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Relevance of the TAPSE/PASP ratio in pulmonary arterial hypertension

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ABSTRACT

Background: The ratio of echocardiography-derived tricuspid annular plane systolic excursion (TAPSE) and pulmonary arterial systolic pressure (PASP) has recently been reported as an independent prognostic parameter in heart failure. The TAPSE/PASP ratio has not been evaluated in detail in patients with pulmonary arterial hypertension (PAH).

Methods: We analyzed TAPSE/PASP in 290 patients with PAH entered into the Giessen Pulmonary Hypertension Registry between November 2003 and July 2014. The prognostic relevance of TAPSE/PASP was assessed with multivariate Cox regression models, adjusting for clinical covariates, echocardiographic parameters, or hemodynamics, and was confirmed by Kaplan–Meier analyses.

Results: When stratified by tertile of TAPSE/PASP (low: <0.19 mm/mmHg; middle: 0.19–0.32 mm/mmHg; high: >0.32 mm/mmHg), patients in the low tertile showed significantly compromised hemodynamic, functional, and echocardiographic status compared with patients in the middle and high tertiles. In all multivariate models, TAPSE/PASP remained independently associated with overall mortality: the hazard ratio (95% confidence interval) was 1.87 (1.35–2.59) when adjusting for clinical covariates ($p < .001$), 5.21 (2.17–12.5) when adjusting for echocardiographic parameters ($p < .001$), 1.92 (1.30–2.83) when adjusting for hemodynamics ($p = .001$), and 4.13 (2.02–8.48) when adjusting for a selection of previously identified independent echocardiographic and hemodynamic prognostic indicators ($p < .001$). Kaplan–Meier analyses showed better overall survival in the middle and high tertiles versus the low tertile (log-rank $p < .001$).

Conclusions: The TAPSE/PASP ratio is a meaningful prognostic parameter in patients with PAH and is associated with hemodynamics and functional class.

1. Introduction

Pulmonary arterial hypertension (PAH) is characterized by an elevated mean pulmonary arterial pressure (mPAP) and an increased pulmonary vascular resistance (PVR) [1]. During the course of the disease, maladaptive right ventricular (RV) hypertrophy and/or dilatation occur, eventually resulting in RV failure [2, 3]. Several echocardiographic parameters of RV function including tricuspid annular plane systolic excursion (TAPSE) and pulmonary arterial systolic pressure (PASP) have been shown to be of prognostic relevance in patients with PAH [4, 5]. The ratio of TAPSE/PASP has been described as an index of in vivo RV shortening in the longitudinal axis versus developed force in patients with heart failure [6], and was introduced as a non-invasive, indirect measurement of RV contractile function and RV-pulmonary arterial (PA) coupling [6–8]. The TAPSE/PASP ratio has been validated as an important clinical and prognostic parameter in patients with heart failure with and without pulmonary hypertension (PH) [7–11], and was identified as an independent and strong predictor

Abbreviations: BMI, body mass index; CI, confidence interval; CO, cardiac output; dPAP, diastolic pulmonary arterial pressure; ERA, endothelin receptor antagonist; FAC, fractional area change; HIV, human immunodeficiency virus; HR, hazard ratio; IQR, interquartile range; LV, left ventricular; mPAP, mean pulmonary arterial pressure; PA, pulmonary arterial; PAC, pulmonary arterial capacitance; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary arterial wedge pressure; PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension; PP, pulse pressure; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; RV S′, systolic annular tissue velocity of the lateral tricuspid annulus; SD, standard deviation; sGC, soluble guanylate cyclase stimulator; sPAP, systolic pulmonary arterial pressure; SV, stroke volume; SvO_2, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; Tei, myocardial performance; TR, tricuspid regurgitation; WHO, World Health Organization.

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of outcome in patients with combined post- and pre-capillary PH [12]. Moreover, a close relationship of the TAPSE/PASP ratio with pulmonary arterial capacitance (PAC; a measure of the compliance of the pulmonary artery and RV afterload) and PVR has been shown [8, 12].

