parental informed consent, 30 children under the age of 1 year were enrolled into this prospective study between February 2004 and March 2006. All patients underwent elective cardiac operation with cardiopulmonary bypass (CPB) to achieve complete biventricular repair. Routine postoperative echocardiography examination showed no residual intracardiac shunt in the patients. The study was performed in accordance with the most recent version of the Helsinki Declaration.

Preoperative history, echocardiogram, and catheterization data were reported by the attending cardiologist. Procedure and intraoperative data were collected by reviewing the surgical notes and anesthesia reports. Anesthesia and CPB was performed with standard technique according to the institutional protocol of the clinic. Hypothermia was induced according to the individual operation protocol (28-30 °C). Indication of ultrafiltration was at the discretion of the attending anesthesiologist and was used in two patients.

Hemodynamic status was assessed by routinely monitored parameters such as heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), peripheral oxygen saturation, and 2-channel electrocardiogram. Pulse-pressure product (PPP) was calculated as a product of HR and MAP. Echocardiography was performed daily. The systolic left ventricle function of the patients was evaluated by fractional shortening (FS) which was calculated using M-mode echocardiography from the standard long-axis view as follows: left ventricular end-diastolic diameter - left ventricular end-systolic diameter / left ventricular end-diastolic diameter x 100 (percent). The right ventricular systolic pressure (RVSP) was calculated from the peak velocity of the tricuspid regurgitation jet (V) using the Bernoulli equation, where the right atrial systolic pressure (RA) was measured directly from central venous line or estimated ($RVSP\text{-}RA = 4(V)^2$).

Transpulmonary thermodilution (TPTD) measurements enabled intermittent calculation of cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI) and additional parameters, e.g. global ejection fraction (GEF), global end diastolic volume index (GEDI), intrathoracic blood volume index (ITBI), and extravascular lung water index (ELWI). Indexed hemodynamic parameters were calculated following estimation of body surface area from body height and body weight. Hemodynamic parameters were recorded after induction of anesthesia, prior to skin incision (PRE), after termination of CPB, following skin closure (POP) and 12, 24, 48 and 72 hours after arrival (POP12, POP24, etc.) at the postoperative intensive care unit (ICU), and in case of severe circulatory alterations.

Thermodilution measurements were performed in duplicate or triplicate with 3 ml cold injectate into the right internal jugular vein through a double lumen catheter (PiCCO system V4.12, Pulsion Medical Systems, Munich, Germany; Philips CMS System, Endower, Massachusetts). The average of the results of the measurements performed at the same time point was used for statistical analysis. For thermodilution, a 3 french (Fr) thermistor tipped arterial catheter (PV 2013L07 Pulsiocath, Pulsion Medical Systems, Munich, Germany) was inserted into the femoral artery of the study patients after induction of anesthesia. Catheters were removed when patients were ready to be discharged from the ICU, in cases of possible catheter-related infection (in 1 patient on the first postoperative day), and in cases of limb ischemia (none of our patients). Participation in the study and catheter-related complications caused no delay in discharge from the ICU.

Natriuretic peptide levels were determined from blood samples (2 ml) drawn at the same time points when hemodynamic measurements were taken. Venous serum samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes. Within 1 hour, the samples were centrifuged at 3000 g for 10 minutes at +4°C. Plasma samples were stored at –20°C before the analysis. NT-proANP (antiserum to NT-proANP$_{46-79}$) and NT-proBNP (antiserum to NT-proBNP$_{10-29}$) contents were determined by radioimmunoassay. The sensitivities of the assays were 60 pmol/l and 40 pmol/l, respectively. NT-proXNP was determined by specific antisera recognizing the recombinant hybrid peptide (NT-proBNP$_{1-37}$-NT-proANP$_{29-98}$). The detection limit of

the assay is considered 80 pmol/l. Patients were treated without any information of natriuretic peptide values.

Inotropic support, fluid balance (ml/kg) and urine output (ml/kg) data were collected during the first postoperative 72 hours. The cumulative index of inotropic support was quantified by the total inotropic dose proposed by Wernovsky, which was modified after the introduction of milrinone treatment: dopamine (µg/kg/min) + dobutamine (µg/kg/min) + 100 X epinephrine (µg/kg/min) + 100 X norepinephrine (µg/kg/min) + 20 X milrinone (µg/kg/min). Partial arterial oxygen tension (PaO_2/FiO_2), base excess, and core-peripheral temperature difference were recorded hourly. Laboratory values, including C-reactive protein (CRP), blood urea nitrogen (BUN) and serum creatinine, were determined at PRE, POP24 and POP48. CKMB and lactate dehydrogenase (LDH) were also measured upon arrival in the ICU. The estimated creatinine clearance (CCl) was calculated according to the Schwartz-formula.

