Usefulness of *N*-Terminal Pro-Brain Natriuretic Peptide to Predict Mortality in Adults With Congenital Heart Disease

Jana Rubáčková Popelová, MD, PhD[a,b,*], Karel Kotaška, PhD[c], Markéta Tomková, Mgr[a,d], and Jakub Tomek, Mgr[e]

Natriuretic peptides are often elevated in congenital heart disease (CHD); however, the clinical impact on mortality is unclear. The aim of our study was to evaluate the prognostic value of *N*-terminal pro-brain natriuretic peptide (NT-proBNP) in the prediction of all-cause mortality in adults with different CHD. In this prospective longitudinal mortality study, we evaluated NT-proBNP in 1,242 blood samples from 646 outpatient adults with stable CHD (mean age 35 ± 12 years; 345 women). Patients were followed up for 6 ± 3 (1 to 10) years. The mortality rate was 5% (35 patients, mean age 40 ± 14 years, 17 women). Median NT-proBNP (pg/ml) was 220 in the whole cohort, 203 in survivors, and 1,548 in deceased patients. The best discrimination value for mortality prediction was 630 pg/ml with 74% sensitivity and 84% specificity. During the follow-up, the survival rate was 65% for those with median NT-proBNP ≥630 pg/ml and 94% for NT-proBNP <630 pg/ml; p <0.0001. There was only 1% mortality among 388 patients with at least 1 NT-proBNP value ≤220 pg/ml compared with 41% mortality among 54 patients with at least 1 NT-proBNP value >1,548 pg/ml. Even the first (baseline) measurements of NT-proBNP were strongly associated with a high risk of death (log_{10} NT-proBNP had hazard ratio 7, p <0.0001). In conclusion, NT-proBNP assessment is a useful and simple tool for the prediction of mortality in long-term follow-up of adults with CHD. **(Am J Cardiol 2015;116:1425−1430)**

Natriuretic peptides are powerful independent markers of prognosis in patients with symptomatic or asymptomatic heart failure, coronary artery disease, pulmonary hypertension, acquired valve disease, and general population but not in the healthy population without cardiovascular risk factors.[1−8] Patients with low level of *N*-terminal pro-brain natriuretic peptide (NT-proBNP) have excellent prognosis irrespective of echocardiographic findings.[2,9] For patients with advanced chronic heart failure, natriuretic peptides have been accepted as a gold standard in predicting mortality.[8,10,11] It is less clear which levels of NT-proBNP may be considered normal and which have negative prognostic impact in the population of adults with congenital heart disease (ACHD).[12,13] The average (reference) values of NT-proBNP for the main congenital heart diagnoses in adulthood were proposed by 2 larger studies.[14,15] The usefulness of natriuretic peptides for mortality prediction in ACHD has been studied in smaller studies for specific complex lesions.[16−19] The aim of our study was to assess the prognostic value of NT-proBNP for mortality prediction in a large cohort of ACHD during long-term follow-up. To the best of our knowledge, this is the largest study in ACHD evaluating NT-proBNP in mortality prediction.

Methods

During the period 2003 to 2013, we measured NT-proBNP prospectively in 646 consecutive adults with different congenital heart lesions referred to our center. All blood samples were obtained during the planned outpatient visit. Only adult patients in stable state were included in this study; those referred to hospitalization with manifest heart failure or arrhythmia during the first visit were excluded. Patients with renal failure and creatinine level >160 μmol/l were not included in the study.

The first NT-proBNP measurement was considered baseline. Repeated NT-proBNP assessments were performed during the controls in our center. All patients were regularly followed up either in our tertiary referral center for ACHD or by local cardiologists. The mortality rate of our patients was confirmed by the confrontation of all patients with the National Mortality Register. If the death happened outside the hospital, we tried to find out the cause of the death by a telephone call to the family, local cardiologist, or general practitioner.

Blood samples for NT-proBNP were withdrawn during the outpatient visit in the morning in a sitting position at rest from a peripheral vein together with blood samples for routine

[a]Department of Cardiac Surgery, Hospital Na Homolce, Prague, Czech Republic; [b]Pediatric Heart Centre, Faculty Hospital Motol, Prague, Czech Republic; [c]Department of Medical Biochemistry and Clinical Biochemistry, 2nd Faculty of Medicine, Charles University, Faculty Hospital Motol, Prague, Czech Republic; [d]Nuffield Department of Medicine and [e]Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom. Manuscript received May 23, 2015; revised manuscript received and accepted July 30, 2015.

