ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 650–660
Published online 24 November 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14216

ORIGINAL ARTICLE

Dynamic aspects of ventricular interaction during exercise in HFpEF and in pre-capillary pulmonary hypertension

Mathias Claeys[1,2], Thibault Petit[1,3], Jan Bogaert[2,4], Andre La Gerche[1,5], Jan Los[1,6], Marion Delcroix[2,7], Rik Willems[1,2], Guido Claessen[1,2] and Piet Claus[1]*

[1]*Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium;* [2]*University Hospitals Leuven, Leuven, Belgium;* [3]*Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium;* [4]*Department of Imaging and Pathology, KU Leuven, Leuven, Belgium;* [5]*Baker Heart and Diabetes Institute, Melbourne, Australia;* [6]*Department of Cardiology, Radboud UMC, Nijmegen, Netherlands; and* [7]*Department of Chronic Disease, Metabolism and Ageing, KU Leuven, Leuven, Belgium*

Abstract

Aims The contribution of adverse ventricular interdependence remains undervalued in heart failure or pulmonary vascular disease, and not much is known about its dynamic nature during exercise and respiration. In this study, we evaluated ventricular interaction during exercise in patients with heart failure with preserved ejection fraction (HFpEF) and patients with chronic thromboembolic pulmonary hypertension (CTEPH) as compared with healthy controls.

Methods and results Forty-six subjects (10 controls, 19 CTEPH patients, and 17 HFpEF patients) underwent cardiac magnetic resonance imaging during exercise. Ventricular interaction was determined through analysis of the septal curvature (SC) of a mid-ventricular short-axis slice at end-diastole, end-systole, and early-diastole, both in expiration and inspiration. Exercise amplified ventricular interaction in CTEPH patients and to a lesser extent in HFpEF patients ($P < 0.05$ for decrease in SC with exercise). Adverse interaction was most profound in early-diastole and most pronounced in CTEPH patients ($P < 0.05$ interaction group * exercise) because of a disproportionate increase RV afterload ($P < 0.05$ to both controls and HFpEF) and diastolic pericardial restraint ($P < 0.001$ for interaction group * exercise) during exercise. Inspiration enhanced diastolic interdependence in CTEPH and HFpEF patients ($P < 0.05$ vs. expiration). Both at rest and during exercise, SC strongly correlated with RV volumes and pulmonary artery pressures (all $P < 0.05$).

Conclusions Exercise amplifies adverse right–left ventricular interactions in CTEPH, while a more moderate effect is observed in isolated post-capillary HFpEF. Given the strong link with RV function and pulmonary hemodynamic, assessing ventricular interaction with exCMR might be valuable from a diagnostic or therapeutic perspective.

Keywords Ventricular interdependence; Cardiac magnetic resonance; HFpEF; Right ventricle; Exercise

Received: 23 May 2022; Revised: 13 September 2022; Accepted: 7 October 2022
**Correspondence to: Piet Claus, Department of Cardiovascular Sciences, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. Email: piet.claus@kuleuven.be*
Guido Claessen and Piet Claus are joint senior authors.

Introduction

Ventricular interdependence, or the direct force transmission between both ventricles, originates directly from the cross-talk brought about by the interventricular septum, shared myocardial fibres, and the enclosing pericardium.[1] Ventricular interactions are dynamic, persist throughout the cardiac cycle, and are large enough to have meaningful impact on cardiac function. As the interventricular septum plays a crucial role in mediating ventricular interactions, ventricular interdependence can be easily examined through evaluation of septal motion by cardiac imaging.[2] Historically, ventricular interdependence has mainly been evaluated in the context of right ventricular (RV) pressure or volume overload.[3] Recently, however, also its role in patients with heart failure is increasingly recognized. Specifically, in patients with heart failure with preserved ejection fraction (HFpEF), recent evidence suggests that, in addition to left

© 2022 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

ventricular (LV) diastolic dysfunction, pericardial restraint, and the ensuing ventricular interdependence may contribute to the disproportionate increase in filling pressures during exercise.[4,5] Moreover, the upstream transfer of rising LV filling pressures during exercise contributes to RV afterload and could further exacerbate adverse ventricular interaction.

Exercise intolerance is a cardinal manifestation of both pulmonary vascular diseases and HFpEF, and numerous studies have already demonstrated the incremental value of exercise evaluation in both conditions.[6] Unfortunately, parameters of ventricular interaction, even despite their dynamic nature, are generally only assessed at rest, and the effect of respiration is often discarded. The goal of this study was therefore to gain further insight into the dynamic influence of exercise and respiration on ventricular interdependence and to explore differences between pre-capillary and post-capillary hypertension. Using exercise cardiac magnetic resonance (CMR) imaging with simultaneous haemodynamic measurements, we compared cardiac function and parameters of ventricular interaction of patients with pre-capillary pulmonary hypertension [due to chronic thromboembolic pulmonary hypertension (CTEPH)] with HFpEF patients and isolated post-capillary pulmonary hypertension. To provide a reference frame, we also included healthy controls.

Methods

Subjects

HFpEF and CTEPH patients were recruited from the heart failure clinic and the centre for pulmonary vascular diseases at our institution. HFpEF was defined by symptoms of heart failure, normal LV ejection fraction (LVEF $\geq$50%), and elevated left heart filling pressures on RHC [pulmonary arterial wedge pressure (PAWP), $>$15 mmHg at rest or $\geq$25 mmHg with exercise], although CTEPH patients were diagnosed according to current guidelines.[7,8] Patients with significant valvular heart disease, coronary artery disease, hypertrophic or infiltrative cardiomyopathy, primary renal or hepatic disease, or significant ventilatory disease (FEV_1 $<$ 50%, TLC or VC $<$ 70%) were excluded. Control subjects without prior cardiopulmonary disease volunteered to participate after responding to local advertisements. All were asymptomatic and had a normal ECG, transthoracic echocardiogram, and right heart catheterization at rest. Finally, to be included, all participants had to able to perform at least 50 W on an upright bicycle stress test. The study conformed to the Declaration of Helsinki and was approved by the local Ethics Committee. All participants provided written informed consent.

