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RESEARCH ARTICLE

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Asymmetric right ventricular myocardial work correlates with gold standard measurements of cardiac function in pulmonary hypertension

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Abstract

Right ventricular (RV) (dys)function determines outcomes in pulmonary hypertension (PH). We previously found that asymmetric RV myocardial work (MW) corresponds with inefficient RV function in experimental PH models. We therefore aimed to investigate regional distribution of RV MW and its correlation with catheter hemodynamics in children with PH. RV MW was calculated by longitudinal strain and simultaneous catheter pressure measurements in 14 patients with PH. Wasted MW was defined as the ratio of inappropriate myocardial lengthening to favorable shortening work. Segment-wise and averaged MW and wasted MW were evaluated at baseline and during pulmonary vasodilation therapy with oxygen and nitric oxide, and their relationship to hemodynamic measurements was analyzed. We found that MW was higher for the lateral wall than the septum: $1013 \pm 374\,\text{mmHg} \cdot \%$ versus $532 \pm 190\,\text{mmHg} \cdot \%$ at baseline. Wasted MW ratio did not differ significantly between wall regions. Pulmonary vasodilators slightly reduced mean pulmonary artery pressure and was accompanied by a more symmetrical MW distribution. Averaged MW correlated with the rate of RV pressure development (dP/dt maximum) and decay (dP/dt minimum) at all conditions ($p \leq 0.047$). The results suggest that MW contribute to, and may be used as a marker of, systolic and diastolic efficiency in the PH RV.

KEYWORDS

myocardial work, pulmonary hypertension, right ventricular function, right ventricular strain, speckle tracking echocardiography

INTRODUCTION

Pulmonary hypertension (PH) carries high morbidity and mortality driven by right ventricular (RV) failure.[1,2] The increased RV afterload leads to RV hypertrophy, impaired systolic and diastolic function, and ultimately RV failure. Pressure-volume loops are the gold-standard measure to assess ventricular function,[3] with the area encapsulated by the loop reflecting external ventricular work. However, the need for invasive cardiac catheterization with conductance catheters limits its clinical application. Myocardial deformation analysis is useful to

assess RV function in PH.[4,5] However, reduced myocardial shortening without accounting for the increased afterload may be misinterpreted as intrinsically impaired myocardial function.

Russel et al. introduced noninvasive myocardial work (MW) of the left ventricle (LV) by calculating the pressure-strain loop area using a catheter-derived pressure reference curve.[6] They further calculated LV efficiency by comparing MW during contraction with MW during inappropriate myocardial wall stretching (wasted work).[7] Several studies have investigated LV MW and inefficiency,[8,9] and application of noninvasive MW is being explored in clinical practice.[10] A few clinical studies have calculated RV MW by using the standardized pressure curve for the LV and the tricuspid regurgitation jet.[11–14] While WU et al.[11] described RV MW in healthy individuals, Butcher et al.[13] reported a correlation between RV MW and invasive measures of stroke volume and stroke volume index in patients with heart failure and reduced LV ejection fraction. Both Butcher et al.[12] and Berg-Hansen et al.[14] included patients with PH and found a good correlations between RV global constructive work and invasively derived RV stroke work index.

To date, no studies have described RV MW using simultaneously acquired, high-fidelity, invasive RV pressures. We previously investigated RV MW in experimental PH models, showing that asymmetric MW between the RV lateral wall and septum, and increased wasted work in the septum, are associated with RV fibrosis and dysfunction.[15] Therefore, regional disparities and inefficient RV MW, may be an important contributor to RV dysfunction in PH. However, this has not been studied in PH patients, and the relationship to invasive hemodynamics is unknown. Accordingly, by using high-fidelity micromanometer catheter data and simultaneously acquired echocardiographic strain data in patients with PH, we aimed to investigate:

(a) The distribution of RV MW and wasted work ratio (WWR), and their change during pulmonary vasodilation therapy.
(b) The correlation of RV MW and WWR with invasively measured RV hemodynamics.

We hypothesized that calculated RV MW and wasted work in children with PH correlate with invasive RV hemodynamics. Based on our experimental studies, we further hypothesized that RV MW and WWR are asymmetrically distributed between the septum and RV lateral wall, and that pulmonary vasodilation is associated with less wasted MW. We further used this data to compare MW during systole and isovolumic relaxation (IVR), as defined by published vendor-based guidelines,[16] with the true pressure-strain loop area.

METHODS

Study population

We retrospectively analyzed data collected from prospectively enrolled children with PH due to various causes, undergoing clinically indicated cardiac catheterization at the Hospital for Sick Children in Toronto between 2008 and 2013. Heart catheterization with high-fidelity micromanometer catheters for pressure assessment and simultaneous protocolized echocardiography were performed under a prospective research protocol. For patients with available and adequate echocardiographic and pressure data, patient records were re-assessed to identify the outcomes of PH-related hospitalizations, syncope, need for atrial septostomy, lung transplantation, and death. Patients were followed-up until November 2019. A control group of age and sex matched healthy individuals was included for comparison of echocardiographic strain data and peak instantaneous MW (as further described below).

Right heart catheterization

Procedures were performed under general anesthesia or conscious sedation, as previously described.[5] RV pressures were recorded throughout the cardiac cycle at a frequency of 1 kHz using high-fidelity micromanometer catheters (Millar Instruments Inc.). Based on these pressure recordings, the peak changes in maximum and minimum pressure change over time (RV dP/dt maximum and RV dP/dt minimum, respectively), RV systolic pressure (RVSP), and RV end-diastolic pressure (RVEDP) were determined. Using fluid-filled catheters, the mean pulmonary artery (PA) pressure and pulmonary vascular resistance, indexed for body surface area (PVRi), were calculated. Pulmonary blood flow was measured using the Fick method, with oxygen consumption measured by mass spectrometry. RV stroke work was calculated as PA blood flow indexed to body surface area multiplied by mean PA pressure and divided by heart rate. All measurements were recorded at baseline (21% oxygen) and during the sequential vasodilator challenge consisting of 70% inspired oxygen and 20 ppm inhaled nitric oxide (iNO).

