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ORIGINAL PAPER

Right atrial emptying fraction non-invasively predicts mortality in pulmonary hypertension

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Abstract Right-sided heart failure is the most common cause of death in pulmonary hypertension (PH). Echocardiographic measurements of right atrial (RA) size are associated with worse outcome in PH, however the association between RA function and death in PH has not been well-described. 160 PH patients (World Health Organization groups 1–5) underwent cardiac magnetic resonance imaging (cMRI) and right heart catheterization (RHC) within 6 weeks of each other at a tertiary care academic medical center in the United States. We measured cMRI RA maximum and minimum volumes indexed to body surface area and calculated RA emptying fraction (RAEF). We evaluated the relationship between RAEF and clinical variables with death using Cox proportional hazard models. 57 deaths occurred during a median follow-up of 3.5 years (36% died overall, 10% per year). RAEF was directly correlated in univariate analyses with right ventricular (RV) ejection fraction, left ventricular (LV) ejection fraction, LV size, cardiac index, absence of tricuspid and pulmonic regurgita-tion, absence of pericardial effusion, estimated glomerular filtration rate, 6-minute walk distance, and pulmonary arterial oxygen saturation, whereas it was inversely correlated with death, BNP, heart rate, mean RA pressure, mean PA pressure, pulmonary and systemic vascular resistance, RV size, and RA size. Using multivariate analyses, RAEF had a robust inverse association with death after adjusting for measured risk factors (HR per 5% change in RAEF: 0.83 [95% CI 0.73–0.94], p=0.003). In PH patients, decreased RAEF by cMRI is independently associated with worse survival after adjustment for other risk factors.

Keywords Pulmonary heart disease · Magnetic resonance imaging · Atrium · Right heart failure

Introduction

Pulmonary hypertension (PH) is a diverse disease that is found in up to 10% of patients undergoing routine echocardiography in a clinical setting [1]. Direct invasive hemodynamic assessment is required for confirmation of the diagnosis and initiation of PH therapy. PH-associated morbidity and mortality remain high despite available treatments including oral medications, continuous intravenous therapy, lung transplantation, and additional interventions aimed to counteract the specific causes of the various forms of PH [2–4]. Although prognostic scores have been developed for idiopathic PH (IPAH) [2, 5, 6], diagnostic and treatment algorithms for patients with PH at large remain cumbersome while the ability of individual tests to inform clinical decision-making remain limited.

There is a growing consensus that the cause of death across all five PH groups is heavily influenced by right heart failure [2]. Thus there has been a focus on right

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ventricular (RV) structure, function, and remodeling in PH [7–11]. Interestingly, the main clinical endpoints used in trials might generally be considered as surrogate markers of right heart function and reserve: World Health Organization (WHO) functional classification, 6-minute walk distance (6MWD), exercise testing, cardiac biomarkers, and anatomic/functional echocardiographic parameters [5, 12–19]. Echocardiographic studies have demonstrated the prognostic value in IPAH of tricuspid annular plane systolic excursion (TAPSE), RV myocardial performance index, right atrial (RA) size, and pericardial effusion [20–24]. Although echocardiography is the mainstay of evaluating the right heart in routine clinical practice, cardiac magnetic resonance imaging (cMRI) is considered the gold standard of RV imaging; it allows for a reproducible and accurate evaluation of the structural and functional characteristics of this chamber that can otherwise be challenging to image [25, 26]. Stroke volume index, RV ejection fraction (RVEF), and indexed RV end-diastolic and end-systolic volumes, as assessed by cMRI, have been shown previously as important non-invasive prognostic markers in IPAH [27–31]. There has even been recent work examining the added benefit of RA functional and structural measurements in prognostic scores for IPAH patients [6, 32, 33]. In the absence of primary abnormalities of the tricuspid valve, RA enlargement is generally viewed as a manifestation of high RA pressure due to functional tricuspid regurgitation (TR) or elevated RV diastolic pressure, both consequences of RV failure. However, the association between RA structure and function and RV failure and death in all types of PH has not been well-described. Moreover, prognostic classification for idiopathic IPAH patients remains imperfect [2, 5, 6] and prognostic classification for other types of PH patients is even less well defined. The purpose of our study is to evaluate the association of RA structure and function with RVEF as well as with time to death in PH patients. We assessed RA and RV parameters by cMRI given its uniquely accurate and reproducible ability to view these chambers. We hypothesized that cMRI-determined RA emptying fraction (RAEF) is directly associated with RVEF and is inversely associated with death independently from RVEF (and other commonly assessed risk factors) in patients with PH.