Study design

Firstly, cardiopulmonary exercise testing with continuous monitoring of expiratory gases was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany). Through breath-by-breath analysis minute ventilation, oxygen consumption and carbon dioxide production were assessed. Additional measures included peak heart rate, peak power, and the ventilatory equivalent for carbon dioxide. Secondly, within 24 h, all subjects underwent exercise CMR imaging with simultaneous invasive pressure measurements through a 7-Fr MRI-compatible pulmonary artery catheter (Edwards Lifesciences, CA, USA) and a 20-G radial arterial catheter. Pressures were recorded through MRI-compatible transducers connected to a PowerLab recording system (ADInstruments, Oxford, UK) and analysed offline using LabChart V6.1.1 (ADInstruments, Oxford, UK). Images were acquired during free breathing at rest, and during exercise at 25%, 50% of peak power achieved during CPET. Workloads were imposed nearly instantaneously and were maintained for ≈3 min at each stage, 30 s to achieve a physiological steady state, and then 2–3 min for image acquisition and will hereinafter be referred to as rest, low, and moderate intensity.

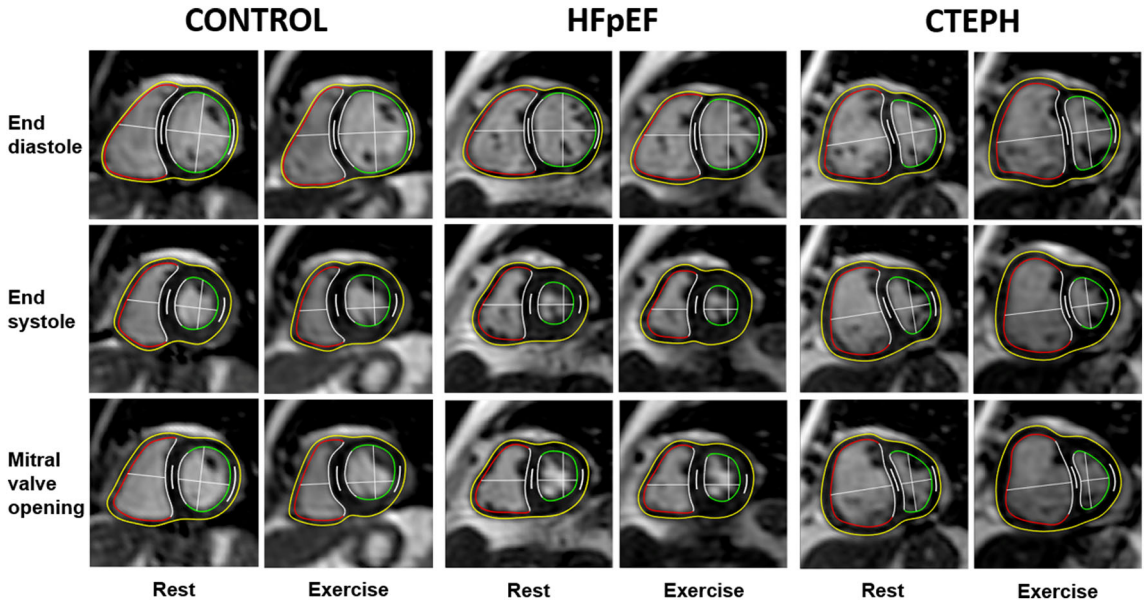
CMR equipment, image acquisition, and analysis

Cardiac function was assessed using a free-breathing real-time exercise CMR method that we previously validated against invasive standards and that has been described in depth elsewhere.[9] Detailed information can be found in the Supporting Information. To assess ventricular interdependence, the LV and RV endocardial and epicardial borders of a mid-ventricular short-axis slice were traced during expiration and inspiration at end-diastole (ED), at end-systole (ES), and at early-diastole [defined as mitral valve opening (MVO)] both at rest and during low-intensity and moderate-intensity exercise. Using custom software, septal curvature (SC) was calculated as the reciprocal of the mean radius of curvature of the midline of the mid-septal segment (60% of total septal length to avoid tethering effects of RV insertion points) as illustrated in *Figure 1*. A negative SC denotes septal bowing into the LV. In HFpEF patients, right atrial pressure was used a surrogate for pericardial pressure.[10] LV transmural pressure was calculated as pulmonary capillary wedge pressure minus right atrial pressure. Pulmonary vascular reserve (P/Q slope) was evaluated through the relationship between mean pulmonary artery pressure and cardiac output.

Statistics

Data were analysed using SPSS Statistics version 27 (IBM Corporation, Armonk, NY, USA). Normality was ensured

Figure 1 Methodology. Illustrative mid-ventricular slice of control subject (A), HFpEF (B), and CTEPH (C) patient at ED (upper row), ES (middle row), MVO (lower row) both at rest (left column) and exercise (right column) with traced epicardial (yellow), RV endocardial (red), and LV endocardial (green) border.



(Shapiro–Wilk test), and variables are presented as means (± standard deviation) or as medians (with 25% and 75% percentiles) accordingly. Categorical data were compared using a Chi^2 test and continuous variables with either a Kruskal–Wallis *H* test or a one-way analysis of variance (ANOVA) with the Bonferroni post hoc correction. The cardiac response to exercise and the evolution of ventricular interaction were assessed using repeated measures ANOVA with exercise intensity and respiration as within-subject effect and subject group as between-subject effect. In a separate analysis, age was added as a covariate to the model. The relationship between SC, volumes, and pressures was determined using Pearson correlation coefficients. Intraobserver and interobserver reproducibility (see *Table S1*) was assessed at rest and during exercise in a sample of 10 subjects using the intra-class correlation coefficient (two-way mixed and absolute agreement quoted). A *P*-value of <0.05 was considered statistically significant. Sample size calculation is provided in the supplements.

Results

Baseline characteristics

Forty-six subjects (10 controls, 19 CTEPH patients, and 17 HFpEF patients) were included in the study. The baseline characteristics and the results of the cardiopulmonary exercise test are summarized in *Table 1*. HFpEF patients were older and had a higher BMI compared with both other groups. Parameters of peak exercise capacity were significantly lower and pulmonary artery pressures higher in CTEPH and HFpEF patients compared with controls. Finally, HFpEF patients had higher right atrial and pulmonary capillary wedge pressures compared with both other groups.