However, to the best of our knowledge, the TAPSE/PASP ratio has not been explored in detail in patients presenting with PAH. Our present study therefore had the following aims: 1) to assess the prognostic value of the TAPSE/PASP ratio in PAH and 2) to explore the relationship between TAPSE/PASP and hemodynamic parameters including PAC.

2. Methods

2.1. Study design and patients

We analyzed patients with PAH enrolled between November 2003 and July 2014 in the Giessen PH Registry, a prospectively recruiting single-center registry in Germany [13]. The analysis included consecutive patients with complete echocardiographic and invasive hemodynamic data at the time of enrollment and complete follow-up data. Follow-up data were retrieved from the Giessen PH Registry up to May 2017. A multidisciplinary board, including pulmonary physicians and radiologists, assessed the diagnosis in all patients with PAH before enrollment. All of the patients were receiving targeted PAH therapies based on clinical grounds and best standard of care, and changes in PAH medication were based on clinical decisions. The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of the Faculty of Medicine at the University of Giessen (Approval No. 186/16, 266/11). All participating patients gave written informed consent to be enrolled in the Giessen PH Registry.

2.2. Right heart catheterization

All patients underwent right heart catheterization by insertion of a Swan-Ganz catheter under local anesthesia according to standard techniques in the left or right jugular vein. Pressure values were continuously assessed [mPAP, right atrial pressure (RAP), pulmonary arterial wedge pressure (PAWP), and systolic and diastolic pulmonary arterial pressure (sPAP and dPAP, respectively)] and the cardiac output (CO) was measured using the direct Fick method [1], as available. PVR and cardiac index were calculated as [PVR = (mPAP − PAWP)/CO; cardiac index = (CO/body surface area)] [1]. PAC was calculated as [PAC = stroke volume (SV)/pulse pressure (PP) = (CO/heart rate)/(sPAP − dPAP)] [14].

2.3. Right heart echocardiography

All echocardiographic measurements, including TAPSE, were obtained from the Giessen PH Registry and were entered into this registry at enrollment. The measurements were obtained using a Vivid E9 and a Vivid S5 (GE Healthcare, Wauwatosa, WI, USA), with supervision by experienced examiners at the time of the original assessments to ensure adherence to echocardiographic guidelines [15–17]. TAPSE was measured in the four-chamber apical view by placing the M-mode cursor through the lateral tricuspid annulus. The peak excursion of the lateral annulus represented the TAPSE (in mm). RV systolic pressure was assessed by estimating the pressure gradient across the tricuspid valve (based on the tricuspid regurgitation [TR] jet, applying the simplified Bernoulli equation) and adding the RAP (estimated based on the collapse and diameter of the inferior vena cava) [15, 18]. Right atrial (RA) size was quantified by measuring the RA area in end-systole, and the systolic annular tissue velocity of the lateral tricuspid annulus (RV S′) was also measured [15]. Tei index was measured as the ratio of isovolumic contraction time and isovolumic relaxation time divided by ejection time [15]. The degrees of RA and RV enlargement, obtained from the four-chamber apical view, were described as none, mild, moderate, or severe based on visual assessment by an experienced examiner at the time of enrollment [19]. TR severity was classified as none, mild, moderate, or severe at enrollment [15]. For further analyses, patients with no or mild enlargement were grouped together, as were patients with no or mild TR.

2.4. Outcome

The primary outcome was overall mortality, which was assessed using follow-up data from the Giessen PH Registry.

2.5. Statistical analyses

SPSS version 23.0 (IBM, Armonk, NY, USA) was used for statistical analyses. Normally distributed data are expressed as mean ± standard deviation (SD); non-normally distributed data are expressed as median [interquartile range (IQR)]. Patients were divided into subgroups based on TAPSE/PASP ratio tertiles. Between-group differences were analyzed with one-way ANOVA, the Kruskal–Wallis test, and (for categorical parameters) the Pearson Chi-square test as appropriate, with $p < .05$ considered statistically significant. For further analysis, variables were ln-transformed in cases of a non-normal distribution (see for example Fig. S1 online).