Continuous parameters are presented as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. For comparison of natriuretic peptide values at different time points, repeated measures of ANOVA analysis was used. Pearson's correlation analysis was used to investigate the associations of different continuous variables. When data from all the postoperative measurements were analyzed together, weighted correlations were calculated after calculating the mean of the analyzed parameters for every subjects. ROC analysis was used to determine the diagnostic and prognostic value of natriuretic peptides indicative of CI lower than 3 $l/min/m^2$ and mechanical ventilation longer than 72 hours. For parametric analyses, non-normally distributed parameters were transformed to their natural logarithm to correct the intrinsic skew in their distribution. A p value < 0.05 was considered significant. SPSS for Windows 11.5 and 16 (SPSS Inc., Chicago, IL) was used for all statistical evaluation.

Results

Fifteen patients underwent arterial switch operation because of transposition of the great arteries. Nine patients had ventricular septal closure, other congenital heart defects were double outlet right ventricle (n=3), total anomalous pulmonary venous return (n=2) and a truncus arteriosus communis. Of the 30 enrolled patients, the natriuretic peptide levels were evaluated in 26 patients. In these patients, median age was 46 (IQR: 10-157) days, median weight was 3.9 (3.5-4.9) kg. Median CPB time was 117 (60-149) minutes, aorta cross-clamp time was 69 (29-92) minutes. Nine patients were treated with delayed sternal closure; twelve patients were mechanically ventilated more than 72 hours; none of the patients died.

The median baseline level of NT-proANP was 1915 (1055-4542) pmol/l, more than twice as high as that of NT-proBNP [700 (126-1784) pmol/l]. The baseline NT-proXNP value was between that of the other natriuretic peptides [1375 (238-6063) pmol/l]. A significant postoperative increase compared to baseline was found for NT-proBNP levels reaching the peak value 24 hours after the operation. Peak levels of NT-proANP, NT-proBNP and NT-proXNP after the operation were 2565 (1991-5404), 2221 (1223-5180) and 4031 (1165-10200) pmol/l, respectively. NT-proXNP level correlated significantly with the simultaneously measured NT-proANP level ($r = 0.60$, $p < 0.001$), but more strongly with NT-proBNP level ($r = 0.89$, $p < 0.001$) and the arithmetic sum of both peptides throughout the perioperative period ($r = 0.88$, $p < 0.001$).

Baseline NT-proXNP level correlated with the age ($r = -0.72$, $p < 0.001$) and the weight of the patients ($r = -0.47$, $p = 0.026$). Preoperative creatinine level (53.3 ± 13.1 μmol/l) correlated with baseline NT-proXNP ($r = 0.53$, $p = 0.013$). The duration of operation and the duration of CPB were associated with the preoperative NT-proXNP level ($r = 0.58$, $p = 0.005$ and $r = 0.62$ $p = 0.002$, respectively) and the peak postoperative NT-proXNP level ($r = 0.64$, $p < 0.001$ and $r = 0.67$, $p < 0.001$, respectively). NT-proBNP showed similar correlations with the duration of operation and CPB.

The mean preoperative value of cardiac index (CI) was 3.6 l/min/m^2 (SD: 1.1 l/min/m^2). Cardiac function temporarily declined following CPB. The lowest value of CI was 2.5 ± 1.1 l/min/m^2 at 12 hours after the operation; it reached the baseline level 24 hours after surgery (3.6 ± 1.7 l/min/m^2), and further improved (POP48: 4.2 ± 2.8 l/min/m^2). The time course of stroke volume index (SVI) was similar to that of CI.

In the postoperative period, natriuretic peptide levels correlated significantly with the simultaneously assessed hemodynamic parameters (Table 1.). NT-proXNP correlated stronger with the hemodynamic parameters except for ELWI than the arithmetic sum of NT-proANP and NT-proBNP. The correlation between NT-proXNP and CI remained significant after adjusting for age ($r = 0.60$, $p = 0.018$) or weight ($r = 0.81$, $p < 0.001$).

