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Early View

Research letter

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

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Take-home message: 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.

To the Editor:

The adaptation of right ventricular (RV) systolic function to afterload is a major determinant of outcome in pulmonary hypertension (PH) [1]. The gold standard measurement of RV-pulmonary arterial (PA) coupling is the ratio of end-systolic to arterial elastances (Ees/Ea) 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 Ees/Ea 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 PH. 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].

PH secondary to chronic lung diseases (PH-LD) is most often mild to moderate, with many patients having a mean pulmonary artery pressure (mPAP) below 35 mmHg. A small percentage of patients referred for evaluation in dedicated centres may have severe PH with mPAP 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 12/2004 and 03/2012. Follow-up data were retrieved from the Giessen PH Registry up to 02/2018. 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 mPAP of ≥21 mmHg (21–24 mmHg with pulmonary vascular resistance (PVR) ≥3 Wood Units, or ≥25 mmHg alone), with mPAP ≥35 mmHg alone or mPAP ≥25 mmHg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$) sub-defining severe PH-LD. 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; mPAP: 34 [28–41] mmHg; PVR: 5.5 [3.8–7.9] Wood Units; cardiac index: 2.5 ± 0.7 $L \cdot min^{-1} \cdot m^{-2}$). Seventy-eight patients (45.3%) had PH due to chronic obstructive pulmonary disease (PH-COPD), which was classified as severe in 21 patients (12.2%). The remaining 94 patients (54.7%) had PH due to interstitial lung disease (PH-ILD),

which was classified as severe in 44 patients (25.6%). The patients with PH-COPD had a reduced forced expiratory volume in 1 second (FEV1) of 51±23% predicted (pred.) and a FEV1/forced vital capacity (FVC) ratio of 57±14%. The FEV1/FVC ratio was higher in severe vs. non-severe PH-COPD while FEV1 was not different (FEV1/FVC: 63±12% pred. vs. 55±15% pred., p=0.049; FEV1: p=0.088; independent t-test). We found no correlation between FEV1/FVC or FEV1 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·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 gender) showed a significant ability of the TAPSE/PASP ratio (dichotomised at 0.26 mm·mmHg^{-1}; odds ratio: 9.37; 95% confidence interval: 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 odds ratio for PH-COPD: 18.60; 95% confidence interval: 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 FEV1/FVC ratio in COPD with severe vs. 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 PH 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 PH), 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.

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Conflict of interest

Dr Tello has declared no conflict of interest. Dr Ghofrani has received consultancy fees from Bayer, Actelion, Pfizer, Merck, GSK, and Novartis; fees for participation in advisory boards from Bayer, Pfizer, GSK, Actelion, and Takeda; lecture fees from Bayer HealthCare, GSK, Actelion, and Encysive/Pfizer; industry-sponsored grants from Bayer HealthCare, Aires, Encysive/Pfizer, and Novartis; and sponsored grants from the German Research Foundation, Excellence Cluster Cardiopulmonary Research, and the German Ministry for Education and Research. Ms Heinze and Dr Krueger have declared no conflicts of interest. Dr Naeije has relationships with drug companies including AOPOrphan Pharmaceuticals, Actelion, Bayer, Reata, Lung Biotechnology Corporation, and United Therapeutics. In addition to being an investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards. Ms Raubach has declared no conflict of interest. Dr Seeger has received speaker/consultancy fees/fees for participation in advisory boards from Pfizer, Novartis, United Therapeutics, Actelion, Vectura, Savara, Medspray, and Bayer Pharma AG. Dr Sommer has declared no conflict of interest. Dr Gall has received fees from Actelion, AstraZeneca, Bayer, BMS, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer, and United Therapeutics. Dr Richter has received support from United Therapeutics and Bayer Pharma AG, and speaker fees from Actelion, Mundipharma, Roche, and OMT.

References

1. Vonk Noordegraaf A, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, Kawut SM, Langleben D, Lumens J, Naeije R. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. *The European respiratory journal* 2019: 53(1): 1801900.

2. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The Relationship Between the Right Ventricle and its Load in Pulmonary Hypertension. *J Am Coll Cardiol* 2017: 69(2): 236-243.

