MRI feature tracking strain in pulmonary hypertension: utility of combined left atrial volumetric and deformation assessment in distinguishing post- from pre-capillary physiology

Kai'En Leong (✉ leongkaien@gmail.com)

Imperial College Healthcare NHS Trust <https://orcid.org/0000-0001-5556-9825>

Luke Howard

Imperial College Healthcare NHS Trust

Francesco Lo Guidice

Imperial College Healthcare NHS Trust

Holly Pavey

University of Cambridge

Rachel Davies

Imperial College Healthcare NHS Trust

Gulammehdi Haji

Imperial College Healthcare NHS Trust

Simon Gibbs

Imperial College London

Deepa Gopalan

Imperial College Healthcare NHS Trust

Research Article

Keywords: Left atrial strain, pulmonary hypertension, pre-capillary, post-capillary, feature tracking, MRI

Posted Date: July 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-693423/v1>

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Version of Record: A version of this preprint was published at Frontiers in Cardiovascular Medicine on March 17th, 2022. See the published version at <https://doi.org/10.3389/fcvm.2022.787656>.

Abstract

Aims

Pulmonary hypertension (PH) is dichotomized into pre- and post-capillary physiology by invasive catheterization. Imaging, particularly strain assessment, may aid in classification and be helpful with ambiguous haemodynamics.

We sought to define cardiac MRI (CMR) feature tracking biatrial peak reservoir and biventricular peak systolic strain in pre- and post-capillary PH and examine the performance of peak left atrial strain in distinguishing the 2 groups compared to TTE.

Methods and results

Retrospective cross-sectional study from 1 Jan 2015 to 31 Dec 2020; 48 patients (22 pre- and 26 post-capillary) were included with contemporaneous TTE, CMR and catheterization. Mean pulmonary artery pressures were higher in the pre-capillary cohort (55 ± 14 mmHg vs 42 ± 9 mmHg; $p < 0.001$) as was pulmonary vascular resistance (median 11.7 WU vs 3.7 WU; $p < 0.001$). Post-capillary patients had significantly larger left atria (60 ± 22 ml/m² vs 25 ± 9 ml/m²; $p < 0.001$). There was no difference in right atrial volumes between groups (60 ± 21 ml/m² vs 61 ± 29 ml/m²; $p = 0.694$), however peak RA strain was lower in post-capillary PH patients ($8.9 \pm 5.5\%$ vs $18.8 \pm 7.0\%$; $p < 0.001$). In the post-capillary group, there was commensurately severe peak strain impairment in both atria (LA strain $9.0 \pm 5.8\%$, RA strain $8.9 \pm 5.5\%$). CMR LAVi and peak LA strain had a multivariate AUC of 0.98 (95% CI 0.89-1.00; $p < 0.001$) for post-capillary PH diagnosis which was superior to TTE.

Conclusion

CMR volumetric and deformation assessment of the left atrium can highly accurately distinguish post- from pre-capillary PH.

Introduction

Pulmonary hypertension (PH) is a haemodynamic diagnosis with diverse aetiologies and variable prognoses [1]. Dichotomisation into pre- and post-capillary physiology is based on left ventricular (LV) filling pressures (mean pulmonary arterial wedge pressure/mPAWP). Consequently, right heart catheterization remains the reference standard [1].

Pre-capillary (mPAWP ≤ 15 mmHg) PH encompasses most of the WHO classification groups (1, 3, 4 and 5) while post-capillary PH (mPAWP > 15 mmHg) relates to left heart disease (group 2) [1–3].

With post-capillary PH (particularly heart failure with preserved ejection fraction/HFpEF patients), diagnostic ambiguity may arise during catheterization. Chronic mPAWP elevation may cause fragmentation/fibrosis of the alveolar-capillary interface with resultant pulmonary vascular resistance

(PVR) increment [4, 5]. Diuresis may pseudo-normalise prior mPAWP elevation causing misdiagnosis of pre-capillary PH. This hemodynamic scenario may be clarified by the diastolic pressure gradient (DPG; diastolic pulmonary artery pressure/PAP – mPAWP) and is valuable in being less preload sensitive, thus identifying pulmonary vascular remodelling in post-capillary PH [6]. A DPG cut-point of < 7 mmHg identifies 'isolated post-capillary PH' and an elevated DPG indicates 'mixed pre/post-capillary PH' and is associated with increased mortality [5, 6].