Materials and methods

Study population, inclusion criteria, and assessed variables

Data were retrospectively collected on a cohort of 172 consecutive patients initially seen at the University of Texas Southwestern Medical Center (Dallas, TX) between 2008 and 2010 with a diagnosis of PH, including WHO groups

I–V. We excluded six patients who did not have a cMRI and right heart catheterization (RHC) performed within 6 weeks of each other around the time of the index clinic visit. We excluded another six patients whose mean pulmonary arterial pressure was not ≥25 mmHg by RHC. Classification of PH type was made according to the clinical classification scheme of the Fifth World Symposium (Nice, France, 2013) [34]. In the evaluation for PH subtype, data closest to the RHC date was collected from chart review, including pulmonary function testing (PFT) and 6MWD. The diagnosis of PH was determined by two independent physicians (KD and KMC).

Patient charts were reviewed for the following variables (closest to but within 6 months of the RHC): age, sex, height, weight, ethnicity, comorbid medical conditions, medications, WHO PH etiology, WHO functional class, BNP level, troponin, estimated glomerular filtration rate (eGFR by the Modified Diet in Renal Disease equation), hemoglobin, heart rate (during cMRI), 6MWD, PFT results (single breath carbon monoxide diffusing capacity=DLCOc, forced vital capacity=FVC, forced expiratory volume in one second=FEV1), hemodynamic measurements (mean arterial pressure=MAP, systemic arterial oxygen saturation, mean RA pressure=mRAP, mean pulmonary arterial pressures=mPAP, PA oxygen saturation, mean pulmonary capillary wedge pressure=PCWP, Fick cardiac index=CI, Fick systemic vascular resistance=SVR, and Fick pulmonary vascular resistance=PVR), echocardiographic measurements (graded tricuspid regurgitation and graded pulmonic regurgitation), and presence of pericardial effusion (graded either by echocardiogram or cMRI). We analyzed cMRI studies performed within 6 weeks of RHC for the following: indexed RV end-diastolic volume=RVEDVOI, RVEF, indexed left ventricular end-diastolic volume=LVEDVOI, left ventricular ejection fraction=LVEF, and indexed left ventricular mass=LVMASSI, indexed RA end-diastolic and end-systolic volumes=RAEDVOI and RAESVOI, RA ejection fraction=RAEF. Survival and organ transplantation were determined by chart review upon study completion.

Imaging procedures

All cMRIs were performed on a GE 1.5-T scanner (GE Healthcare, Milwaukee, Wisconsin) using steady-state free precession cine short-axis images. Cardiac volume and mass measurements were performed using MASS software (MEDIS, Leiden, Netherlands) with prospective ECG gating on the acquisition sequence. RA areas were measured from the apical four chamber view only, by tracing the endocardial contour at the time of maximum distension [RA end-diastolic (ED) area], which occurs at LV end-systole, and at the time of smallest RA area [RA end-systolic (ES) area]. Measurements were made in accordance with published recommendations on four chamber measurements of

Fig. 1 Representative examples of right atrial measurement by cardiac MRI. **a** RA end-systolic area and length. **b** RA end-diastolic area and length
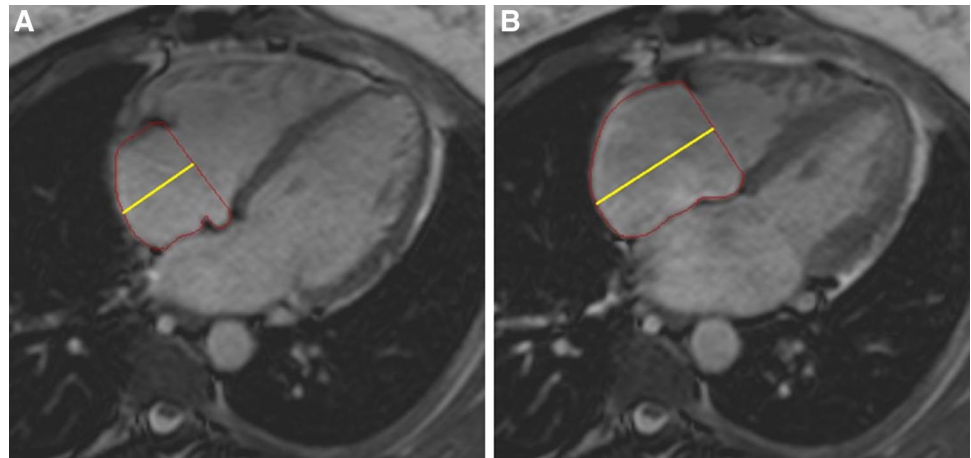
RA area [35]. RA length was measured from the midpoint of the tricuspid annular plane to the back wall of the right atrium (Fig. 1). To approximate volumes, the single plane area-length method was used. RAEF was calculated as the difference between cMRI derived RA maximum volume (RAmax) and RA minimum volume (RAmin), divided by RAmax. All volumes were indexed to BSA. Only four chamber views that excluded the LV outflow tract throughout the cardiac cycle were used for analysis. For quality control, all measurements of RA parameters were performed by a single physician (KD) after satisfactory completion of a training set of images (within 10 % of measured training set values). Contours were redrawn by a second physician (SM) on 5 % of randomly selected subjects to assess for intra- and inter-observer variability in the newly acquired cMRI measures.

