A simple echocardiographic estimate of right ventricular–arterial coupling to assess severity and outcome in pulmonary hypertension on chronic lung disease

To the Editor:

The adaptation of right ventricular (RV) systolic function to afterload is a major determinant of outcome in pulmonary hypertension [1]. The gold standard measurement of RV–pulmonary arterial (PA) coupling is the ratio of end-systolic to arterial elastances (E_{es}/E_a) which is optimal for RV flow output at minimal energy cost at values between 1.5 and 2 [2]. Progressive RV–PA uncoupling is associated with maintained RV dimensions down to E_{es}/E_a values of around 0.8 [3]. Thus, the evaluation of RV–PA coupling would theoretically allow monitoring of the transition from compensated to decompensated RV function in pulmonary hypertension. However, measuring RV–PA coupling at the bedside is technically demanding and invasive. Therefore, simpler imaging surrogates are being evaluated. One of those is the ratio of tricuspid annular plane systolic excursion (TAPSE) as a surrogate of contractility and systolic pulmonary artery pressure (PASP) as a surrogate of afterload, both measured using echocardiography (M-mode for TAPSE and Doppler assessment of the maximum velocity of tricuspid regurgitation for PASP) [4]. The TAPSE/PASP ratio has emerged as a potent predictor of outcome in heart failure [5] as well as in pulmonary arterial hypertension (PAH) [6].

Pulmonary hypertension secondary to chronic lung diseases (PH-LD) is most often mild to moderate, with many patients having a mean pulmonary artery pressure (PAP) <35 mmHg. A small percentage of patients referred for evaluation in dedicated centres may have severe pulmonary hypertension with mean PAP in the range reported in PAH [7]. However, RV function is often altered even in mild-to-moderate PH-LD, and is an important determinant of survival and functional status in PH-LD [7, 8]. We therefore explored the functional significance and prognostic relevance of the TAPSE/PASP ratio in PH-LD.

We analysed patients with PH-LD and idiopathic PAH (iPAH) enrolled in the prospectively recruiting Giessen PH Registry [9]. The diagnosis of PH-LD was established by a multidisciplinary board before enrolment in the Giessen PH registry [9] between December 2004 and March 2012. Follow-up data were retrieved from the Giessen PH Registry up to February 2018. The analysis included consecutive patients with complete echocardiographic (day 1) and invasive haemodynamic data (day 2) and complete follow-up. The patients with iPAH (n=193) were a subset of a previously reported cohort of 290 patients with PAH [6]. The investigation 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.

As recently updated [7], PH-LD was defined by a mean PAP of ⩾21 mmHg (21–24 mmHg with pulmonary vascular resistance (PVR) ⩾3 Wood Units, or ⩾25 mmHg alone), with mean PAP ⩾35 mmHg alone or mean PAP ⩾25 mmHg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$) sub-defining severe PH-LD.

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The ratio of tricuspid annular plane systolic excursion to systolic pulmonary artery pressure is a simple echocardiographic parameter that reflects haemodynamic severity and predicts survival in pulmonary hypertension due to lung diseases. http://bit.ly/2KgLAbR

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Normally distributed data were expressed as mean±SD; non-normally distributed data were expressed as median (interquartile range). Receiver operating characteristic (ROC) analyses and the Youden Index were used to determine thresholds for discrimination of PH-LD severity. Logistic regression models were built to assess the ability of the TAPSE/PASP ratio to discriminate severe and non-severe PH-LD and to predict survival. In all analyses, $p<0.05$ was considered significant.