Table 1. Correlations between natriuretic peptide levels and hemodynamic parameters

	NT-proANP		NT-proBNP		NT-proXNP		Summa NT-proANP + NT-proBNP	
	r	*p*	r	*p*	r	*p*	r	*p*
HR	0,46	0,073	0,54	**0,033**	0,53	**0,034**	0,52	**0,039**
MAP	-0,45	0,077	-0,84	**<0,001**	-0,87	**<0,001**	-0,81	**<0,001**
CI	-0,69	**0,003**	-0,71	**0,002**	-0,85	**<0,001**	-0,71	**0,002**
SVI	-0,75	**0,002**	-0,66	**0,010**	-0,80	**<0,001**	-0,72	**0,004**
SVRI	0,67	**0,009**	0,52	0,055	0,65	**0,012**	0,54	**0,045**
GEF	-0,35	0,22	-0,62	**0,018**	-0,67	**0,009**	-0,61	**0,022**
GEDI	-0,70	**0,005**	-0,33	0,25	-0,48	0,079	-0,40	0,15
ITBI	-0,64	**0,007**	-0,38	0,14	-0,50	**0,047**	-0,39	0,14
ELWI	0,75	**0,003**	0,64	**0,020**	0,67	**0,012**	0,72	**0,005**
PPP	-0,29	0,17	-0,23	0,27	-0,24	0,24	-0,32	0,11

Significant values are indicated by bold. CI, cardiac index; ELWI, extravascular lung water index; GEDI, global end-diastolic volume index; GEF, global ejection fraction; HR. heart rate; ITBI, intrathoracic blood volume index; MAP, mean arterial pressure; NT-proANP, N-terminal pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; NT-proXNP, the concentration of the new hybrid peptide; SVI, stroke volume index; SVRI, systemic vascular resistance index; PPP, pulse pressure product..

Besides, CI correlated with HR ($r = -0.61$, $p = 0.013$). Other conventionally measured parameters such as MAP and pulse-pressure product, and parameters measured by echocardiography i.e. FS and calculated pressure of the right ventricle showed no correlation with CI. Among laboratory values, creatinine levels correlated significantly with CI ($r = -0.77$, $p < 0.001$) and NT-proXNP levels ($r = 0.76$, $p < 0.001$) throughout the postoperative period. Other measured laboratory and clinical values were not associated with these parameters. Neither the urine output nor the fluid balance was related to CI and NT-proXNP.

In ROC analysis, a postoperative NT-proBNP level of 2051 pmol/l was diagnostic for CI lower than 3 $l/min/m^2$ with 79% sensitivity and 95% specificity (AUC: 0.87 ± 0.06), whereas a postoperative NT-proXNP level of 3079 pmol/l was diagnostic for that with 89% sensitivity and 90% specificity (AUC: 0.91 ± 0.05). The length of mechanical ventilation and ICU stay did not correlate with the baseline or the peak natriuretic peptide levels. NT-proBNP and NT-proXNP, but not NT-proANP level at 24 hours after surgery were correlated to the length of mechanical ventilation ($r = 0.51$, $p = 0.015$ and $r = 0.47$, $p = 0.027$, respectively). The area under the curve (AUC) of NT-proBNP and NT-proXNP at 24 hours after surgery for prolonged mechanical ventilation (> 72h) in ROC analysis was 0.81 ± 0.10 and 0.72 ± 0.11, respectively.

In a subgroup of 12 patients who underwent anatomic corrections of transposition of the great arteries, hemodynamic parameters were compared before and after sternal closure and after extubation (Table 2.). Most hemodynamic parameters improved throughout the postoperative period. After sternal closure, CI and SVI were significantly higher; SVRI, HR and ELWI were significantly lower compared to the open chest measurements. There were also significant differences in CI, SVI, HR, GEF and ELWI before and after extubation. The latter measurements were made in patients with a stable cardiorespiratory condition, thus we considered these results as normal values in this population. The CI value was in the adult reference range, whereas GEDI and ITBI were lower, ELWI was higher than that.