Cardiac volumes and function during exercise

The cardiac response to exercise is depicted in *Table 2* and *Figure S2*. In control subjects, stroke volume and ejection fraction increased significantly during exercise, which was primarily driven by a significant reduction in end-systolic volume. In CTEPH patients and to a lesser extent in HFpEF patients, RV end-systolic volumes increased more than end-diastolic volumes because of the exercise-induced afterload increase (higher P/Q slope, $P < 0.001$ between groups). Hence, RV ejection fraction declined in both groups during exercise. LV volumes, on the other hand, either remained unchanged (HFpEF) or declined in tandem (CTEPH). LV stroke volume and ejection fraction therefore remained stable during exercise. Global biventricular volume increased minimally in all groups (*Figure 2A*, $P = 0.926$ between groups), but there were marked differences in the behaviour of LV and RV volumes during exercise. RV/LV volume ratio increased significantly in CTEPH patients ($P < 0.001$), increased slightly in HFpEF patients ($P = 0.015$), and remained unchanged in controls (*Figure 2*, $P < 0.001$ for interaction

Table 1 Baseline characteristics

	Controls (n = 10)	HFpEF (n = 17)	CTEPH (n = 19)	P-value
Age	46 ± 10	72 ± 8*†	53 ± 15	<0.001
Gender (male)	6	7	11	0.596
BSA (m^2)	2.0 (1.8–2.2)	2.0 (1.8–2.2)	1.9 (1.8–2.0)	0.537
BMI ($kg.m^{-2}$)	27 ± 4	31 ± 5†	27 ± 4	0.014
Cardiopulmonary exercise test				
Peak VO_2 ($mL.min^{-1}.kg^{-1}$)	30.3 ± 8.6	14.7 ± 4.1*	14.5 ± 3.6*	<0.001
Pred peak VO_2 (%)	102 ± 20	84 ± 21*	59 ± 18*	<0.001
Peak power (W)	215 (140–275)	80 (60–110)*	80 (60–95)*	<0.001
Peak HR (b.p.m.)	178 (151–181)	120 (90–126)*	125 (116–143)*	<0.001
VE/VCO_2	27 (25–30)	36 (32–41)*†	47 (43–56)*	<0.001
Right heart catheterization				
RAP (mmHg)	4 ± 2	10 ± 4*†	6 ± 4	0.001
sPAP (mmHg)	28 ± 5	47 ± 14*†	72 ± 14*	<0.001
mPAP (mmHg)	18 ± 3	29 ± 8*†	42 ± 9*	<0.001
dPAP (mmHg)	13 ± 3	20 ± 6*†	27 ± 7*	<0.001
PAWP (mmHg)	9 ± 4	18 ± 4*†	9 ± 3	<0.001
PVR ($dyn.s.cm^{-5}$)	N/A	224 (100–257)	575 (430–933)	<0.001
CI ($L.min^{-1}.m^{-2}$)	N/A	2.3 ± 0.4	2.3 ± 0.5	0.976

BSA, body surface area; BMI, body mass index; CI, cardiac index; d/m/sPAP, diastolic/mean/systolic pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atria pressure; VE/VCO2, ventilator efficiency slope; VO_2, oxygen consumption.
P values for between-group difference.

group * exercise). Right atrial and pulmonary arterial wedge pressures increased significantly during exercise in HFpEF patients (both $P < 0.001$ for rest-to-peak), whereas LV transmural pressure only increased minimally ($P = 0.048$ for rest-to-peak).

Dynamics of septal curvature across the cardiac cycle

The dynamics of average (expiration and inspiration combined) SC at end-diastole, end-systole, and mitral valve opening (i.e. end relaxation/early diastole) can be appreciated *Figure 3* and are also represented in *Figure S3*. At rest, a similar change was seen in the three groups (*Figure 3A*, $P = 0.064$ for interaction group * cardiac cycle) with slightly lower SC at ED compared with ES in controls and HFpEF patients and a significantly lower SC at MVO compared with ES in CTEPH patients. At moderate exercise intensity, the dynamics of SC differed across the groups (*Figure 3B*, $P < 0.001$ for interaction group * cardiac cycle) with a more pronounced decrease in SC at ED and especially at MVO in HFpEF and CTEPH patients.

Effect of exercise on ventricular interaction

The effect of exercise on average (expiration and inspiration combined) SC is outlined in *Figure 3* and *Table S2*. Throughout the cardiac cycle, there were significant differences between the three groups (between-group difference, all $P < 0.01$), but SC was only differentially affected by exercise at MVO ($P = 0.024$ for interaction group * exercise). In controls, SC did not change with exercise either at ED, ES, or MVO (main effect of exercise both $P > 0.05$). Conversely, in CTEPH and to a lesser extent in HFpEF patients, SC decreased significantly during exercise at ED and MVO (main effect of exercise all $P < 0.01$), although no effect was observed at ES (main effect of exercise $P > 0.05$). CTEPH patients had consistently lower SC compared with both other groups, whereas in HFpEF patients, SC was only significantly lower compared with controls at MVO during exercise. Other parameters of ventricular interaction, such as eccentricity index or the ratio of RV to LV diameter displayed similar changes during exercise (*Figure S4*).

Effect of respiration on ventricular interaction

The effect of respiration did not differ between groups (interaction group * respiration all $P > 0.05$; *Figure 4*). Inspiration enhanced end-diastolic ventricular interaction at rest in CTEPH and HFpEF patients and during exercise in HFpEF patients (*Figure 4A*). At end systole on the other hand, respiration did not influence SC, neither at rest nor during exercise (*Figure 4B*). Finally, at MVO, a significant effect was noted in CTEPH patients at rest and in all groups during exercise (*Figure 4C*). Detailed description of average, expiratory, and inspiratory SC values are available in Tables *S2*–*S4*.

Association between ventricular interaction, RV end-diastolic volume, and pulmonary artery pressures

Both at rest and during moderate exercise, strong correlations were noted between SC and RVEDV (r between

