


Echocardiographic pressure–strain loop-derived stroke work of the right ventricle: validation against the gold standard

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Abstract

Aims Commercially available integrated software for echocardiographic measurement of stroke work (SW) is increasingly used for the right ventricle, despite a lack of validation. We sought to assess the validity of this method [echo-based myocardial work (MW) module] vs. gold-standard invasive right ventricular (RV) pressure–volume (PV) loops.

Methods and results From the prospectively recruiting EXERTION study (NCT04663217), we included 42 patients [34 patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) and 8 patients with absence of cardiopulmonary disease] with RV echocardiography and invasive PV catheterization. Echocardiographic SW was assessed as RV global work index (RVGWI) generated via the integrated pressure–strain MW software. Invasive SW was calculated as the area bounded by the PV loop. An additional parameter derived from the MW module, RV global wasted work (RVGWW), was correlated with PV loop measures. RVGWI significantly correlated with invasive PV loop-derived RV SW in the overall cohort [$\rho = 0.546$ ($P < 0.001$)] and the PAH/CTEPH subgroup [$\rho = 0.568$ ($P < 0.001$)]. Overall, RVGWW correlated with invasive measures of arterial elastance (Ea), the ratio of end-systolic elastance (Ees)/Ea, and end-diastolic elastance (Eed) significantly.

Conclusions Integrated echo measurement of pressure–strain loop-derived SW correlates with PV loop-based assessment of RV SW. Wasted work correlates with invasive measures of load-independent RV function. Given the methodological and anatomical challenges of RV work assessment, evolution of this approach by incorporating more elaborated echo analysis data and an RV reference curve might improve its reliability to mirror invasively assessed RV SW.

Keywords Right ventricular myocardial work; Echocardiography; Stroke work; Pressure–volume curve; Pulmonary hypertension

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Background

Right ventricular (RV) function is significantly associated with prognosis and symptoms in pulmonary hypertension (PH)¹ and in various cardio-pulmonary diseases.² One of

the major parameters derived from invasive catheterization is RV stroke work (SW), which represents the active cardiac work in each contraction.³ Different invasive and non-invasive surrogates have been previously investigated for the calculation of RV SW,^{4,5} but without validation by

gold-standard pressure–volume (PV) loops from conductance catheterization. In direct comparison with PV loops, pressure–strain loops may provide an alternative method for the non-invasive assessment of SW, as suggested by Russell *et al.* in 2012.⁶ A semi-automated myocardial work (MW) module was recently introduced, which allows bed-side ready analysis and might pave the way for MW to become a diagnostic tool for clinical routine across various diseases.^{7,8} The module has already been applied to the right ventricle,^{9,10} but RV validation data are lacking.

Aims

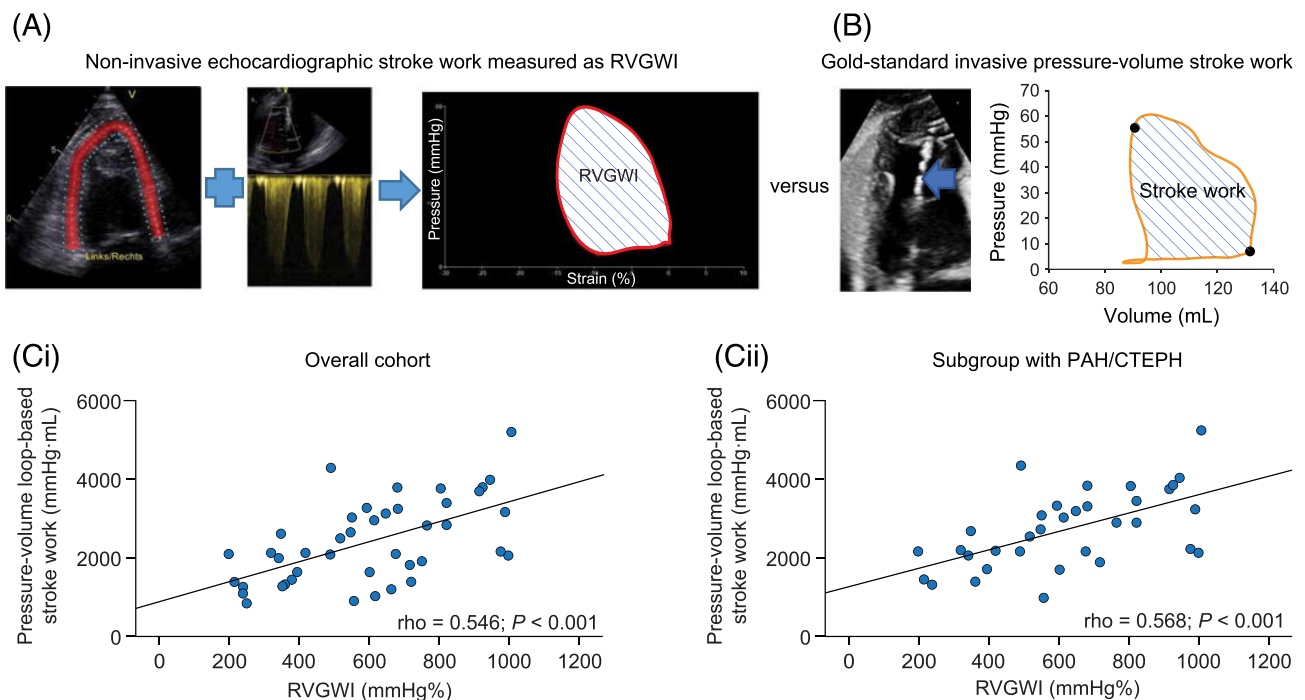
The aim of our current study is to validate the semi-automated MW module against RV conductance catheterization, which is the invasive gold standard to assess RV SW and RV–pulmonary arterial (PA) coupling.