Guidelines [1] have suggested clinical, echocardiographic (TTE) and ECG features that increase pre-catheterisation suspicion for post-capillary PH. However, these are inadequately sensitive/specific, prompting development of additional imaging parameters to enhance discrimination. With TTE, Scalia and colleagues [7] proposed ePLAR (ratio of TR Vmax to E/medial e') and Venkateshvaran et al [8] described ePLAGS (ratio of TR Vmax to peak LA strain) with high predictive ability. A single parameter of cardiac MRI (CMR) assessed LAVi < 43 ml/m² has been shown to have excellent performance in distinguishing IPAHA from HFpEF [9]. With non-gated CT, reduced LA size with a trans-axial LA/RA ratio < 0.7 identified pre-capillary PH from HFpEF patients [10].

Contemporarily, interest in deformation imaging has increased with strain assessment offering additive diagnostic and prognostic value in various pathologies [11, 12]. However, most data relate to the echocardiographic speckle tracking technique, although CMR feature tracking (FT) strain appears reasonably concordant [13]. Reduced peak LA reservoir strain has been shown to have superior correlation with elevated LV filling pressures over standard parameters like E/e' and LAVi [14–16]. Accordingly, with pre- and post-capillary dichotomisation contingent on invasive mPAWP measurement, it is plausible that LA strain may be the optimal imaging surrogate.

Importantly, left and right atrial deformation has mainly been examined separately and the pattern of biatrial impairment in pre- versus post-capillary PH is poorly defined.

We sought to characterise CMR FT biatrial peak reservoir and biventricular peak systolic strain in pre- and post-capillary PH patients and examine the performance of peak LA strain in distinguishing the 2 groups compared to other discriminatory parameters [7, 9].

Methods

Patients

This was a retrospective cross-sectional study with all patients referred for PH assessment to a single high volume PH centre between 1 Jan 2015 and 31 Dec 2020 screened for eligibility. Only consecutive patients who had all investigations (CMR, TTE and catheterization) performed by our service were included. Patients were excluded if any of the 3 tests were performed prior to referral and not repeated by us. Medical records were reviewed to determine PH classification groups according to current guidelines [1], atrial fibrillation (AF) history and all cause deaths during the period of analysis.

This study has been approved by the Heath Research Authority (HRA) and NHS Research Ethics Service (REC) (IRAS ID 280472/Protocol 20HH5838) with waivers of informed consent due to the retrospective design.

Right heart catheterization

Patients were allowed only oral clear fluids prior to catheterization. Vascular access was via right internal jugular (ultrasound-guided) or occasionally right antecubital venous puncture. A Swan-Ganz catheter was used for all pressure measurements (mean of 3 readings recorded in sinus rhythm or 5 in AF). PAWP tracings were obtained in end-expiration. Cardiac output (CO) measurements were made using the thermodilution or Fick method. PVR (Wood units/WU) was calculated by $(\text{mPAP} - \text{mPAWP}) \div \text{CO}$.

Hemodynamic definitions

Patients were classified as having pre-capillary PH if their invasive mPAP was ≥ 25 mmHg and mPAWP ≤ 15 mmHg. A designation of post-capillary PH was applied if the mPAWP was > 15 mmHg [1]. Amongst post-capillary PH patients, 'isolated post-capillary PH' was diagnosed if the DPG was < 7 mmHg $\pm$ PVR ≤ 3 WU and 'mixed pre/post-capillary PH' if the DPG was ≥ 7 mmHg $\pm$ PVR > 3 WU [1, 5].

TTE and ePLAR

All patients had Doppler parameters and left atrial volume (LAV) measured in accordance with current guidelines [17]. ePLAR was selected as the echocardiographic comparator due to its integration of multiple Doppler estimates of hemodynamic parameters and was calculated as described: $\text{ePLAR} = \text{TR Vmax} \div \text{E/medial e'}$ [7].

Reduced medial (but preserved lateral) mitral annular e' velocities may be observed in pre-capillary PH [18] and can cause incorrect conclusion of raised LV filling pressures when the E/e' parameter is computed using the medial e' velocity. As such, guidelines propose utilisation of E/lateral e' for estimation of LV filling pressures in pre-capillary PH [19]. Accordingly, we calculated additional 'ePLAR variants' using the lateral e' velocity ($\text{TR Vmax} \div \text{E/lateral e'}$) and the average (medial and lateral) E/e' ($\text{TR Vmax} \div \text{average E/e'}$).