In order to define gender-specific thresholds for normal RAEF, RA measurements were performed in a previously described healthy reference subpopulation of the Dallas Heart Study that underwent cMRI [36]. Low RAEF and low RAEDVOl were defined as RAEF or RAEDVOI less than the fifth percentile of gender-specific values respectively in this healthy normal population.

Clinical outcomes

Patients were followed from the date of initial clinical examination until death or the end of follow-up on January 31, 2014. Death of a participant was determined using the National Death Index and was corroborated with the patient's medical record. All-cause mortality was used as the primary outcome variable.

Statistical analysis

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA). Continuous data are presented as median plus interquartile range (25th and

75th percentiles), and categorical data are presented as percentages with significance determined by the Jonckheere–Terpstra trend test. Intra- and inter-observer reproducibility was determined through the use of intraclass correlation coefficients (ICC) by mixed modeling. Multivariable Cox regression analyses were generated to test the association between death and RAEF (continuous and tertiles). Models were adjusted for the described variables. Assumptions for the Cox regression models were satisfied through the use of Schoenfeld residuals. All reported p values are two-sided with $p < 0.05$ considered statistically significant.

Results

Validation of intra- and inter-observer reproducibility (as described in the "Materials and methods" section) showed that our analyses of RAEF and RAEDVOI were highly reproducible. Intra-observer ICC for our primary reader was 0.99 and 0.97 for RAEDVOI and RAEF, respectively. Inter-observer ICC between our primary and secondary readers was 0.97 and 0.90 for RAEDVOI and RAEF, respectively.

Of the 160 total outpatients that we studied, 83 were incident and 57 died during a median follow-up of 3.5 years. Patients were predominantly white, female, and middle-aged (Table 1). WHO group 1 PH was the most prevalent type of PH within each tertile with an idiopathic etiology being the most common WHO group 1 subtype for each tertile. RAEF tertile associated most strongly with measures of RV structure and function that included strong direct associations with cardiac index, PA oxygen saturation, and RVEF, and strong inverse associations with mean RA pressure, RAEDVOI, RAESVOI, RVEDVOI and BNP (Tables 1, 2).

Univariate analyses of survival compared with cardiac MRI measurements listed within Table 2 demonstrated significantly improved survival with higher RAEF ($p < 0.0001$, HR 0.83 per 5 % increase in RAEF, CI [0.77, 0.90]) or RVEF