Methods

Study design and patients

We prospectively analysed consecutive patients enrolled into the EXERTION study (ClinicalTrials.gov identifier: NCT04663217; ethics committee approval number 117/16). Diagnosis of pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) was made by a multidisciplinary board, according to current guidelines.^{11,12} Control patients were initially referred for suspicion of PH and dyspnoea on exertion. Post hoc, patients' PH diagnosis was updated to the current guidelines.¹² Patients with left heart disease or chronic thromboembolic disease without PH or atrial fibrillation/flutter at the time of evaluation were excluded. MW analysis was not feasible in 17 patients [e.g. atrial flutter/fibrillation at time of evaluation, missing tricuspid regurgitation (TR) signal, and region of interest (ROI) implausible]. Thirteen patients with left heart disease and three patients with chronic thromboembolic disease without PH were excluded.

Figure 1 Measurement of right ventricular (RV) stroke work. (A) Echocardiographic RV pressure–strain loop built by the Automated Function Imaging software myocardial work module (Echo PAC Version 204, GE Vingmed Ultrasound). Based on non-invasive pulmonary artery systolic pressure, longitudinal strain, and the timings of opening and closure of the pulmonary and tricuspid valves, the software generates the RV global work index (RVGWI), representative of stroke work. (B) Invasively measured pressure–volume loop obtained via conductance catheterization (blue arrow). The area bounded by the pressure–volume loop represents RV stroke work. (C) Correlation of echocardiographic RVGWI with invasive pressure–volume loop-derived RV stroke work (i) in the overall cohort ($n = 42$) and (ii) in the subgroup with pulmonary arterial hypertension (PAH)/chronic thromboembolic pulmonary hypertension (CTEPH) ($n = 34$).



Integrated myocardial work module

We applied the MW module (Automated Function Imaging, EchoPAC 204) to the right ventricle (Figure 1A), as described previously.¹⁰ Pulmonary valve event timings were determined by pulsed wave Doppler. Tricuspid valve event timings were assessed from direct visualization in the right ventricle-focused four-chamber view. To adapt to the right ventricle, we traced the right ventricle-focused view for *all* chamber views requested by the software (i.e. the same RV view of the same cycle was traced three times). The ROI was manually aligned to the RV structures by the operators. We used systolic pulmonary artery pressure (PASP) estimated from the TR jet peak velocity [without adding estimated mean right atrial (RA) pressure], as recommended.¹³ We entered diastolic pulmonary artery pressure (DPAP) calculated as $1.5 \times [\text{mean pulmonary artery pressure (PAMP)} - (\text{PASP}/3)]$.⁹ Echocardiographic PAMP was obtained by the following formula: mean RV–RA gradient to mean RA pressure. The mean RV–RA gradient was calculated by tracing the TR velocity–time integral.^{9,10} The derived MW parameters were RV global work index (RVGWI) and RV global wasted work (RVGWW).

