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BRIEF COMMUNICATION

Loss of right ventricular outflow function in pulmonary hypertension

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KEYWORDS:
right ventricular outflow tract; echocardiography; pulmonary hypertension; right ventricle; 3D analysis

Right ventricular outflow tract (RVOT) function is not systematically quantified by three-dimensional (3D) echocardiography. We tested the hypothesis that loss of RVOT function in pulmonary hypertension (PH) is related to disease severity independently of other echocardiographic parameters. In this observational study, patients with PH, disease controls, and a matched healthy control group underwent 3D echocardiography and RVOT analysis using ReVISION software. The study included 43 patients (38 with PH, 5 disease controls) and 43 healthy controls. Median 3D RVOT-ejection fraction (EF) was 30.4% in the patients and 44.2% in the healthy controls ($p < 0.001$). Patients with low 3D RVOT-EF (< 30.4%) were more frequently categorized in higher-risk groups and had a higher incidence of clinical worsening than those with high 3D RVOT-EF. Even in patients with RV-EF ≥35%, those with low 3D RVOT-EF had worse outcomes. Segmental RVOT analysis identifies high-risk patients even with normal overall RV function.

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For the diagnosis and treatment of pulmonary hypertension (PH), a comprehensive examination of right ventricular (RV) function is important as it is closely related to PH symptoms and prognosis.[1-3] The proportion of RV volume taken up by the RV outflow tract (RVOT) contributes up to 15% to overall RV efficiency.[4] However, comprehensive assessment of RVOT function remains outside the standard of practice. We hypothesized that the loss of RVOT function is independently associated with disease severity. We, therefore, aimed to investigate the clinical relevance of RVOT function using advanced three-dimensional (3D)-echocardiographic analysis techniques,

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highlighting the additional clinical value of RVOT-ejection fraction (EF) measured alongside established routine echocardiographic RV metrics in PH.

We prospectively analyzed patients enrolled in the EXERTION Study (NCT04663217) between November 2020 and March 2022, with PH diagnoses confirmed or excluded via right heart catheterization. Ethical approval was obtained from the University of Giessen (Approval No. 117/16). An age- and gender-matched control group of 43 healthy individuals was analyzed from a normative study at Semmelweis University, Budapest (Approval No. 169/2018).

The EXERTION cohort underwent standard right heart catheterization[5] and 3D echocardiography with a Philips EPIQ 7G unit. A 3D RV casts were reconstructed using IntelliSpace Cardiovascular Workstation software. RV volumetry showed high interobserver agreement, as reported previously[6] (Figure S1). The control group underwent 3D echocardiography using Philips EPIQ 7 or GE Vivid E95 machines.

For segmental analysis, 3D RV mesh models were exported to ReVISION software (Argus Cognitive Inc.). RVOT-EF was calculated, as described previously.[7,8]

Patients with PH were categorized into risk groups using the REVEAL Lite 2 score (based on World Health Organization functional class, heart rate, systolic blood pressure, 6-minute walk distance, B-type natriuretic peptide [BNP] or N-terminal pro-BNP levels, and estimated glomerular filtration rate) and followed until August 5, 2023 for clinical worsening, defined as a 15% reduction in 6-minute walk distance, worsening World Health Organization class, or clinical deterioration resulting in hospitalization, pulmonary arterial hypertension (PAH) therapy adjustment, diuretic increase, lung transplantation, or death.[9]

Normality was assessed by the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots. Normally and non-normally distributed variables are presented as mean ± standard deviation and median [interquartile range], respectively. Correlations were determined using Spearman's rho. A 3D RVOT-EF and pulmonary vascular resistance (PVR) were classified as low/high based on cut-offs of 30.4% (the median in the EXERTION cohort) and 2 Wood Units, respectively. Differences were analyzed by Student's *t*-test or Mann-Whitney U test. Survival was assessed using Kaplan-Meier, univariable, and multivariable Cox regression analyses. $P < 0.05$ was considered significant. SPSS 29.0 and R 4.0.4 were used.