CMR

All patients underwent comprehensive CMR on a 1.5T Siemens Aera scanner (Erlangen, Germany) using a 32 channel phased array surface coil as part of routine care. Cine imaging was performed with breath-held steady state free precession sequences to derive contiguous parallel short axis slices of both ventricles from base to apex, as well as standard long axis slices of the heart. Slice prescription parameters were 8mm thickness/2mm gap for short axis imaging with 1.5-2 mm in-plane spatial resolution, and 33–45 msec temporal resolution with 25–30 reconstructed cardiac phases.

CMR post processing and FT strain

CMR studies were analysed using Circle Cardiovascular Imaging (CVI42, version 5.12.1, Calgary, Canada). Volumetric analysis was performed as per guidelines [20].

Myocardial and atrial deformation FT was also performed using CVI42 (Fig. 1). Chamber endo- and epicardial borders were traced at ventricular end-diastole to define strain zero baseline (R-R gating) and strain quantification was performed automatically by the software using a deformable myocardial model [13, 21–23].

3 repeat measurements of peak biatrial reservoir and peak systolic biventricular global longitudinal strain (GLS) were performed, and the average recorded.

10 patients were randomly selected for strain measurement by a second investigator (DG) to assess inter-observer variability. Intra-observer variability was assessed with one investigator (KL) re-measuring atrial and ventricular strain after 1 month.

Statistical analysis

Continuous normal data are presented as mean ($\pm$ 1 standard deviation). Non-normal data are presented as median (inter-quartile range). Continuous data was compared with the two tailed Student's t test or Mann Whitney U test for normal and non-normal data respectively. Categorical variables are displayed as n (%) and differences assessed using Fisher's exact test. Intraclass correlation coefficient (ICC) estimates and their 95% confidence intervals for inter- and intra-observer variability in strain assessment were calculated. Correlation analysis was performed using Pearson correlation coefficient or Spearman rank test where data was non-normal. TTE and CMR measurement of LAV was compared with Bland-Altman analysis. Univariate and multivariate stepwise logistic regression was performed to identify variables that identified post- from pre-capillary PH. Receiver operating characteristic (ROC) curves with area under the curve (AUC) values were used to compare discriminative ability of the various parameters and the optimal cut-points were defined by the Youden index. Univariate and multivariate logistic regression models were also fitted to assess the effect of RVEDVi, RVESVi, RVEF, RV GLS, RAVi, peak RA strain, LVEDVi, LVESVi, LVEF, LV GLS, LAVi and peak LA strain on mortality. Pre-specified confounding variables included age, gender, body surface area and AF history. A p-value of ≤ 0.05 was considered statistically significant.

Results

CMR FT strain reproducibility

Measurement of FT biatrial and biventricular strain was feasible in all patients. There was excellent inter- and intra-observer agreement. Intra-observer (KL) ICC for the RA, LA, RV and LV were 0.99 (0.97-1.0), 1.0 (0.99-1.0), 0.99 (0.95-1.0) and 0.97 (0.87–0.99) respectively.

Inter-observer (DG, KL) ICC were 0.98 for RA (0.90–0.99), 1.0 for LA (0.98-1.0), 0.99 for RV (0.96-1.0) and 0.97 for LV (0.88–0.99).

Patient characteristics

A total of 48 patients were included (22 pre- and 26 post-capillary). Pre-capillary PH patients were mainly female and younger, with lower BMI and preserved renal function. Only 1 pre-capillary PH patient had an AF history compared to 20 (77%) post-capillary patients ($p < 0.001$) (Table 1).

Table 1

– Baseline patient characteristics. Abbreviations: PAH, pulmonary arterial hypertension; CTD, connective tissue disease; HIV, human immunodeficiency virus; CHD, congenital heart disease; SD, systolic dysfunction (LVEF $< 50\%$); DD, diastolic dysfunction.

