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Original Research

PULMONARY HYPERTENSION

Serum N-Terminal Brain Natriuretic Peptide as a Prognostic Parameter in Patients With Pulmonary Hypertension*

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Study objectives: **Baseline prognostic assessment in patients with pulmonary hypertension (PH) may help in the selection of treatment. High plasma levels of natriuretic peptide type B have been reported in patients with right ventricular (RV) dysfunction and suggest poor prognosis in patients with idiopathic pulmonary arterial hypertension (IPAH). We prospectively assessed the correlation of N-terminal brain natriuretic peptide (NT-proBNP) with echocardiographic and hemodynamic indexes of RV function as well as with baseline functional status and long-term survival of PH patients.**

Patients and design: **Fifty-five consecutive patients with a mean (± SD) age of 41 ± 15 years and severe PH (including 36 patients with IPAH) were followed up for up to 36 months. Serum samples for NT-proBNP were secured, and 6-min walk test (6 MWT), RV catheterization, and echocardiography were all performed on the same day, before the introduction of targeted treatment.**

Results: **The median baseline serum NT-proBNP concentration was 1,674 pg/mL (range, 51 to 10,951 pg/mL). NT-proBNP concentration correlated with 6MWT distance ($r = 0.6$; $p < 0.001$), cardiac index, pulmonary vascular resistance, and right atrial pressure (RAP), but not with pulmonary arterial pressure. NT-proBNP levels were also related to the ratio of the diastolic area of the RV and the LV, and to pericardial effusion during echocardiography. Receiver operating characteristic analysis identified ≥ 1,400 pg/mL as the best NT-proBNP threshold predicting fatal outcome for the entire study group as well as for IPAH patients (sensitivity, 88% and 100%, respectively; specificity, 53% and 56%, respectively). In multivariate analysis, NT-proBNP, troponin T, and RAP were identified as independent factors for poor prognosis for the entire study group, while only NT-proBNP and RAP were identified as markers for poor prognosis in the IPAH subgroup.**

Conclusions: **NT-proBNP level is related to the right heart morphology and dysfunction in PH patients. A serum NT-proBNP level of ≥ 1,400 pg/mL was found to be useful in identifying patients with poor long-term prognosis both in the whole studied group and in the IPAH subgroup.** ***(CHEST 2006; 129:1313–1321)***

Key words: echocardiography; natriuretic peptides; prognosis; pulmonary arterial hypertension; pulmonary heart disease; troponin T

Abbreviations: BNP = brain natriuretic peptide; IPAH = idiopathic pulmonary arterial hypertension; LV = left ventricle/ventricular; NT-proBNP = N-terminal brain natriuretic peptide; PAP = pulmonary artery pressure; PH = pulmonary hypertension; RAP = right atrial pressure; ROC = receiver operating characteristic; RV = right ventricle/ventricular; 6MWT = 6-min walk test; WHO = World Health Organization

The accurate assessment of prognosis in patients with pulmonary hypertension (PH) is difficult. Moreover, the optimal timing for invasive procedures such as atrial septostomy or lung transplantation remains controversial and contributes to the high mortality rate among patients on the waiting lists.[1] Many parameters, as assessed at baseline, may be used to predict a worse prognosis in patients with PH (*eg*, poor functional status, low 6MWT distance, worse hemodynamic indexes, and detectable troponin T lev-

el).[2–4] Although echocardiography is the screening test for diagnosis and is helpful in the monitoring of treatment and prognosis in patients with severe PH,[5–7] its inherent limitations suggest the need for an alternative, noninvasive, simple, and rapid method.

Natriuretic peptide type-B (BNP) is of proven value in the diagnosis of and prognosis of patients with left ventricular (LV) dysfunction, mainly as a "rule-out" test for heart failure that is comparable with echocardiography.[8–11] It was shown that plasma BNP levels increase in proportion to the degree of right ventricular (RV) dysfunction[12] and functional status in patients with PH.[13] However, the correlation of BNP level and echocardiography in patients with PH has not been assessed so far. Importantly, both high baseline levels of plasma BNP and its increase during a 3-month follow-up period are strong independent prognostic factors in patients with primary PH.[14]

BNP is cleaved into an inactive part N-terminal BNP (NT-proBNP) and the biologically active hormone BNP. High NT-proBNP level correlated with poor outcome in patients with acute pulmonary embolism.[15] Having a somewhat longer plasma half-life than BNP, and a much higher plasma concentration,[16] NT-proBNP could also be of prognostic value in patients with chronic PH. We tried to determine whether NT-proBNP is related to echocardiographic, functional, and hemodynamic variables in PH patients. We also assessed the potential value of the initial serum NT-proBNP level in predicting poor long-term outcome in patients with severe PH.