The EXERTION cohort comprised 43 patients (38 with PH confirmed and 5 with PH excluded [disease controls]) (Table 1 and Figure S2). Median 3D RVOT-EF was 30.4 [18.5-36.9]% and 44.2 [37.6-49.3]% in the EXERTION and healthy control cohorts, respectively ($p < 0.001$; Table S1). Healthy and disease controls showed no significant

Table 1 Baseline Characteristics of the Patient Cohort

Characteristics	Total	Group 1 Low PVR, high 3D RVOT-EF	Group 2 High PVR, high 3D RVOT-EF	Group 3 High PVR, low 3D RVOT-EF	*p* Group 1 versus 2	*p* Group 2 versus 3
Patients, *n* (%)	43 (100)	5 (12)	16 (37)	22 (51)		
Male/female, *n/n*	16/27	3/2	4/12	9/13	0.323[a]	
Age, years	70.0 [60.0-77.0]	44.0 [36.0-54.0]	70.5 [58.5-77.5]	71.5 [61.5-79.0]	0.008[b]	0.711[b]
BMI, kg/m^2	26.6 [23.5-32.4]	31.0 [26.2-34.7]	27.4 [24.6-34.6]	24.7 [23.2-31.7]	0.65[b]	0.315[b]
BNP, pg/ml	110.0 [16.0-318.0]	14.0 [5.0-68.0]	36.0 [13.0-102.5]	277.5 [97.0-451.0]	0.321[b]	< 0.001[b]
eGFR, ml/min/1.73 m^2	75.9 ± 28.6	118.0 ± 16.1	80.1 ± 26.0	63.4 ± 22.4	0.007[c]	0.041[c]
Heart rate, beats/min	69.6 ± 13.1	67.6 ± 10.7	67.6 ± 12.3	71.5 ± 14.4	0.997[c]	0.385[c]
Diagnosis, *n* (%)						
Non-PH (disease control)[d]	5 (12)	5 (100)	0	0		
PAH (PH group 1)	16 (37)	0	6 (38)	10 (45)		
PH-HFpEF (PH group 2)	6 (14)	0	4 (25)	2 (9)		
CTEPH (PH group 4)	16 (37)	0	6 (38)	10 (45)		
NYHA functional class, *n* (%)						
II	13 (30)	4 (80)	6 (38)	3 (14)		
III	28 (65)	1 (20)	10 (63)	17 (77)		
IV	2 (5)	0	0	2 (9)		
Right heart catheterization						
mPAP, mm Hg	35.7 ± 12.3	15.6 ± 3.0	34.8 ± 8.7	40.9 ± 10.9	< 0.001[c]	0.076[c]
PVR, WU	5.3 [2.7-7.6]	1.2 [1.0-1.5]	5.1 [2.9-6.4]	6.6 [3.5-9.6]	< 0.001[b]	0.089[b]

(*continued on next page*)

Table 1 (*Continued*)

