Ventricular mass as a prognostic imaging biomarker in incident pulmonary arterial hypertension

To the Editor:

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature that leads to right ventricular (RV) failure and premature death. Because RV failure is the leading cause of mortality in PAH, the prognostic value of cardiac magnetic resonance (CMR) imaging, a powerful tool for assessing the RV, has been the subject of much recent investigation. Several studies have demonstrated that CMR measures of ventricular volumes and right ventricular ejection fraction (RVEF) predict mortality in PAH [1–5]. Fewer studies, however, have examined the prognostic value of ventricular mass metrics in PAH. Rajaram *et al.* [5] demonstrated significant associations between RV mass and ventricular mass index (VMI), the ratio of RV mass to left ventricular (LV) mass, and mortality in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH). LV mass has been shown to predict time to clinical worsening in idiopathic pulmonary arterial hypertension (IPAH) [6]. Small studies have shown that VMI correlates more strongly with invasive haemodynamics than does RV mass alone [7, 8], suggesting added value in a metric incorporating measures of both RV and LV mass.

Between July 2007 and September 2014, we enrolled 89 patients suspected of having PAH with the aim of investigating relationships between ventricular mass and survival in incident PAH cases. All subjects underwent CMR within 48 h of a right heart catheterisation that defined the presence or absence of PAH. CMR images were acquired and interpreted by a trained radiologist with expertise in cardiac imaging (S.L. Zimmerman) as previously described [9]. Patients found to have PAH were managed in accordance with contemporary guidelines, including prescription of pulmonary vasodilator therapies. Subjects were followed until death or the end of the study period.

CMR metrics were indexed for body surface area, and adjusted for age and sex, as previously described [3]. Relationships between mortality and clinical characteristics, haemodynamics, and CMR metrics were assessed with univariable Cox proportional hazard (CPH) models. CMR variables were scaled to $\log_{1.1}$ for comparison of hazard ratios (HRs). Variables significant in univariable analysis ($p<0.20$) and other biologically relevant variables were incorporated into separate bivariable CPH models. Collinearity was assessed with pairwise correlation and collinear variables were excluded from bivariable models. A p-value <0.05 was considered statistically significant.

Of the 89 subjects enrolled, 64 met diagnostic criteria for PAH and were included in the analytic cohort. 42 were classified as having CTD-PAH (with 40 having scleroderma-related PAH) and 22 were judged to have IPAH. Subjects were mean±SD 57±11 years of age and mostly female (91%) with CTD-PAH (66%). The only statistically significant difference in CMR metrics between disease subtypes was a higher mean left ventricular end-diastolic mass index (LVEDMI) in subjects with CTD-PAH (96±28%predicted) compared with IPAH (79±17%predicted) ($p<0.05$). Mean RV mass index did not differ significantly in IPAH (113±72% predicted) *versus* CTD-PAH (121±69% predicted). There were 30 deaths (46% mortality) over a median follow-up time of 4.2 years (interquartile range 2.4–5.5 years).

Unadjusted HRs for mortality are shown in table 1. RV and LV mass metrics, including LVEDMI, LVEDMI % predicted, right ventricular end-diastolic mass index (RVEDMI), RVEDMI % predicted and VMI, were all significantly associated with mortality. Each 10% increase in VMI was associated with 11%

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Increased right ventricular mass and VMI, the ratio of RV mass to LV mass, are predictors of mortality in incident, treatment-naive PAH. These findings challenge the notion that RV hypertrophy is adaptive in pulmonary hypertension. http://ow.ly/qzvt30ntJze

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TABLE 1 Univariable Cox proportional hazard ratios for mortality for all subjects with pulmonary arterial hypertension