Materials and Methods

Study Population

In 55 consecutive patients (43 women and 12 men; mean [± SD] age, 41 ± 15 years) with PH who received diagnoses and were treated between June 1999 and January 2004, serum samples were collected at the time of baseline functional, echocardiographic, and hemodynamic assessment. PH was diagnosed according to World Health Organization (WHO) Evian/Venice classification.[17] The study group consisted of 36 patients with idiopathic pulmonary arterial hypertension (IPAH), 10 patients with PH associated with collagen vascular disease, 4 patients with PH associated with congenital systemic-to-pulmonary shunts, and 1 patient with portal pulmonary arterial hypertension. The remaining five patients had PH due to chronic thrombotic disease not suitable for surgical treatment. Pharmacologic treatment varied among patients; 20 patients received oral beraprost, 7 patients received bosentan, 1 patient received inhaled iloprost, 15 patients received treprostinil subcutaneously, and 10 patients received oral sildenafil. At the time of this study, IV epoprostenol was not available in Poland.

Baseline Assessment

The baseline assessment had been performed before targeted therapy was started. According to the previously described protocol,[4] echocardiographic examination was performed on the day of right heart catheterization using a Swan-Ganz 7F fluid-filled catheter. The exercise capacity of our patients was estimated with an "unencouraged" 6-min walk test (6MWT). The patients were followed up for 36 months for a mean duration of 770 ± 336 days (range, 11 to 1,095 days), and no patient was lost to follow-up.

Measurement of Cardiac Biomarkers

Serum NT-proBNP was measured (Elecsys proBNP immunoassay; Roche Diagnostics; Basel, Switzerland) in peripheral venous blood samples that were collected in the morning of the day of the 6MWT. To compare local normal values with those suggested by the producer (< 125 pg/mL),[18] NT-proBNP levels were also measured in nine healthy volunteers with a median age of 40 years (age range, 23 to 59 years).

Cardiac troponin T levels were assessed with a highly sensitive test (electrochemiluminescence method ECLIA; Roche Diagnostics). According to the manufacturer data, concentrations of troponin T of > 0.01 ng/mL were considered to be abnormal. The local Institutional Bioethical Committee approved the protocol of this study. All participating patients gave their informed consent.

Statistical Analysis

Log transformation was used to normalize the distribution of serum NT-proBNP levels. Correlations between serum NT-proBNP and hemodynamic, echocardiographic, and 6MWT variables were evaluated by Pearson correlation coefficients. The optimal cutoff value of the baseline NT-proBNP level for the prediction of death was selected according to receiver operating characteristic (ROC) analysis. The proportion of patients surviving was estimated by the Kaplan-Meier method and was compared with the log rank-test. The prognostic value was tested by univariate and multivariate Cox proportional hazards regression analysis.

Baseline functional, hemodynamic, and echocardiographic parameters and NT-proBNP serum level were compared in survivors and nonsurvivors with the Wilcoxon test. A p value of < 0.05 was considered to be statistically significant. All analyses were performed using a statistical software package (STATISTICA, version 6.1; StatSoft; Tulsa, OK).

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Results

At the time of right-heart catheterization, all patients presented with precapillary PH with a significantly elevated mean pulmonary artery pressure (PAP) of 60.2 ± 17.5 mm Hg (Table 1). The mean baseline serum NT-proBNP concentration was 2,369 ± 2,429.5 pg/mL (similar to the mean concentration of 2,562 ± 2,713 pg/mL in the subgroup of IPAH patients), with a median value 1,674 pg/mL (range, 51 to 10,951 pg/mL), which again is similar to the 1,795 pg/mL (range, 1,529 to 10,951 pg/mL) in IPAH patients (Table 2) [almost 15 times the designated upper limit of normal].[18] In nine healthy volunteers, the mean concentration was 46 ± 24 pg/mL (range, 22 to 87 pg/mL). High serum NT-proBNP concentration predicted worse exercise endurance in our PH patients showing a strong negative correlation with distance walked on the 6MWT ($r = -0.6$; $p < 0,001$).