Echocardiography

Echocardiography was performed simultaneously with micromanometer catheter pressure measurements, using a Vivid 7 or E9 system with transducers appropriate for the patient's size (General Electric). Dedicated two-

dimensional RV apical views (frame rate 60–120 frames/s) were prospectively obtained as part of the research protocol. These images were reassessed for the current study and speckle tracking (STE) longitudinal strains (LS) measured. For each patient, analyses were performed at baseline and during pulmonary vasodilation therapy with oxygen and iNO. For STE analysis (EchoPAC v.113, GE), endocardial borders were traced with the region of interest adjusted to the wall thickness. The RV free wall and interventricular septum were divided into three segments: basal, mid, and apical, as proposed by consensus guidelines.[17] Tracking was visually assessed throughout the cardiac-cycle, and the region of interest adjusted to ensure accurate tracking. Segments that tracked well (visually and by EchoPAC assessment) were accepted, whereas segments that tracked poorly were not analyzed. Peak systolic strain of the basal and mid segments was measured. When present, segmental systolic prestretching was measured and added to the peak strain to yield total systolic shortening. RV fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE) were calculated.[18] TAPSE values were normalized for age using published *z*-scores.[19]

Calculation of MW

Strain data were resampled to 1 kHz, corresponding to the sample rate of invasive pressure measurements. The invasive pressure and strain data were synchronized using the electrocardiogram QRS onset as a reference. Systolic and diastolic phases and valve timings were determined by blood Doppler measurements. MW, as a function of the time, was calculated as the product of the rate of segmental shortening and the instantaneous RV pressure in each available myocardial segment. Positive (constructive) work was defined as work performed by myocardial shortening in systole and lengthening during IVR. Negative (wasted) work was defined as work performed by myocardial lengthening in systole and shortening during IVR. Net MW was calculated at the sum of constructive and wasted work. WWR was calculated as wasted work divided by constructive work, and for clarity expressed as an absolute value. The true pressure-strain loop area, which accounts for the work exerted by the blood on the myocardium during diastole, was calculated for comparison. Values of MW and WWR were calculated using Excel 2013 (Microsoft Corporation). Values were averaged for the lateral wall segments (lateral wall MW and WWR), septal wall segments (septal wall MW and WWR), and all available segments (averaged MW and WWR).

In both patients and controls, RV peak instantaneous MW was calculated as the product of total systolic shortening and RVSP. For the controls, RVSP was estimated to 28 mmHg based on a previous invasive study in healthy children.[20]

Statistical methods

Categorical variables are expressed as frequencies and proportions. Continuous variables are presented as the mean ± standard deviation. The paired T test was used to compare differences between lateral and septal wall work and to compare between values at baseline and during pulmonary vasodilation therapy. Due to the nonlinear distribution of the WWR, the same comparisons were done with Related-Samples Wilcoxon Signed Rank Test. For linear regression between invasive parameters and global and segmental MW/WWR, the amount of explained variance is expressed as the R^2 value. Two-tailed p values < 0.05 were considered significant. Statistical analyses were performed using SPSS Statistics 25 (IBM Corp.) and SigmaPlot 12.5 (Systat Software Inc.) software.

The first author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

RESULTS

Of the 22 patients, six were excluded due to incorrectly stored digital data. Another two patients were excluded due to a lack of raw echo data. Baseline characteristics of the included patients ($n = 14$), including the etiology of PH, are shown in Table 1, which compares patients who experienced the outcome of death/lung transplant and transplant-free survivors. All patients underwent an oxygen challenge, and 13/14 patients were additionally challenged with inhaled NO. Invasive measurements (mean PA pressure, RVSP, RVEDP, RV dP/dt maximum, RV dP/dt minimum, PVRi, and indexed RV stroke work) under the three conditions (baseline, oxygen, and NO) are shown in Table 2. The mean follow-up duration was 6.5 ± 2.4 years. During this period, four patients underwent lung transplantation ($n = 1$) or died ($n = 3$). No patient underwent atrial septostomy. Among patients alive during the follow-up period, there was no history of syncope or PH-related hospitalizations.

Echocardiographic LS measurement of the RV apical segments was not performed in approximately half of the patients at each stage due to poor tracking and was therefore not included in work analyses. RV total systolic shortening of lateral wall and septal segments in both

TABLE 1 Patient characteristics.

Variable	Included patients		
	All patients $n = 14$	**Transplant free survivors $n = 10$**	**Lung transplant/death $n = 4$**
Age (years), Median (range)	4.3 (0.6–13.7)	3.7 (1.4–5.8)	10.8 (0.6–13.7)
Female gender	9 (64%)	5 (50%)	4 (100%)
Diagnosis			
Idiopathic PH	1	–	1
Lung disease	2	2	–
CHD	7	5	2
BPD and CHD	4	3	1
BMI (kg/m^2), Median (range)	16.5 (14.1–21.7)	15.4 (14.1–18.9)	19.0 (16.6–21.7)
Pulmonary vasodilator therapy			
Mono therapy	7	5	2
Dual therapy	2	1	1
Triple therapy	0	0	0

Note: For patients with lung disease alone ($n = 3$), diagnoses included primary pulmonary hypertension, bronchopulmonary dysplasia (BPD), and lung metastases. For patients with congenital heart disease (CHD) alone ($n = 7$), diagnoses included atrial septal defect (ASD), ventricular septal defect (VSD), patent arterial duct (PDA), transposition of the great arteries (TGA) with ASD and VSD, left atrial isomerism with ASD and, in one case, an additional portal shunt. For patients with BPD and CHD ($n = 4$), CHD diagnoses included ASD or VSD and/or PDA. Pulmonary vasodilators were either phosphodiesterase 5 inhibitor (sildenafil), endothelin receptor antagonist (bosentan), or home oxygen.

Abbreviation: BMI, body mass index.

patients and controls are presented in Table 3. Representative pressure-strain loops depicting MW and WWR distributions in patients are shown in Figure 1.

