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BRIEF COMMUNICATION

Right ventricular pressure-strain relationship-derived myocardial work reflects contractility: Validation with invasive pressure-volume analysis

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Three-dimensional (3D) echocardiography-derived right ventricular (RV) ejection fraction (EF) and global longitudinal strain (GLS) are valuable RV functional markers; nevertheless, they are substantially load-dependent. Global myocardial work index (GMWI) is a novel parameter calculated by the area of the RV pressure-strain loop. By adjusting myocardial deformation to instantaneous pressure, it may reflect contractility.

To test this hypothesis, we enrolled 60 patients who underwent RV pressure-conductance catheterization to determine load-independent markers of RV contractility and ventriculo-arterial coupling. Detailed 3D echocardiography was also performed, and we calculated RV EF, RV GLS, and using the RV pressure trace curve, RV GWMI.

While neither RV EF nor GLS correlated with Ees, GMWI strongly correlated with Ees. In contrast, RV EF and GLS showed a relationship with Ees/Ea. By dividing the population based on their Reveal Lite 2 risk classification, different characteristics were seen among the subgroups.

RV GMWI may emerge as a useful clinical tool for risk stratification and follow-up in patients with RV dysfunction.
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Abbreviations: 2D, 2-dimensional; 3D, 3-dimensional; Ea, arterial elastance; Eed, end-diastolic elastance; Ees, end-systolic elastance; Ees/Ea, ventriculo-arterial coupling; EF, ejection fraction; GLS, global longitudinal strain; GMWI, global myocardial work index; LV, left ventricular; RV, right ventricular; RVSP, right ventricular systolic pressure

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Myocardial contractility represents the intrinsic ability of the myocardium to shorten independently of loading conditions and, as such, is the target feature of ventricular performance for patient evaluations. In clinical practice, the assessment of myocardial function is most commonly performed using echocardiography with a constantly augmenting technical toolkit. Importantly, even advanced echocardiographic metrics, such as 3-dimensional (3D) echocardiography-derived ejection fraction (EF) or global longitudinal strain (GLS) are heavily dependent on loading conditions; therefore, they can not be considered reliable markers of contractility.[1] Increased afterload can significantly diminish the value of GLS despite maintained or even increased contractile function; thus, GLS rather reflects ventriculo-arterial coupling (Ees/Ea).[1] To mitigate the afterload dependency of left ventricular (LV) GLS, the concept of myocardial work by adjusting strain to the instantaneous LV pressure has been validated and subsequently introduced in clinical practice.[2] Previous experimental work demonstrated that the global myocardial work index (GMWI) correlates with gold-standard pressure-volume analysis-derived measures of contractility in different hemodynamic overload conditions, whereas EF or GLS is not.[3] Importantly, the issue of load-dependency may culminate in the right side of the heart: right ventricular (RV) systolic performance is even more intensely exposed to alterations in afterload, yet the concept of myocardial work has not been thoroughly tested in its context. Available data are based on a 2-dimensional (2D) echocardiography, which carries significant limitations due to the RV's complex shape, contraction pattern, and hemodynamics, impeding an identical approach to the LV.

Accordingly, our present study aimed to calculate RV myocardial work using 3D echocardiography-derived RV GLS and examine its relationship with the gold-standard invasive measurement of RV contractility.

This research constitutes a post-hoc analysis of data collected from the EXERTION study (ClinicalTrials.gov Identifier: NCT04663217). The study adhered to the principles outlined in the Declaration of Helsinki and was approved by the local Ethics Committee of the Faculty of Medicine at the University of Giessen (Approval Number: 117/16). Written informed consent was obtained from all participating patients. Subjects were either undergoing an initial invasive diagnostic evaluation for suspected pulmonary hypertension or were already diagnosed with pulmonary hypertension. All patients underwent 3D echocardiography and RV pressure-conductance catheterization. The median duration between the pressure-conductance catheterization and echocardiography was 1 day. Importantly, no therapeutic modifications were applied between the 2 examinations. Using the Reveal Lite 2 risk stratification score, low- ($n = 23$), intermediate- ($n = 20$), or high-risk ($n = 17$) groups were identified. The technical details of the echocardiographic examinations and the RV pressure-conductance catheterization were described in detail previously.[4] Briefly, 3D echocardiography datasets were analyzed using the 4D RV-Function 2 software (TomTec Imaging GmbH, Unterschleissheim, Germany) to calculate RV volumes and EF. The reader of the 3D echocardiographic data was blinded to the clinical characteristics and the Reveal Lite 2 risk categories of the patients. Intra- and interobserver variability of the most relevant echocardiographic parameters were previously assessed, confirming good reproducibility.[5] To assess the 3D GLS, reconstructed 3D mesh models were imported into the ReVISION software (Argus Cognitive, Inc., Lebanon, NH, USA), employing a previously reported methodology.[6]