NT-proBNP and Echocardiographic Findings

Serum NT-proBNP concentration correlated with several echocardiographic indexes, which illustrated the degree of RV overload and were suggestive of poor prognosis in PH patients,[5] positively with a diastolic RV/LV ratio area ($r = 0.6$; $p < 0.001$), with the presence of pericardial effusion ($r = 0.51$; $p = 0.002$), and inversely with acceleration time of the RV ejection ($r = -0.61$; $p < 0.001$) [Table 3]. Similar results concerned patients with IPAH (Table 3). Interestingly, no correlation with peak jet velocity and the gradient of tricuspid regurgitation was found in both groups.

Serum NT-proBNP level at baseline reflected RV function in all PH patients as well as in the IPAH subgroup. It correlated with prognostically important hemodynamic variables, inversely with cardiac index and mixed venous saturation, and positively with right atrial pressure (RAP) and pulmonary

Table 1—*Baseline Clinical Characteristics, Exercise Capacity, Echocardiographic and Hemodynamic Parameters, and Comparison Between Survivors and Nonsurvivors

Variables	All Patients (n = 55)	Survivors (n = 39)	p Value	Nonsurvivors (n = 16)
Age, yr	41 ± 15.1	40.4 ± 15.1	NS	43.7 ± 15.6
Female gender	43 (76)	29 (74)	NS	15 (93)
Heart rate, beats/min	78 ± 15	76 ± 15.2	NS	81 ± 14.4
Systolic BP, mm Hg	114 ± 15	114 ± 13.8	NS	113 ± 17.8
Diastolic BP, mm Hg	78 ± 11	78 ± 10	NS	77 ± 12.8
WHO functional class†	2.3 ± 0.48	2.23 ± 0.4	0.002	2.6 ± 0.49
6MWT distance, m	381 ± 110	407 ± 97	0.007	323 ± 119
Borg dyspnea score	1.3 ± 1.9	1.06 ± 1.6	NS	2.0 ± 2.3
Baseline NT-proBNP, pg/mL	2,369 ± 2,429	1,664 ± 1,704	< 0.001	4,088 ± 3,073
NT-proBNp level ≥ 1,400 pg/mL	32 (56)	18 (46)	0.001	14 (88)
Detectable troponin T level	8 (13)	3 (7)	0.03	5 (31)
Echocardiography				
RV diameter, mm	35 ± 10.4	35 ± 11.2	NS	34 ± 8.75
Ratio of RV/LV diastolic areas	2.0 ± 0.74	1.8 ± 0.64	0.005	2.4 ± 0.8
RV area change, %	16.9 ± 10.1	18 ± 11.0	NS	14.4 ± 7.81
Right atrial area, cm^2	24.0 ± 8.8	22 ± 9.6	NS	26 ± 6.16
Diastolic LV eccentricity index	0.54 ± 0.16	0.57 ± 0.15	NS	0.48 ± 0.16
Systolic LV eccentricity index	0.48 ± 0.16	0.50 ± 0.14	NS	0.42 ± 0.15
RV Doppler performance index	0.89 ± 0.41	0.87 ± 0.44	NS	0.93 ± 0.36
Presence of pericardial effusion	15 (26)	6 (15)	0.02	9 (56)
Pericardial effusion score	0.7 ± 1.3	0.34 ± 1.0	0.002	1.5 ± 1.7
IVCinsp, mm	16.4 ± 6.4	14.9 ± 6.01	0.005	20.5 ± 5.8
Pulmonary hemodynamics				
PAP, mm Hg	60.2 ± 17.5	57.8 ± 15.4	NS	65.7 ± 21.2
RAP, mm Hg	9.8 ± 6.5	8.4 ± 5.78	0.01	13.0 ± 7.2
PAOP, mm Hg	8.4 ± 3.4	8.1 ± 3.2	NS	9.2 ± 3.8
CO, L/min	4.2 ± 1.0	4.5 ± 1.0	0.002	3.5 ± 0.77
Cardiac index, $L/min/m^2$	2.4 ± 0.6	2.6 ± 0.63	0.002	2.1 ± 0.37
Mixed venous O_2 saturation, %	56.0 ± 9.6	57.2 ± 9.8	NS	53.2 ± 9.16
PVR, Wood units	13.3 ± 6.1	12.0 ± 5.7	0.01	16.3 ± 6.39
PVRI, Wood units × m^2	22.6 ± 10.1	20.4 ± 9.5	0.01	27.4 ± 10.4

*Values are given as the mean ± SD or No. (%), unless otherwise indicated. CO = cardiac output; IVCinsp = inspiration diameter of inferior vena cava; PAOP = pulmonary artery occlusion pressure, PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; NS = not significant.