Table 1 Patient demographics

	n1	Tertile 1 (N=52)	n2	Tertile 2 (N=55)	n3	Tertile 3 (N=53)	p value
Age (years)	52	61.5 [48.5, 73.5]	55	54.0 [45.5, 67.8]	53	56.3 [41.2, 66.7]	0.0537
BMI (kg/m^2)	52	27.3 [22.8, 32.5]	54	30.9 [25.4, 38.5]	52	30.2 [26.0, 35.5]	0.0952
Female	42/52	80.8%	43/54	79.6%	42/53	79.2%	0.8458
Ethnicity							
White	33/52	63.5%	40/55	72.7%	40/53	75.5%	0.1775
Black	11/52	21.2%	8/55	14.5%	5/53	9.4%	0.0928
Hispanic	5/52	9.6%	5/55	9.1%	6/53	11.3%	0.7697
Other ethnicity	3/52	5.8%	2/55	3.6%	2/53	3.8%	0.6185
Incident patients	32/51	62.7%	24/55	43.6%	27/53	50.9%	0.2354
Dead at study termination	29/52	55.8%	20/55	36.4%	8/53	15.1%	<0.0001
Diabetes	14/52	26.9%	14/55	25.5%	15/53	28.3%	0.8721
High cholesterol	24/52	46.2%	11/55	20%	11/53	20.8%	0.0042
Hypertension	35/52	67.3%	31/55	56.4%	24/53	45.3%	0.0229
Coronary artery disease	12/52	23.1%	5/55	9.1%	6/53	11.3%	0.0874
Atrial fibrillation or flutter	18/52	34.6%	2/55	3.6%	7/53	13.2%	0.0036
Current smoker	3/51	5.9%	6/54	11.1%	3/52	5.8%	0.9774
COPD	8/52	15.4%	7/55	12.7%	5/53	9.4%	0.3564
Interstitial lung disease	11/52	21.2%	12/55	21.8%	13/53	24.5%	0.6783
Obstructive sleep apnea	12/52	23.1%	18/55	32.7%	21/53	39.6%	0.0690
Thyroid disease	15/52	28.8%	13/55	23.6%	21/53	39.6%	0.2280
Medication use							
Aspirin	15/51	29.4%	11/55	20%	11/53	20.8%	0.3000
Coumadin	26/51	51%	18/55	32.7%	17/53	32.1%	0.0489
Statin	17/51	33.3%	10/55	18.2%	7/53	13.2%	0.0126
Digoxin	9/51	17.6%	3/55	5.5%	2/53	3.8%	0.0130
Aldosterone blockade	7/50	14%	10/55	18.2%	11/53	20.8%	0.3707
Calcium channel blocker	9/51	17.6%	9/55	16.4%	8/53	15.1%	0.7249
Transplants							
Lung	1/52	1.9%	0/55	0%	4/53	7.5%	0.0959
Liver	0/52	0%	2/55	3.6%	1/53	1.9%	0.4802
WHO functional class							
Class 1	1/51	2%	3/51	5.9%	6/53	11.3%	0.0518
Class 2	16/51	31.4%	8/51	15.7%	13/53	24.5%	0.4237
Class 3	24/51	47.1%	34/51	66.7%	30/53	56.6%	0.3355
Class 4	10/51	19.6%	6/51	11.8%	4/53	7.5%	0.0671
WHO group 1 etiology	25/52	48.1%	37/55	67.3%	25/53	47.2%	0.9152
Idiopathic	20/52	38.5%	21/55	38.2%	17/53	32.1%	0.4948
WHO group 2 etiology	12/52	23.1%	6/55	10.9%	10/53	18.9%	0.5764
WHO group 3 etiology	8/52	15.4%	7/55	12.7%	10/53	18.9%	0.6202
WHO group 4 etiology	5/52	9.6%	2/55	3.6%	7/53	13.2%	0.5089
WHO group 5 etiology	2/52	3.8%	3/55	5.5%	1/53	1.9%	0.5941

Continuous data are presented as median plus interquartile range (25th and 75th percentiles) and categorical data as percentages

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *WHO* World Health Organization

(p=0.001, HR 0.86 per 5% increase in RVEF, CI [0.78, 0.94]). RAEF itself was directly associated with RVEF by univariate analysis (ρ=0.39, p<0.001).

Kaplan–Meier analysis demonstrated a significant association between RAEF tertile and patient mortality (p<0.0001) with a stepwise increase in mortality moving from high RAEF to moderate RAEF to low RAEF (Fig. 2, p<0.05 for each pairwise comparison). There was no significant association between RAEDVOI tertile and patient mortality (p=0.46) by Kaplan–Meier estimation (Fig. 3).