	Pre-capillary (n = 22)	Post-capillary (n = 26)	p-value
Age (years)	48 $\pm$ 17	71 $\pm$ 11	< 0.001
Sex (%)	Male 6 (27%) Female 16 (73%)	Male 12 (46%) Female 14 (54%)	0.237
BMI (kg/m ²)	27.5 $\pm$ 7.4	33.1 $\pm$ 7.4	0.009
Serum creatinine (μ mol/L)	77 $\pm$ 15	114 $\pm$ 74	0.007
AF at TTE (%)	0	15 (58%)	< 0.001
Any history of documented AF (%)	1 (5%)	20 (77%)	< 0.001
Clinical classification	Idiopathic PAH – 14 (64%) Heritable PAH – 1 (5%) CTD associated PAH – 4 (18%) HIV associated PAH – 1 (5%) CHD associated PAH – 2 (9%)	SD – 1 (4%) DD – 25 (96%)	-
Deceased	7 (32%)	0	0.002
Catheterization-CMR interval (days)	3 (1–63)	1 (0–7)	0.154
Catheterization-TTE interval (days)	33 (1–110)	36 (22–64)	0.626
TTE-CMR interval (days)	18 (1–43)	39 (22–78)	0.025

Amongst the 26 post-capillary PH patients, there were 16 with isolated post-capillary physiology (DPG < 7 mmHg) and 10 with mixed pre/post-capillary hemodynamics.

7 patients (all pre-capillary; 32%) died. All post-capillary PH patients were alive at time of analysis.

Hemodynamic findings

Mean PA pressures (mPAP) were higher in the pre-capillary cohort as was PVR. Cardiac index (CI) was similar between groups. Mean RA pressures (mRAP) were higher in post-capillary PH patients (Table 2).

Table 2
– Invasive haemodynamic parameters.

	Pre-capillary (n = 22)	Post-capillary (n = 26)	p-value
PA systolic (mmHg)	89 ± 21	65 ± 17	< 0.001
PA diastolic (mmHg)	36 ± 13	26 ± 6	0.002
mPAP (mmHg)	55 ± 14	42 ± 9	< 0.001
mPAWP (mmHg)	10 ± 3	22 ± 5	< 0.001
mRAP (mmHg)	9 ± 6	14 ± 5	0.003
PVR (Wood units)	11.7 (7.8–18.0)	3.7 (2.4–5.7)	< 0.001
Cardiac index (L/min/m ²)	2.0 (1.8–2.5)	2.1 (1.9–2.6)	0.282

Imaging findings

Echocardiography

TR Vmax was lower but transmitral E wave velocity was higher in post-capillary PH patients. ePLAR and all ePLAR variants were significantly higher in pre-capillary patients in context of greater TR Vmax and lower LV filling pressure estimates by E/e'. Lastly, TTE LAVi was smaller in the pre-capillary group (Table 3).

Table 3
– TTE parameters.

	Pre-capillary (n = 22)	Post-capillary (n = 26)	p-value
TR Vmax (m/s)	4.2 ± 0.8	3.7 ± 0.5	0.009
Transmitral E (cm/s)	56 ± 19	96 ± 28	< 0.001
Medial e' (cm/s)	6 ± 2	6 ± 2	0.785
Lateral e' (cm/s)	11 ± 4	9 ± 3	0.223
E/medial e'	10.0 ± 3.9	17.9 ± 8.7	< 0.001
E/lateral e'	5.8 ± 2.7	11.1 ± 4.7	< 0.001
Average E/e'	7.9 ± 2.9	14.5 ± 6.3	< 0.001
ePLAR (E/medial e')	0.48 (0.29–0.59)	0.22 (0.17–0.34)	< 0.001
Variant ePLAR (E/lateral e')	0.79 (0.51–1.10)	0.36 (0.27–0.47)	< 0.001
Variant ePLAR (average E/e')	0.51 (0.39–0.76)	0.25 (0.21–0.37)	< 0.001
LAVi (ml/m²)	23 ± 7	45 ± 17	< 0.001

Table 4
– CMR volumetric and FT strain assessment.

