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Mortality in pulmonary arterial hypertension due to congenital heart disease: Serial changes improve prognostication

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ABSTRACT

Background: Adult patients with pulmonary arterial hypertension due to congenital heart disease (PAH-CHD) suffer from high mortality. This underlines the importance of adequate risk stratification to guide treatment decisions. Several baseline parameters are associated with mortality, however, their prognostic value may weaken after years of follow-up. Therefore we investigated the prognostic value of serial changes in standard clinical parameters in PAH-CHD.

Methods: In this prospective observational cohort study we included consecutive PAH-CHD adults, between 2005 and 2016. Control visits to the outpatient clinic were standardized, including functional, biochemical and echocardiographic tests, according to the guidelines. The prognostic value of serial changes was determined with time-dependent Cox regression.

Results: Ninety-two patients with PAH-CHD were included (age 43 ± 15 years, 34% male, 38% Down, 73% Eisenmenger). During a median follow-up of 6.0 (IQR 3.7-9.3) years, 35 (38%) patients died. Serial changes in World Health Organization functional classification (WHO-FC, HR 18.34 for onset class IV), six-minute walk distance (6-MWD, HR 0.65 per 50 m), oxygen saturation at peak exercise (peak SaO_2, HR 0.74 per 5%), NTproBNP (HR 2.25 per 1000 ng/l) and echocardiographic right ventricular function (TAPSE, HR 0.80 per 0.5 cm) significantly predicted mortality. Moreover, serial changes in these parameters were more potent predictors compared to baseline parameters, based on reduction in −2 log likelihood.

Conclusions: Serial changes in standard clinical parameters have more prognostic value compared to baseline parameters in PAH-CHD. Our results emphasize the importance of screening for serial changes since periodical assessment could guide treatment decisions to delay disease progression.

1. Introduction

Pulmonary arterial hypertension (PAH) is a potential and serious complication of congenital heart disease (CHD), associated with a poor prognosis [1–3]. PAH due to CHD (PAH-CHD) is characterized by increased pulmonary vascular resistance resulting in right ventricular remodeling, dysfunction and eventually failure. During this process, PAH-CHD patients are at risk for clinical events such as hospitalization for heart failure, arrhythmias and ultimately death.

Identifying patients with a high mortality risk is important because their prognosis can be improved by intensifying their treatment [4]. Currently, timing of initiation of PAH-specific combination therapy and determination of follow-up intensity depend on the value of baseline parameters with an established association with mortality [5,6]. In order to delay clinical deterioration, PAH guidelines recommend to evaluate PAH-CHD patients twice a year using functional, biochemical and echocardiographic parameters [7,8]. However, these PAH guidelines are based upon studies combining various PAH aetiologies, thus hampering their use in PAH-CHD patients specifically.

Although there have been several PAH-CHD studies in which baseline parameters have been associated with mortality [8], the prognostic value of these baseline parameters may weaken after years of follow-up. Observation of serial changes in these parameters over time may better reflect prognosis. A limited number of studies explored the prognostic value of serial changes in standard clinical parameters [9–12], however, not all parameters have been described, nor the underlying coherence.

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Knowledge about which serial changes in parameters influence mortality, might improve risk stratification by capturing disease progression in an earlier state.

In the current study we investigated the prognostic value of serial changes in standard clinical parameters in PAH-CHD. Moreover, we evaluated the parameter specific impact on the length of survival.

2. Methods

2.1. Study population

The current study was part of a prospective observational study on PAH-specific therapy in adult patients with PAH-CHD [13]. We included all consecutive adults with PAH-CHD, also patients with Down syndrome, referred to the outpatient clinic of two tertiary referral centers between January 2005 and May 2016. Both patients with open and closed systemic-to-pulmonary shunts were included. PAH diagnosis was based on right heart catheterization or, in case of a clinical profile of Eisenmenger syndrome or severe PAH, on echocardiography [8]. Before 2014, bosentan monotherapy 62.5 mg twice daily was started in all patients after their first visit, increasing the dose to 125 mg twice a day after four weeks, as tolerated. From 2014, therapy naive patients started macitentan monotherapy 10 mg once a day. Approval of the research protocol by the local ethics committee was obtained. Informed consent was not required, as all investigations were performed for routine clinical care.

2.2. Data collection

Patients from the outpatient clinic were evaluated every six months with a standardized evaluation protocol including functional (arterial oxygen saturation at peak exercise (peak SaO_2), six-minute walk distance (6-MWD)), biochemical (hemoglobin, urea, N-terminal pro brain natriuretic peptide (NTproBNP) and creatinine) and echocardiographic parameters (tricuspid annular plane systolic excursion (TAPSE), velocity of the tricuspid annular systolic motion (RV S′) and systolic pulmonary arterial pressure (SPAP)).

The six-minute walk test was performed according to the American Thoracic Society guidelines with continuous pulse oximetry monitoring [14]. Arterial oxygen saturation and heart rate were recorded prior to the test and directly at the end of the six-minute walk test.