Table 2 Cardiac volumes, function, and haemodynamics during exercise

	Level	Controls (n = 10)	HFpEF (n = 17)	CTEPH (n = 19)	P	Group Interaction
HR (min^{-1})	Rest	68 ± 14	68 ± 10	74 ± 13	0.148	
	Low	101 ± 10	92 ± 18	103 ± 13	0.014	
	Mod	125 ± 12	100 ± 22	117 ± 18		
Power (W)	Rest	0 ± 0	0 ± 0	0 ± 0	<0.001	
	Low	53 ± 19	24 ± 8 *	22 ± 8 *	<0.001	
	Mod	103 ± 37	43 ± 15 *	42 ± 16 *		
LVEDVi ($mL.m^{-2}$)	Rest	78 ± 22	65 ± 12	58 ± 13 *	0.002	
	Low	81 ± 21	66 ± 16	55 ± 12 *	0.001	
	Mod	83 ± 24	66 ± 16 †	53 ± 12 *		
LVESVi ($mL.m^{-2}$)	Rest	29 ± 12	25 ± 8	23 ± 8	0.173	
	Low	27 ± 9	25 ± 10	21 ± 9	0.503	
	Mod	26 ± 10	24 ± 9	20 ± 9		
RVEDVi ($mL.m^{-2}$)	Rest	77 ± 24	68 ± 15 †	91 ± 28	0.020	
	Low	79 ± 24	72 ± 16 †	97 ± 28	0.011	
	Mod	79 ± 26	73 ± 17 †	101 ± 27		
RVESVi ($mL.m^{-2}$)	Rest	31 ± 13	30 ± 11	57 ± 26*	<0.001	
	Low	26 ± 10	35 ± 14†	63 ± 26*	<0.001	
	Mod	24 ± 11	35 ± 16†	68 ± 24*		
SVi ($mL.m^{-2}$)	Rest	49 ± 12	40 ± 7	35 ± 8*	<0.001	
	Low	55 ± 14	41 ± 10*	34 ± 6*	<0.001	
	Mod	57 ± 14	42 ± 8*†	33 ± 7*		
LVEF (%)	Rest	64 ± 9	62 ± 7	61 ± 9	0.390	
	Low	68 ± 6	62 ± 9	63 ± 9	0.270	
	Mod	69 ± 7	65 ± 8	64 ± 10		
RVEF (%)	Rest	61 ± 7	57 ± 10†	40 ± 11*	<0.001	
	Low	69 ± 6	52 ± 12*†	37 ± 11*	<0.001	
	Mod	71 ± 5	53 ± 14*†	34 ± 8*		
CI ($L.min^{-1}.m^{-2}$)	Rest	3.1 ± 0.8	2.6 ± 0.4	2.6 ± 0.7	<0.001	
	Low	5.5 ± 1.7	3.6 ± 0.5*	3.5 ± 0.7*	<0.001	
	Mod	7.2 ± 2.4	3.9 ± 0.8*	3.9 ± 1.0*		
SBP (mmHg)	Rest	140 ± 22	143 ± 21	133 ± 17	0.102	
	Low	170 ± 22	169 ± 29	156 ± 28	0.016	
	Mod	192 ± 25	178 ± 24	164 ± 31		
sPAP (mmHg)	Rest	20 ± 6	42 ± 14	75 ± 20	<0.001	
	Low	32 ± 8	67 ± 19	104 ± 18	0.001	
	Mod	39 ± 9	73 ± 20	114 ± 18		
RAP (mmHg)	Rest	3 ± 1	9 ± 4	6 ± 4	<0.001	
	Low	5 ± 2	16 ± 8	14 ± 5	0.002	
	Mod	7 ± 2	18 ± 9	19 ± 6		
P/Q slope (mmHg.min. L^{-1})	n/a	1.8 (1.0–2.8)	4.2 (3.7–7.6)*†	9.3 (7.6–11.5)*	<0.001	

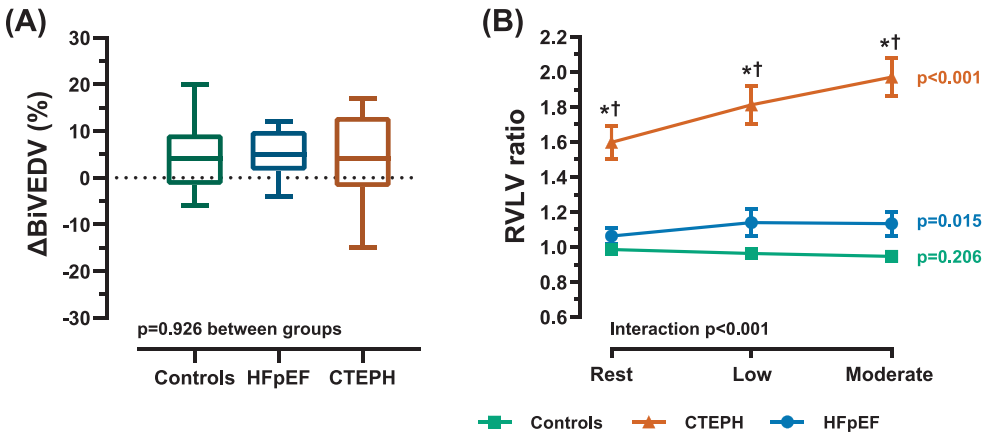
CI, cardiac index: ED/SVi, indexed end-diastolic/systolic volume; EF, ejection fraction; HR, heart rate; mod, moderate; P/Q, mean pulmonary artery pressure to cardiac output; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure, SVi, indexed stroke volume. P values for between-group difference.

−0.535 and −0.702, all $P < 0.001$) and sPAP (r between −0.672 and −0.788, all $P < 0.001$) throughout the cardiac cycle (*Figure 5* and *Table S6*). Likewise moderate to strong correlations were noted with total pulmonary vascular resistance (r between −0.369 to −0.700, all $P < 0.05$, *Table S6*). In addition, SC at moderate exercise intensity also correlated with P/Q slope at end-diastole and mitral valve opening (r − 0.402 and r − 0.409, respectively, both $P < 0.01$) but not at end systole (r − 0.160). Finally, at end systole, SC correlated (r 0.679 at rest, r 0.641 at moderate exercise, both $P < 0.001$; *Figure S5*) with a surrogate of the interventricular pressure gradient (the delta of systolic blood pressure and systolic pulmonary artery pressures, i.e. sBP–PAP). Because we did not measure PAWP during the XMR protocol, similar analyses could not be obtained with other potential surrogates at end-diastole (pulmonary arterial wedge pressure, RAP) or at mitral valve opening (sPAP, pulmonary arterial wedge pressure).

Discussion

Using exercise CMR imaging, we evaluated the effects of exercise and breathing on ventricular interdependence in healthy controls and HFpEF and CTEPH patients. We demonstrate that ventricular interaction differs across the three groups and is influenced by exercise and respiration. Specifically, exercise enhanced adverse right–left ventricular interactions in CTEPH patients and had a more limited effect in HFpEF patients with isolated post-capillary PH and no effect in controls subjects. Inspiration enhanced diastolic right–left

Figure 2 Global ventricular volume and RV/LV volume ratio. Relative change in biventricular volume from rest to moderate exercise intensity and evolution of RV/LV volume ratio during exercise in controls and CTEPH and HFpEF patients. Data presented as Tukey boxplots or as mean ± SEM. Interaction *P*-value between exercise and subject group. Coloured *P*-value denotes main effect of exercise. $^{*,\dagger}P < 0.05$ Bonferroni post hoc to controls and HFpEF, respectively.