†According to the criteria of the Primary Pulmonary Hypertension World Symposium.

Table 2—*NT-proBNP Levels in Survivors and Nonsurvivors in 36 IPAH and 19 Non-IPAH Patients***

Variables	All Patients (n = 36†/19‡)	Survivors (n = 27†/12‡)	p Value	Nonsurvivors (n = 9†/7‡)
Baseline NT-proBNP level, pg/mL				
IPAH	2,562 ± 2,713	1,721 ± 1,885	< 0.001	5,084 ± 3,332
Non-IPAH	2,003 ± 1,783	1,535 ± 1,268	NS	2,807 ± 2,324
NT-proBNP level ≥ 1,400 pg/mL, %				
IPAH	22 (61)	13 (48)	0.005	9 (100)
Non-IPAH	10 (52)	5 (26)	0.026	5 (71)

*Values are given as the mean ± SD or No. (%), unless otherwise indicated. See Table 1 for abbreviation not used in the text.
†IPAH patients.
‡Non-IPAH patients.

vascular resistance (Table 3). Interestingly, no correlations between NT-proBNP and serum creatinine levels were found in our groups.

Prognostic Value of NT-proBNP

Among the 55 patients studied, 16 patients (29%) died during the mean follow-up period of 770 ± 336 days (range, 11 to 1,095 days). The mortality in the IPAH subgroup was similar, with 9 of 36 patients (25%) dying in this period. Those who died differed significantly from survivors at baseline; they had worse functional class and walked a shorter distance in 6 min. On echocardiography, nonsurvivors presented more often with signs of pericardial effusion and increased RV/LV ratio. Also, the incidence of a detectable troponin T level was higher in nonsurvivors. Their hemodynamic parameters indicated more compromised RV function. Surprisingly, no statistically significant difference was found in the level of PAP between the groups. The characteristics of patients divided in survivors and nonsurvivors are shown in Table 1.

Baseline high serum NT-proBNP level was related to poor prognosis. An initial serum NT-proBNP cutoff value of 1,400 pg/mL for prediction of death was identified by ROC analysis (area under the curve for the entire study group, 0.74; area under the curve for the IPAH subgroup, 0.82) and was the same in both groups (Fig 1). A serum NT-proBNP concentration of 1,400 pg/mL showed 88% sensitivity, 53% specificity, and a high negative predictive value of 91% for fatal outcome. The results for the IPAH

Table 3—*Correlations Between Selected Baseline Clinical, Hemodynamic, and Echocardiographic Data and NT-proBNP Levels in Patients With Severe PH Compared to Patients With IPAH***

Parameters	All Patients (n = 55)		IPAH Patients (n = 36)	
	r Value	p Value	*r* Value	p Value
Age	0.05	NS	0.01	NS
WHO functional class	0.45	< 0.001	0.51	0.001
6MWT distance	− 0.60	< 0.001	− 0.67	< 0.001
Serum creatinine level	− 0.15	NS	− 0.25	NS
Detectable troponin T level	0.29	NS	0.3	NS
Echocardiographic variables				
RV/LV diastolic area	0.6	< 0.001	0.7	< 0.001
RV diameter	0.29	0.04	0.42	0.014
AcT	− 0.61	< 0.001	− 0.66	< 0.001
Tei index	0.44	0.001	0.45	0.009
IVC inspiration	0.47	< 0.001	0.7	< 0.001
Pericardial effusion	0.51	0.002	0.5	0.002
TVPG	0.08	NS	− 0.02	NS
Hemodynamic data				
mPAP	0.21	NS	0.29	NS
CI	− 0.65	< 0.001	− 0.73	< 0.001
mRAP	0.45	< 0.001	0.66	< 0.001
PVR	0.43	< 0.001	0.53	0.001
Mixed venous O_2 saturation	− 0.48	< 0.001	− 0.56	< 0.001

*AcT = RV acceleration time; IVC = diameter of inferior vena cava; mPAP = mean PAP; mRAP = mean RAP; PVR = pulmonary vascular resistance; TVPG = tricuspid valve peak gradient. See Table 1 for abbreviations not used in the text.