Characteristics	Total	Group 1 Low PVR, high 3D RVOT-EF	Group 2 High PVR, high 3D RVOT-EF	Group 3 High PVR, low 3D RVOT-EF	*p* Group 1 versus 2	*p* Group 2 versus 3
Cardiac index, liter/min/m^2	2.6 ± 0.6	3.5 ± 0.6	2.6 ± 0.3	2.5 ± 0.6	< 0.001[c]	0.582[c]
PAWP, mm Hg	10.3 ± 4.6	6.4 ± 1.9	11.1 ± 5.2	10.7 ± 4.3	0.067[c]	0.807[c]
PAC, ml/mm Hg	2.0 [1.3-3.5]	8.8 [7.3-10.2]	2.4 [1.8-3.5]	1.6 [1.1-2.1]	< 0.001[b]	0.014[b]
PP, mm Hg	37.0 ± 18.0	12.8 ± 1.5	33.4 ± 13.8	45.0 ± 17.2	0.004[c]	0.032[c]
Echocardiography						
3D RV EDV, ml	122.6 [101.3-149.9]	101.3 [96.0-113.0]	108.4 [86.3-134.4]	143.1 [114.8-190.6]	0.78[b]	0.002[b]
3D RV ESV, ml	70.8 [53.8-95.5]	50.9 [45.4-55.4]	58.7 [38.0-73.4]	92.6 [64.4-134.0]	0.354[b]	< 0.001[b]
3D RV SV, ml	51.6 [45.4-60.1]	48.4 [45.8-63.4]	52.4 [43.4-61.0]	51.6 [45.0-63.2]	0.869[c]	0.929[c]
RV EDD, mm	46.1 ± 8.1	35.8 ± 3.4	41.8 ± 6.2	51.5 ± 5.5	0.056[c]	< 0.001[c]
RV EDA, cm²	27.4 ± 7.9	21.2 ± 3.6	24.1 ± 6.8	31.3 ± 7.4	0.376[c]	0.004[c]
RV ESA, cm²	19.2 ± 7	12.7 ± 2.9	15.4 ± 4.8	23.4 ± 6.4	0.492[c]	< 0.001[c]
3D RV-EF, %	42.7 ± 9.8	51.1 ± 5.9	48.7 ± 6.9	36.3 ± 8.0	0.492[c]	< 0.001[c]
3D RV FWS, %	−22.1 ± 6.1	−29.5 ± 5.8	−23.8 ± 3.7	−19.2 ± 5.8	0.016[c]	0.008[c]
3D RV 4-chamber strain, %	−17.5 ± 4.5	−21.9 ± 2.6	−19.0 ± 2.7	−15.3 ± 4.8	0.055[c]	0.009[c]
RV FAC, %	29.5 ± 12.5	41.8 ± 4.6	34.1 ± 12.1	23.2 ± 10.5	0.188[c]	0.005[c]
TAPSE, mm	20.2 ± 3.8	23.1 ± 3.6	20.8 ± 3.3	19.1 ± 4.0	0.186[c]	0.182[c]
TAPSE/PASP, mm/mm Hg	0.35 [0.2-0.6]	1.0 [0.9-1.0]	0.4 [0.3-0.5]	0.2 [0.2-0.3]	< 0.001[b]	0.008[b]
ReVISION software analysis						
3D RVOT-EF, %	30.4 [18.5-36.9]	38.9 [38.8-41.4]	36.2 [31.8-40.9]	19 [10.7-23.2]	0.46[b]	< 0.001[b]
3D RVOT EDV, ml	17.9 [13.7-23.0]	17.9 [17.1-20.4]	14.2 [12.2-18.2]	19.3 [14.6-27.2]	0.109[b]	0.011[b]
3D RVOT ESV, ml	11.9 [8.8-17.1]	11.0 [10.7-12.0]	8.8 [7.8-11.9]	17.1 [11.5-23.2]	0.275[b]	< 0.001[b]
3D RVOT SV, ml	4.9 ± 2.1	7.3 ± 1.1	5.6 ± 1.5	3.8 ± 2.1	0.03[c]	0.008[c]

3D, three-dimensional; BMI, body mass index; BNP, B-type natriuretic peptide; CTEPH, chronic thromboembolic pulmonary hypertension; EDA, end-diastolic area; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESA, end-systolic area; ESV, end-systolic volume; FAC, fractional area change; FWS, free wall strain; HFpEF, heart failure with preserved ejection fraction; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association; PAC, pulmonary arterial capacitance; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PP, pulse pressure; PVR, pulmonary vascular resistance; RV, right ventricular; RVOT, right ventricular outflow tract; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; WU, Wood Units.

Values are presented as *n/n, n (%), mean ± standard deviation, or median [interquartile range]. All echocardiographic measurements marked as "3D" were performed using 3D echocardiography; other echocardiographic measurements were performed using 2-dimensional echocardiography.*

[a]Pearson chi-square test overall.

[b]Mann-Whitney U test.

[c]Student's *t*-test.

[d]Disease control patients were initially referred for suspicion of PH and dyspnea on exertion; in these patients, pulmonary vascular disease (defined as PVR > 2 WU) was excluded by invasive assessment, and relevant concomitant cardiopulmonary disease was also excluded.

difference in 3D RVOT-EF ($p = 0.216$). Among the patients with PH, 58% had low 3D RVOT-EF (i.e., below median), and the median follow-up was 20 (10-26) months, with 17 clinical worsening events.

A 3D RVOT-EF correlated significantly with mean pulmonary arterial pressure (rho = −0.59), PVR (rho = −0.50), pulmonary arterial capacitance (rho = 0.55), and end-diastolic diameter (rho = −0.74) (all $p < 0.001$) (Figure S3).

We assessed the clinical relevance of 3D RVOT-EF by grouping patients based on PVR and 3D RVOT-EF (Table 1). Three distinct groups were observed: group 1 with low PVR and high 3D RVOT-EF; group 2 with high PVR and high 3D RVOT-EF; and group 3 with high PVR and low 3D RVOT-EF. In patients belonging to groups 2 or 3, PVR did not show statistically significant differences. Despite the comparable afterload elevation, patients in group 3 showed significantly higher BNP values, more advanced RV dilatation, and lower total RV-EF than those in group 2 (Figure S4). Notably, although statistical significance was not reached, RVOT-EF outperformed RV end-diastolic volume and RV end-diastolic diameter in discriminating risk (Table S2).