Conductance catheterization

Guided by echocardiography, a 4F PV catheter (CA-Nr 41063, CD Leycom, Zoetermeer, the Netherlands) was positioned in

the RV apex for real-time acquisition of PV loops (Figure 1B). End-systolic elastance (Ees) was calculated as end-systolic pressure (ESP)/[end-systolic volume – volume at zero pressure (V0)].¹⁴ Arterial elastance (Ea) was calculated as ESP/stroke volume. The ratio of Ees/Ea defines RV–PA coupling.¹⁵ SW was calculated as the area bounded by the PV loop. End-diastolic elastance (Eed) was calculated from a curvilinear adjustment of end-diastolic pressure/volume ratios, as described previously.¹⁶

Statistical analyses

Adherence to a Gaussian distribution was determined by visual assessment of histograms. Data are expressed as mean \pm standard deviation (SD) or median [interquartile range (IQR)]. Differences between groups were analysed with the Pearson χ^2 test, the independent-samples Mann–Whitney *U* test, or the independent-samples *t*-test, as appropriate. Correlations between variables were determined by Spearman's rho. Intra-observer and inter-observer variability was assessed using intra-class correlation coefficients (ICCs) and 95% confidence intervals (CIs) in 10 random patients. For all analyses, $P < 0.05$ was considered statistically significant. SPSS Version 28.0 (IBM, Armonk, NY, USA) was used.

Table 1 Patient characteristics, right ventricular myocardial work, and invasive pressure–volume loop measurements

	PAH/CTEPH	Control	<i>P</i> value
Patients, <i>n</i>	34	8	
Male/female, <i>n/n</i>	10/24	1/8	0.328
Age, years	66 [53–73]	51 [37–62]	0.044
BMI, kg/m ²	29 \pm 7	28 \pm 6	0.576
Diagnosis, <i>n</i> (%)			
PAH, Group I	17		
CTEPH	17		
Right heart catheterization			
Mean pulmonary artery pressure, mmHg	38 [28–50]	17 [12–19]	<0.001
Pulmonary vascular resistance, Wood units	5.7 [3.4–8.1]	1.1 [0.8–1.4]	<0.001
Cardiac index, L/min/m ²	2.6 \pm 0.6	3.4 \pm 0.8	0.003
Pulmonary artery wedge pressure, mmHg	9 \pm 4	9 \pm 3	0.635
Echocardiography			
RVGWI, mmHg%	607 [412–820]	498 [276–705]	0.289
RVGWW, mmHg%	60 [30–115]	24 [15–34]	0.006
RVGLS, %	–16 \pm 5 ^a	–21 \pm 3	0.010
PASP, mmHg	52 \pm 19	28 \pm 12	0.002
DPAP, mmHg	26 [19–31]	15 [13–21]	0.002
Pressure–volume loop measurements			
Ea, mmHg/mL	0.65 [0.45–0.93]	0.24 [0.16–0.26]	<0.001
Ees, mmHg/mL	0.73 [0.55–0.98]	0.38 [0.26–0.62]	0.003
Ees/Ea ratio	1.03 [0.90–1.44]	1.63 [1.26–2.10]	0.002
Eed, mmHg/mL	0.18 [0.14–0.27]	0.14 [0.06–0.20]	0.075
SW, mmHg/mL	2630 [2046–3292]	1240 [1044–1428]	<0.001

BMI, body mass index; CTEPH, chronic thromboembolic pulmonary hypertension; DPAP, pulmonary artery diastolic pressure; Ea, arterial elastance; Eed, end-diastolic elastance; Ees, end-systolic elastance; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; RVGLS, right ventricular global longitudinal strain; RVGWI, right ventricular global work index; RVGWW, right ventricular global wasted work; SW, stroke work.

Values represent mean \pm standard deviation or median [interquartile range], unless otherwise specified.