Table 2. Hemodynamic parameters in the postoperative period

	Open chest (1) n = 47	Closed chest (2) n = 91	After extubation (3) n = 7	ANOVA *p*	1 vs. 2 *p*	1 vs. 3 *p*	2 vs. 3 *p*
CI (l/min/m^2)	2,1 ± 0,6	3,1 ± 1,1	4,0 ± 0,6	**<0,001**	**<0,001**	**<0,001**	**0,005**
SVI (ml/m^2)	15,5 ± 3,3	22,7 ± 7,5	33,1 ± 4,3	**<0,001**	**<0,001**	**<0,001**	**<0,001**
MAP (Hgmm)	57 ± 10	61 ± 9	68 ± 7	**0,002**	0,10	**0,003**	0,059
SVRI (dyn*s/cm^5/m^2)	1639 ± 243	1411 ± 396	1150 ± 295	**<0,001**	**0,005**	**<0,001**	0,067
HR (BPM)	165 ± 17	145 ± 18	128 ± 8	**<0,001**	**<0,001**	**<0,001**	**0,003**
GEF (%)	22,3 ± 11,3	25,6 ± 6,0	35,8 ± 8,0	**<0,001**	0,16	**<0,001**	**0,002**
GEDI (ml/m^2)	298 ± 120	355 ± 123	404 ± 103	**0,016**	0,05	0,06	0,76
ITBI (ml/m^2)	398 ± 134	454 ± 147	489 ± 125	0,067			
ELWI (ml/kg)	37,3 ± 6,6	32,4 ± 8,5	20,2 ± 7,0	**<0,001**	**0,021**	**<0,001**	**0,002**

Data are expressed as mean ± standard deviation (SD). Significant values are indicated by bold. CI, cardiac index; ELWI, extravascular lung water index; GEDI, global end-diastolic volume index; GEF, global ejection fraction; HR. heart rate; ITBI, intrathoracic blood volume index; MAP, mean arterial pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index.

Conclusions

1. We presented the perioperative time course of NT-proANP and NT-proBNP in neonates and infants undergoing open heart surgery. NT-proANP did not change significantly, whereas NT-proBNP significantly increased reaching the peak value 24 hours after the operation. The postoperative elevation of NT-proBNP might be a marker of myocardial damage related to open heart surgery.

2. The level of the new virtual natriuretic peptide analyte, NT-proXNP, significantly correlated to the simultaneously measured NT-proANP level, and more strongly to the NT-proBNP level and the arithmetic sum of both peptides throughout the perioperative period. According to our results, the NT-proXNP assay can simultaneously detect the activation of ANP and BNP systems in the investigated population regardless of whether they are activated alone or together.

3. The baseline NT-proXNP value was between the level of NT-proANP and NT-proBNP. The preoperative time course of NT-proXNP followed that of the other natriuretic peptides. We proved the clinical applicability of the novel immunoassay in children under the age of 1 year undergoing open heart surgery.

4. We described the values of the hemodynamic parameters in neonates and infants undergoing heart surgery. The hemodynamic parameters improved during the postoperative period as the myocardium recovered. The application of transpulmonary thermodilution was safe and reliable following pediatric cardiac surgery. The invasive hemodynamic monitoring provided by the method adds useful information for the evaluation of the circulatory state in neonates and infant following open heart surgery.

5. The reference value of cardiac index in children in a stable cardiorespiratory condition did not differ from adult reference values. However, the other measured hemodynamic values differed from the adult normal values reported by the manufacturer. We found that lower GEDI and ITBI values and higher ELWI values were tolerable for neonates following arterial switch operation. Age related

and disease specific reference values of the transpulmonary thermodilution parameters are yet to be determined in children.

6. Natriuretic peptide levels had strong inverse correlations with cardiac index throughout the postoperative period. NT-proXNP enabled a better assessment of cardiac function than the other natriuretic peptides alone or the arithmetic sum of NT-proANP and NT-proBNP. The additional correlations of the natriuretic peptide levels and the hemodynamic parameters indicate that natriuretic peptides, and particularly NT-proXNP, are good markers of hemodynamic function not only in chronic heart failure, but in acute settings as well.

7. Conventionally measured parameters such as heart rate, mean arterial pressure and pulse-pressure product exhibited weaker correlations with CI than natriuretic peptide levels. Parameters measured by echocardiography i.e. fractional shortening and calculated pressure of the right ventricle were not correlated to CI. Clinical and laboratory values, except for creatinine level and creatinine clearance, showed no correlation with CI or NT-proXNP. According to our findings, natriuretic peptides and NT-proXNP are indicators of hemodynamic parameters following pediatric cardiac surgery that can only be measured by invasive hemodynamic monitoring.

8. Elevated postoperative NT-proBNP and NT-proXNP level were diagnostic for low cardiac output with high sensitivity and specificity following cardiac surgery in infants. Besides, their levels at 24 hours after surgery had good prognostic values for mechanical ventilation longer than 72 hours. NT-proXNP is a novel non-invasive diagnostic tool which may be applicable for the global assessment of different aspects of hemodynamic function and for the follow up of patients following pediatric open heart surgery.