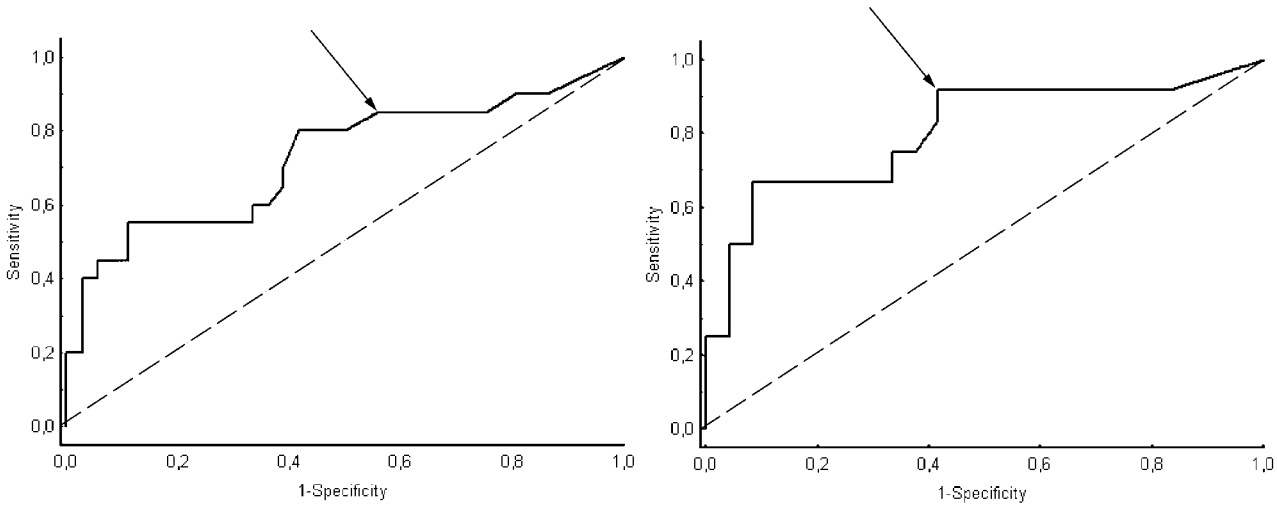

FIGURE 1. ROC analysis for serum NT-proBNP level in the prognosis of death in patients with PH. *Left*: entire study group. *Right*: subgroup of patients with IPAH. Dashed line = no discrimination; solid line = NT-proBNP; arrow = NT-proBNP level of 1,400 pg/mL.

group were 100%, 56%, and 100%, respectively. Survival was significantly better in patients with a NT-proBNP concentration of $< 1{,}400$ pg/mL (Fig 2). During a 3-year follow-up period, 2 of 23 patients (8%) died in the group of patients with NT-proBNP concentration of $< 1{,}400$ pg/mL compared with 14 of 32 patients (44%) in the group of patients with NT-proBNP concentration of $\geq 1{,}400$ group. Among 36 patients with IPAH, 9 patients (41%) from the group with NT-proBNP concentrations of $\geq 1{,}400$ pg/mL died. In contrast, all 12 IPAH patients (100%) with NT-proBNP levels $< 1{,}400$ pg/mL survived. A cutoff value of $\geq 3{,}400$ pg/L would have higher specificity (100%) but a lower sensitivity (45%) for predicting death at 3 years, with respective values of 100% and 50% in the IPAH group.

Cumulative survival estimated by the Kaplan-Meier method was significantly lower at 36 months when the initial NT-proBNP level exceeded 1,400 pg/mL ($p = 0.02$ [log-rank test]). This was also true when the survival analysis was limited to 36 patients with IPAH ($p = 0.001$ [log-rank test]).

Many factors that are indicative of increased mortality risk were identified in the univariate analysis. This included WHO functional class, distance walked on the 6MWT and level of dyspnea measured on the Borg scale, cardiac index, RAP, pulmonary