	Pre-capillary (n = 22)	Post-capillary (n = 26)	p-value
LAVi (ml/m²)	25 ± 9	60 ± 22	< 0.001
Peak LA strain (%)	22.6 ± 8.4	9.0 ± 5.8	< 0.001
RAVi (ml/m²)	60 ± 21	61 ± 29	0.694
Peak RA strain (%)	18.8 ± 7.0	8.9 ± 5.5	< 0.001
LA/RA volume ratio	0.33 (0.29–0.65)	1.0 (0.83–1.30)	< 0.001
LVEDVi (ml/m²)	48 (43–54)	64 (46–73)	0.018
LVESVi (ml/m²)	17 (16–25)	22 (15–30)	0.178
LV stroke volume indexed (ml/m²)	30 (26–34)	36 (29–43)	0.006
LVEF (%)	62 (59–66)	63 (59–67)	0.656
LV GLS (%)	-13.3 ± 3.2	-13.4 ± 2.9	0.910
RVEDVi (ml/m²)	119 (97–136)	76 (69–88)	< 0.001
RVESVi (ml/m²)	82 (61–98)	39 (31–50)	< 0.001
RV stroke volume indexed (ml/m²)	39 (34–44)	38 (30–50)	0.885
RVEF (%)	35 ± 9	49 ± 9	< 0.001
RV GLS (%)	-10.1 ± 3.7	-13.7 ± 3.1	< 0.001
LVEDV/RVEDV ratio	0.44 (0.32–0.56)	0.78 (0.62–0.92)	< 0.001

CMR

Pre-capillary PH patients had smaller left atria and ventricles relative to the right. The post-capillary group had significantly larger left atria. There was no difference in RAVi between groups, however peak RA strain was lower in post-capillary patients.

Amongst post-capillary patients, there was commensurately severe biatrial impairment of peak strain (LA 9.0 ± 5.8%, RA 8.9 ± 5.5%).

All patients had preserved LVEF however longitudinal function assessed by LV GLS was similarly impaired in both groups. RVEF was more impaired in pre-capillary patients with concomitant/proportional RV GLS reduction.

7 (of 22, 32%) pre-capillary PH patients died. After adjustment for age, gender, BSA and AF history, RV GLS was the only independent imaging parameter predictor of mortality (OR 1.62 [1.15–2.64]; $p = 0.017$ vs RVEF mortality OR 1.15 [1.02–1.36]; $p = 0.051$).

Distinguishing post- from pre-capillary PH

10 parameters (4 TTE, 6 CMR) were assessed for their ability to distinguish (1) pre- from all post-capillary, (2) pre- from isolated post -capillary (DPG < 7 mmHG) and (3) pre- from mixed pre/post-capillary PH (DPG $\geq$ 7 mmHg).

Of all (TTE and CMR) parameters, CMR LAVi had the greatest AUC for all 3 hemodynamic comparisons (AUC 0.96 for pre- vs all post-capillary PH) followed by peak LA strain (AUC 0.92) (Fig. 2 & Table 5).

Table 5
– Comparison of predictive ability/AUC of 10 discriminator parameters.

	Area under the curve (95% CI)					
	Pre- vs all post-capillary PH	p-value	Pre- vs isolated post-capillary PH (DPG < 7 mmHg)	p-value	Pre- vs mixed pre/post-capillary PH (DPG ≥ 7 mmHg)	p-value
TTE						
ePLAR (E/medial e')	0.84 (0.71–0.93)	< 0.001	0.84 (0.68–0.94)	< 0.001	0.85 (0.68–0.95)	< 0.001
Variant ePLAR (E/lateral e')	0.89 (0.76–0.96)	< 0.001	0.88 (0.73–0.96)	< 0.001	0.91 (0.75–0.98)	< 0.001
Variant ePLAR (average E/e')	0.88 (0.75–0.95)	< 0.001	0.88 (0.73–0.96)	< 0.001	0.88 (0.71–0.97)	< 0.001
TTE LAVi	0.89 (0.77–0.96)	< 0.001	0.86 (0.71–0.95)	< 0.001	0.94 (0.79–0.99)	< 0.001
CMR						
Peak LA strain	0.92 (0.80–0.98)	< 0.001	0.88 (0.74–0.96)	< 0.001	0.97 (0.84–1.00)	< 0.001
CMR LAVi	0.96 (0.86–1.00)	< 0.001	0.94 (0.82–0.99)	< 0.001	0.98 (0.86–1.00)	< 0.001
LA/RA volume ratio	0.91 (0.79–0.97)	< 0.001	0.91 (0.77–0.98)	< 0.001	0.91 (0.75–0.98)	< 0.001
LVEDV/RVEDV ratio	0.87 (0.75–0.95)	< 0.001	0.94 (0.81–0.99)	< 0.001	0.78 (0.60–0.91)	0.002
RVEF	0.87 (0.74–0.95)	< 0.001	0.90 (0.75–0.97)	< 0.001	0.83 (0.65–0.94)	< 0.001
RV GLS	0.76 (0.62–0.87)	< 0.001	0.80 (0.64–0.91)	< 0.001	0.71 (0.52–0.86)	0.023