Subjects also underwent RV pressure-conductance catheterization (CA-No. 41063, CD Leycom, Zoetermeer, Netherlands). The multi-beat method was used to calculate Ees and Ea as described previously.[5] First, sequential resting pressure-volume loops were recorded. Then, patients were instructed to perform a Valsalva maneuver to achieve preload reduction and a progressive leftward shift of the pressure-volume loop. The end-systolic pressure-volume points were connected by a regression line to determine the end-systolic pressure-volume relationship, and Ees was defined as the slope of that line. Ea was calculated as the ratio of RV systolic pressure (RVSP) to stroke volume. End-diastolic elastance (Eed) was measured as the slope of the end-diastolic pressure-volume relationship. Using these measures, we also quantified Ees/Ea. Two expert readers performed data analysis and interpretation.

In myocardial work analysis, we followed previously published principles.[2] GLS curves and invasively-acquired RV pressure recordings were exported and analyzed using our custom-made software. The isovolumetric phases were identified using the second derivative squared method by expert consensus reading on the RV pressure tracing. By inspecting the RV volume curve, isovolumetric phases were also identified by expert consensus reading, and corresponding time points were applied to the GLS curve. Due to the different temporal resolutions of the datasets, the timestamps of the pressure and strain tracings were normalized in each section, and strain values were interpolated for the timestamps of the RV pressure recording. Then, the 4 sections of each recording were concatenated, and pressure–strain loops were constructed and plotted. The instantaneous power was calculated by multiplying the inverse of the strain rate (obtained by differentiating the strain curve) and the instantaneous RV pressure. GMWI was computed by integrating the power over time from the beginning of isovolumetric contraction until the end of isovolumetric relaxation.

The normal distribution of the variables was confirmed using the Shapiro-Wilk test. Pearson's correlation coefficient was used for correlation analysis. ANOVA, followed by Tukey's post-hoc test, was used to compare the different risk categories. A p value < 0.05 was considered statistically significant.

The study included 60 patients, with an average age of 65 ± 14 years, and 65% were female.

RV EF ($r = -0.143$, $p = 0.275$) and GLS ($r = -0.067$, $p = 0.611$) did not correlate with Ees, but rather with Ees/Ea (RVEF: $r = 0.552$, $p < 0.001$; GLS: $r = 0.460$, $p < 0.001$). In contrast, GMWI inversely correlated with Ees/Ea ($r = -0.439$, $p < 0.001$) but, importantly, showed a strong