Table 2 Measured parameters at baseline

	n1	Tertile 1 (N=52)	n2	Tertile 2 (N=55)	n3	Tertile 3 (N=53)	p value
Heart cath hemodynamics							
Heart rate (bpm)	51	82 [70, 92]	53	80 [70, 90]	51	75 [66, 85]	0.0451
MAP (mmHg)	51	94.3 [83.3, 105.0]	54	97.7 [87.7, 105.3]	51	96.3 [86.0, 105.3]	0.8605
Fick CI (L/min/m^2)	47	2.18 [1.84, 2.62]	43	2.46 [2.02, 3.09]	46	3.05 [2.52, 3.39]	<0.0001
Fick SVR (Woods units)	49	19.3 [14.5, 23.5]	53	17.1 [14.1, 20.3]	51	13.3 [11.8, 18.0]	0.0002
Arterial O$_2$ saturation (%)	47	0.95 [0.92, 0.97]	46	0.96 [0.93, 0.98]	46	0.96 [0.94, 0.98]	0.0851
Mean RA pressure (mmHg)	51	13 [8, 17]	55	7 [3, 12]	52	7 [4, 9.5]	<0.0001
Mean PA pressure (mmHg)	51	45.0 [33.7, 53.7]	55	43.7 [33.3, 54.0]	52	31.3 [24.8, 49.3]	0.0121
Fick PVR (Woods units)	46	6.8 [3.8, 11.7]	42	6.4 [4.1, 9.9]	45	3.1 [2.1, 5.8]	0.0008
PA O$_2$ saturation (%)	51	0.57 [0.48, 0.63]	53	0.64 [0.58, 0.7]	52	0.69 [0.64, 0.72]	<0.0001
Mean PCWP (mmHg)	50	12 [7, 15]	54	10 [5, 15]	52	11 [8, 14]	0.6646
Cardiac MRI measurements							
RVEDVOI (mL/m^2)	49	103.4 [85.5, 123.0]	52	81.7 [69.6, 101.4]	51	70.3 [62.7, 91.4]	<0.0001
RVEF (%)	50	42 [29, 51]	52	50 [36, 59]	53	56 [47, 60]	<0.0001
LVEDVOI (mL/m^2)	48	49.8 [37.0, 61.8]	52	50.1 [40.3, 58.9]	51	54.5 [47.9, 71.1]	0.0252
LVEF (%)	50	64 [56, 70]	52	66 [62, 76]	53	70 [67, 74]	0.0008
LVMASSI (g/m^2)	49	63.4 [45.6, 79.2]	52	59.0 [49.7, 72.2]	51	57.4 [48.1, 67.7]	0.4721
RAEDVOl (mL/m^2)	52	131.4 [84.4, 181.3]	55	90.1 [64.7, 109.5]	53	73.6 [60.1, 102.6]	<0.0001
RAESVOl (mL/m^2)	52	118.9 [78.9, 152.8]	55	59.7 [43.5, 74.8]	53	37.5 [28.8, 53.7]	<0.0001
RAEF (%)	52	10.8 [3.7, 17.8]	55	32.6 [28.6, 36.7]	53	46.6 [41.1, 50.6]	<0.0001
Range (female)	42	0.6–14.0	43	15.7–37.3	42	37.6–65.8	
Range (male)	10	0.1–25.5	11	25.6–39.3	11	40.0–67.2	
Echocardiographic measurements							
Pericardial effusion							
None or trace	27/50	54.0%	35/52	67.3%	41/53	77.4%	0.0122
Small	3/50	6.0%	9/52	17.3%	7/53	13.2%	0.2750
Moderate	18/50	36.0%	8/52	15.4%	5/53	9.4%	0.0008
Large	2/50	4.0%	0/52	0%	0/53	0%	0.0750
Tricuspid regurgitation							
None or trace	11/49	22.4%	19/52	36.5%	27/51	52.9%	0.0016
Mild	24/49	49.0%	23/52	44.2%	19/51	37.3%	0.2364
Moderate	9/49	18.4%	9/52	17.3%	4/51	7.8%	0.1327
Severe	5/49	10.2%	1/52	1.9%	1/51	2.0%	0.0509
Pulmonic regurgitation							
None or trace	30/49	61.2%	30/50	60.0%	41/50	82.0%	0.0264
Mild	15/49	30.6%	19/50	38.0%	7/50	14.0%	0.0626
Moderate	3/49	6.1%	1/50	2.0%	2/50	4.0%	0.5948
Severe	1/49	2.0%	0/50	0%	0/50	0%	0.2153
Pulmonary function testing							
FEV1 (%)	45	65 [57, 83]	50	67 [61, 87]	44	76 [61.4, 92]	0.1477
FVC (%)	45	67 [56, 76]	50	74 [59, 88]	44	76 [63, 88]	0.0610
DLCOc (mL/min/mmHg)	23	9.7 [6.2, 16.8]	24	14.3 [9.1, 20.4]	25	11.1 [8.4, 15.7]	0.7098
6MWD (min)	44	285 [154, 355]	51	362 [296, 420]	50	341 [240, 435]	0.0239

Table 2 continued

	n1	Tertile 1 (N=52)	n2	Tertile 2 (N=55)	n3	Tertile 3 (N=53)	p value
Blood markers							
Hemoglobin (g/dL)	51	12.0 [10.6, 13.8]	54	12.8 [11.3, 14.1]	51	12.5 [10.7, 14.0]	0.6626
BNP (pg/mL)	46	483 [261, 1224]	54	190 [69, 408]	50	56 [27, 209]	<0.0001
Troponin I (ng/mL)	47	0.1 [0, 0.1]	50	0.1 [0, 0.1]	47	0.1 [0, 0.1]	0.4395
eGFR (cc/min/1.7 m²)	49	59 [45, 60]	52	60 [60, 60]	51	60 [60, 60]	0.0016

Continuous data are presented as median plus interquartile range (25th and 75th percentiles) and categorical data as percentages