Echocardiographic parameters also had excellent, albeit smaller AUC. ePLAR (E/medial e') had the smallest AUC of all (0.84 for pre- vs all post-capillary PH) while variant ePLAR (E/lateral e') and TTE LAVi performed similarly well (AUC 0.89).

Consistent with prior data [9], a CMR LAVi of > 39 ml/m² had 85% sensitivity and 95% specificity for distinguishing post- from pre-capillary PH. Compared to CMR LAVi, a peak LA strain cut-point of < 12% had excellent sensitivity at 81% and greater specificity at 100% (Table 6). Stepwise logistic regression

showed that CMR LAVi and peak LA strain had a combined multivariate AUC of 0.98 (95% CI 0.89-1.00; $p < 0.001$) for (all) post-capillary PH diagnosis.

Table 6
– Discriminator cut-points for (all) post-capillary PH diagnosis.

Cut-point for (all) post-capillary PH diagnosis		Likelihood ratio for post-capillary PH diagnosis		Sens	Spec
		+LR	-LR		
TTE					
ePLAR (E/medial e')	≤ 0.29	2.9	0.5	65%	77%
Variant ePLAR (E/lateral e')	≤ 0.48	3.7	0.2	85%	77%
Variant ePLAR (average E/e')	≤ 0.39	4.4	0.2	81%	82%
TTE LAVi (ml/m ²)	> 25	5.1	0.1	92%	82%
CMR					
Peak LA strain (%)	< 12	-	0.2	81%	100%
CMR LAVi (ml/m ²)	> 39	18.6	0.2	85%	95%
LA/RA volume ratio	> 0.72	4.9	0.1	88%	82%
LVEDV/RVEDV ratio	> 0.56	4.4	0.2	81%	82%
RV GLS (%)	≤ -10.4	2.2	0.2	88%	59%
RVEF (%)	> 42	4.2	0.3	77%	82%

For identification of mixed pre/post-capillary PH, similar performance was seen for all parameters, with marginal differences in variant ePLAR and peak LA strain cut-points (Supplementary Table 1).

Comparison of TTE and CMR LAV

Non-indexed LAV was underestimated by TTE compared to CMR (bias $\pm$ SD; -16.5 ± 18 ml) (Fig. 3).

Correlation analysis

Both CMR LAVi (r 0.61, 95% CI 0.39–0.76; $p < 0.001$) and peak LA strain (r -0.58, 95% CI -0.75 to -0.36; $p < 0.001$) were significantly correlated with mPAWP. A similar relationship was seen for mRAP and peak RA strain (r -0.53, 95% CI -0.71 to -0.30; $p < 0.001$). There was however no association between mRAP and RAVi (r 0.001, 95% CI -0.28 to 0.29; $p = 0.993$) (Fig. 4).

Amongst post-capillary PH patients, there was a significant positive correlation between mRAP and mPAWP (r 0.57, 95% CI 0.24 to 0.79; p = 0.002) (Fig. 5) which was stronger than that observed in the pre-capillary group (r 0.50, 95% CI 0.09 to 0.76; p = 0.019). Lastly, there was no correlation between mRAP and mPAP in post-capillary patients (r 0.19, 95% CI -0.22 to 0.53; p = 0.365) (Fig. 5).

Discussion

In this work, we have shown that CMR LA volumetric and deformation assessment can accurately distinguish post- from pre-capillary PH and was superior to TTE.

TTE's predictive performance for post-capillary PH was optimised when variant ePLAR (E/lateral e') was utilised, with an augmented AUC of 0.89 compared to ePLAR (E/medial e' ; AUC 0.84).