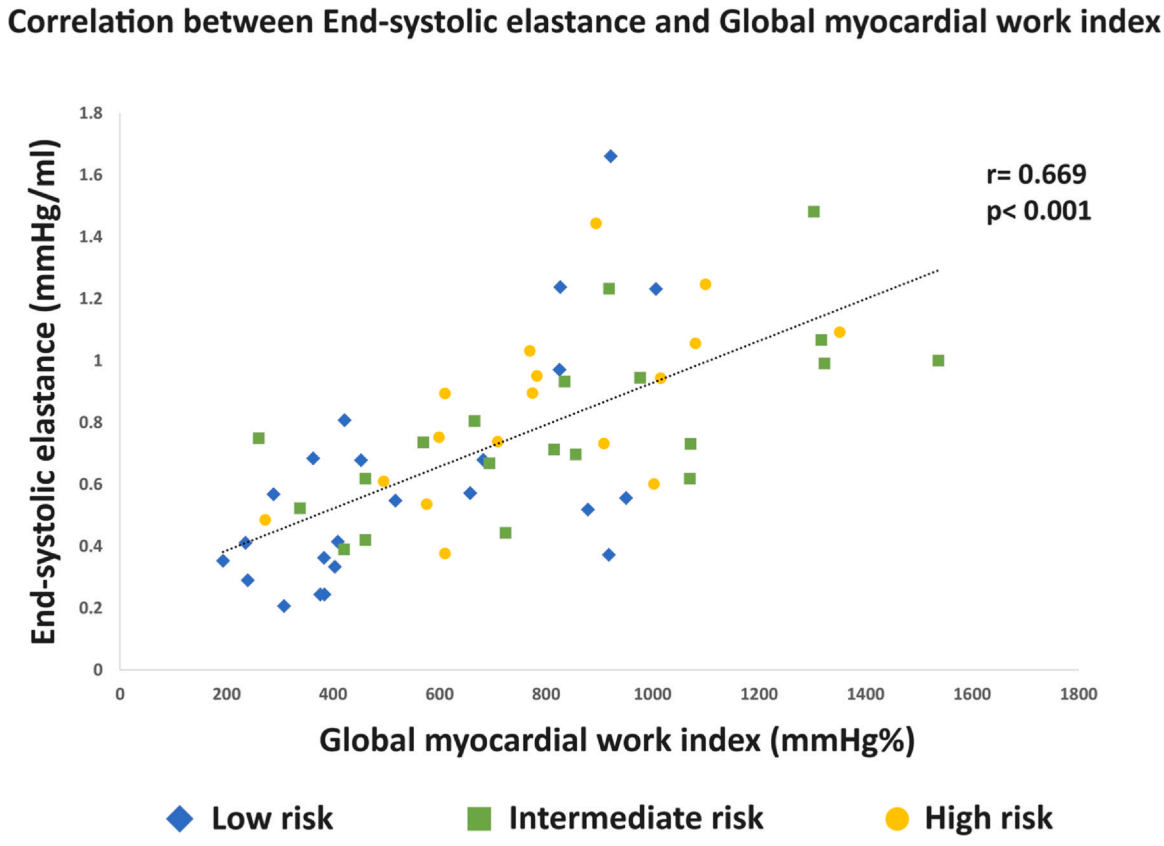

Fig. 1 Global myocardial work index significantly correlated with end-systolic elastance. The patients' Reveal Lite 2 risk classification is shape and color-coded (*blue square*: low risk, *green square*: intermediate risk, *yellow circle*: high risk).

direct correlation with Ees ($r = 0.669$, $p < 0.001$) (Figure 1). RV EF ($r = -0.517$, $p < 0.001$) and GLS ($r = -0.446$, $p < 0.001$) correlated inversely with Eed, whereas GMWI correlated directly with Eed ($r = 0.356$, $p = 0.005$).

By dividing the patients based on their Reveal Lite 2 risk classification, every 3D echocardiographic and invasive hemodynamic marker showed significant differences (Table 1). By post-hoc analysis, the low-risk group had comparable EF and GLS to intermediate patients, while GMWI was significantly higher in the latter group. Ees/Ea significantly decreased in the intermediate group, while RVSP was higher. High-risk patients significantly differed in every measure compared to the low-risk group. By comparing intermediate and high risk, EF and GLS were significantly lower in the latter, while GMWI and the invasive hemodynamic measures did not differ (Table 1). Representative cases of each group are depicted in Figure 2.

Our findings indicate that similarly to the observations in the LV, RV EF and GLS reflect ventriculo-arterial coupling rather than myocardial contractility. On the other hand, the fusion of 3D echocardiography-derived GLS with instantaneous RV pressures allows the quantification of RV

Table 1 Three-Dimensional Echocardiographic and Invasive Hemodynamic Data of the Patients by Reveal Lite 2 Risk Categories

	Low risk ($n = 23$)	Intermediate risk ($n = 20$)	High risk ($n = 17$)	p value
EF (%)	48.8 ± 6.6	44.0 ± 9.4[a]	35.0 ± 7.8[b]	< 0.001
GLS (%)	-18.6 ± 3.6	-17.0 ± 4.5[a]	-13.3 ± 3.9[b]	< 0.001
GMWI (mm Hg%)	550 ± 267[c]	831 ± 361	797 ± 265[b]	< 0.01
Ees (mm Hg/ml)	0.61 ± 0.36	0.79 ± 0.28	0.85 ± 0.28[b]	< 0.05
Ees/Ea	1.53 ± 0.49[c]	1.16 ± 0.30	1.01 ± 0.31[b]	< 0.001
RVSP (mm Hg)	33.7 ± 13.0[c]	60.6 ± 29.0	77.1 ± 25.4[b]	< 0.001

Ees, end-systolic elastance; Ees/Ea, ventriculo-arterial coupling; EF, ejection fraction; GLS, global longitudinal strain; GMWI, global myocardial work index; RVSP, right ventricular systolic pressure.

The values are mean ± standard deviation.

[a]Intermediate vs. high $p < 0.05$.

[b]Low vs. high $p < 0.05$.

[c]Low vs. intermediate $p < 0.05$.