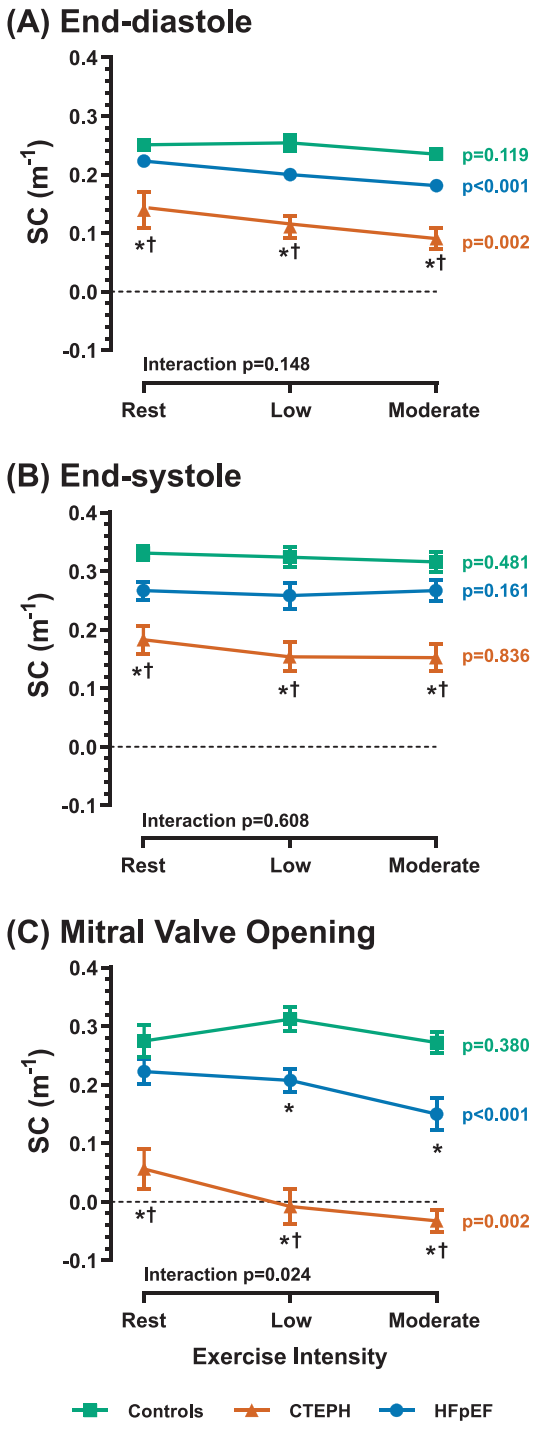
interactions, particularly in CTEPH and HFpEF patients. Finally, associations were noted between SC and RV volumes or pulmonary artery pressures, both at rest and during exercise, suggesting that non-invasive evaluation of ventricular interdependence with exCMR might be attractive in the evaluation of treatments lowering right ventricular afterload or those specifically targeting adverse ventricular interdependence.

Influence of exercise on ventricular interdependence

Ventricular interdependence is an undervalued feature of both pulmonary vascular disease and heart failure and generally only assessed at rest.[3,4,11–13] In the current study, we therefore examined ventricular interdependence during exercise in CTEPH and HFpEF patients while comparing with healthy control subjects. In CTEPH patients, we observed a strong increase in ventricular interdependence during exercise, whereas a more modest effect was observed in HFpEF patients. In contrast, SC remained largely unchanged in controls. The disparity between the groups is most likely explained by the differences in RV afterload during exercise. Pulmonary artery pressures are flow dependent but increase disproportionally in those with pulmonary vascular disease or heart failure.[14] In pulmonary hypertension, the heightened RV afterload prolongs RV contraction and results in an interventricular relaxation dyssynchrony causing a rapid left-to-right septal motion in early LV diastole.[15–17] The magnitude of the septal shift correlates with invasive haemodynamics and has shown to be marker of disease severity.[18,19] Hence, the increased early diastolic septal shift observed in our CTEPH cohort during exercise can be interpreted as a sign of worsening relaxation dyssynchrony. Similarly, also in HFpEF patients, the most profound differences with controls were observed at early diastole and potentially hint to the presence of some form of relaxation dyssynchrony during exercise in HFpEF subjects as well. Although still fairly limited in our cohort, relaxation dyssynchrony could become more important in those with combined pre-capillary and post-capillary pulmonary hypertension (CpC-PH) and thus might contribute, along with heightened right-sided congestion, to the increased ventricular interdependence and impaired RV reserve observed in this subtype.[20]

In addition to prolonged RV contraction, also diastolic pericardial constraint appears to have contributed to the observed differences in CTEPH patients. But the pericardium is capable of adapting chronically, acute ventricular volume changes, such as occur during exercise or acute volume overload, leading to a swift increase in pericardial restraint once the critical inflection point of the pericardial stress–strain relationship is surpassed.[21,22] In both CTEPH and HFpEF patients, RV volumes increased with exercise, but only in CTEPH patients, LV volumes declined. As RV stroke volume remained unchanged with exercise, the decline in LV volumes is a manifestation of increased diastolic ventricular interdependence, which corresponds with the significantly lower SC observed in CTEPH patients at ED. In contrast, in our HFpEF cohort, the small increase in RV volumes during exercise was not accompanied by a decline in LV volumes and resulted in only small changes in the RV/LV volume ratio and the end-diastolic SC with exercise. This is in keeping with a study by Parasuraman *et al*. who also did not observe a decline in LV volumes in HFpEF patients during exercise and corroborates earlier reports that pericardial restraint likely plays only a minor role in non-obese HFpEF patients with isolated

Figure 3 Effect of exercise on ventricular interaction. Evolution of average (expiration and inspiration combined) SC with exercise at (A) end-diastole, (B) end-systole, and (C) mitral valve opening in controls and CTEPH and HFpEF patients. Data presented as mean ± SEM. Interaction *P*-value between exercise and subject group. Coloured *P*-value denotes main effect of exercise $^{*,\dagger}P < 0.05$ Bonferroni post hoc to controls and HFpEF, respectively.



post-capillary PH.[20,23,24] In contrast, reports by Gorter *et al.* and Obokata *et al.* demonstrated that adverse ventricular interdependence does contribute to blunted cardiac output augmentation in HFpEF patients with combined pre-capillary and post-capillary PH and in those with an obesity-related HFpEF phenotype (BMI $>$ 35 kg.m^{-2}).[20,24] Thus, our results confirm that diastolic pericardial restraint is not universal in HFpEF, exemplifying the substantial pathophysiological heterogeneity of the disease.