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*Corresponding author: Tel: (+420)-605513540; fax: (+420)-257272941.
E-mail address: jana.popelova@homolka.cz (J.R. Popelová).

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Table 1
Characteristics of the 646 adult patients with congenital heart disease (CHD)

Diagnosis	Pts	N of NT-proBNP samples	Pts after repair N (%)	Pts without radical repair N (%)	N of deaths/ deaths after radical repair	Rate of deaths within dg group	Rate of deaths within all 35 deaths
Pulmonary atresia	24	46	18 (75 %)	6 (25 %)	2/2	8 %	6 %
Congenitally corrected transposition of the great arteries	22	43	9 (41 %)	13 (59 %)	0	0	0
Ventricular septal defect*	34	57	22 (65 %)	12 (35 %)	0	0	0
Fontan correction†	(27)	(57)	(27) (100 %)	0 (0)	0	0	0
Single ventricle† incl. Tricuspid atresia	48	92	31 (65 %)	17 (35 %)	5/1	10 %	14 %
Eisenmenger syndrome or severe pulmonary hypertension*	51	106	15 (29 %)	36 (71 %)	6/2	12 %	17 %
Coarctation of the aorta	25	38	22 (88 %)	3 (12 %)	0	0	0
Ebstein anomaly	49	120	31 (63 %)	18 (37 %)	6/3	12 %	17 %
Transposition of the great arteries	86	185	84 (98 %)	2 (2 %)	9/8	10 %	26 %
Tetralogy of Fallot	96	188	92 (96 %)	4 (4 %)	2/1	2 %	6 %
Atrial septal defect	90	142	57 (63 %)	33 (37 %)	1/1	1 %	2.8 %
Atrio-ventricular septal defect	29	50	25 (86 %)	4 (14 %)	3/3	10 %	8.6 %
Truncus arteriosus	3	3	3 (100 %)	0	0	0	0
Pulmonary stenosis	29	44	23 (79 %)	6 (21 %)	1/1	3%	2.8 %
Congenital aortic valve disease	56	118	16 (29 %)	40 (71 %)	0	0	0
Other	4	10	3 (75 %)	1 (25 %)	0	0	0
Together	646	1242	451 (70 %)	195 (30 %)	35/22		100 %

dg = diagnosis.
* Patients with ventricular septal defect, atrial septal defect, or any other lesion with severe pulmonary hypertension are included only in the Eisenmenger group.
† All patients with Fontan correction are included also in the single ventricle group.

biochemistry and blood count evaluation. Serum samples were analyzed immediately after the transport to the laboratory. Serum levels of NT-proBNP were measured using commercially available electrochemiluminescence sandwich immunoassay (Elecsys 2010; Roche, Mannheim, Germany).

The Kaplan−Meier analysis with the log-rank Mantel−Cox test was used for evaluation of survival curves. The negative and positive predictive values, sensitivity, specificity, and area under the curve (AUC) were assessed for different NT-proBNP cut-off values. The effect of $\log_{10}$ NT-proBNP on survival was assessed by Cox proportional hazard ratio (HR) analysis and resulting significance, HR, and confidence intervals of HR were reported; fulfillment of Cox proportional hazards assumptions were tested using R function cox.zph. The Mann−Whitney *U* test was used to compare the differences in NT-proBNP values between survivors and deceased patients. The value of $p < 0.05$ was considered statistically significant. The GraphPad Prism version 6.0 (San Diego, California) and R software version 3.1.2 were used to perform the statistical analysis.

The study was approved by the local ethics committee. All patients were informed about the purpose of NT-proBNP assessment and gave their informed consent with the NT-proBNP analysis.

Results

The mean follow-up was 6 ± 3 (1 to 10) years in the period between 2003 and 2013. The mean age of our patients was 35 ± 12 years (18 to 79 years), there were 301 men and 345 women. The overview of different CHD diagnoses, number of patients and blood samples, history of repair, and deaths are summarized in Table 1.

Most patients (70%) had a history of radical repair of their CHD, mostly in childhood (58%), less frequently in adulthood (12%); the remaining 30% did not have any operation or had only a palliative shunt. The group with unrepaired CHD comprised patients with severe inoperable lesions and patients with mild lesions not indicated for surgery. Most patients (81%) were only mildly symptomatic (New York Heart Association [NYHA] classes I to II) and 19% had NYHA classes III to IV. Cyanosis with oxygen saturation ≤90% was present in 7% of patients without radical correction (Eisenmenger syndrome, Ebstein anomaly, functionally single ventricle or palliated tetralogy of Fallot). All our patients had normal creatinine levels except one with mild renal failure and serum creatinine 150 μmol/l. Repeated NT-proBNP assessment was performed in 46% of the whole cohort (295 patients).

