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Early View

Research letter

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Ventricular Mass as a Prognostic Imaging Biomarker in Incident PAH

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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 RV 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 demonstrated significant associations between RV mass and ventricular mass index (VMI, the ratio of RV mass to left ventricular mass) and mortality in connective tissue disease-associated PAH (CTD-PAH) [5]. Left ventricular (LV) mass has been shown to predict time to clinical worsening in idiopathic PAH (IPAH) [6]. Small studies have shown that VMI correlates more strongly with invasive hemodynamics 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 hours of a right heart catheterization (RHC) 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.Z.) 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 (BSA) and adjusted for age and sex as previously described [3]. Relationships between mortality and clinical characteristics, hemodynamics, 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. Forty-two were classified as having CTD-PAH (with 40 having scleroderma related-PAH, or SSc-PAH), and 22 were judged to have IPAH. Subjects were 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 LV 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 the Table. RV and LV mass metrics, including LVEDMI, LVEDMI %predicted, RV end-diastolic mass index (RVEDMI), RVEDMI %predicted, and VMI were all significantly associated with mortality. Each 10% increase in VMI was associated with 11% 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 non-collinear covariates: age, sex, race, 6-minute walk distance (6MWD), disease subtype, cardiac index (CI), pulmonary vascular resistance (PVR), LV end-systolic volume (LVESV), stroke volume to end-systolic volume (SV/ESV), tricuspid annular plane systolic excursion (TAPSE), and stroke volume over pulse pressure (SV/PP). Similarly, the significance and magnitude of the relationship between VMI and mortality also persisted with adjustment for non-collinear covariates (age, sex, race, 6MWD, disease subtype, CI, 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-PA coupling, and VMI and RVEDMI %predicted in our cohort (r= -0.7, p<0.01). RV-PA coupling reflects the RV's 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 remodeling 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 and colleagues [1]. It is known that in PAH, the pressure-overloaded RV bows into the LV due to ventricular interdependence imposed by pericardial constraint, thereby under-filling the LV [13, 14]. This under-filling and unloading of the LV may lead to atrophic LV remodeling 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 LV becomes impacted by RV hypertrophy and atrophic LV remodeling occurs.

Our study has several limitations. It was conducted within a single center, 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. Further, 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.

References

1. van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD, Postmus PE, Vonk-Noordegraaf A: **Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension**. *European heart journal* 2007, **28**(10):1250-1257.
2. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk-Noordegraaf A: **Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy**. *Journal of the American College of Cardiology* 2011, **58**(24):2511-2519.
3. Swift AJ, Capener D, Johns C, Hamilton N, Rothman A, Elliot C, Condliffe R, Charalampopoulos A, Rajaram S, Lawrie A *et al*: **Magnetic Resonance Imaging in the Prognostic Evaluation of Patients with Pulmonary Arterial Hypertension**. *American journal of respiratory and critical care medicine* 2017, **196**(2):228-239.
4. Swift AJ, Rajaram S, Campbell MJ, Hurdman J, Thomas S, Capener D, Elliot C, Condliffe R, Wild JM, Kiely DG: **Prognostic value of cardiovascular magnetic resonance imaging measurements corrected for age and sex in idiopathic pulmonary arterial hypertension**. *Circulation Cardiovascular imaging* 2014, **7**(1):100-106.
5. Rajaram S, Swift AJ, Capener D, Elliot CA, Condliffe R, Davies C, Hill C, Hurdman J, Kidling R, Akil M *et al*: **Comparison of the diagnostic utility of cardiac magnetic resonance imaging, computed tomography, and echocardiography in assessment of suspected pulmonary arterial hypertension in patients with connective tissue disease**. *The Journal of rheumatology* 2012, **39**(6):1265-1274.
6. Yamada Y, Okuda S, Kataoka M, Tanimoto A, Tamura Y, Abe T, Okamura T, Fukuda K, Satoh T, Kuribayashi S: **Prognostic value of cardiac magnetic resonance imaging for idiopathic pulmonary arterial hypertension before initiating intravenous prostacyclin therapy**. *Circulation journal : official journal of the Japanese Circulation Society* 2012, **76**(7):1737-1743.
7. Saba TS, Foster J, Cockburn M, Cowan M, Peacock AJ: **Ventricular mass index using magnetic resonance imaging accurately estimates pulmonary artery pressure**. *The European respiratory journal* 2002, **20**(6):1519-1524.
8. Katz J, Whang J, Boxt LM, Barst RJ: **Estimation of right ventricular mass in normal subjects and in patients with primary pulmonary hypertension by nuclear magnetic resonance imaging**. *Journal of the American College of Cardiology* 1993, **21**(6):1475-1481.
9. Kelemen BW, Mathai SC, Tedford RJ, Damico RL, Corona-Villalobos C, Kolb TM, Chaisson NF, Harris TH, Zimmerman SL, Kamel IR *et al*: **Right ventricular remodeling in idiopathic and scleroderma-associated pulmonary arterial hypertension: two distinct phenotypes**. *Pulmonary circulation* 2015, **5**(2):327-334.
10. Haddad F, Doyle R, Murphy DJ, Hunt SA: **Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure**. *Circulation* 2008, **117**(13):1717-1731.
11. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ: **Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle**. *Circulation* 2008, **117**(11):1436-1448.
12. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, Naeije R, Newman J, Oudiz RJ, Provencher S *et al*: **Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology**. *J Am Coll Cardiol* 2013, **62**(25 Suppl):D22-33.
13. Marcus JT, Gan CT, Zwanenburg JJ, Boonstra A, Allaart CP, Gotte MJ, 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**. *Journal of the American College of Cardiology* 2008, **51**(7):750-757.

14. Vonk-Noordegraaf A, Marcus JT, Gan CT, Boonstra A, Postmus PE: **Interventricular mechanical asynchrony due to right ventricular pressure overload in pulmonary hypertension plays an important role in impaired left ventricular filling**. *Chest* 2005, **128**(6 Suppl):628S-630S.

Table. Univariable Cox proportional hazard ratios for mortality for all subjects with PAH

Variable	HR (95% CI)	HR (95% CI), Variables Scaled to $Log_{1.1}$
Clinical Characteristics		
Age, y	1.02 (0.99-1.06, 0.17)	
Sex (female)	1.18 (0.28-5.01, NS)	
Race (Caucasian)	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)	
Hemodynamics		
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/min	0.72 (0.54-0.95, <0.05)	
CI, L/min/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/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/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/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)
RV EF, %	0.98 (0.95-1.005, 0.11)	0.93 (0.85-1.02, 0.11)
RV EF, % predicted	0.99 (0.98-1.01, NS)	0.97 (0.88-1.06, NS)
RVESVI, mL/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/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, p=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)

All data are presented as HR (95% confidence interval, p value). NS: p>0.20, not significant.
NYHA FC: New York Heart Association Functional Class; 6MWD: six minute walk distance; CTD: connective tissue disease; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; CO: cardiac output; CI: cardiac index; 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; 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/ESV; stroke volume over end systolic volume; SV/PP: stroke volume over pulse pressure.