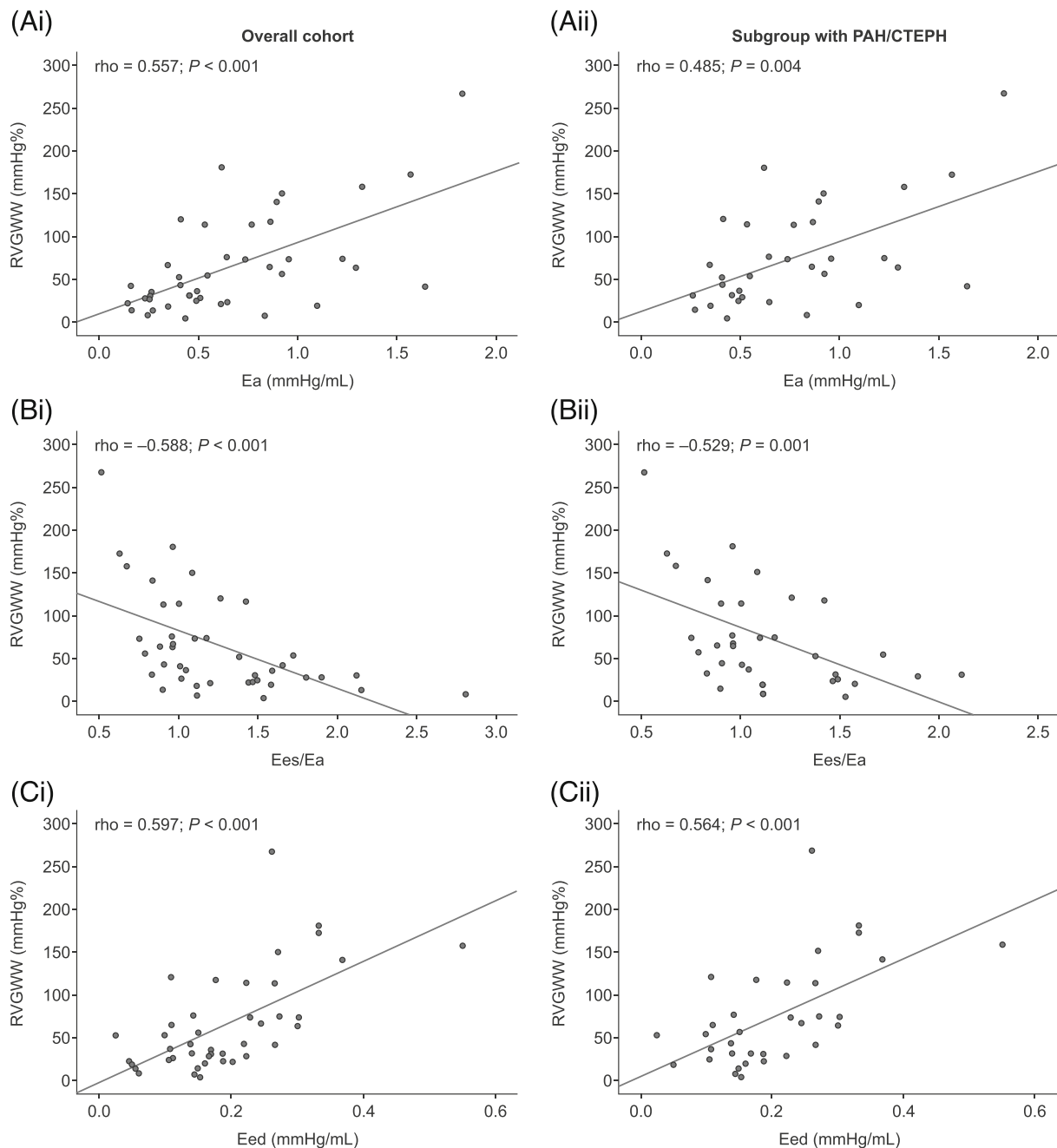
^a34.

Results

Overall, 42 patients were included. Patient characteristics and echocardiographic and invasive PV loop measurements are presented in *Table 1*. Eight patients were controls. RVGWI (derived from the MW module) showed significant correlations with invasively measured conductance SW in

the overall cohort and in the PAH/CTEPH subgroup (*Figure 1C,ii*). As illustrated in *Figure 2*, RVGWW and conductance catheter-derived indices of afterload (Ea), RV-PA coupling, and diastolic stiffness (Eed) were significantly correlated in the overall cohort and within the PAH/CTEPH subgroup. ICC showed acceptable intra-observer and inter-observer agreement of RVGWI [inter-observer, 0.978 (0.910–0.994);

Figure 2 Correlation of right ventricular global wasted work (RVGWW) with invasive conductance catheter parameters (A) arterial elastance (Ea), (B) end-systolic elastance (Ees)/Ea, and (C) end-diastolic elastance (Eed) in (i) the overall cohort ($n = 42$) and (ii) the subgroup with pulmonary arterial hypertension (PAH)/chronic thromboembolic pulmonary hypertension (CTEPH) ($n = 34$). Correlations were assessed using Spearman's rho coefficient.



intra-observer, 0.990 (0.961–0.998)] and RVGWW [inter-observer, 0.964 (0.856–0.991); intra-observer, 0.916 (0.664–0.979) (95% CIs)].