In total, 172 patients with PH-LD were included (age: 58±26 years; mean PAP: 34 (28–41) mmHg; PVR: 5.5 (3.8–7.9) Wood Units; cardiac index: 2.5±0.7 $L \cdot min^{-1} \cdot m^{-2}$). 78 (45.3%) patients had pulmonary hypertension due to chronic obstructive pulmonary disease (PH-COPD), which was classified as severe in 21 (12.2%) patients. The remaining 94 (54.7%) patients had pulmonary hypertension due to interstitial lung disease (PH-ILD), which was classified as severe in 44 (25.6%) patients. The patients with PH-COPD had a reduced forced expiratory volume in 1 s (FEV_1) of 51±23% predicted and a FEV_1/forced vital capacity (FVC) ratio of 57±14%. The FEV_1/FVC ratio was higher in severe *versus* non-severe PH-COPD while FEV_1 was not different (FEV_1/FVC: 63±12% pred *versus* 55±15% pred, p=0.049; FEV_1: p=0.088; independent t-test). We found no correlation between FEV_1/FVC or FEV_1 and the TAPSE/PASP ratio in severe and non-severe PH-COPD (data not shown). The patients with PH-ILD had reduced total lung capacity (TLC; 71±21% pred) and vital capacity (VC; 61±22% pred). Neither parameter differed between severe and non-severe PH-ILD (TLC: p=0.699; VC: p=0.838; independent t-test). There were no correlations between TLC or VC and the TAPSE/PASP ratio in severe and non-severe PH-ILD (data not shown).

In the patients with severe PH-LD, TAPSE/PASP ratios and PVR values were in the same range as those observed in the patients with iPAH and significantly lower and higher, respectively, than those observed in the patients with non-severe PH-LD (figure 1a).