Variable	HR (95% CI, p-value)	HR (95% CI, p-value) with variables scaled to $\log_{1.1}$
Clinical characteristics		
Age years	1.02 (0.99–1.06, 0.17)	
Female sex	1.18 (0.28–5.01, NS)	
Caucasian race	0.21 (0.03–1.52, 0.12)	
NYHA FC III–IV	1.11 (0.53–2.36, NS)	
6MWD m	1.00 (0.99–1.00, 0.08)	
Presence of CTD	1.79 (0.79–4.05, 0.17)	
Haemodynamics		
mPAP mmHg	1.01 (0.98–1.04, NS)	
PAWP mmHg	0.97 (0.88–1.07, NS)	
PVR Wood units	1.06 (1.00–1.13, 0.06)	
CO $L{\cdot}min^{-1}$	0.72 (0.54–0.95, <0.05)	
Cardiac index $L{\cdot}min^{-1}{\cdot}m^{-2}$	0.70 (0.41–1.19, 0.18)	
LV metrics		
LVESV mL	0.97 (0.94–0.99, <0.05)	0.90 (0.83–0.98, <0.05)
LVEDV mL	0.98 (0.97–0.99, <0.01)	0.88 (0.80–0.97, <0.05)
LVEDVI $mL{\cdot}m^{-2}$	0.98 (0.96–1.01, NS)	0.95 (0.86–1.06, NS)
LVEDVI % predicted	0.98 (0.97–1.00, 0.17)	0.94 (0.85–1.06, 0.17)
LVEDMI $g{\cdot}m^{-2}$	1.02 (1.001–1.03, <0.05)	1.15 (1.02–1.30, <0.05)
LVEDMI % predicted	1.01 (1.001–1.03, <0.05)	1.15 (1.02–1.30, <0.05)
RV metrics		
RVEDVI $mL{\cdot}m^{-2}$	1.01 (0.99–1.02, NS)	1.05 (0.93–1.17, NS)
RVEDVI % predicted	1.00 (0.99–1.01, NS)	1.07 (0.95–1.19, NS)
RVEF %	0.98 (0.95–1.005, 0.11)	0.93 (0.85–1.02, 0.11)
RVEF % predicted	0.99 (0.98–1.01, NS)	0.97 (0.88–1.06, NS)
RVESVI $mL{\cdot}m^{-2}$	1.01 (1.00–1.02, NS)	1.05 (0.98–1.12, NS)
RVESVI % predicted	1.00 (0.99–1.00, 0.06)	1.06 (0.99–1.14, 0.06)
RVEDMI $g{\cdot}m^{-2}$	1.02 (1.01–1.04, <0.01)	1.11 (1.04–1.19, <0.01)
RVEDMI % predicted	1.01 (1.003–1.01, <0.01)	1.12 (1.05–1.19, <0.01)
TAPSE mm	0.93 (0.86–0.999, <0.05)	0.93 (0.86–1.01, 0.07)
Composite metrics		
VMI	4.6 (1.44–14.7, <0.01)	1.11 (1.03–1.19, <0.01)
SV/ESV	0.24 (0.07–0.80, <0.05)	0.93 (0.87–0.99, <0.05)
SV/PP	0.65 (0.43–1.00, 0.05)	0.93 (0.87–0.99, <0.05)

HR: hazard ratio; NYHA FC: New York Heart Association functional class; 6MWD: 6-min walk distance; CTD: connective tissue disease; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; CO: cardiac output; LV: left ventricular; LVESV: left ventricular end-systolic volume; LVEDV: left ventricular end-diastolic volume; LVEDVI: left ventricular end-diastolic volume index; LVEDMI: left ventricular end-diastolic mass index; RV: right ventricular; RVEDVI: right ventricular end-diastolic volume index; RVEF: right ventricular ejection fraction; RVESVI: right ventricular end-systolic volume index; RVEDMI: right ventricular end-diastolic mass index; TAPSE: tricuspid annular plane systolic excursion; VMI: ventricular mass index; SV; stroke volume; ESV: end-systolic volume; PP: pulse pressure; NS: not significant (p>0.20).

higher mortality and each 10% increase in RVEDMI % predicted was associated with 12% higher mortality. Each 10% increase in LVEDMI % predicted was associated with 15% higher mortality.