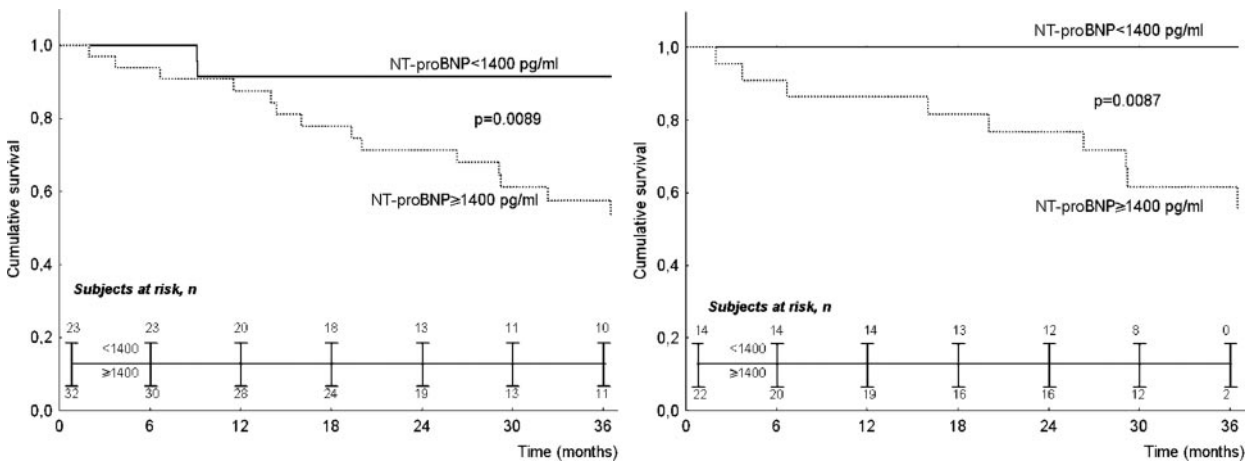

FIGURE 2. Cumulative survival estimated by Kaplan-Meier curves was significantly worse at 36 months with initial NT-proBNP levels of $\geq 1{,}400$ pg/mL (dotted line) than NT-proBNP levels of $< 1{,}400$ pg/mL (solid line). *Left*: entire study group. *Right*: subgroup with IPAH. $p = 0.02$ for overall group, and $p = 0.001$ for IPAH (log-rank test).

vascular resistance, ratio of RV and LV diastolic areas, presence of pericardial effusion and troponin T status, initial level of NT-proBNP, as well as NT-proBNP concentration ≥ 1,400 pg/mL at the baseline (Table 4). In the univariate analysis, which was limited to IPAH patients, mean PAP, and systolic and diastolic LV eccentricity index were related to mortality risk, while troponin T level and cardiac index were not statically significant risk factors of death in this subgroup (Table 4). The type of targeted therapy did not influence 3-year survival, but overall survival in our IPAH patients was statistically significantly better when compared to that predicted by National Institutes of Health equation (Fig 3).

According to stepwise multivariate analysis, the best model predicting survival in a 3-year follow-up consisted of RAP > 10 mm Hg, detectable troponin T level, and NT-proBNP level (Table 5). In the analysis limited to IPAH patients, only RAP and NT-proBNP concentration entered the best model for predicting 3-year survival.

Discussion

BNP is released from the myocytes of ventricles that are on stretch. The very high serum NT-proBNP concentrations observed in the patients with chronic PH who were studied most probably result from increased RV wall stretch and marked hypertrophy of the RV walls. Our data indicate that, similarly to BNP,[12] NT-proBNP also is a good indicator of RV function in patients with chronic PH. Serum NT-proBNP level correlated with the hemodynamic parameters, except for mean PAP. Importantly, PAP was found to be of lesser importance in the prognostic assessment of patients with severe PH.[7,19–21]

Interestingly, there are no data available so far relating serum NT-proBNP concentration to the echocardiographic characteristics of patients with PH. We observed a correlation of serum NT-proBNP concentration with prognostically significant echocardiographic indexes of RV overload. These findings could be of practical importance,

Table 4—*Univariate Cox Proportional Hazard Analysis of Selected Variables Tested in Whole Group of 55 Patients With Severe PH Compared to 36 Patients With IPAH