Work distribution

MW was significantly higher in the lateral versus septal wall at baseline and during oxygen and iNO ($p < 0.001$ at baseline, $p = 0.024$ with oxygen and $p = 0.012$ with iNO) (Table 2). Reduced positive septal work corresponded to septal flattening and reduced contraction in early systole. Negative septal work corresponded to septal stretching, particularly in late systole (Figure 2). The WWR did not differ significantly between the lateral and septal segments.

Calculated noninvasive peak instantaneous MW for both patients and controls is presented in Table 3. Compared with controls, patients had higher peak instantaneous MW in both the lateral and septal wall and a higher lateral-septal difference.

Effects of pulmonary vasodilators

The mean PA pressure at baseline was 40.3 ± 15.1 mmHg, with no significant change during pulmonary vasodilation therapy with oxygen (38.8 ± 15.3 mmHg, $p = 0.169$) and a small but statistically significant decrease with iNO (37.8 ± 13.2 mmHg, $p = 0.014$). The effects of these agents on invasive and echo parameters are shown in Table 2. Echo parameters, including global and segmental total systolic shortening, did not change significantly with pulmonary vasodilators.

Averaged and segmental MWs and WWR are shown in Table 2. Mean MW for the lateral wall decreased with both oxygen and iNO ($p = 0.034$ and $p = 0.007$, respectively) and mean MW averaged decreased with iNO. Mean MW for the septum did not change significantly. There was no significant change in WWR during pulmonary vasodilation therapy (Figure 3).

When comparing MW calculated for systole and IVR with MW calculated from the whole loop area (diastole included), MW derived from the whole loop area was lower for both lateral wall, septum and averaged MW. The asymmetric distribution between the lateral wall and the septum was more pronounced. However, intersegmental distribution of MW derived from the whole loop area did not change significantly with pulmonary vasodilators. This may have stemmed from the concomitant reduction in both systolic and diastolic pressure inducing a leftward shift of the loop but no significant area change (Figure 4).

TABLE 2 Study variables.

Variable	Condition		
	Baseline ($n = 14$)	Oxygen ($n = 14$)	Nitric ($n = 13$)
Myocardial work (mmHg · %)			
Lateral segments	1013 ± 374 ($n = 12$)	802 ± 342[a]	777 ± 387[a] ($n = 12$)
Septal segments	532 ± 190	573 ± 205 ($n = 13$)	408 ± 198 ($n = 13$)
Averaged (apical segments excluded)	744 ± 241 ($n = 12$)	693 ± 236 ($n = 13$)	606 ± 225[a] ($n = 12$)
Lateral-septal difference	481 ± 184	239 ± 335	347 ± 339
Wasted work ratio			
Lateral segments	0.05 ± 0.07 ($n = 12$)	0.13 ± 0.17	0.09 ± 0.09 ($n = 12$)
Septal segments	0.12 ± 0.17	0.09 ± 0.10 ($n = 13$)	0.21 ± 0.39 ($n = 13$)
Averaged (apical segments excluded)	0.10 ± 0.12 ($n = 12$)	0.11 ± 0.11 ($n = 13$)	0.14 ± 0.21 ($n = 12$)
Whole cycle loop area (mmHg · %)			
Lateral segments	910 ± 374 ($n = 12$)	753 ± 328	777 ± 357 ($n = 12$)
Septal segments	278 ± 167	266 ± 182 ($n = 13$)	273 ± 179 ($n = 13$)
Averaged (apical segments excluded)	608 ± 231 ($n = 12$)	500 ± 235 ($n = 13$)	523 ± 235 ($n = 12$)
Lateral-septal difference	604 ± 333	468 ± 257	508 ± 257
Invasive measurements			
Mean PA pressure (mmHg)	40.3 ± 15.1	38.8 ± 15.3[b]	37.8 ± 13.2[a,b]
RV systolic pressure (mmHg)	52.9 ± 16.6	53.4 ± 17.3	46.0 ± 15.1[a,b]
RV end diastolic pressure (mmHg)	9.4 ± 3.1[b]	9.8 ± 3.1	7.5 ± 3.5
RV dP/dt minimum (mmHg/s)	−852 ± 398[b]	−809 ± 374[b]	−749 ± 324[a,b]
RV dP/dt maximum (mmHg/s)	605 ± 192[b]	554 ± 162[b]	525 ± 178[b]
PVRi (WU/m^2)	10.5 ± 6.6	8.2 ± 5.4[a] ($n = 13$)	9.1 ± 5.7
Indexed PA blood flow (L/min/m^2)	3.49 ± 1.71	3.63 ± 1.15[a] ($n = 12$)	3.76 ± 1.89[b] ($n = 11$)
RV indexed stroke work (mmHg · L/m^2)	1.42 ± 0.95	1.36 ± 0.71	1.51 ± 1.05[b]
Echocardiographic measurements			
Total systolic shortening (%)			
Lateral segments	−28.5 ± 7.4 ($n = 12$)	−24.6 ± 6.7	−26.5 ± 5.9 ($n = 12$)
Septal segments	−14.1 ± 3.8	−14.1 ± 3.5 ($n = 13$)	−13.3 ± 3.5 ($n = 13$)
Averaged (apical segmentsexcluded)	−21.7 ± 4.5 ($n = 12$)	−19.1 ± 4.4 ($n = 13$)	−19.8 ± 4.0 ($n = 12$)
TAPSE *Z*-score	−1.7 ± 2.2	−1.8 ± 2.2	−0.9 ± 2.2
Fractional area change (%)	31.5 ± 10.2 ($n = 11$)	32.9 ± 10.5 ($n = 11$)	31.8 ± 10.8 ($n = 11$)

Note: Calculated RV myocardial work and wasted work ratio, echocardiographic parameters of right ventricular (RV) function, hemodynamic measurements by right heart catheterization. When data from less than 14 patients is available, the patient number is given by ($n =$).

Abbreviations: PA, pulmonary artery; TAPSE, tricuspid annular systolic plane excursion.

[a]Indicates statistically significant changes from baseline.

[b]Indicates statistically significant correlation with myocardial work as described in the main text.