The discriminatory ability of LAV was maximised as a CMR parameter, circumventing TTE limitations of suboptimal acoustic windows with certain body habitus. Additionally, the LA long axis plane is typically divergent from that of the LV, causing TTE volumetric underestimation without atrial-focussed imaging [24, 25].

This is also the first study to contrast biatrial and biventricular CMR FT deformation parameters in the same PH cohort. There are several notable findings.

7 pre-capillary PH patients died and after adjustment, RV GLS was the only independent predictor of mortality. In a canine PH model by PA banding, early compensation was characterised by preserved systolic but impaired RV diastolic function, and increased RA distensibility (increased reservoir strain) [26]. The latter would be counterpoise for RV diastolic dysfunction and avert clinical heart failure but with worsening PH severity/chronicity, RV-PA then RV-RA uncoupling would ensue with diminution of RA reservoir function causing symptoms [27, 28]. Strain cut-points have been proposed to accompany this trajectory of maladaptation [27, 29, 30] with RV-PA decoupling occurring at RV GLS $>$ -15.29% and later stage RV-RA decoupling corresponding to a RA reservoir strain $<$ 16%. In this cross-sectional work, pre-capillary PH patients had a mean RV GLS of -10.1% and peak RA strain of 18.8% suggesting uncoupled RV-PA but preserved RV-RA relationships and underlie our finding of lack of mortality prediction by peak RA strain.

Both pre- and post-capillary PH patients had similarly severe RA dilatation however post-capillary patients had lower RA peak strain and higher mRAP despite the similar volumes.

Tello et al [27] have shown peak RA strain to reflect RV diastolic rather than systolic function and our data would imply more pronounced RV diastolic dysfunction in post-capillary PH patients compared to the pre-capillary group.

Right ventricular diastolic dysfunction in left heart disease is poorly characterised. Independent of RVSP elevation, Yu and colleagues [31] have demonstrated similar magnitude diastolic abnormalities of trans-tricuspid inflow in HFrEF patients without PH (normal RVSP) and PH patients (LVEF $>$ 55%; mainly COPD

and valvular heart disease). This would suggest a separate/additional mechanism for RV diastolic dysfunction other than PH. Importantly, a close correlation existed between RV and LV diastolic parameters but not between RV diastolic function and LV size/systolic function.

Recent data from Patel et al [32] indicate that whilst CMR RV extracellular volume (ECV) increment was seen to a similar degree in PAH and post-capillary PH patients, a significant correlation between RV ECV and PVR was only seen in PAH patients. This would again suggest additional PH-independent mechanisms contributing to diffuse RV fibrosis in post-capillary patients.

Su et al [33] has shown significant correlation between LV diastolic dysfunction and diffuse LV myocardial fibrosis (by CMR ECV) in HFpEF. In a porcine CTEPH model [34], RV afterload elevation was associated with increased RV expression of pro-fibrotic genes. Notably, the latter was not observed in the LV, with no change in LV myocardial interstitial collagen content.

Summarily, it would appear that biventricular fibrosis is seen in post-capillary PH whereas RV fibrosis predominates in pre-capillary PH.

Our work adds further to these data. Our post-capillary cohort comprised mainly of HFpEF patients with commensurately severe biatrial peak strain reduction. As depicted in Fig. 5, mRAP was significantly correlated with mPAWP but not with mPAP in post-capillary PH patients. Post-capillary PH patients had greater reduction in RA strain than pre-capillary patients despite the latter having higher mPAP.

These observations would suggest that clinically significant RV diastolic dysfunction occurs in both pre- and post-capillary PH however in pre-capillary patients, when symptomatic, represents late stage disease (RV-RA uncoupling) following RV-PA uncoupling in the context of progressive afterload elevation [27]. Conversely in post-capillary PH, we propose that RV diastolic dysfunction is an earlier event, likely coincident with and reflective of LV diastolic dysfunction in keeping with the paradigm of ventricular interdependence [35] rather than simply reflecting transmitted pressures across the pulmonary circulation.

Both groups had similarly preserved LVEF but reduced GLS. The pathophysiology underlying this subclinical dysfunction is likely disparate between groups. In pre-capillary PH patients with higher mPAP, PVR, RV volumes and greater RV dysfunction, abnormal septal configuration and reduced LV preload are likely principal mechanisms for LV GLS impairment [36, 37]. In post-capillary PH patients, commonly older and more co-morbid, the dominant mechanism is likely diffuse myocardial fibrosis [33, 38–40].