Conclusions

Our study aimed to validate echocardiography-based SW analysis against gold-standard RV PV loop-based (invasive) SW and RV–PA coupling (i.e. RV PV loops). Our study shows that RVGWI derived from the left ventricular (LV)-based semi-automated pressure–strain software is associated with invasive RV SW in a mixed population of PAH/CTEPH patients and controls, as well as in the solely PAH/CTEPH subgroup. This can be considered a major step forward, because until now, various surrogates and simplifications for the calculation of RV SW have co-existed and were solely based on LV reference.¹⁷ In general, SW is considered an index of the work performed by the myocardium¹⁸ and is calculated as the product of volume and pressure.¹⁹

As the left ventricle-based semi-automatic integrated MW module relies solely on non-invasive measurements, this method offers for bed-side assessments. However, several pitfalls remain when this approach is transferred to the right ventricle. First, although we found a significant correlation between RVGWI and invasive RV SW, the correlation is moderate. This is the consequence of the integrated MW module being built on an LV pressure reference curve with different pressure properties. However, as mean pulmonary artery pressure increases from normal values to the level seen in severe PH, the shape of the RV PV loop changes markedly²⁰ and ESP becomes closer to systolic RV pressure. Thus, the left ventricle-based software might not be appropriate for patients with mild PH or without PH. Second, the current standard acquisition of the right ventricle is solely focused on the four-chamber view, the tracing includes repeated measures, and the region of RV septal wall might be influenced by LV function. The moderate correlation between invasive and echocardiographic RV SW in the overall cohort may therefore be partly attributed to the anatomic RV properties and heterogeneous remodelling. Third, diastolic properties are exclusively based on valvular event timing in the integrated MW module (and not adjusting for the diastolic pressure entered), whereas the invasive PV loop area calculation includes an exact determination of diastolic and end-diastolic pressures. This also limits the degree of correlation between invasive and echocardiographic measurements. Moreover, given the various limitations of the transfer of the application from the LV to the RV. It is mandatory to develop a specific RV MW software, adjusting for the anatomy of the RV, integrating 4D volumes or strain, and taking into account the specific shape of the reference pressure curve.

Interestingly, we found correlations of wasted work (RVGWW) with load-independent RV parameters including RV–PA coupling. RVGWW as defined by the MW software is equal to the work contributing to myocardial lengthening during systole and shortening during isovolumic relaxation. In general, wasted work is defined as an index of dyssynchronous ventricular contractions.⁷ RV dyssynchrony, as assessed by the SD of time to peak strains, was described by Badagliacca and co-workers as a clinically relevant pathological feature.^{21,22} In turn, RV dyssynchrony directly relates to wall stress, increased afterload, and diastolic dysfunction and mirrors RV maladaptation in chronic pressure and volume overload.²² Therefore, the association of higher RVGWW with RV–PA uncoupling mirrors progressive RV dyssynchrony, which is associated with the increase of pulmonary pressures and the impairment of RV global strain²³ in the state of uncoupling. This is of clinical relevance, as an increase in RVGWW implies that work is being done by the ventricle but does not contribute to ejection. Interestingly, there is evidence of improvement of RVGWW after intervention, thus signalling reversibility of this abnormality.²⁴

The associations found in our study, and further evolution of the echo-based approach as discussed above, might pave the way for longitudinal non-invasive assessment of RV contractile function. Of note, Hulshof and co-workers showed with a non-automatic approach that RV strain–area loops are of prognostic relevance.²⁵ Moreover, Butcher and co-workers were able to demonstrate the prognostic relevance of RVGWI as a measure of SW with association to pulmonary vascular resistance, further emphasizing the clinical value of this approach.¹⁰

This is the first study to validate the integrated echocardiographic measurement of pressure–strain loop-derived MW for the RV against the invasive gold standard for the evaluation of RV function.

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Conflict of interest

The authors have filed a European patent application (EP 20190939.7) for the echocardiography-derived method for quantification of right ventricular pressure–volume loops. Dr Richter has received support from Bayer; speaker fees from Bayer, Janssen-Cilag GmbH, and OMT; and consultancy

fees from Bayer and Janssen-Cilag GmbH. Dr Douschan reports personal fees and non-financial support from Actelion, non-financial support from Astra Zeneca, non-financial support from Bayer, non-financial support from GSK, personal fees and non-financial support from MSD, non-financial support from Novartis, non-financial support from Teva, non-financial support from Boehringer Ingelheim, non-financial support from Vifor, and non-financial support from Menarini outside the submitted work. 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 Cardio-pulmonary Research, and the German Ministry for Education and Research. Dr Seeger has received speaker/consultancy fees from Abivax, Bayer AG, Liquidia Technologies, Pieris Pharmaceuticals, United Therapeutics, and Vectura. Dr Gall

has received fees from Actelion, AstraZeneca, Bayer, BMS, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer, and United Therapeutics. Dr Tello has received speaking fees from Actelion and Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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