Correlation of MW with invasive and echocardiographic measurements

Averaged MW correlated with dP/dt maximum and dP/dt minimum (Figure 5) in all three conditions (dP/dt maximum and minimum at baseline: $R^2 = 0.493$, $p = 0.007$ and $R^2 = 0.800$, $p = < 0.001$; oxygen: $R^2 = 0.530$, $p = 0.005$ and $R^2 = 0.683$, $p = < 0.001$; iNO: $R^2 = 0.338$, $p = 0.047$ and $R^2 = 0.638$, $p = 0.002$, respectively). This correlation was also found for the pressure-strain loop area ($p \leq 0015$ for both

TABLE 3 Baseline strain and peak instantaneous myocardial work.

	Patients ($n = 14$)	Controls ($n = 14$)	p Value
Total systolic shortening (%)			
Lateral segments	-28.5 ± 7.4 ($n = 12$)	-33.1 ± 5.7	0.085
Septal segments	-14.1 ± 3.8	-21.0 ± 2.6	<0.001
Averaged (apical segments excluded)	-21.0 ± 4.9 ($n = 12$)	-27.0 ± 3.1	0.002
Peak instantaneous myocardial work (mmHg · %)			
Lateral segments	1437 ± 491 ($n = 12$)	926 ± 158	0.004
Septal segments	708 ± 195	588 ± 74	0.047
Averaged (apical segments excluded)	1083 ± 307 ($n = 12$)	757 ± 87	0.004
Lateral-septal difference	707 ± 410	338 ± 175	0.011

Note: Right ventricular peak systolic strain and calculated noninvasive peak instantaneous myocardial work (peak systolic strain multiplied by RV systolic pressure) in patients and controls. For patients, invasive RV systolic pressure is used, while for controls, an estimated RV systolic pressure of 28 mmHg is used. Statistical significance of the differences between patients and controls is given by the p value. When data from less than 14 patients is available, the patient number is given by ($n =$).

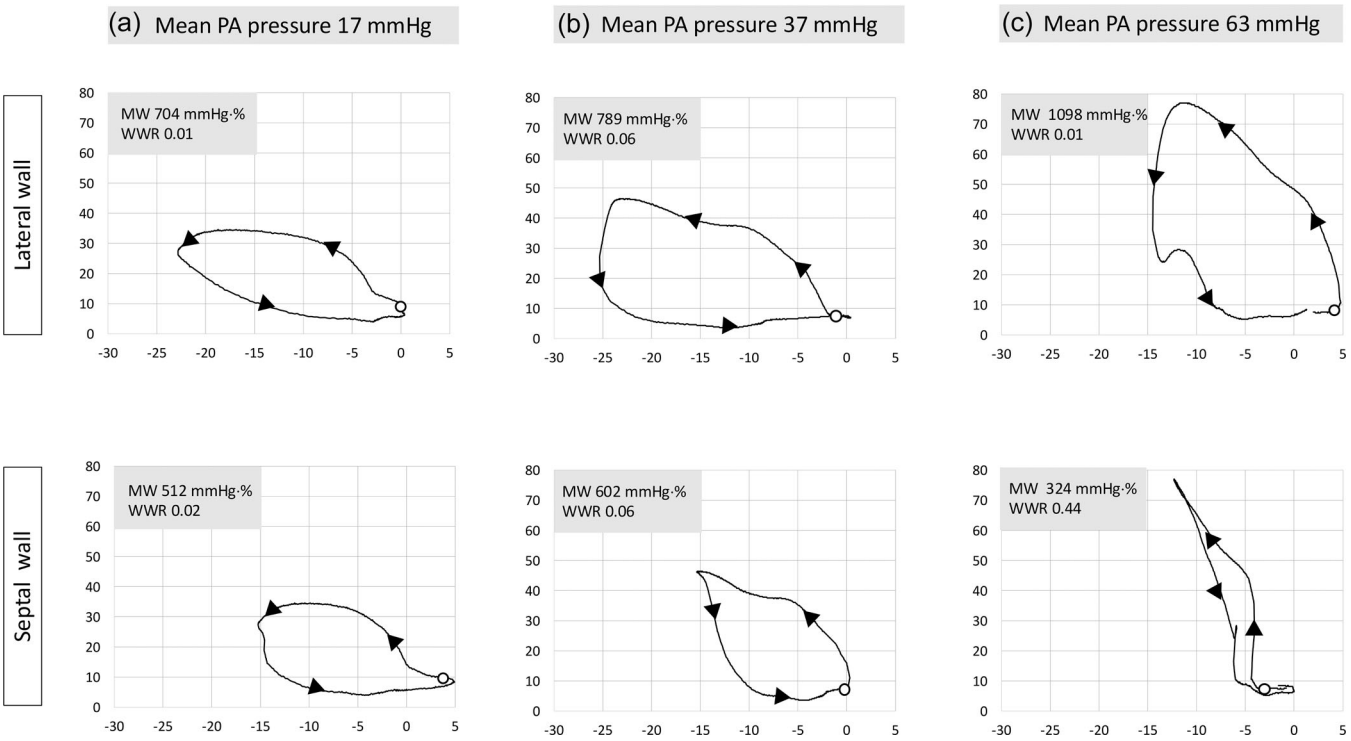

FIGURE 1 Right ventricular pressure-strain loops of the lateral wall and the septal wall from three different patients with mean pulmonary artery (PA) pressure at baseline, varying from normal (a) to moderately (b) and severely (c) elevated. Strain (%) is illustrated on the x-axis and pressure (mmHg) on the y-axis. The small circle on the loop indicates tricuspid valve closure and arrows indicate loop direction.

dP/dt maximum and minimum at all stages). Total systolic shortening did not correlate with either dP/dt maximum or dP/dt minimum. Averaged MW correlated with mean PA pressure during pulmonary vasodilation therapy (oxygen: $R^2 = 0.325$, $p = 0.042$, iNO: $R^2 = 0.364$, $p = 0.038$), with systolic RV pressure during iNO ($R^2 = 0.415$, $p = 0.024$), with RVEDP at baseline ($R^2 = 0.336$, $p = 0.038$), with indexed PA blood flow during iNO ($R^2 = 0.406$, $p = 0.026$), and with indexed stroke work during iNO ($R^2 = 0.510$, $p = 0.009$). Averaged MW did not correlate with PVRi at any condition. No correlations were found between averaged or lateral wall MW and TAPSE or FAC.