Lastly, our data contributes to the literature regarding determination of congruence between CMR and TTE deformation assessment. Inoue and colleagues [41] showed similar findings of peak LA strain reduction in post-capillary (vs pre-capillary) PH patients using speckle tracking TTE, and proposed a comparable discriminatory peak strain cut-point.

Subsequent to this, prospective validation of the diagnostic performance of combined CMR LA volumetric and strain assessment may enhance the current PH workup algorithm. Study into the

prognostic value of CMR FT strain in PH would also be invaluable in view of present paucity of imaging prognostic markers, specifically with examination of change in deformation parameters following targeted therapy.

Conclusion

Comprehensive CMR FT deformation assessment offers additional physiologic insights in PH beyond sole volumetric evaluation and may enhance the current PH workup algorithm.

Limitations

This was a retrospective study from a single institution. The relatively small cohort size ($n = 48$) was due to exclusion of a large proportion of patients who had part of their PH workup completed externally prior to referral. There was a significant interval between all investigations, with potential for change in loading conditions with medical therapy however, this does not appear to have affected the predictive ability of assessed TTE and CMR parameters. The strength of imaging-hemodynamic correlation also was maintained and consistent with published data. Additionally, the time interval reflects real world service provision at our institution. Amongst post-capillary PH patients, there was a larger proportion with an AF history but this would be congruent with the post-capillary phenotype. With CMR FT LA strain, we acknowledge the limitation of single cardiac cycle atrial strain assessment in AF compared to averaging in TTE but again, this does not appear to have affected the predictive ability of CMR LA strain. Lastly, atrial strain was not assessed using a dedicated algorithm but rather by a ventricular algorithm from a specific vendor.

Abbreviations

AF

atrial fibrillation

CI

cardiac index

CMR

cardiac MRI

CO

cardiac output

CTEPH

chronic thromboembolic pulmonary hypertension

DPG

diastolic pressure gradient

ECV

extracellular volume

ePLAGS

echocardiographic pulmonary to left atrial global strain ratio

ePLAR

echocardiographic pulmonary to left atrial ratio

FT

feature tracking

GLS

global longitudinal strain

HFpEF

heart failure with preserved ejection fraction

HFrEF

heart failure with reduced EF

IPAH

idiopathic pulmonary arterial hypertension

LAVi

left atrial volume index

LV

left ventricle

LVEDVi

left ventricular end diastolic volume index

LVEF

left ventricular ejection fraction

LVESVi

left ventricular end systolic volume index

mPAP

mean pulmonary arterial pressure

mPAWP

mean pulmonary arterial wedge pressure

mPVR

mean pulmonary vascular resistance

mRAP

mean right atrial pressure

PA

pulmonary artery

PH

pulmonary hypertension

RAVi

right atrial volume index

RV

right ventricle

RVEDVi

right ventricular end diastolic volume index

RVEF

right ventricular ejection fraction

RVESVi

right ventricular end systolic volume index

RVSP

right ventricular systolic pressure

SVi

stroke volume index

TPG

transpulmonary gradient

TR

tricuspid regurgitation

TTE

transthoracic echocardiogram

Vmax

Doppler maximum velocity

Declarations

All authors declare no conflict of interest in relation to this manuscript. No funding has been received for this work.

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Figures

Figure 1

CMR LA volumetric and deformation assessment. Combined CMR LAVi and peak LA strain multivariate AUC 0.98 for (all) post-capillary PH diagnosis.

Cut-points for post-capillary PH diagnosis

ePLAR (E/medial e') ≤ 0.29

TTE LAVi $> 25 \text{ ml/m}^2$

Variant ePLAR (E/lateral e') ≤ 0.48

CMR peak LA strain $< 12\%$

CMR LAVi $> 39 \text{ ml/m}^2$

Figure 2

Comparison of selected TTE and CMR discriminator AUC.

Figure 3

Bland-Altman comparison of TTE and CMR non-indexed LAV. Shading represents + SD. Dotted line indicates mean bias.

Figure 4

Biatrial pressure-volumetric/strain correlation in entire cohort.

Figure 5

mRAP-mPAP and mRAP-mPAWP relationships in post-capillary PH patients.

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