References

Related publications:

1. **Breuer T**, Sápi E, Skoumal R, Tóth M, Ala-Kopsala M, Vuolteenaho O, Leppäluoto J, Ruskoaho H, Szatmári A, Székely A. N-terminal pro-brain natriuretic peptide level inversely correlates with cardiac index after arterial switch operation in neonates. *Pediatric Anesthesia* 2007; 17: 782-8. IF: 1.461.
2. **Breuer T**, Skoumal R, Horkay F, Merkely B, Ala-Kopsala M, Leppäluoto J, Vuolteenaho O, Ruskoaho H, Tóth M., Székely A. Strong relationship between NT-proXNP levels and cardiac output following cardiac surgery in neonates and infants. *Acta Anaesthesiologica Scandinavica* 2010; 54: 502-9. IF: 2.260.
3. Székely A, **Breuer T**, Sápi E, Székely E, Szatmári A, Tóth M, Hauser B, Gál J. Transpulmonary thermodilution in neonates undergoing arterial switch surgery. *Pediatric Cardiology* 2010; doi: 10.1007/s00246-010-9828-0 [in pr.]. IF: 1.151.
4. **Breuer T**, Székely A. A nátriuretikus peptidek rövid jellemzése és az új, virtuális nátriuretikus peptid (NT-proXNP). *Aneszteziológia és Intenzív Terápia* [in press].

Other publications:

1. Székely A, **Breuer T**. Az altatógázok prekondicionáló és kardioprotektív tulajdonságai. *Lege Artis Medicinae* 2005; 15: 905-912.
2. **Breuer T**, Barankay A, Tassani P. Remifentanil a kardiovaszkuláris anesztéziában – 10 év tapasztalatai. *Aneszteziológia és Intenzív Terápia* 2007; 37: 55-61.
3. Székely A, Balog P, Benkő E, **Breuer T**, Székely J, Kertai DM, Horkay F, Kopp MS, Thayer JF. Anxiety predicts mortality and morbidity after coronary artery and valve surgery – A 4-year follow-up study. *Psychosomatic medicine* 2007; 69: 625-31. IF: 3.109.

4. Székely A, Sápi E, **Breuer T**, Kertai DM, Bodor G, Vargha P, Szatmári A. Aprotinin and renal dysfunction after pediatric cardiac surgery. *Pediatric Anesthesia* 2008; 18: 151-9. IF: 1.469.
5. **Breuer T**, Barankay A, Wiesner G, Tassani P. Az inhalációs és az intravénás anesztézia kardioprotektív hatása szívműtétek során. *Aneszteziológia és Intenzív Terápia* 2008; 38: 53-59.
6. Martin K, Wiesner G, **Breuer T**, Lange R, Tassani P. The risks of aprotinin and tranexamic acid in cardiac surgery: 1-year follow-up of 1188 consecutive patients. *Anesthesia Analgesia* 2008; 107: 1783-90. IF: 2.590.
7. **Breuer T**, Martin K, Wilhelm M, Wiesner G, Schreiber C, Hess J, Lange R, Tassani P. The blood sparing effect and the safety of aprotinin compared to tranexamic acid in paediatric cardiac surgery. *European Journal of Cardio-Thoracic Surgery* 2009; 35: 167-71. IF: 2.397.
8. Székely A, Cserép Z, Sápi E, **Breuer T**, Nagy CA, Vargha P, Hartyánszky I, Szatmári A, Treszl A. Risks and predictors of blood transfusion in pediatric patients undergoing open heart operations. *Annals of Thoracic Surgery* 2009; 87: 187-97. IF: 3.644.
9. **Breuer T**, Sápi E, Hartyánszky IL, Cserép Z, Vargha P, Treszl A, Kertai MD, Gál J, Tóth M, Szatmári A, Székely A. Impact of blood glucose values in patients with and without insulin treatment following paediatric cardiac surgery. *Interventional Medicine and Applied Science* 2010; 2: 10-16.
10. Martin K, **Breuer T**, Gertler R, Hapfelmeier A, Schreiber C, Lange R, Hess J, Wiesner G. Tranexamic acid versus ε-aminocaproic acid: Efficacy and safety in pediatric cardiac surgery. *European Journal of Cardio-Thoracic Surgery* 2010; doi:10.1016/j.ejcts.2010.09.041 [in press]. IF: 2.397.
11. Martin K, Knorr J, **Breuer T**, Gertler R, MacGuill M, Lange R, Tassani P, Wiesner G. Seizures after open heart surgery: Comparison of ε-aminocaproic acid and tranexamic acid. *Journal of Cardiothoracic and Vascular Anesthesia* [in press]. IF: 1.062.