6MWD 6-minute walk distance, *CI* cardiac index, *DLCOc* single breath carbon monoxide diffusing capacity, *eGFR* estimated glomerular filtration rate, *FEV1* forced expiratory volume in one second, *FVC* forced vital capacity, *LVEDVOI* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVMASSI* left ventricular mass index, *MAP* mean arterial pressure, *PA* pulmonary arterial, *PCWP* pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance, *RA* right atrial, *RAEDVOI* right atrial end-diastolic volume index, *RAEF* right atrial ejection fraction, *RAESVOI* right atrial end-systolic volume index, *RVEDVOI* right ventricular end-diastolic volume index, *RVEF* right ventricular ejection fraction, *SVR* systemic vascular resistance
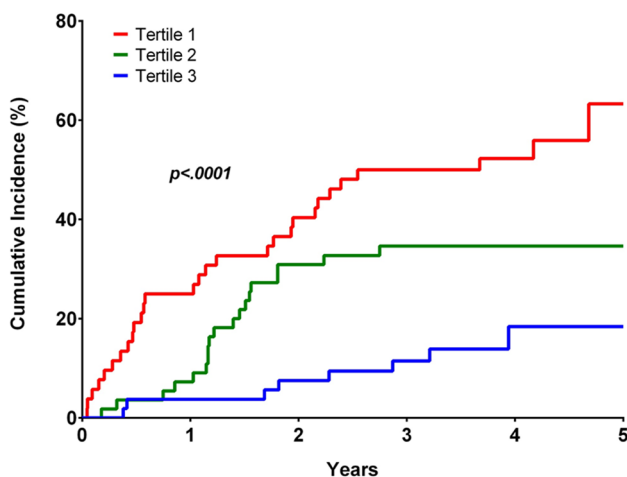
Fig. 2 Kaplan–Meier survival curves stratified by RAEF tertile. Lower RAEF correlated with higher mortality. Each pairwise comparison was statistically significant (p<0.05). *RAEF* right atrial ejection fraction

A Kaplan–Meier plot assessing all four combinations of RAEF (normal vs. low, cutpoint ≤31.1%/23.4% based on fifth percentile for women/men of sex-specific healthy normal values in the Dallas Heart Study) and RAEDVOI (normal vs. high, cutpoint ≥49.0/57.8 mL based on 95th percentile for women/men of sex-specific healthy normal values in the Dallas Heart Study) demonstrates that RAEF, rather than RAEDVOI, drives the association with mortality in these PH patients (Fig. 4, p=0.001 overall and p<0.05 for all but two pairwise comparisons: normal RAEF/normal RAEDVOI vs. normal RAEF/high RAEDVOI and low RAEF/normal RAEDVOI vs. low RAEF/high RAEDVOI).

RAEF was robustly associated with overall survival in several multivariate analyses (Fig. 5). The inverse relationship between RAEF tertile (tertile 3 vs. tertiles 1 or 2 as shown for each of these statistical models) and overall survival remained significant for all of the following multivariate adjustments: (1) age and sex; (2) age, sex, BNP, 6MWD,