Inspiration enhances diastolic interaction during exercise

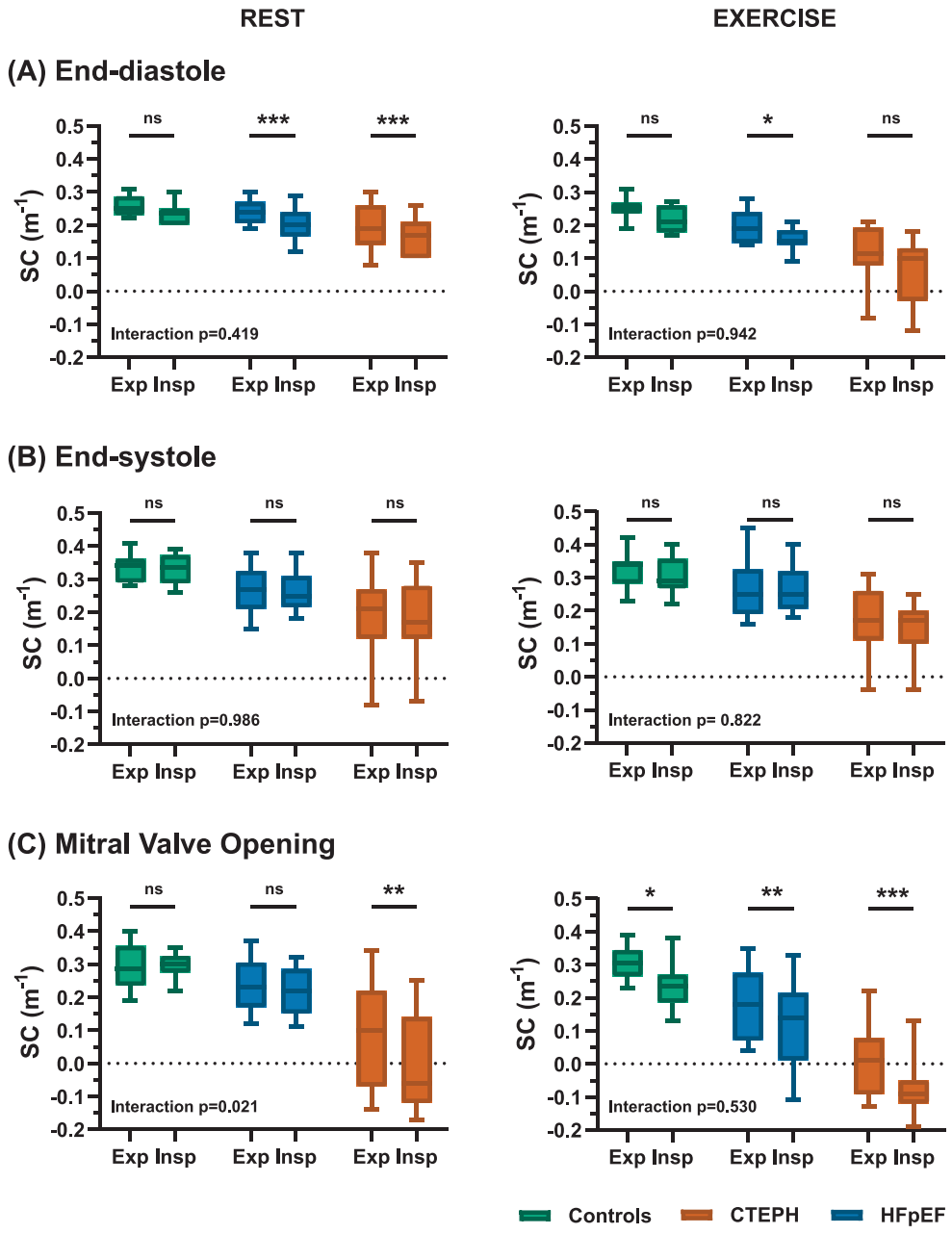
During exercise, venous return to the heart is augmented by venoconstriction and activation of the skeletal muscle and the abdominothoracic pumps. During inspiration, the decrease in intrathoracic pressure is transmitted to the heart and is known to augment right heart filling. Previously, we have demonstrated in healthy subjects that the reciprocal effects of respiration on LV and RV volumes persist during exercise.[25] In the current study, we expand upon these findings and examine the dynamic nature of respiration on ventricular interdependence during exercise in CTEPH and HFpEF patients. In general, inspiration had a similar effect on SC in the different groups and the associated increased venous return to the right heart enhanced early and to a lesser extent also late diastolic interaction during exercise. The observed effect was small and most pronounced in CTEPH and HFpEF patients, again signalling increased ventricular interdependence compared with controls.

Ventricular interdependence as therapeutic target?

Although contemporary PH treatment mainly targets RV afterload, it has been speculated that strategies aimed at mitigating the deleterious consequences of increased afterload on cardiac function (e.g. adverse ventricular interdependence) might confer additional benefit. For instance, small proof-of-concept studies have suggested that cardiac pacing might counter adverse ventricular interdependence in patients with pulmonary hypertension.[26–29] Whether this then also improves patient outcome remains to be proven, but the substantial increase in ventricular interdependence during exercise suggests, at least in theory, that this may merit further consideration as an ancillary treatment.

Likewise, also in heart failure, ventricular interdependence is increasingly considered as a potential therapeutic target. Borlaug *et al.* demonstrated that limited pericardiotomy attenuates the increase in LV filling pressure that develops