Multivariate Cox proportional-hazards regression models were used to assess prognostic relevance. The minimum number of events per adjustment variable in the multivariate Cox regression analysis was set at 10, based on previous recommendations [20]. We therefore built four different multivariate Cox models to avoid overfitting. For model 1, covariate selection was based on clinical relevance [8] and included the TAPSE/PASP ratio as a continuous variable, along with age, gender, body mass index, arterial hypertension, atrial fibrillation, diabetes mellitus, and World Health Organization (WHO) functional class. Model 2 included the TAPSE/PASP ratio as a continuous variable and the following echocardiographic parameters (also as continuous variables): TAPSE, PASP, RA size, RV S′, Tei index, and left ventricular ejection fraction. TAPSE and PASP were included in the model despite showing strong collinearity with the TAPSE/PASP ratio [$r = 0.695$ ($p < .001$) and $r = 0.756$ ($p < .001$), respectively], to allow direct comparison of their prognostic impact. Model 3 included the TAPSE/PASP ratio as a continuous variable and the following hemodynamic parameters (also as continuous variables): PVR, mPAP, CO, PAC, mixed venous oxygen saturation (SvO_2), PP, SV, RAP, and PAWP. Model 4 included the TAPSE/PASP ratio as a continuous variable and previously identified independent hemodynamic [21–23] and echocardiographic prognostic parameters [4, 24–26] (also as continuous variables): CO, SvO_2, RAP, TAPSE, PASP, RA size, and Tei index. The prognostic relevance of the TAPSE/PASP ratio was also evaluated by Kaplan–Meier analyses with log-rank tests. For the Cox regression and Kaplan–Meier analyses, $p < .01$ was considered statistically significant.

3. Results

3.1. Patients

In total, 290 patients with PAH were included in the analysis (Table 1) and were stratified into tertiles according to TAPSE/PASP ratio (low: <0.19 mm/mmHg; middle: 0.19–0.32 mm/mmHg; high: >0.32 mm/mmHg). The majority of the patients were diagnosed with idiopathic PAH and were in WHO functional class III, presenting with severe precapillary PH with substantially elevated PVR and mPAP. Patients in the low and middle TAPSE/PASP tertiles showed a significantly more compromised hemodynamic status than those in the high tertile, with substantially increased mPAP, RAP, and PVR and decreased cardiac index, SvO_2, and PAC. Moreover, patients in the low tertile presented with a larger RA size, higher PASP, lower TAPSE, more compromised Tei index, higher rate of severe RA/RV enlargement, higher rate of severe TR, and lower RV S′ than patients in the middle and high tertiles. The initiation of specific vasoactive treatment after enrollment did not differ significantly between the tertile groups, although a numerical trend towards a higher rate of prostanoid and triple combination treatment was observed in the low tertile.

3.2. Prognostic relevance of TAPSE/PASP in PAH

The mean ± SD follow-up period was 81.3 ± 55.7 months [median [IQR]: 72.5 [89.4] months], during which 145 (50.0%) of the patients died. The median [IQR] follow-up time in TAPSE/PASP tertiles 1, 2, and 3 was 64.0 [89.5] months, 85.0 [85.5] months, and 73.5 [106.3] months, respectively.

In multivariate analyses including TAPSE/PASP as a continuous variable, model 1 (adjusting for clinical covariates) showed a significant, independent association of the TAPSE/PASP ratio with overall mortality. Of note, age and body mass index also remained significantly associated with mortality in this model. In model 2 (adjusting for echocardiographic parameters), only the TAPSE/PASP ratio remained significantly associated with overall mortality. The TAPSE/PASP ratio was also independently associated with overall mortality in model 3, along with CO, mPAP, SvO_2, and PAC. In addition, after adjusting for previously identified independent hemodynamic and echocardiographic prognostic parameters (model 4), the TAPSE/PASP ratio remained significantly associated with overall mortality (Table 2).

The prognostic significance of the TAPSE/PASP ratio was confirmed by Kaplan–Meier analyses which showed significantly better overall survival in the middle and high TAPSE/PASP tertiles compared with the low tertile (log-rank $p < .001$; Fig. 1). Five-year overall survival was 58.1%, 73.0%, and 70.0% in the low, middle, and high TAPSE/PASP tertiles, respectively (Fig. 1).