Thirty-five patients (5%) died during follow-up at the mean age of 40 ± 14 years, 17 were women. The most frequent diagnoses in the deceased group were transposition of the great arteries after Mustard or Senning correction or without correction (26% of deaths), Ebstein anomaly (17%), Eisenmenger syndrome or severe pulmonary hypertension (17%), and unoperated or palliated complex CHD with functionally single ventricle (14% of deaths; Table 1). Interestingly, there was no death in the Fontan group of patients. Low or zero mortality was found also in coarctation of the aorta, tetralogy of Fallot, pulmonary stenosis, atrial septal defect type secundum, congenitally corrected transposition of the great arteries, ventricular septal defect, and congenital aortic valve disease (Table 1). The cause of death was cardiovascular in 97%. Most patients (28; 80%) died from heart failure either without relation to operation (25 patients) or in the

Table 2
NT-proBNP in the prediction of death

NT-proBNP cut-off (pg/ml)	Type of cut-off	Samples	Sensitivity	Specificity	PPV	NPV	AUC
220	Median of all samples	1242	92 %	53 %	10 %	99 %	**0.85**
1548	Median of deceased	77	49 %	93 %	36 %	97 %	
203	Median of survivors	1165	94 %	51 %	10 %	99 %	
630	**Maximal sensitivity and specificity**	**1242**	**74 %**	**84 %**	**18 %**	**98 %**	

AUC = area under curve; NPV = negative predictive value; PPV = positive predictive value.

Table 3
Median values of NT-proBNP in alive and deceased patients with particular congenital heart diagnoses

Diagnosis	Survivors		Deceased	
	NT-proBNP (pg/ml)	Patients	NT-proBNP (pg/ml)	Patients
Pulmonary atresia	296	22	3264	2
Congenitally corrected transposition of the great arteries	211	22	-	0
Ventricular septal defect*	170	34	-	0
Fontan correction†	220	(27)	-	0
Single ventricle† incl. Tricuspid atresia	470	43	1184	5
Eisenmenger syndrome or severe pulmonary hypertension*	351	45	2706	6
Coarctation of the aorta	101	25	-	0
Ebstein anomaly of the tricuspid valve	250	43	304	6
Transposition of the great arteries	220	77	4352	9
Tetralogy of Fallot	183	94	300	2
Atrial septal defect	206	89	2410	1
Atrio-ventricular septal defect	195	26	1548	3
Truncus arteriosus	144	3	-	0
Pulmonary stenosis	101	28	1412	1
Congenital aortic valve disease	118	56	-	0
Other	80	4	-	0
Together	203	611	1548	35

* Patients with ventricular septal defect, atrial septal defect, or any other lesion with severe pulmonary hypertension are included only in the Eisenmenger group.

† All patients with Fontan correction are included also in the single ventricle group.

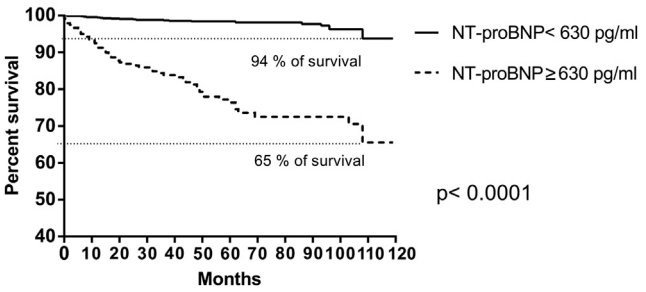

Figure 1. Kaplan–Meier survival curve stratified according to the cut-off value of NT-proBNP 630 pg/ml.

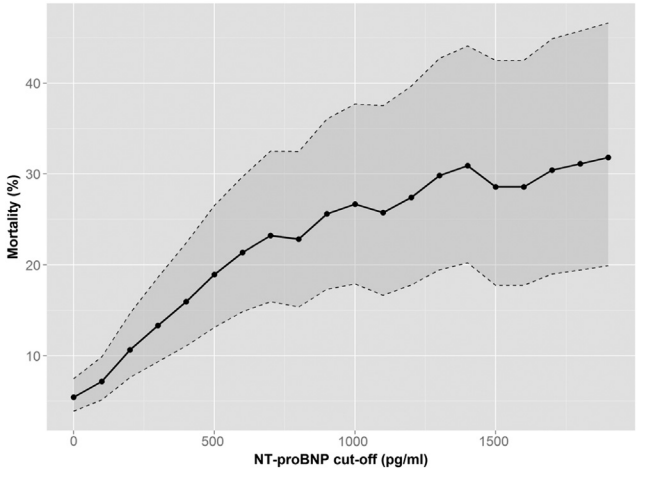

Figure 2. The relation between the cut-off values of baseline NT-proBNP (pg/ml) and the mortality rate in patients with NT-proBNP higher than each of the cut-off values. 95% confidence intervals are shown in *dashed lines*.