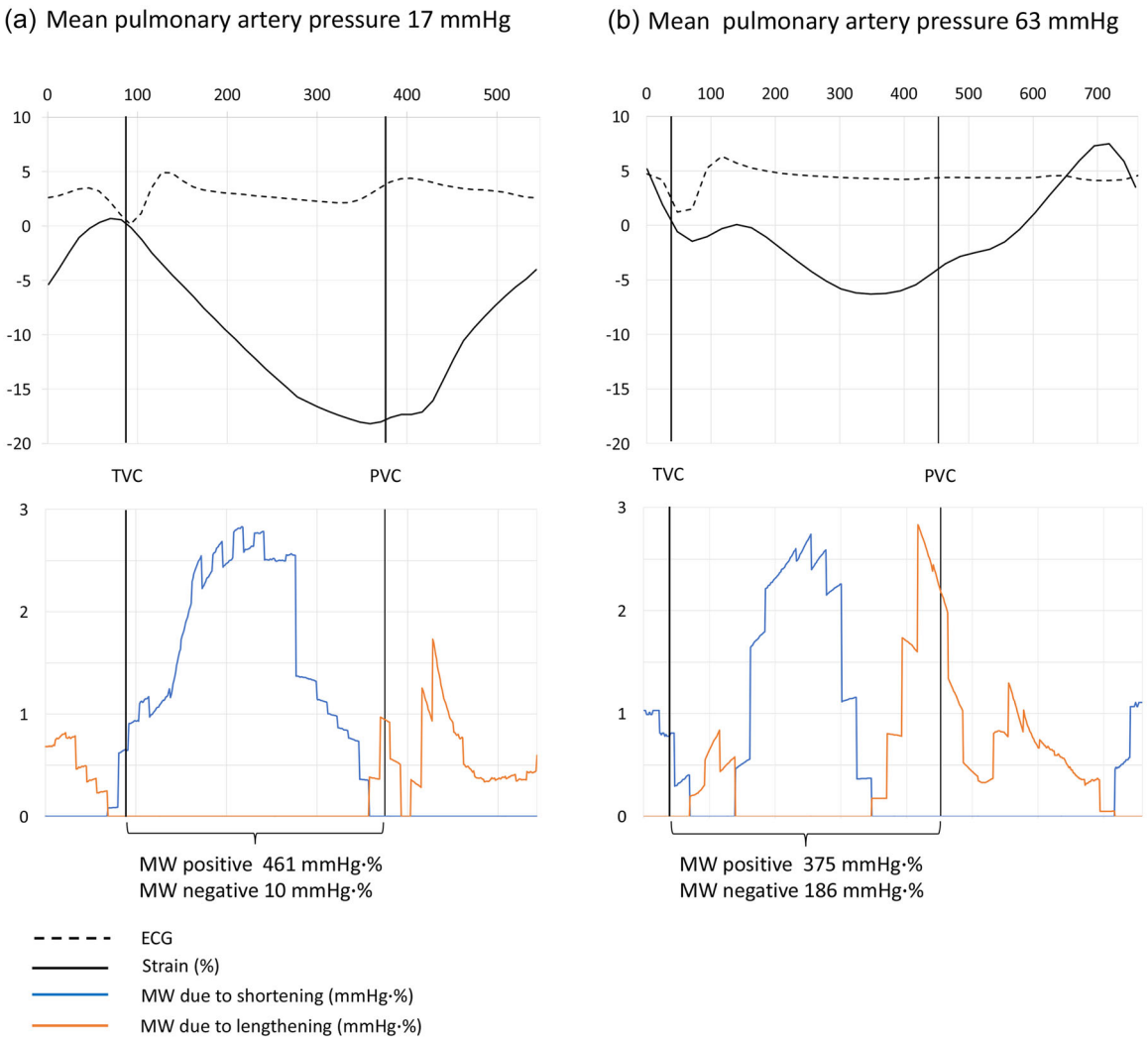

FIGURE 2 Graphs illustrating strain of the septum (upper curve) and simultaneously acquired myocardial septal work (lower graph) in a patient with mild (a) and severe (b) pulmonary hypertension, both at baseline. The patient with higher mean pulmonary artery pressure has lower positive myocardial work, higher negative myocardial work and substantially higher wasted work ratio, calculated from tricuspid valve closure (TVC) to pulmonary valve closure (PVC).

Visual examination of the pressure-strain curve configuration suggested increased septal WWR in patients with increased mean PA pressure (Figure 1), and a trend toward lower septal WWR in those with lower mean PA pressure but the difference did not reach statistical significance in this small cohort.

DISCUSSION

We calculated RV MW in children with PH who underwent clinically indicated cardiac catheterization using simultaneously acquired echo and high-fidelity pressure-tipped catheter measurements. The main results show that:

(a) MW, but not WWR, was asymmetrically distributed between the RV lateral wall and septum.
(b) Pulmonary vasodilation therapy tended to redistribute MW more symmetrically between RV segments.
(c) MW correlated with the rate of RV pressure development and decay at baseline and during pulmonary vasodilation therapy.