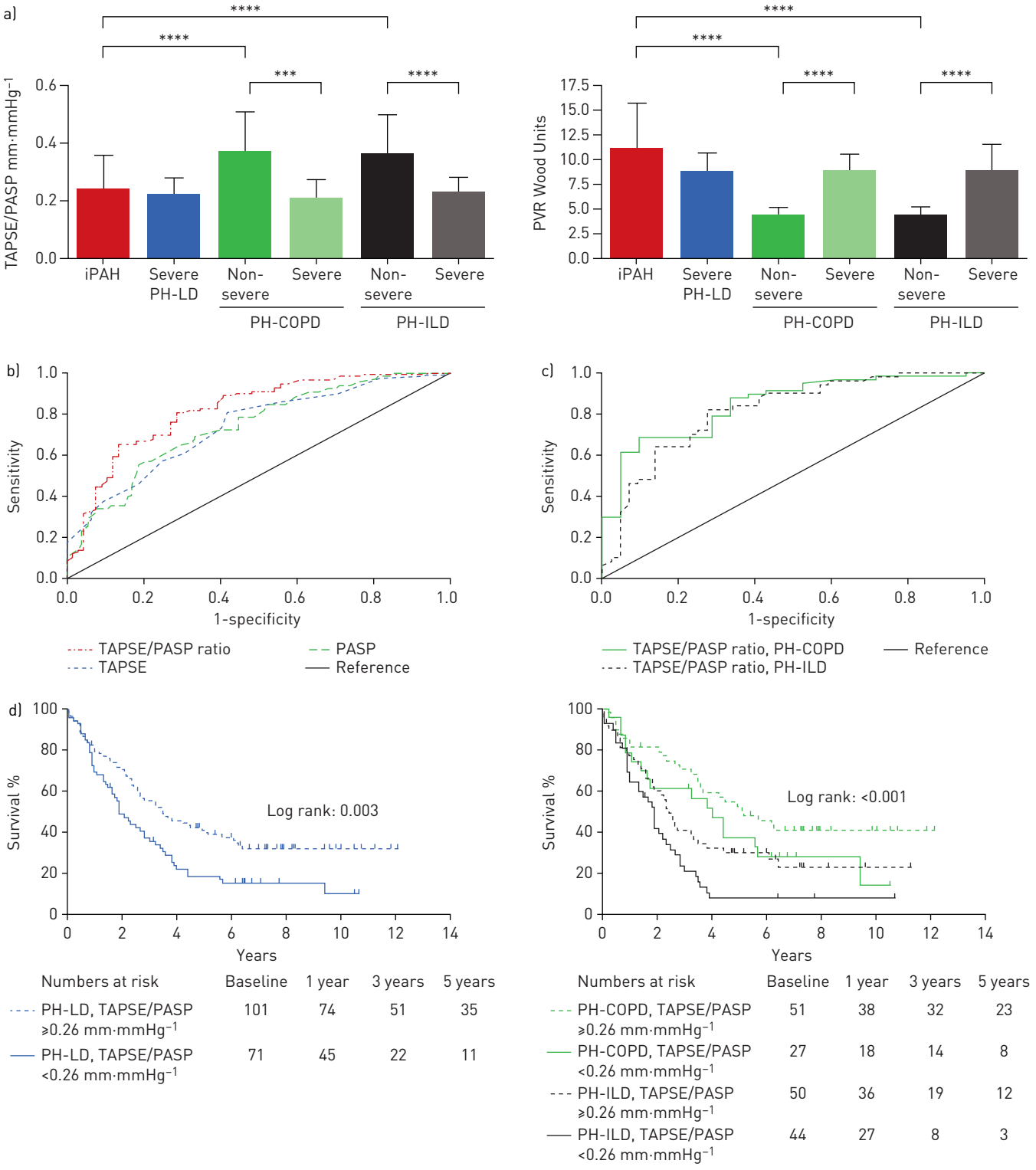
ROC analysis identified a cut-off of 0.26 $mm \cdot mmHg^{-1}$ for TAPSE/PASP with a sensitivity of 80.6% and a specificity of 71.2% to discriminate between severe and non-severe PH-LD, which was superior to TAPSE or PASP alone (figure 1b). Logistic multivariate analysis (adjusting for age and sex) showed a significant ability of the TAPSE/PASP ratio (dichotomised at 0.26 $mm \cdot mmHg^{-1}$; OR: 9.37; 95% CI: 4.56–19.26; p<0.001) to discriminate the haemodynamic phenotypes. In addition, ROC analysis showed that TAPSE/PASP is also able to discriminate between severe and non-severe PH-COPD and severe and non-severe PH-ILD (figure 1c). This was supported by logistic multivariate analysis (multivariate OR for PH-COPD: 18.60; 95% CI: 4.45–77.75; p<0.001; and PH-ILD: 8.44; 95% confidence interval: 3.34–21.36; p<0.001). Interestingly, the TAPSE/PASP ratio predicted survival in PH-COPD as well as in PH-ILD (figure 1d).

Previous studies reported only mild-to-moderate alterations in lung function tests in patients with severe PH secondary to COPD [10, 11], and better lung function in severe PH-COPD compared with non-severe PH-COPD [12, 13]. This is supported by our data showing a higher FEV_1/FVC ratio in COPD with severe *versus* non-severe PH, and agrees with the notion of a predominantly vascular phenotype in these patients [11].

Afterload dependent progression of RV function from adaptation over maladaptation and eventually to failure is determining the symptomatic status and prognosis irrespectively of the underlying pulmonary hypertension subgroup [14]. In the present study, the TAPSE/PASP ratio, as an afterload dependent echocardiographic surrogate of RV–PA coupling, showed its clinical utility in PH-LD. This is in line with the previously described prognostic relevance and association to PVR in PAH [6] as well as in heart failure [15]. However, the adequacy of RV adaptation may vary from one patient to another and depend on the presence of co-morbidities, as has been shown for example in patients with systemic sclerosis [1, 2]. Nevertheless, the impact of chronic infections or an inflammatory state on RV–PA coupling in PH-LD patients need further investigation.