Moreover, low 3D RVOT-EF was associated with an increased REVEAL Lite 2 risk score, despite global RV function being above risk-indicating thresholds (Figure S5). Right atrial data and tricuspid regurgitation did not significantly impact the observed association between RVOT function and clinical outcomes. Kaplan-Meier analysis

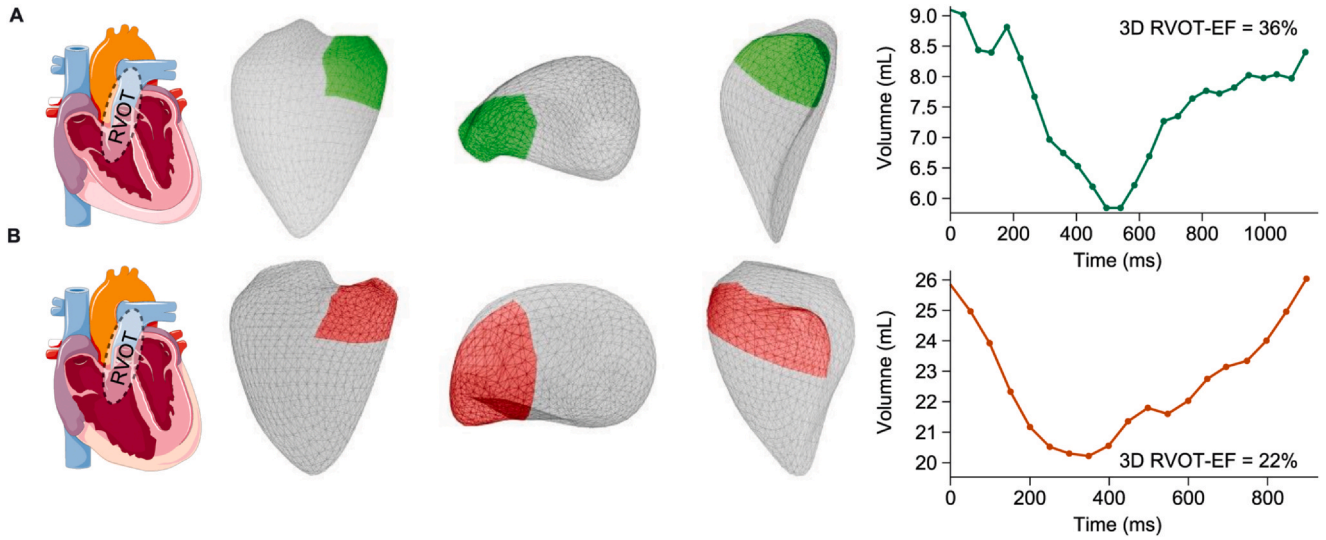

Figure 1 A 3D imaging of the RVOT and calculation of 3D RVOT-EF. ReVISION software was used to generate a segmented 3D representation of the RVOT, allowing measurement of RVOT volume over time and calculation of RVOT-EF; examples are shown from patients with (A) high and (B) low 3D RVOT-EF. 3D, three-dimensional; EF, ejection fraction; RVOT, right ventricular outflow tract.

showed a significantly higher incidence of clinical worsening in patients with low 3D RVOT-EF than in those with high 3D RVOT-EF (Graphic abstract). Univariable Cox regression analysis indicated that 3D RVOT-EF was significantly associated with clinical worsening (hazard ratio: 0.94; 95% confidence interval: 0.89-0.98; $p = 0.003$). Different multivariable models adjusting for relevant confounders confirmed the independent association of RVOT-EF and clinical worsening (Table S3).

Taken together, our findings highlight a crucial aspect of RVOT function in the context of PH. The transition from RV adaptation to maladaptation in response to increased afterload—resulting in loss of EF, contractility, and coupling—is a key feature of PH.[1] The RVOT links the right ventricle and pulmonary vessels, playing a critical role in their coupling. Our findings show that loss of the unique segmental function of the RVOT has significant clinical implications. Even when global RV function is above risk thresholds, risk-associated changes can still be detected through 3D subanalyses. This underscores the importance of the RV compartmental structure in maintaining overall performance.[4]