The significance and magnitude of the relationship between RVEDMI % predicted and mortality persisted in multiple bivariable models adjusting for noncollinear covariates: age, sex, race, 6-min walk distance (6MWD), disease subtype, cardiac index, pulmonary vascular resistance (PVR), LV end-systolic volume, stroke volume (SV)/end-systolic volume (ESV), tricuspid annular plane systolic excursion (TAPSE), and SV/pulse pressure. Similarly, the significance and magnitude of the relationship between VMI and mortality also persisted with adjustment for noncollinear covariates (age, sex, race, 6MWD, disease subtype, cardiac index, PVR and TAPSE). By contrast, the relationship between LVEDMI % predicted and mortality was attenuated, and its significance was lost with adjustment for 6MWD, TAPSE and disease subtype.

Our results suggest that RV mass and VMI are candidate prognostic markers in incident PAH. While RV volumes and RVEF were not significantly associated with mortality in the overall cohort,

associations existed in a survival analysis limited to the IPAH subgroup (data not shown). This finding should be interpreted with caution due to the small size of our cohort, though the pattern aligns with previous work demonstrating differences in the prognostic significance of RV volumetrics in IPAH *versus* CTD-PAH [3].

Associations between increased RV mass and mortality call into question whether RV hypertrophy is always adaptive in PAH. If instances in which RV hypertrophy may be maladaptive were identified, RV mass metrics might offer earlier prognostic insights than RV volumes or RVEF, which are indicators of dilatation and dysfunction. RV hypertrophy typically occurs earliest in the disease course, then progresses to RV dilatation, dysfunction, and ultimately RV failure and death [10, 11]. While RV hypertrophy is generally considered adaptive in PAH, other changes, such as dilatation, are considered maladaptive, with a continuum existing between adaptive and maladaptive change [12]. We noted significant negative correlations between SV/ESV, the noninvasive estimate of RV–pulmonary artery (PA) coupling, and VMI and RVEDMI % predicted in our cohort ($r=-0.7$, $p<0.01$). RV-PA coupling reflects the RV ability to adapt to increased afterload in PAH. These negative correlations between measures of coupling and measures of RV hypertrophy provide a basis for speculation that RV hypertrophy may represent maladaptive RV remodelling in some instances.

There may be added value in incorporation of LV metrics into assessments of RV function and adaptation in PAH. Higher LV end-diastolic volumes were associated with decreased risk of mortality in our cohort, a finding also reported by Van Wolferen *et al.* [1]. It is known that in PAH, the pressure-overloaded right ventricle bows into the left ventricle due to ventricular interdependence imposed by pericardial constraint, thereby underfilling the left ventricle [13, 14]. This underfilling and unloading of the left ventricle may lead to atrophic LV remodelling over time, which may explain the observed decrease in predicted LV mass in our cohort, with mean LVEDMI 79% and 96% predicted in IPAH and CTD-PAH subgroups respectively. As a ratiometric, VMI may thus reflect a degree of RV change further along the continuum toward maladaptive change, when the left ventricle becomes impacted by RV hypertrophy and atrophic LV remodelling occurs.

Our study has several limitations. It was conducted within a single centre, with a modestly sized cohort composed of a high proportion of patients with scleroderma-associated PAH. Thus, these results should be interpreted as hypothesis generating rather than conclusive. Furthermore, there were relatively few patients with IPAH, limiting our power to detect differences between disease subtypes. Our analysis is also limited to associations with baseline CMR metrics only, as few patients within the cohort underwent follow-up CMR. Future studies are needed to examine the prognostic value of mass metrics as possible early markers of maladaptive change in larger cohorts of incident PAH patients with different disease subtypes and to assess the prognostic significance of changes in serially measured mass metrics over time.

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