Fig. 3 Kaplan–Meier survival curves stratified by RAEDVOI. There was not a statistically significant relationship between RAEDVOI and survival in this patient cohort. *RAEDVOI* right atrial end-diastolic volume index
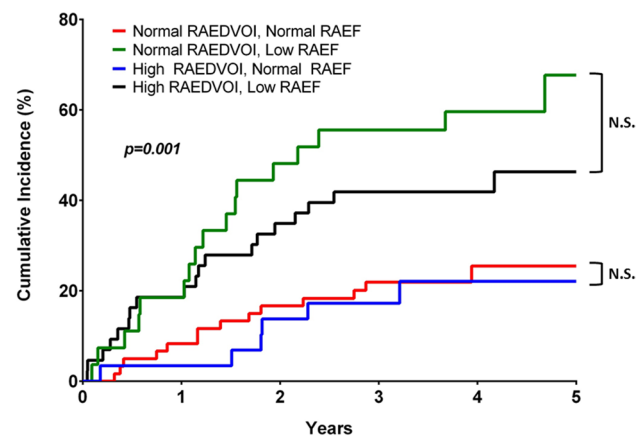
Fig. 4 Kaplan–Meier survival curves showing the relationship between RAEF and RAEDVOI. Lower RAEF correlated with higher mortality, but RAEDVOI did not correlate with a change in mortality. Each pairwise comparison was statistically significant (p<0.05) except as marked (N.S.). *RAEF* right atrial ejection fraction, *RAEDVOI* right atrial end-diastolic volume index
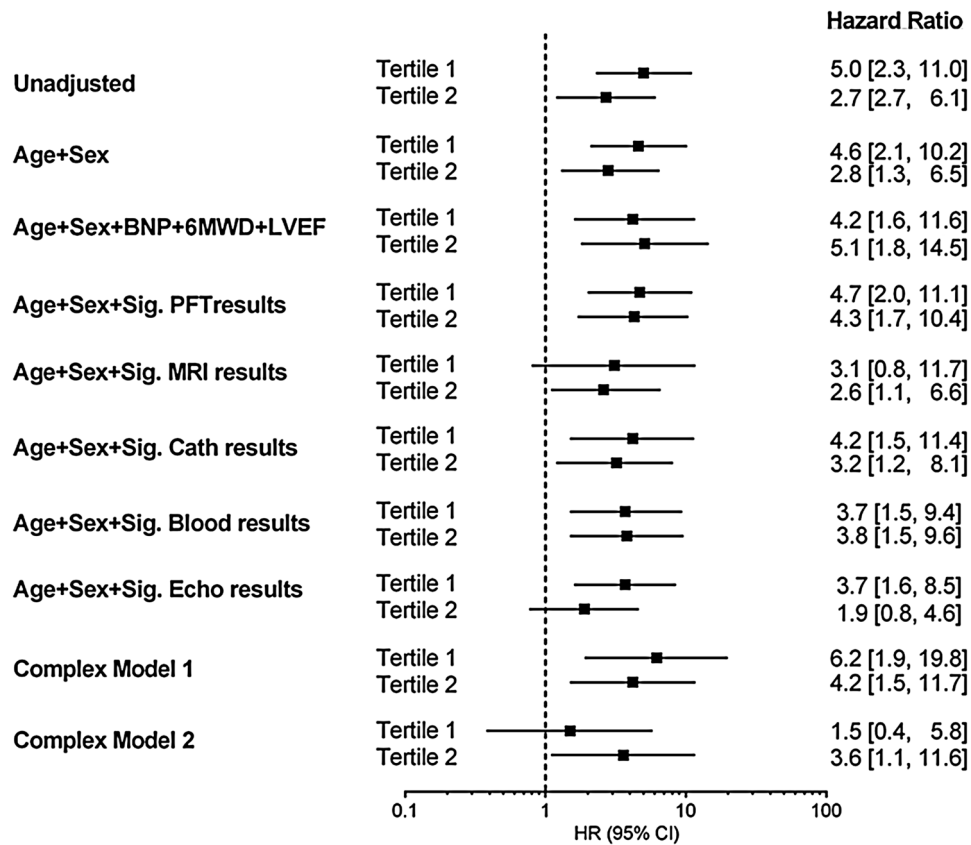
Fig. 5 Multivariate analyses of survival by RAEF tertile after correction for the listed measurements. Forest plot of multiple statistical models that each compare tertile 3 RAEF mortality vs. either tertile 1 or 2 mortality as indicated following adjustment for the listed measurements. The results cumulatively show that RAEF has a robust association with mortality despite adjustment for multiple other measured variables. Sig = statistically significant (p < 0.05) between RAEF tertiles as listed in Table 2. Complex Model 1 = age, sex, BNP, pericardial effusion, mean right atrial pressure, mean pulmonary arterial pressure, Fick pulmonary vascular resistance, left ventricular ejection fraction, right ventricular ejection fraction, right ventricular end-diastolic volume index, and right atrial end-diastolic volume index. Complex Model 2 = age, sex, and all variables (other than RAEF) that reached statistical significance (p < 0.05) in Table 2. *RAEF* right atrial ejection fraction

and LVEF; (3) age, sex, and 6MWD; (4) age, sex, RVEDVOI, RVEF, LVEDVOI, LVEF, RAEDVOI, and RAESVOI; (5) age, sex, heart rate, CI, SVR, PVR, pulmonary oxygen saturation, mRAP, and mPAP; (6) age, sex, BNP, and eGFR; (7) age, sex, pericardial effusion, tricuspid regurgitation, and pulmonic regurgitation; (8) Complex Model #1 age, sex, BNP, pericardial effusion, mRAP, mPAP, PVR, LVEF, RVEF, RVEDVOI, and RAEDVOI; and (9) Complex Model #2 age, sex, and all variables (other than RAEF) that reached statistical significance in Table 2. In multivariate model 8 above (= Complex Model #1), the hazard ratio for survival per 5 % increase in RAEF = 0.83 (95 % CI 0.73–0.94, p = 0.003).

Discussion

Direct visualization of pulmonary vascular changes in PH patients is not possible antemortem, but a growing consensus links the ultimate cause of death in PH patients to closely related right heart structure and function. Our results extend this association using a high-fidelity imaging technique (cMRI) for the right side of the heart, and we show in this retrospective cohort analysis that RAEF has a robust inverse correlation with the likelihood of mortality even after adjusting for other measured risk factors. It is notable to show that RAEF serves as an independent risk factor for death since (1) the predominant focus on the right heart in PH has been on the RV rather than the RA and (2) RAEF varies even amongst those with preserved RVEF. Although speculative, it is possible that the latter finding may reflect a sensitivity of RA function to both RV diastolic and RV systolic function. This study is also notable in that it included patients with all types of PH rather than just IPAH.