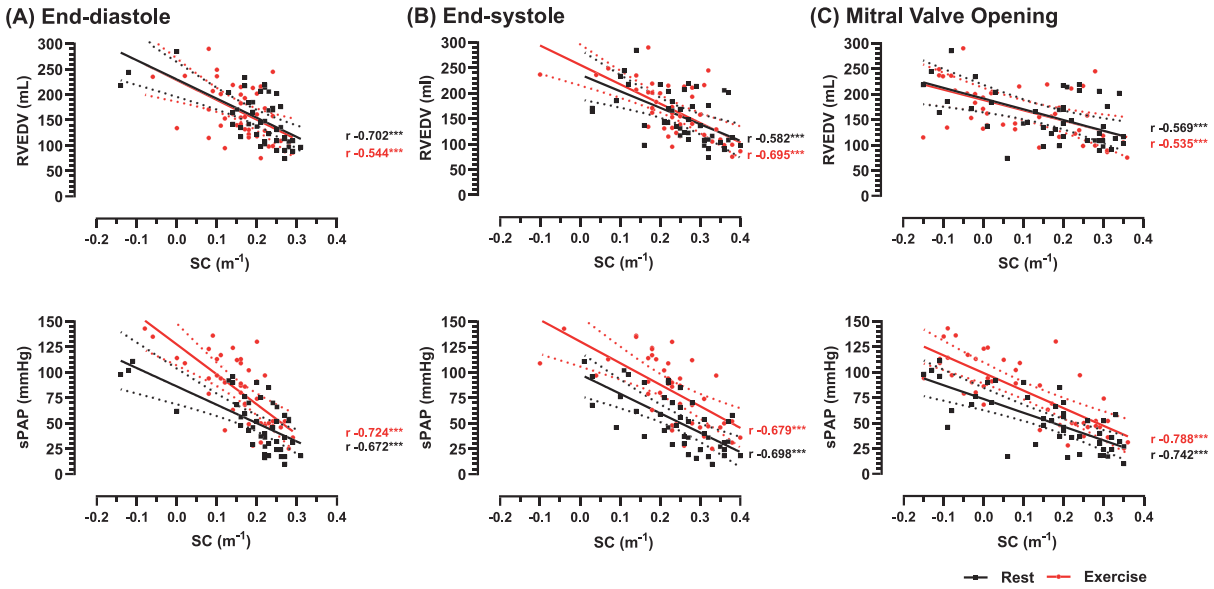
Figure 4 Effect of respiration on ventricular interaction. Tukey boxplots showing the effect of respiration on SC both at rest (left) and during moderate exercise intensity (right) at (A) end-diastole, (B) end-systole, and (C) early-diastole in controls and CTEPH and HFpEF patients. Interaction p-value denotes the interaction between respiration and subject group. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ Bonferroni post hoc for comparison between expiration (exp) and inspiration (insp).



during acute volume loading.[5,30] From our results, it would appear unlikely that the limited increase in ventricular interaction we observed in our cohort of HFpEF patients with isolated post-capillary pulmonary hypertension would be sufficient for a substantial haemodynamic benefit during exercise. However, in other HFpEF subtypes with more pronounced interdependence such as obesity-related HFpEF and certainly those with associated pre-capillary pulmonary vascular disease (i.e. combined post-capillary and pre-capillary pulmonary hypertension), the potential benefit might be larger than suggested by our data.[20,24] The strong link between SC and exercise haemodynamics certainly provides a rationale for patient selection based on exercise imaging. Given its gold-standard accuracy and feasibility, exercise

DOI: 10.1002/ehf2.14216

Figure 5 Association between ventricular interaction, RV end-diastolic volume, and haemodynamics at rest and at moderate exercise intensity in all subjects. Pearson correlation of average (expiration and inspiration combined) SC at rest and during moderate exercise intensity with RV end-diastolic volume (left), systolic pulmonary artery pressure (middle), and right atrial pressure (right) at (A) end-diastole, (B) end-systole, and (C) early-diastole. $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$.



CMR imaging would appear particularly attractive in this regard.

Limitations

Firstly, the small sample size increases the probability for Type II statistical errors and multiple comparisons increase the likelihood of Type I errors. Nevertheless, the accuracy of our exercise CMR method enables evaluation of relevant differences with high statistical significance despite the modest cohort size. Secondly, HFpEF patients were older than both other groups, which might have impacted the exercise response. However, there was no difference in SC between the youngest and oldest HFpEF tertile and integration of age as a covariate in the model did not alter the relation between the predictor and outcome variables (see *Table S5*). Thirdly, because we retained maximal clinical feasibility, we opted to analyse ventricular interaction from a single mid-ventricular slice, instead of considering the full septal shape. This could have lowered sensitivity for mild or more complex septal motion patterns. Moreover, because the intraventricular septum is not necessarily a perfect circular arc with a single radius of curvature, SC may vary depending on the local geometry and the measured length of arc, and thus, its relation to ventricular interdependence is inevitably confounded by a certain amount of error, bias, or variability. Fourthly, the limitation in temporal resolution did not allow evaluation of ventricular interdependence at higher heart rate and workloads. Nonetheless, as pulmonary pressures increase nearly linearly with cardiac output, the observed effects would be even more pronounced at peak exercise. Finally, as we did not perform biventricular pressure measurements, we cannot relate our findings to the timing and magnitude of the interventricular pressure gradient.

Conclusions

Exercise enhances adverse right–left ventricular interactions in pre-capillary pulmonary hypertension, although only a modest effect is observed in isolated post-capillary HFpEF. Inspiration further enhances diastolic ventricular interdependence, particularly in HFpEF and CTEPH patients. Given the strong link between SC and RV volumes or pulmonary haemodynamics, assessing ventricular interaction with exercise imaging might be valuable from a diagnostic or therapeutic perspective.

Conflict of interest

MC: none; TP: none; JB: none; ALG has received grants from the Fund for Scientific Research Flanders (FWO) and from the National Health and Medical Research Council (NHMRC) of Australia; JL: none; MD received fees as speaker, investigator, consultant, or steering committee member for Actelion, Bayer, Bellarophon, Eli Lilly, GlaxoSmithKline, MSD, Pfizer,

and Reata; and a research grant from Actelion; RW is supported as a postdoctoral clinical researcher by the Fund for Scientific Research Flanders (FWO); GC is supported by a postdoctoral research grant from the Frans Van De Werf Fund for Clinical Cardiovascular Research by the UZ Leuven Future Fund and by a Mathilde Horlait-Dapsens Scholarship; PC: none.

Funding

This study was funded by a grant (Project G.0465.10N) from the Research Foundation Flanders (FWO), Brussels, Belgium.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Observer variability for echocardiographic measures

Table S2. Average Septal Curvature (expiration + inspiration)

Table S3. Expiratory Septal Curvature

Table S4. Inspiratory Septal Curvature

Table S5. Average septal curvature in HFpEF patients according to age tertile and effect of age as covariate on average septal curvature during exercise.

Table S6. Pearson correlations of SC with volumes and hemodynamics.

Figure S1. exCMR setup and ventricular volume analysis.

Figure S2. Ventricular volumes and cardiac function at rest and during exercise.

Figure S3. Evolution of septal curvature across the cardiac cycle.

Figure S4. Effect of exercise on Eccentricity Index and RVLV ratio

Figure S5. Association between ventricular interaction and the approximated end-systolic interventricular pressure gradient at rest and at moderate exercise intensity in all subjects.