	Patients With PH (n = 55)			Patients With IPAH (n = 36)		
Variables	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
Age	1.01	0.97–1.04	NS	1.02	0.96–1.07	NS
Diagnosis	1.09	068–1.72	NS			
Treatment selected	0.52	0.23–1.17	NS	1.08	0.36–3.2	NS
Heart rate	1.02	0.99–1.05	NS	1.01	0.96–1.06	NS
Systolic BP	0.99	0.95–1.02	NS	0.94	0.89–1.0	NS
Diastolic BP	0.98	0.95–1.02	NS	0.97	0.92–1.03	NS
WHO functional class	3.7	1.35–9.94	0.01	5.33	1.33–21.4	0.0181
6MWT distance	0.99	0.98–0.99	0.001	0.99	0.98–0.99	0.0062
Borg dyspnea score	1.27	0.99–1.63	0.05	1.11	0.77–1.62	NS
Baseline NT-proBNP level	3	1.45–6.18	0.002	5.31	1.83–15.44	0.0021
NT-proBNp level ≥ 1,400 pg/mL	5.1	1.17–22.7	0.02	8.1	1.66–39.9	0.009
Detectable troponin T level	4.5	1.56–12.92	0.005	2.86	0.58–13.9	0.1923
RV diameter	1.08	0.99–1.17	NS	1.01	0.95–1.06	NS
RV/LV diastolic area	2.91	1.4–6.03	0.004	5.59	1.95–16	0.0013
RV area change	0.98	0.93–1.03	NS	0.95	0.88–1.03	NS
Right atrial area	1.02	0.97–1.07	NS	1.02	0.96–1.09	NS
Diastolic LV eccentricity index	0.06	0.001–2.74	NS	0.00039	0–0.23	0.0225
Systolic LV eccentricity index	0.11	0.002–6.34	NS	0.00087	0–0.46	0.0329
Tei index	1.01	0.34–3.01	NS	1.27	0.36–4.45	NS
Presence of pericardial effusion	3.8	1.46–9.93	0.006	5.46	1.36–22.0	0.0167
Pericardial effusion score	1.4	1.1–1.89	0.007	1.56	1.07–2.28	0.0205
IVCinsp	1.1	1.02–1.2	0.011	1.22	1.06–1.39	0.0048
mPAP	1.01	0.99–1.03	NS	1.03	1.0–1.06	0.0337
mRAP	1.08	1.01–1.16	0.017	1.15	1.04–1.27	0.0045
PAOP	1.07	0.92–1.24	NS	1.05	0.84–1.32	NS
CO	0.42	0.23–0.77	0.005	0.52	0.26–1.04	0.0661
Cardiac index	0.18	0.05–0.61	0.005	0.31	0.08–1.16	0.0842
Mixed venous O_2 saturation	0.96	0.92–1.00	NS	0.95	0.9–1.0	NS
PVR	1.06	1.00–1.13	0.029	1.08	1.0–1.17	0.0321
PVRI	1.04	1.00–1.08	0.034	1.05	1.0–1.1	0.0417

*CI = confidence interval. See Tables 1 and 3 for abbreviations not used in the text.

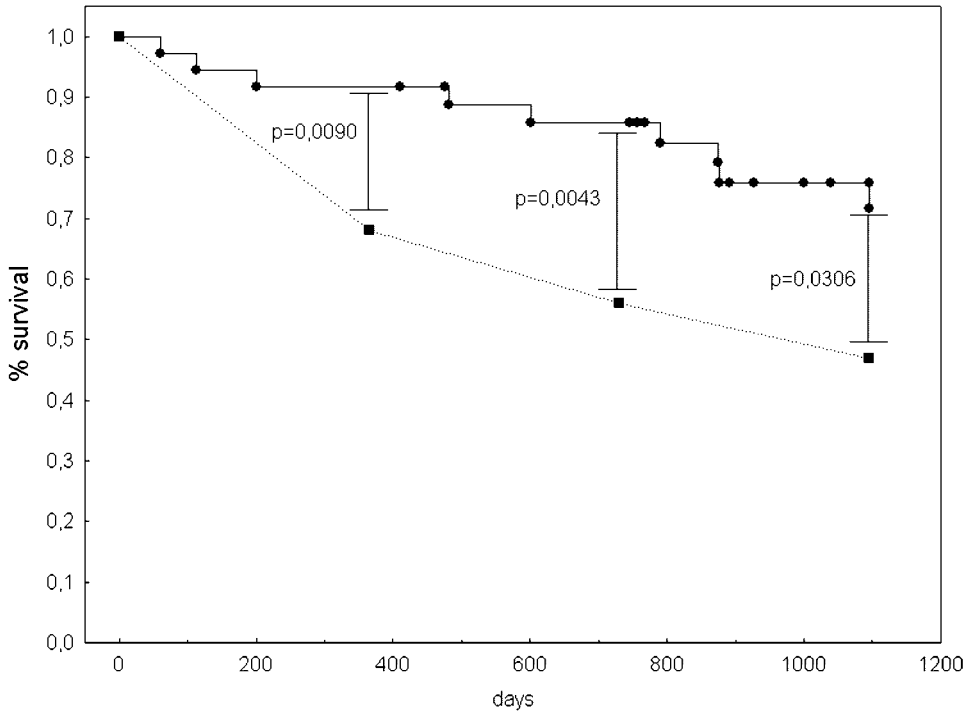

FIGURE 3. Three-year survival observed in the present study in 36 patients with IPAH and predicted by the National Institutes of Health equation ($p < 0.05$ at 1, 2, and 3 years). ■ = expected survival; ● = observed survival.