RV pressure loading in PH, when severe and/or progressive, leads to RV failure. While echo parameters can indicate reduced RV function, they may not accurately reflect RV compensation for the increased load. An RV with preserved contractile function and normal pressure loading performs less work than an RV with equal contractile function in the setting of PH. Our calculations of peak instantaneous MW, demonstrate that even when contractile function, measured by strain, is reduced compared with healthy controls, the performed work can be higher in patients due to the increased

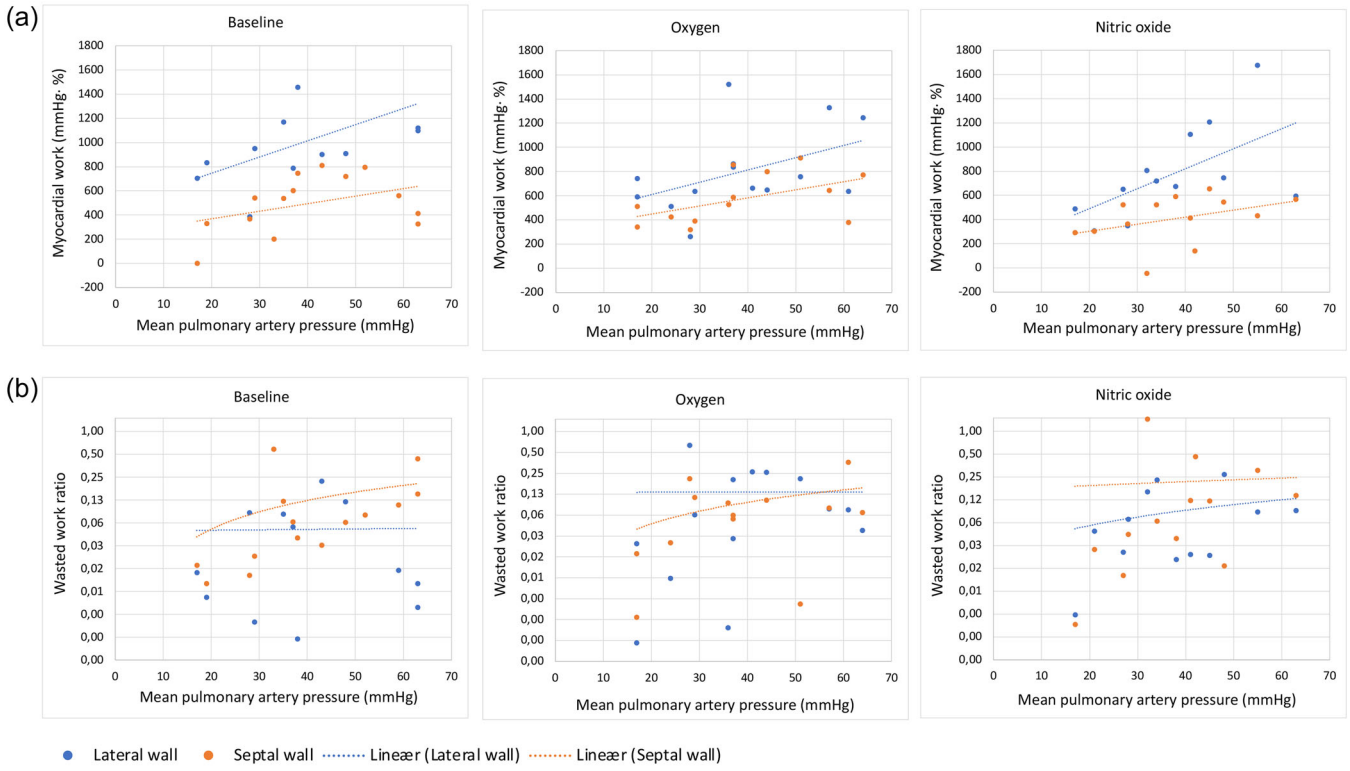

FIGURE 3 (a) Relationship between lateral and septal wall myocardial work (MW) and mean pulmonary artery pressure under all conditions (at baseline and during pulmonary vasodilation therapy with oxygen and nitric oxide). (b) Relationship between lateral and septal wall wasted work (WWR) and mean pulmonary artery pressure under all conditions.

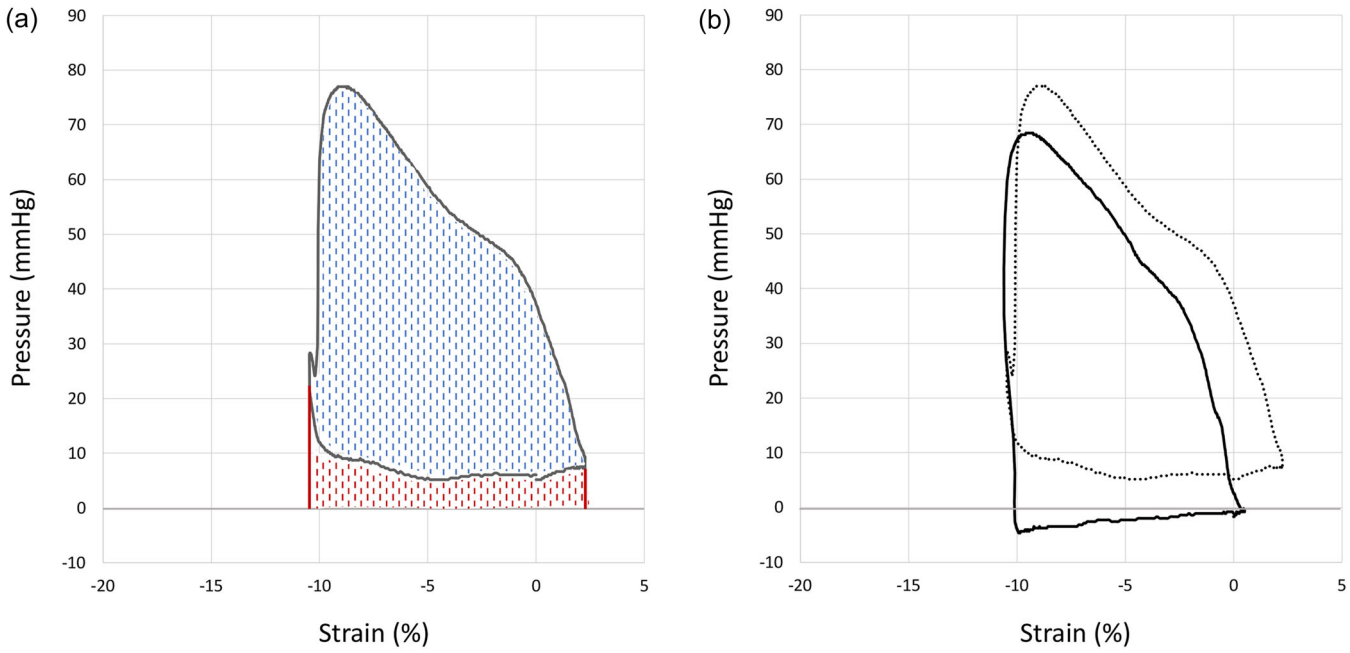

FIGURE 4 (a) Illustration of myocardial work calculations representing the true loop area (blue) and the area included when calculating work without adjusting for the diastolic component (blue + red). (b) Pressure-strain loops at baseline and with inhaled nitric oxide (solid line) illustrating a parallel shift of the curve but no significant change in loop area.