Limitations to the present findings are the absence of invasive validation of the TAPSE/PASP ratio, the high proportion of patients with severe PH-LD (probably related to the fact that the UGMLC is a national tertiary referral centre for pulmonary hypertension), and the currently unclear therapeutic relevance. Other parameters such as FAC and global longitudinal strain, have not been investigated in our study but might also be associated with contractility/coupling and outcome. In addition, variability in load condition might influence the TASPE/PASP ratio due to its afterload dependency.

In conclusion, the TAPSE/PASP ratio is a straightforward and clinically relevant measurement to differentiate between the haemodynamic phenotypes of patients with PH-LD. The TAPSE/PASP ratio might prove to be an important non-invasive tool for the evaluation of future therapeutic interventions in patients with PH-LD.



Numbers at risk	Baseline	1 year	3 years	5 years
PH-LD, TAPSE/PASP ≥0.26 mm·mmHg^{-1}	101	74	51	35
PH-LD, TAPSE/PASP <0.26 mm·mmHg^{-1}	71	45	22	11

Numbers at risk	Baseline	1 year	3 years	5 years
PH-COPD, TAPSE/PASP ≥0.26 mm·mmHg^{-1}	51	38	32	23
PH-COPD, TAPSE/PASP <0.26 mm·mmHg^{-1}	27	18	14	8
PH-ILD, TAPSE/PASP ≥0.26 mm·mmHg^{-1}	50	36	19	12
PH-ILD, TAPSE/PASP <0.26 mm·mmHg^{-1}	44	27	8	3

FIGURE 1 The tricuspid annular plane systolic excursion (TAPSE)/ systolic pulmonary artery pressure (PASP) ratio as an indicator of haemodynamic severity and prognosis in pulmonary hypertension secondary to chronic lung disease (PH-LD). a) TAPSE/PASP ratio and pulmonary vascular resistance (PVR) in patients with idiopathic pulmonary arterial hypertension (iPAH) and patients with pulmonary hypertension due to chronic obstructive pulmonary disease (PH-COPD) or interstitial lung disease (PH-ILD) stratified by haemodynamic severity (bar charts show median and interquartile range; ****p<0.0001; ***p<0.001; between-group differences were analysed with the Kruskal-Wallis test). b) Receiver operating characteristic analyses of the TAPSE/PASP ratio (area under the curve (AUC): 0.825; p<0.001), TAPSE (AUC: 0.736; p<0.001) and PASP (AUC: 0.739; p<0.001) for discriminating between severe and non-severe PH-LD (diagonal segments were produced by ties). c) Receiver operating characteristic analyses of the TAPSE/PASP ratio for discriminating between severe and non-severe PH-COPD (AUC: 0.847; p<0.001) and PH-ILD (AUC: 0.815; p<0.001) (diagonal segments were produced by ties). d) Kaplan–Meier survival curves in patients with PH-LD and subsets with PH-ILD and PH-COPD stratified by the TAPSE/PASP ratio.

Khodr Tello[1], Hossein A. Ghofrani[1,2,3], Charlotte Heinze[1], Karsten Krueger[4], Robert Naeije[5], Christina Raubach[1], Werner Seeger[1], Natascha Sommer[1], Henning Gall[1,6] and Manuel J. Richter[1,6]
[1]Dept of Internal Medicine, Justus-Liebig-University Giessen, Universities of Giessen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research (DZL), Giessen, Germany. [2]Dept of Pneumology, Kerckhoff Heart, Rheuma and Thoracic Center, Bad Nauheim, Germany. [3]Dept of Medicine, Imperial College London, London, UK. [4]Institute of Sports Science, Department of Exercise and Health, Leibniz University Hannover, Hannover, Germany. [5]Erasme University Hospital, Brussels, Belgium. [6]These authors have contributed equally to this work.

Correspondence: Manuel J. Richter, Dept of Internal Medicine, Justus-Liebig-University Giessen, Universities of Giessen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research (DZL), Klinikstrasse 33, 35392 Giessen, Germany. E-mail manuel.richter@innere.med.uni-giessen.de

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