indirectly suggesting that NT-proBNP assessment could replace or reduce the number of echocardiographic examinations conducted during follow-up. Moreover, we found serum NT-proBNP level also to be a marker of functional capacity in patients with severe chronic PH, as indicated by its relationship to 6MWT distance.

Most importantly, the initial high NT-proBNP concentration was a strong, independent prognostic factor of poor prognosis in our patients with severe chronic PH as well as in the subgroup of patients with IPAH. Long-term mortality in patients with serum NT-proBNP levels of > 1,400 pg/mL reached 44% (41% in IPAH patients), while serum levels of this biomarker < 1,400 pg/mL had a high negative predictive value for fatal outcome. NT-proBNP level and detectable troponin T seem to be independent markers of poor prognosis in this group. These biomarkers together with high RAP made the best prognostic model for PH patients. In a smaller group of patients with IPAH, detectable troponin T level was not a statistically significant indicator of 3-year survival when assessed at baseline. We suppose that troponin T is released by the severely damaged RV muscle cells and that a detectable level of this enzyme is a rather "late" indicator of poor prognosis. For patients with IPAH, the serum level of NT-proBNP and high RAP reflect prognosis. Whether increasing the number of patients in the IPAH subgroup would result in the reappearance of a prognostic value for the baseline troponin T test after 3 years, as was reported at 2 years,[4] remains to be checked.

From observation,[4] it is probable that baseline troponin status was less related to outcome, as it

Table 5—*Multivariate Cox Proportional Hazard Analysis**

Variables	Hazard Ratio	95% CI	p Value
RAP > 10 mm Hg	3.39 (15.4)	1.09–10.5 (1.38–165)	0.034 (0.024)
Detectable troponin T level	4.02 (7.01)	1.11–14.53 (0.68–71)	0.034 (0.1)
NT-proBNP level, log value	3.19 (11.8)	1.37–7.42 (2.48–55.0)	0.007 (0.001)

*Values are given for PH group (IPAH group). See Table 4 for abbreviation not used in the text.

could have changed in some patients during the period of follow-up due to treatment or progression of the disease.

The importance of these models as well as their components, including NT-proBNP concentration, is also highlighted by the fact that it predicted prognosis despite the various treatments administered. This may imply that the timing of introducing the currently available treatments is of greater importance than the actual type of drug or the mode of its administration. This may be due to therapies not including what remains of the "gold standard" therapy (*ie*, long-term IV epoprostenol therapy), which certainly has been demonstrated to have a survival benefit regardless of the disease severity at the time of the chronic IV epoprostenol therapy initiation. However, the data regarding the impact of long-term IV epoprostenol therapy on survival in IPAH patients certainly demonstrates that the initiation of therapy in patients who are in functional class III results in a better long-term outcome than the initiation of therapy in patients in functional class IV.[19,21] Our data suggest that not only can BNP levels of > 180 ng/mL be used for the prognostic assessment of PAH patients, as indicated by the American College of Chest Physicians guidelines published in 2004,[22] but also NT-proBNp levels of $\geq 1{,}400$ ng/mL can be used for the prognostic assessment of PAH patients.

Cardiac biomarkers, which are simple to assess and are reproducible, have emerged as promising tools for the risk assessment of patients with chronic severe PH. We hope that biological markers such as troponin T and NT-proBNP can assist in a noninvasive follow-up and qualification for invasive treatment in this group of patients.

Conclusions

NT-proBNP level is related to right heart morphology and dysfunction as assessed by echocardiography and right heart catheterization in PH patients. Baseline serum NT-proBNP levels of $\geq 1{,}400$ pg/mL identified the group of PH patients with poor long-term prognosis, and the same cutoff value seems to be useful in the prognostic evaluation of patients with IPAH.

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