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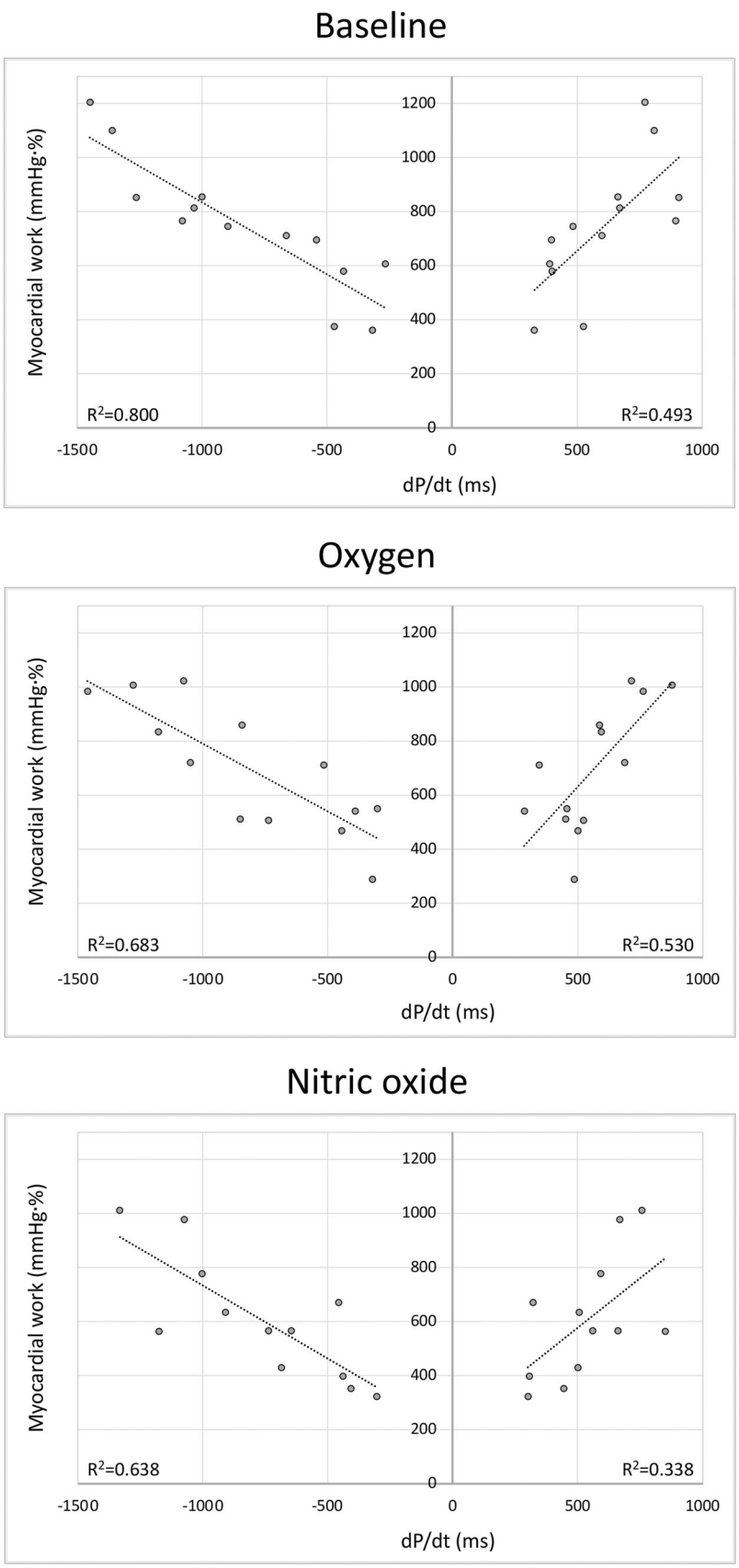

FIGURE 5 Linear regression analysis of correlation between right ventricular myocardial work (MW) and right ventricular dP/dt maximum (to the right of the *y*-axis) and dP/dt minimum (to the left of the *y*-axis) under all conditions (at baseline and during pulmonary vasodilation therapy with oxygen and inhaled nitric oxide).

pressure load. This finding is in line with estimates of RV MW in the adult population[14] and illustrates the clinical relevance of the MW method.

By incorporating echocardiographic measurements of function and invasive measurements of pressure, MW allows for a more comprehensive evaluation of RV performance in relation to its loading. MW further correlates with myocardial oxygen consumption and metabolic demand. Further, functional assessment by strain usually utilizes maximal shortening at a specific point, while effective shortening occurring later in the cardiac cycle is not accounted for. Ventricular work as reflected by pressure-volume relations is clinically relevant in PH,[21-23] but obtaining RV volume changes may be more challenging than determining strain. Furthermore, while pressure-volume relations assess global pump work, MW allows for the analysis of regional differences in MW and work efficiency. It has been shown that identifying and correcting regional differences in MW of the LV, such as that in patients with left bundle branch block and acute coronary syndrome, can provide a clinical benefit.[8,9,24] We now expand these concepts to the RV in PH with results suggesting that regional inefficiency due to maldistribution of MW may contribute to RV dysfunction.

Asymmetric MW contributes to RV inefficiency

We found that work was unevenly distributed between myocardial segments, with septal segments having lower MW than lateral wall segments. This asymmetrical work distribution is consistent with the results of experimental and modeling studies in PH. In our experimental PH models, lateral wall MW increased with increased septal WWR associated with RV fibrosis and dysfunction.[15] Similarly, computer models have shown a 100%–200% increase in RV free-wall myofiber work and a 10%–30% decrease in septal myofiber work in acute PH.[25] Although less pronounced, myofiber work changes persisted in chronic PH, with an increase of up to 20% in the RV free-wall, and a 5% decrease in the septum. Our calculation of peak instantaneous MW shows a significantly increased lateral-septal difference in patients compared with healthy controls.