early postoperative period (3 patients). Other causes of death were arrhythmia or sudden death (3 patients), hemoptysis (1 patient), stroke (1 patient), complication of ventricular assist device (1 patient), and tumor (1 patient).

The median of NT-proBNP was 220 (interquartile range 110 to 474) pg/ml in the whole cohort, 203 (101 to 420) pg/ml in the group of survivors, and 1,548 (473 to 3,828) pg/ml in the group of deceased patients (Table 2). The difference between survivors and deceased patients was highly significant ($p < 0.0001$; Mann–Whitney *U* test). The median values of NT-proBNP in survivors and deceased patients with particular congenital heart diagnoses are listed in Table 3.

The optimal discrimination value of NT-proBNP for the prediction of death was 630 pg/ml with 74% sensitivity, 84% specificity, 18% positive predictive value, and 98% negative predictive value. The optimal discrimination value was estimated at a value of maximal specificity and sensitivity. The AUC was 0.85 (Table 2). The long-term survival rate was 94% in the group with NT-proBNP <630 pg/ml compared to 65% survival rate in patients with NT-proBNP ≥630 pg/ml, $p < 0.0001$ (Figure 1).

The use of median of all samples (220 pg/ml) as the discrimination value for mortality had higher sensitivity (92%) but lower specificity (53%). The cutoff 1,548 pg/ml had high specificity (93%) but lower sensitivity (49%; Table 2). There was only 1% mortality (4 patients) in the

Table 4
Maximal and baseline NT-proBNP in the prediction of death

a: Maximal NT-proBNP concentrations

NT-proBNP cut-off (pg/ml)	Type of cut-off	Patients	Sensitivity	Specificity	PPV	NPV	AUC
203	Median of survivors	611	94 %	56%	9.5%	99%	**0.87**
1974	Median of deceased	35	46 %	96%	27%	97%	
220	Median of all patients	646	91 %	58%	10%	99%	

b: Baseline NT-proBNP concentrations

NT-proBNP cut-off (pg/ml)	Type of cut-off	Patients	Sensitivity	Specificity	PPV	NPV	AUC
177	Median of survivors	611	94 %	50 %	9 %	99 %	**0.85**
1099	Median of deceased	35	54 %	92 %	22 %	97 %	
183	Median of all patients	646	94 %	50 %	9 %	99 %	

AUC = area under curve; Baseline concentrations = the first measurement for each patient; Maximal concentrations = the maximal measurement for each patient; NPV = negative predictive value; PPV = positive predictive value; Type of cutoff = median value of NT-proBNP in the given group of patients.

388 patients who had at least 1 of their NT-proBNP value $\leq$220 pg/ml. On the contrary, the mortality rate was as high as 41% (22 deceased patients) in 54 patients with at least 1 NT-proBNP value >1,548 pg/ml during the follow-up. The relation between different NT-proBNP cut-off values and the mortality is shown in Figure 2.

Maximal NT-proBNP was highly predictive of mortality (AUC 0.87) with significantly different survival curves for cut-off value of 630 pg/ml ($p < 0.0001$; Table 4a). Interestingly, also the baseline NT-proBNP was similarly predictive (AUC 0.85) with significantly different survival curves for cut-off value of 630 pg/ml ($p < 0.0001$; Table 4b).

We also assessed the hazard associated with baseline NT-proBNP as a continuous variable after logarithmic transformation (to reduce the effect of extreme values because the distribution of NT-proBNP is highly skewed). Values of baseline $\log_{10}$ NT-proBNP were strongly associated with the high risk of death ($p < 0.0001$, HR 7, 95% confidence interval 4 to 13, Cox proportional HR) with the interpretation that a 10-fold increase in NT-proBNP corresponds to a 7-fold increase in the risk of death. Thus, the sole baseline measurement of NT-proBNP has the potential to predict mortality in ACHD.