Our patient population was a fairly typical one for PH in that it was predominantly composed of white, middle-aged females with WHO group 1 etiology. They had a mortality in the expected range ~10 % per year and received standard contemporary treatments for PH. Their RA function varied

considerably from a median RAEF of 11 % in the lowest tertile to 47 % in the highest tertile, and we showed that RAEF independently associated with patient survival even though it was separately associated with RVEF as well. Indexed RAEDV, by contrast, was associated with survival in this study only in univariate analyses but not using Kaplan–Meier or multivariate analyses. This is in contrast to a recent report from Haddad et al. where they found RAEDV more useful than RAEF in deriving a prognostic echocardiographic 'right heart score' for IPAH patients [6]. While the difference in results between our studies may possibly be explained by the different patient populations or different imaging modalities used (cMRI may more accurately determine the RAEF, for example, and Haddad et al. did not use cMRI for their derivation cohort of patients), this should not distract from the important general conclusion that RA structure and function are important predictors for hard patient outcomes in patients with PH. In fact, subsequent work from the same group has further corroborated our results by showing that in IPAH (as opposed to general PH in our study) there is a clear link between RAEF and patient mortality [33]. Their point estimated hazard ratio of low vs. high echo-determined total RAEF on total mortality was 4.2, which compares favorably with ours at 5.0 (comparing the lowest and highest RAEF tertiles in this study by cMRI without adjusting for other measured factors). We thus have independently established a similar prognostic association between RAEF and mortality in patients with PH using complementary imaging modalities. This at once helps confirm the results and further demonstrates the robustness of this association.

RAEF was associated with RVEF, and each was also associated with survival in univariate analyses. In fact, the point estimated survival HR's per 5 % increase in RAEF and RVEF were nearly identical at 0.83 and 0.86, respectively. When considering that multivariate analyses additionally showed that RAEF has a similar HR for death even after correcting for multiple variables (including RVEF; see in particular Complex Model 1 as described above), it is clear that RAEF seems to serve as an independent prognostic factor for hard patient outcomes in PH. This does not negate the importance of the RV in PH but merely suggests that the RA has a particularly important prognostic role in this disease process.

There are several limitations of this study. The modest size (160 patients after application of exclusion criteria) does not allow for additional post-hoc subgroup analyses, and the general study design (retrospective cohort) has known limitations at establishing an etiologic link between variables such as RAEF and survival. Our patient demographics, while typical of this problem in the United States, may not allow universal extrapolation of our findings. RA volume assessment by Simpson's method of discs would have been a more accurate assessment of RA volume than the calculated single plane area-length measurements used [35]. Our retrospective review of clinically acquired studies prohibited direct volume measurements as the short-axis images of the heart were truncated just basal to the atrioventricular valves and therefore did not cover the entire right atrium. However, the correlation between the area-length measurement and the volumetric measurement of RA volume is relatively good both by echocardiography (r = 0.70 for area-length method vs. 3D echo method [37]) and MRI (r = 0.65 vs. real RA volume [35]). While we assessed RAEF by cMRI, which is not available for patient care in all areas, this parameter can also be estimated by echocardiography as well such that further analyses of echo-derived RAEF in PH will be of interest. Nevertheless, we believe that our findings help support the growing recognition that right heart (RA and RV) structure and function serve important prognostic roles for patients with PH.

The fact that RAEF was associated with overall cardiac function (heart rate, LVEF, RVEF, cardiac index, SVR), PA parameters (oxygen saturation, PA pressures, PVR), serum-derived measurements (BNP, eGFR), 6MWD, and echocardiographic parameters (pericardial effusion, tricuspid regurgitation, pulmonic regurgitation) is intriguing but does not offer specific insight into the etiology of these associations. Future investigation to delineate these complex relationships as well as to evaluate whether serial assessment of RA and RV parameters can offer prognostic reclassification of patients following initiation of PH therapyis needed.

Perspectives

There is a growing appreciation for the importance of the right side of the heart in the prognosis for patients with PH. Both RA size and function have been independently linked to mortality in such individuals. Whether these parameters simply serve as sensitive markers of right heart systolic and diastolic function or whether these parameters are more heavily influenced by other variables remains to be determined. Likewise, it remains to be seen whether serial assessment of these parameters may aid in prognostic reclassification after initiation or change in therapy for PH.

Compliance with ethical standards

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