Some studies have suggested "RV dyssynchrony" in patients with PH.[26] Our results show that these disparate mechanics are due to adverse loading rather than electromechanical dyssynchrony, as 12/14 subjects had a normal QRS duration. Nonetheless, the pattern of dyssynchronous wall motion mimics that seen in the right bundle branch block.[27] Work performed by one segment may be wasted in stretching another segment. In acute RV pressure-loading, prolonged ventricular contraction affects the transseptal pressure gradient,[28,29] leading to reduced shortening and septal stretch. Over time, the cause of disparate mechanics is likely multifactorial. Regionally increased wall stress due to changes in regional loading conditions may lead to regional hypertrophy, apoptosis, and fibrosis,[30] which may contribute to uneven distribution of myocardial properties.[15,31] Taken together, these mechanics lead to ineffective contraction despite the increase in lateral wall work.

Correlation of work with invasive hemodynamics

In our study, averaged work measurements correlated with invasive measurements of RV systolic and diastolic function, as reflected by the rate of pressure development (dP/dt maximum) and decay (dP/dt minimum) over time, under all conditions. In PH, the normally very short or absent isovolumetric contraction period is prolonged due to the increased load which slows myocyte shortening velocity.[29,32] As dP/dt correlates with patient outcomes,[33] the correlation between MW and dP/dt may be clinically relevant.

Clinical relevance

Our study used high-fidelity pressure-tipped catheters, thereby providing reliable RV pressure measurements throughout the cardiac cycle and avoiding potential inaccuracies of pressure-curve estimates or derivations. Moreover, oxygen consumption for calculation of cardiac output was measured with mass spectrometry providing a gold-standard method. We recognize that these are significant advantages for a research study but not widely available in clinical practice. Notwithstanding the limitations of imaging supine and immobilized clinically fragile children in the catheter lab, RV four-chamber views could be acquired, and pressure-strain loops generated for all patients in the lateral wall and septum. Nonetheless, speckle-tracking in the apical segments was less feasible, and this remains a substantial limitation in practice.

The results of the current pilot study cannot yet be automatically applied clinically. However, we note that global MW correlated with invasive hemodynamic markers of systolic and diastolic function (dP/dt max and dP/dt min), despite the inconsistent correlation with mean PAP. This is interesting since we previously showed the benefits of pulmonary vasodilation on diastolic function in cases of persistently high RV pressure

in PH patients.[5] If MW is shown to be a sensitive marker of function in further studies, this method could be relevant even in the catheter laboratory, as the acquisition of pressure-volume loops demands extensive equipment and experience.

Further, our results are in line with our previous experimental study and suggest that the segmental pattern of RV MW may be a marker of the impact of disease severity on RV efficiency and hence adaptation. Interestingly, the pattern tended to be reversed with pulmonary vasodilation therapy, even though the measured reduction in mean PAP was considered small. Thus, it is relevant to study if more pronounced unloading of the RV, at different time points in the clinical course, can help identify development of maladaptive RV function.

Redistribution of adverse regional wall stress and work in PH can also be achieved via RV pacing.[34] Hence, MW analyses may be useful for selecting a suitable candidate, guiding lead placement, and evaluating the response to pacing.[24] As detailed previously, the changes we observed in RV MW distribution after pulmonary vasodilators were similar to those described in animal and modeling studies of RV lateral wall pacing in PH. In those studies, reduction in lateral wall myofiber work was accompanied by increased myofiber work in the LV free-wall and septum and improved RV pump function.[28,34]

Although we have demonstrated, for the first time in children, proof-of-concept for the feasibility of assessing MW during clinical catheter studies, MW acquired noninvasively would be beneficial. However, an RV reference curve for healthy individuals is currently lacking both for children and adults. Our data illustrates that methodological awareness and caution needs to be exercised regarding inclusion of the diastolic contribution to MW calculation, which is currently not accounted for in the noninvasive approach for LV MW. While this may be negligible when systolic pressures are substantially higher than diastolic pressures, when diastolic pressures are elevated, such as occurs in ventricular failure, MW may be overestimated.

Limitations

This exploratory proof-of-concept study is limited by its single center design, retrospective data analysis, and by the small number of patients. For obvious ethical reasons, comparison to a control group was limited to noninvasively collected data. Although catheter and echo data were collected simultaneously and timed by ECG, the acquisition was not done by "beat to beat" synchronization. Based on the available echo data, we studied RV longitudinal work, but circumferential MW may also be important in RV pressure loading. Further, the calculation of regional MW uses RV pressure as a surrogate for force and does not reflect changes in force that results from differences in RV geometry. The high-fidelity micromanometer catheters measured only pressure and not volume (conductance). Therefore, conductance catheter pressure-volume loops as a global RV work reference were not available. Moreover, we were not able to test MW results against other measures of RV systolic function or regional myocardial metabolism, such as cardiovascular magnetic resonance or positron emission tomography, respectively. Furthermore, the small changes in mean PA pressure during oxygen and iNO challenges limited the assessment of changes in MW/WWR during pulmonary vasodilation. Lastly, the correlation of these parameters with changes in clinical status and outcomes requires further study.

AUTHOR CONTRIBUTIONS

Simone Goa Diab analyzed echocardiographic data, performed the myocardial work analyses, designed the figures, and prepared the draft. Ryota Ebata prepared the myocardial work methodology. Dariusz Mroczek and Wei Hui collected and analyzed pressure and echocardiographic data, respectively. Espen W. Remme revised and verified the analytical methods. Thomas Möller carried out statistical analyses and designed the figures. Mark K. Friedberg devised the conceptual ideas, supervised data analysis, and drafted the manuscript. All authors took part in revising the manuscript and have approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was approved by the SickKids Research Ethics Board (REB number 1000018502), and informed consent was obtained from the children's guardians. The study complied with the Declaration of Helsinki.

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