For the evaluation of the NT-proBNP dynamics, we compared the ratio of the last and baseline NT-proBNP value in 295 patients with repeated testing. This ratio was nonsignificantly greater in deceased patients (median 1.33 vs 1.08, $p = 0.198$, Mann−Whitney U test).

Discussion

Our results show that the sole NT-proBNP evaluation has the potential to stratify adult patients with CHD according to the risk of mortality in long-term follow-up. The best discrimination was achieved with the cut-off value of 630 pg/ml. There was 94% survival rate in the next 6 years in patients with NT-proBNP below this limit and only 65% survival rate in those with the values previously mentioned ($p < 0.0001$). We did not find any prognostic difference between the baseline and maximal values of NT-proBNP in the case of repeated testing. It is important to realize that even a single (baseline) NT-proBNP assessment in a patient in stabilized state without signs of heart failure has the power to predict the prognosis. All blood samples in this study were obtained during the planned outpatient visits; the values of NT-proBNP from hospitalized patients would be greater.

The serum levels of NT-proBNP in our 646 patients with ACHD were markedly higher than in general healthy population but also compared with another large ACHD study with patients of similar age.[7,15] The difference might be explained by that our cohort comprised also patients with Eisenmenger syndrome, and our whole group was significantly more symptomatic (19% in NYHA classes III to IV) compared with that of Eindhoven's group with only 1% of patients in NYHA class III.[15]

A smaller study with 49 symptomatic patients with CHD showed that both BNP and atrial natriuretic peptide have strong predictive value for the mortality in symptomatic ambulatory patients during long-term follow-up.[17] The mortality rate in this study was higher than that of our study (22% vs 5%). There was similar rate of symptomatic patients in functional classes III and IV (20% vs 19%) but more cyanotic patients compared with our study (20% vs 7%).

Three other studies identified natriuretic peptides as predictors of mortality in patients with Eisenmenger syndrome or pulmonary hypertension.[18−20] The finding that elevated levels of BNP >140 pg/ml increase the risk of death and heart failure in outpatients with Eisenmenger syndrome is similar to our results.[18] In another study, BNP predicted survival in Eisenmenger syndrome independently on 6-minute walking distance.[19] Also temporal increase of BNP predicts mortality which corresponds well with our experience.[19] We found that patients with at least 1 level of NT-proBNP over 1,548 pg/ml (median of deceased patients) had 41% mortality. Schuuring et al[20] has recently observed that the baseline level of NT-proBNP $\geq$500 ng/l was a significant determinant of mortality in patients with ACHD and pulmonary hypertension, which is very similar to our results for the whole ACHD cohort.

Natriuretic peptides and their relations to clinical and echocardiographic parameters have been recently studied in different particular CHDs.[16,18−28] The neurohormonal

activation in ACHD may persist many years after repair, and it was found even in asymptomatic patients.[13,29] Residual lesions after repair may become more important during the time. From the practical point of view, the ordinary methods of identifying patients at risk are often problematic in ACHD. The evaluation of symptoms may be difficult because most patients with ACHD consider their limited functional capacity normal. They do not report problems unless arrhythmia or intercurrent disease with subsequent heart failure occurs. The result of exercise testing may be dependent on the regular training. The echocardiographic evaluation of ejection fraction may be inaccurate in the abnormal morphology of the ventricles and may be overestimated by volume overload of the right or left ventricle. Nevertheless, it is important to distinguish patients with high risk in ACHD to provide them with appropriate treatment in time. If we wait too long until substantial symptoms develop (NYHA classes III to IV), the prognosis is much worse regardless of the treatment.

In conclusion, our results show that NT-proBNP can be an extremely useful, quick, and simple prognostic marker for identification of patients at high risk. Although it obviously cannot replace regular clinical, echocardiographic, and complex examinations in specialized centers, our results suggest that it can add very valuable prognostic information. Early detection of increased mortality risk allows taking appropriate therapeutic measures in time.

Our study has some limitations: we did not perform repeated measurements of NT-proBNP in all our patients. Repeated testing was more likely performed in patients with more severe disease. We did not compare NT-proBNP with any other prognostic markers, functional class, echocardiographic parameters, or exercise tests. We did not analyze early postoperative changes of NT-proBNP after cardiac surgery for congenital condition in adulthood. On purpose, we did not analyze NT-proBNP during hospitalization for heart failure or arrhythmias. The primary end point of our study was the mortality only; we did not analyze any other adverse events, worsening of heart failure, or hospital admissions. The risk stratification by NT-proBNP was performed on purpose for the whole heterogeneous group of patients with different diagnoses.

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Disclosures

The authors have no conflicts of interest to report.

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