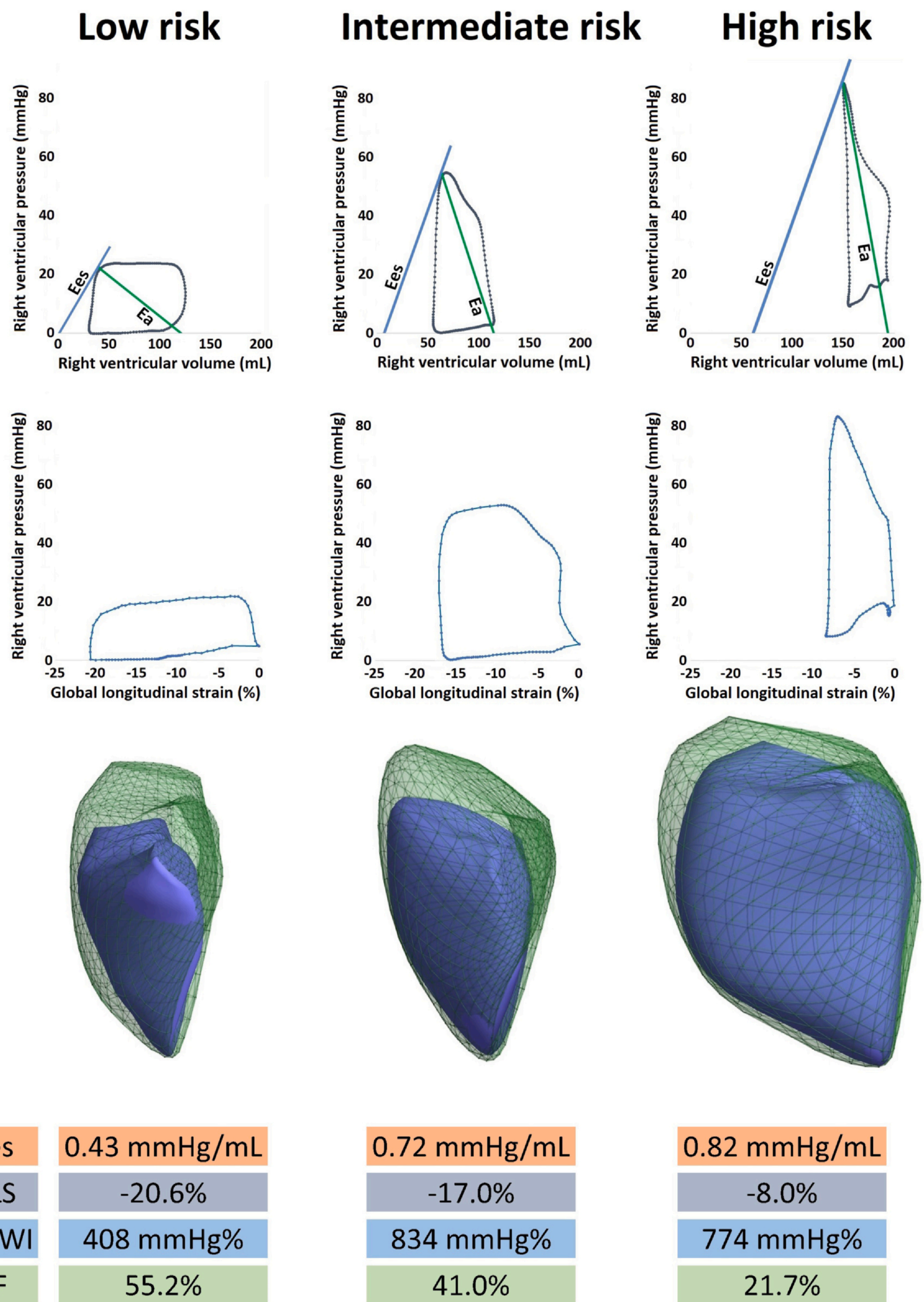

Fig. 2 Representative cases of each Reveal Lite 2 risk category. The low-risk patient demonstrates the lowest end-systolic elastance (Ees) and global myocardial work index while having maintained global longitudinal strain (GLS) and ejection fraction (EF). Higher Ees and GMWI can be observed in the intermediate-risk patient, while both GLS and EF show moderate impairment. In the high risk patient, while Ees and GMWI are numerically comparable to the intermediate patient, EF and GLS are heavily deteriorated. Significant chamber dilation can also be observed as a sign of ventriculoarterial uncoupling (Ees/Ea = 0.67). GMWI, global myocardial work index.

GMWI, which strongly correlates with the gold standard measure of RV contractility. GMWI can display the RV's increased contractile state during RV-PA uncoupling, making it an appealing tool for more precise risk stratification and follow-up for patients with pulmonary hypertension. Further developments should aim at the accurate and non-invasive estimation of the individual RV pressure tracing to allow the everyday clinical use of the RV myocardial work concept.[4]

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