3. Tello K, Dalmer A, Axmann J, Vanderpool R, Ghofrani HA, Naeije R, Roller F, Seeger W, Sommer N, Wilhelm J, Gall H, Richter MJ. Reserve of Right Ventricular-Arterial Coupling in the Setting of Chronic Overload. *Circulation Heart failure* 2019: 12(1): e005512.

4. Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S, Temporelli PL, Arena R. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. *American journal of physiology Heart and circulatory physiology* 2013: 305(9): H1373-1381.

5. Guazzi M, Dixon D, Labate V, Beussink-Nelson L, Bandera F, Cuttica MJ, Shah SJ. RV Contractile Function and its Coupling to Pulmonary Circulation in Heart Failure With Preserved Ejection Fraction: Stratification of Clinical Phenotypes and Outcomes. *JACC Cardiovasc Imaging* 2017: 10(10 Pt B): 1211-1221.

6. Tello K, Axmann J, Ghofrani HA, Naeije R, Narcin N, Rieth A, Seeger W, Gall H, Richter MJ. Relevance of the TAPSE/PASP ratio in pulmonary arterial hypertension. *International journal of cardiology* 2018: 266: 229-235.

7. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, Weissmann N, Seeger W. Pulmonary hypertension

in chronic lung disease and hypoxia. *The European respiratory journal* 2019: 53(1): 1801914.

8. Prins KW, Rose L, Archer SL, Pritzker M, Weir EK, Kazmirczak F, Misialek JR, Thenappan T. Disproportionate Right Ventricular Dysfunction and Poor Survival in Group 3 Pulmonary Hypertension. *American journal of respiratory and critical care medicine* 2018: 197(11): 1496-1499.

9. Gall H, Felix JF, Schneck FK, Milger K, Sommer N, Voswinckel R, Franco OH, Hofman A, Schermuly RT, Weissmann N, Grimminger F, Seeger W, Ghofrani HA. The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2017: 36(9): 957-967.

10. Seeger W, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galie N, Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiery JL. Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol* 2013: 62 (25 Suppl.): D109-116.

11. Kovacs G, Agusti A, Barbera JA, Celli B, Criner G, Humbert M, Sin DD, Voelkel N, Olschewski H. Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease. Is There a Pulmonary Vascular Phenotype? *American journal of respiratory and critical care medicine* 2018: 198(8): 1000-1011.

12. Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducolone A, Ehrhart M, Kessler R, Weitzenblum E. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 2005: 172(2): 189-194.

13. Boerrigter BG, Bogaard HJ, Trip P, Groepenhoff H, Rietema H, Holverda S, Boonstra A, Postmus PE, Westerhof N, Vonk-Noordegraaf A. Ventilatory and cardiocirculatory