References

1. Santamore WP, Dell'Italia LJ. Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. *Prog Cardiovasc Dis*. 1998; **40**: 289–308.
2. Friedberg MK. Imaging right-left ventricular interactions. *JACC Cardiovasc Imaging*. 2018; **11**: 755–771.
3. Naeije R, Badagliacca R. The overloaded right heart and ventricular interdependence. *Cardiovasc Res*. 2017; **113**: 1474–1485.
4. Borlaug BA, Reddy YNV. The role of the pericardium in heart failure: implications for pathophysiology and treatment. *JACC Heart Fail*. 2019; **7**: 574–585.
5. Borlaug BA, Carter RE, Melenovsky V, DeSimone CV, Gaba P, Killu A, Naksuk N, Lerman L, Asirvatham SJ. Percutaneous pericardial resection: a novel potential treatment for heart failure with preserved ejection fraction. *Circ Heart Fail*. 2017; **10**: e003612.
6. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014; **11**: 507–515.
7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016; **37**: 2129–2200.
8. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016; **37**: 67–119.
9. La Gerche A, Claessen G, Van de Bruaene A, Pattyn N, Van Cleemput J, Gewillig M, Bogaert J, Dymarkowski S, Claus P, Heidbuchel H. Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise. *Circ Cardiovasc Imaging*. 2013; **6**: 329–338.
10. Tyberg JV, Taichman GC, Smith ER, Douglas NW, Smiseth OA, Keon WJ. The relationship between pericardial pressure and right atrial pressure: an intraoperative study. *Circulation*. 1986; **73**: 428–432.
11. Janicki JS. Influence of the pericardium and ventricular interdependence on left ventricular diastolic and systolic function in patients with heart failure. *Circulation*. 1990; **81**: III15–III20.
12. Louie EK, Lin SS, Reynertson SI, Brundage BH, Levitsky S, Rich S. Pressure and volume loading of the right ventricle have opposite effects on left ventricular ejection fraction. *Circulation*. 1995; **92**: 819–824.
13. Kanazawa M, Shirato K, Ishikawa K, Nakajima T, Haneda T, Takishima T. The effect of pericardium on the end-systolic pressure-segment length relationship in canine left ventricle in acute volume overload. *Circulation*. 1983; **68**: 1290–1298.
14. Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R, Rubenfire M. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation*. 2013; **128**: 1470–1479.
15. Gillebert TC, Sys SU, Brutsaert DL. Influence of loading patterns on peak length-tension relation and on relaxation in cardiac muscle. *J Am Coll Cardiol*. 1989; **13**: 483–490.
16. Marcus JT, Gan CT-J, Zwanenburg JJM, Boonstra A, Allaart CP, Götte MJW, Vonk-Noordegraaf A. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am Coll Cardiol*. 2008; **51**: 750–757.
17. Palau-Caballero G, Walmsley J, Van Empel V, Lumens J, Delhaas T. Why septal motion is a marker of right ventricu-

lar failure in pulmonary arterial hypertension: mechanistic analysis using a computer model. *Am J Physiol Heart Circ Physiol*. 2017; **312**: H691–H700.
18. Pandya B, Quail MA, Steeden JA, McKee A, Odille F, Taylor AM, Schulze-Neick I, Derrick G, Moledina S, Muthurangu V. Real-time magnetic resonance assessment of septal curvature accurately tracks acute hemodynamic changes in pediatric pulmonary hypertension. *Circ Cardiovasc Imaging*. 2014; **7**: 706–713.
19. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, Ettinger NA, Hill NS, Summer WR, de Boisblanc B, Schwartz T, Koch G, Clayton LM, Jöbsis MM, Crow JW, Long W. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol*. 2002; **39**: 1214–1219.
20. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *Eur Heart J*. 2018; **39**: 2825–2835.
21. Freeman GL, LeWinter MM. Pericardial adaptations during chronic cardiac dilation in dogs. *Circ Res*. 1984; **54**: 294–300.
22. Applegate RJ, Johnston WE, Vinten-Johansen J, Klopfenstein HS, Little WC. Restraining effect of intact pericardium during acute volume loading. *Am J Physiol*. 1992; **262**: H1725–H1733.
23. Parasuraman SK, Loudon BL, Crystal L, Cameron D, Singh S, Schwarz K, Gollop ND, Rudd A, McKiddie F, Phillips JJ, Prasad SK, Wilson AM, Sen-Chowdhry S, Clark A, Vassiliou VS, Dawson DK, Frenneaux MP. Diastolic ventricular interaction in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2019; **8**: e010114.
24. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017; **136**: 6–19.
25. Claessen G, Claus P, Delcroix M, Bogaert J, La Gerche A, Heidbuchel H. Interaction between respiration and right versus left ventricular volumes at rest and during exercise: a real-time cardiac magnetic resonance study. *Am J Physiol Heart Circ Physiol*. 2014; **306**: H816–H824.
26. Lumens J, Arts T, Broers B, Boomars KA, van Paassen P, Prinzen FW, Delhaas T. Right ventricular free wall pacing improves cardiac pump function in severe pulmonary arterial hypertension: a computer simulation analysis. *Am J Physiol Heart Circ Physiol*. 2009; **297**: H2196–H2205.
27. Handoko ML, Lamberts RR, Redout EM, de Man FS, Boer C, Simonides WS, Paulus WJ, Westerhof N, Allaart CP, Vonk-Noordegraaf A. Right ventricular pacing improves right heart function in experimental pulmonary arterial hypertension: a study in the isolated heart. *Am J Physiol Heart Circ Physiol*. 2009; **297**: H1752–H1759.
28. Hardziyenka M, Surie S, de Groot JR, de Bruin-Bon HACMR, Knops RE, Remmelink M, Yong ZY, Baan J Jr, Bouma BJ, Bresser P, Tan HL. Right ventricular pacing improves haemodynamics in right ventricular failure from pressure overload: an open observational proof-of-principle study in patients with chronic thromboembolic pulmonary hypertension. *Europace*. 2011; **13**: 1753–1759.
29. Janoušek J, Kovanda J, Ložek M, Tomek V, Vojtovič P, Gebauer R, Kubuš P, Krejčíř M, Lumens J, Delhaas T, Prinzen F. Pulmonary right ventricular resynchronization in congenital heart disease: Acute improvement in right ventricular mechanics and contraction efficiency. *Circ Cardiovasc Imaging*. 2017; **10**: e006424.
30. Borlaug BA, Schaff HV, Pochettino A, Pedrotty DM, Asirvatham SJ, Abel MD, Carter RE, Mauermann WJ. Pericardiotomy enhances left ventricular diastolic reserve with volume loading in humans. *Circulation*. 2018; **138**: 2295–2297.