Another study showed that, in PAH, RV morphological changes from a normal triangular to an enlarged cylindrical shape may be associated with impaired overall function.[10] As PAH progresses, there is an increase in volume, the contraction sequence is lost, and EF decreases.[10] Early RVOT dysfunction shifts the workload to the apex of the heart, with the inlet tract initially remaining stable but later becoming impaired.[10] Our previous work supports this, showing early RV-arterial uncoupling associated with reduced longitudinal function and advanced uncoupling associated with reduced anteroposterior motion and left ventricular preload.[6]

Applied to the analysis of 3D RVOT-EF, it could be interpreted that early identification of segmental constraints using advanced 3D echocardiography could provide added value by detecting precursors of global dysfunction under sustained high afterload (Figure 1). Our results show that RVOT-EF is inversely associated with afterload and low RVOT-EF is accompanied by low overall 3D RV-EF, even at comparable afterload. As a clinical consequence, low RVOT function was associated with significantly worse risk stratification than high RVOT function.

The study's small sample size limits the reliability of 3D RVOT-EF associations with parameters, risk scores, and outcomes. The patient cohort included disease controls with unexplained dyspnea and suspected PH. The study's cross-sectional design limits the examination of temporal RV changes. Nevertheless, our observations highlight the potential value of 3D RVOT-EF as a tool for assessing risk in patients with PH, even when traditional parameters suggest a more favorable outlook. External validation is warranted.

Author contributions

K.T. and A.K. supervised the project. K.T., A.K., B.B.D.R., and A.Y. contributed significantly to the conception and design of the work. K.T., A.K., B.B.D.R., A.Y., Z.A.R., S.Y., B.K.L., A.F., D.Z., and N.C.K. performed the acquisition, analysis, and/or interpretation of the data for this paper. All authors were involved in the drafting and critical revision of the paper, gave final approval of the version to be published, and agreed to be responsible for all aspects of the paper and for ensuring that issues concerning the accuracy or integrity of any part of the paper are adequately investigated and resolved.

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure statement

Drs. Lakatos, Fábián, and Kovács report personal fees from Argus Cognitive, Inc. Dr. Gall received fees from Actelion, AstraZeneca, Bayer, BMS, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer, and United Therapeutics. Dr. Ghofrani received consultancy fees from Bayer, Actelion, Pfizer, Merck, GSK, and Novartis; fees for participation on 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. Dr. Seeger received speaker/consultancy fees from Pfizer, Bayer Pharma AG, United Therapeutics, and Liquidia. Dr. Yogeswaran reports nonfinancial support from the University of Giessen during the conduct of the study and personal fees from MSD outside the submitted work. Dr. Tello has received speaking fees from Actelion and Bayer. All other authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2024.09.026.

References

1. Rako ZA, Kremer N, Yogeswaran A, Richter MJ, Tello K. Adaptive versus maladaptive right ventricular remodelling. ESC Heart Fail 2023;10:762-75.
2. Guazzi M, Naeije R. Right heart phenotype in heart failure with preserved ejection fraction. Circ Heart Fail 2021;14:e007840.
3. Houston BA, Brittain EL, Tedford RJ. Right ventricular failure. N Engl J Med 2023;388:1111-25.
4. Geva T, Powell AJ, Crawford EC, Chung T, Colan SD. Evaluation of regional differences in right ventricular systolic function by acoustic quantification echocardiography and cine magnetic resonance imaging. Circulation 1998;98:339-45.
5. Yogeswaran A, Richter MJ, Sommer N, et al. Evaluation of pulmonary hypertension by right heart catheterisation: does timing matter? Eur Respir J 2020;56:1901892.
6. Rako ZA, Yogeswaran A, Lakatos BK, et al. Clinical and functional relevance of right ventricular contraction patterns in pulmonary hypertension. J Heart Lung Transplant 2023;42:1518-28.
7. Tokodi M, Staub L, Budai A, et al. Partitioning the right ventricle into 15 segments and decomposing its motion using 3D echocardiography-based models: the updated ReVISION method. Front Cardiovasc Med 2021;8:622118.
8. Lakatos B, Toser Z, Tokodi M, et al. Quantification of the relative contribution of the different right ventricular wall motion components to right ventricular ejection fraction: the ReVISION method. Cardiovasc Ultrasound 2017;15:8.
9. Benza RL, Kanwar MK, Raina A, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. Chest 2021;159:337-46.
10. Calcutteea A, Chung R, Lindqvist P, Hodson M, Henein MY. Differential right ventricular regional function and the effect of pulmonary hypertension: three-dimensional echo study. Heart 2011;97:1004-11.