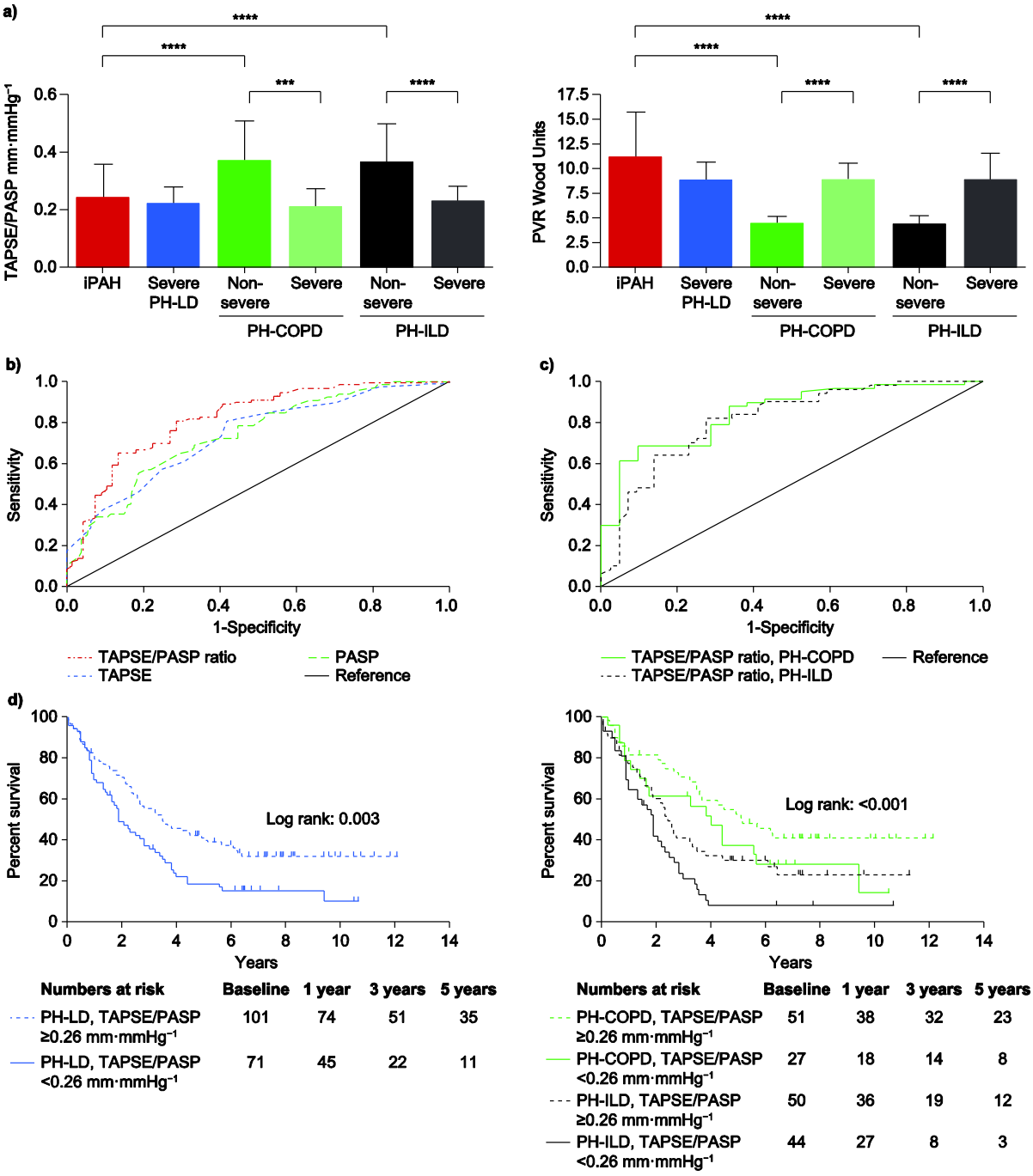
exercise profiles in COPD: the role of pulmonary hypertension. *Chest* 2012: 142(5): 1166-1174.

14. Sanz J, Sanchez-Quintana D, Bossone E, Bogaard HJ, Naeije R. Anatomy, Function, and Dysfunction of the Right Ventricle: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019: 73(12): 1463-1482.

15. Guazzi M, Naeije R. Pulmonary Hypertension in Heart Failure: Pathophysiology, Pathobiology, and Emerging Clinical Perspectives. *J Am Coll Cardiol* 2017: 69(13): 1718-1734.

Figure legend

FIGURE 1 The TAPSE/PASP ratio as an indicator of haemodynamic severity and prognosis in PH-LD. a) TAPSE/PASP ratio and PVR in patients with iPAH and patients with PH-COPD or 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 (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. AUC: area under the curve; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; iPAH: idiopathic pulmonary arterial hypertension; LD: lung disease; PASP: systolic pulmonary artery pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; TAPSE: tricuspid annular plane systolic excursion.


a)
TAPSE/PASP mm·mmHg⁻¹
PVR Wood Units
iPAH
Severe PH-LD
Non-severe
Severe
Non-severe
Severe
PH-COPD
PH-ILD
b)
c)
Sensitivity
1-Specificity
TAPSE/PASP ratio
TAPSE
PASP
Reference
TAPSE/PASP ratio, PH-COPD
TAPSE/PASP ratio, PH-ILD
d)
Percent survival
Years
Log rank: 0.003
Log rank: <0.001
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
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