Echocardiography was performed with a Vivid 7 ultra-sound system (General Electric, Milwaukee, United States of America) according to the guidelines [15]. Pulmonary stenosis was ruled out in all patients. TAPSE was measured in the lateral tricuspid valve annulus using M-mode in the apical 4-chamber view. RV S′ was assessed by pulsed tissue Doppler. SPAP was measured by continuous wave Doppler recording of the maximal tricuspid regurgitation velocity. This was done calculating the systolic transtricuspid gradient using the modified Bernoulli equation, and then adding an assumed right atrial pressure based on inferior vena cava size and collapsibility.

NTproBNP levels were determined by electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Almere, The Netherlands).

2.3. Statistical analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR) as appropriate. Categorical variables are presented as number (percentage). Differences in categorical data were evaluated using the chi-square test. Independent samples *t*-test or Mann-Whitney *U* test was used for comparison of continuous variables between two groups. The relation between baseline parameters and mortality was assessed with Cox proportional-hazards regression analysis. The proportional hazards assumption for baseline parameters and mortality was plotted using Schoenfeld residuals. Serial changes in parameters were assessed with Cox regression analysis with time-dependent covariates [11]. Time "0" was the first full clinical assessment during the study period. Information about survival status was collected from the participating hospitals until May 2016. Univariate statistics identified significant determinants for inclusion in multivariate analysis. The goodness of fit for serial changes in parameters and baseline parameters in multivariate models was determined based on reduction in −2 log likelihood.

In a final step, serial changes in parameters with a significant association with mortality in univariate time-dependent Cox regression were used in a survival model. Cut-offs for these parameters were obtained by maximizing the sensitivity, specificity and positive predictive values for mortality. Patients without any repeated measurements were excluded from these analyses. All reported *p* values were two-sided, and values of $p < 0.05$ were considered significant. Statistical analysis was performed with SPSS 23.0 (IBM Corp, Armonk, NY) and R version 3.3.1.

3. Results

3.1. Patient cohort

All ninety-two adult patients with PAH-CHD (age 43 ± 15 years, 31 (34%) males) which were referred for PAH-specific therapy were included in this study. Demographic and clinical characteristics of all patients are presented in Table 1. Of all patients, 35 (38%) had Down syndrome

Table 1
Baseline characteristics by vital status.

	All $n = 92$	Deceased $n = 35$	Survived $n = 57$	*P*-value
Demographics				
Age, yrs	43 ± 15	50 ± 15	39 ± 14	0.001
Male, n (%)	31 (34)	11 (31)	20 (35)	0.718
Down syndrome, n (%)	35 (38)	15 (43)	20 (35)	0.456
Clinical subgroup				
Eisenmenger syndrome, n (%)	67 (73)	29 (83)	38 (67)	0.110
Systemic to pulmonary shunt, n (%)	10 (11)	3 (9)	7 (12)	
Small defect, n (%)	1 (1)	1 (2)	0 (0)	
Closed defect, n (%)	14 (15)	2 (6)	12 (21)	
Shunt location				
Pre-tricuspid, n (%)	25 (27)	12 (34)	13 (23)	0.461
Post-tricuspid, n (%)	31 (34)	10 (29)	21 (37)	
Complex, n (%)	36 (39)	13 (37)	23 (40)	
WHO functional class				
WHO-FC I, n (%)	1 (1)	0 (0)	1 (2)	0.036
WHO-FC II, n (%)	49 (54)	13 (38)	36 (63)	
WHO-FC III, n (%)	39 (43)	19 (56)	20 (35)	
WHO-FC IV, n (%)	2 (2)	2 (6)	0 (0)	
Laboratory				
Creatinine, μmol/l	77 (67-94)	77 (68-94)	77 (67-95)	0.702
Hemoglobin, mmol/l	10.7 ± 2.3	10.9 ± 2.2	10.6 ± 2.4	0.538
NTproBNP, ng/l	581 (223-1506)	1252 (562-1597)	386 (190-1372)	0.020
Echocardiography				
SPAP, mm Hg	81 ± 25	76 ± 21	84 ± 27	0.219
TAPSE, cm	2.1 ± 1.2	1.8 ± 0.6	2.2 ± 1.5	0.233
RV S′, cm/s	10.1 ± 2.8	9.8 ± 2.8	10.2 ± 2.9	0.579
Exercise test				
Six-minute walk distance, m	375 ± 132	314 ± 129	410 ± 122	0.001
Arterial oxygen saturation rest, %	87 ± 8	84 ± 7	88 ± 8	0.024
Heart rate rest, bpm	83 ± 15	85 ± 16	81 ± 14	0.307

Abbreviations: WHO-FC, World Health Organization functional classification; NTproBNP, N-terminal pro brain natriuretic peptide; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; RV S′, velocity of the tricuspid annular systolic motion.

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