

### Prognostic Importance of Pathophysiologic Markers in Patients With Heart Failure and Preserved Ejection Fraction

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## **SUPPLEMENTARY MATERIAL**

### **Supplementary Methods**

#### ***Comorbidity definitions***

Hypertension was defined by systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg, physician-documented history of hypertension, or current use of antihypertensive medications. Type 2 diabetes mellitus was defined by the presence of physician-documented history of DM or the use of oral hypoglycemic agents or insulin for the treatment of hyperglycemia. Coronary artery disease (CAD) was defined by the presence of physician-documented history of CAD, known coronary stenosis > 50%, history of myocardial infarction, percutaneous intervention, coronary artery bypass grafting, or abnormal stress test results consistent with myocardial ischemia. Obesity was defined by a body mass index  $\geq 30$  kg/m<sup>2</sup>. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m<sup>2</sup>.

**Supplementary Table S1. Reproducibility of RV Wall Thickness and EDV<sub>20</sub> (N=20)**

Parameter	Intraobserver Reliability				Interobserver Reliability		
	Mean±SD	ICC (95% CI)	Mean bias (95% CI)	CV	ICC (95% CI)	Mean bias (95% CI)	CV
RV wall thickness, mm	4.9±1.0	0.97 (0.95, 0.99)	0.005 (-0.10, 0.11)	3.5%	0.95 (0.91, 0.99)	-0.14 (-0.27, 0.002)	5.1%
EDV <sub>20</sub> , ml	77.9±18.4	0.94 (0.89, 0.99)	-3.4 (-6.1, 0.7)	6.2%	0.92 (0.85, 0.99)	-4.6 (-7.4, -1.8)	7.7%

SD, standard deviation; ICC = intraclass correlation; CI, confidence interval; CV = coefficient of variation; RV = right ventricular; EDV<sub>20</sub> = left ventricular end-diastolic volume at an idealized left ventricular end-diastolic pressure of 20 mmHg

**Supplementary Table S2. Comparison of Clinical Characteristics Among Patients With Versus Without Measurable Right Ventricular Wall Thickness**

Clinical characteristic	RV wall thickness measurable (N=362)	RV wall thickness not measurable (N=57)	P-value
Age (years)	65±13	61±11	0.015
Female	232 (64)	28 (49)	0.03*
Race			0.79
White	189 (52)	27 (47)	
Black	138 (38)	24 (42)	
Other	35 (10)	6 (11)	
New York Heart Association functional class			0.42
I	44 (12)	6 (11)	
II	145 (40)	19 (34)	
III	164 (46)	28 (50)	
IV	8 (2)	3 (5)	
<b>Comorbidities</b>			
Coronary artery disease	175 (48)	25 (44)	0.53
Hypertension	274 (76)	49 (86)	0.09
Hyperlipidemia	192 (53)	36 (63)	0.15
Diabetes mellitus	111 (31)	26 (46)	0.03*
Obesity	183 (51)	39 (68)	0.01*
Chronic kidney disease	116 (32)	23 (40)	0.22
Atrial fibrillation	101 (28)	9 (16)	0.05*
Smoker	146 (40)	22 (39)	0.80
Chronic obstructive pulmonary disease	132 (36)	22 (39)	0.76
Obstructive sleep apnea	123 (34)	29 (51)	0.01*
<b>Vital signs and laboratory data</b>			
Heart rate (beats per minute)	74.8±14.2	72.5±13.1	0.26
Systolic blood pressure (mmHg)	124.8±20.3	126.5±18.1	0.57
Diastolic blood pressure (mmHg)	70.2±11.8	70.1±12.1	0.94
Pulse pressure (mmHg)	54.6±17.5	56.4±15.4	0.47
Body mass index (kg/m <sup>2</sup> )	31.6±8.7	38.3±11.3	<0.001
Serum sodium (mEq/l)	138.4±2.9	138.5±3.0	0.99
Blood urea nitrogen (mg/dl)	24.6±16.7	23.9±12.5	0.76
Serum creatinine (mg/dl)	1.6±1.5	1.8±1.7	0.27
Estimated glomerular filtration rate (ml/min/1.73m <sup>2</sup> )	58.9±27.6	52.7±25.0	0.12
Fasting glucose (mg/dl)	118.1±51.4	126.0±71.5	0.32
Hemoglobin (g/dl)	11.9±1.9	11.8±1.8	0.76
B-type natriuretic peptide (pg/ml) (median IQR)	245 (92-568)	115 (54-268)	0.003*
<b>Medications</b>			
ACE-inhibitor or angiotensin II receptor blocker	195 (54)	34 (60)	0.42
β-blocker	242 (67)	38 (67)	0.98
Calcium channel blocker	113 (31)	21 (37)	0.40
Nitrate	47 (13)	6 (11)	0.60
Loop diuretic	54 (15)	7 (12)	0.60
Thiazide diuretic	210 (58)	36 (63)	0.46
Statin	79 (22)	17 (30)	0.18
Aspirin	39 (11)	12 (21)	0.03*

\*Of the variables that were significantly associated with missing RV wall thickness data (P<0.05), only sex was independent of BMI; thus, the 2 main clinical characteristics associated with missing RV wall thickness data were BMI and sex

**Supplementary Table S3. P-values for Interaction Terms in the Cox Proportional Hazard Models for the Combined Outcome of Cardiovascular Hospitalization or Death\***

	<b>EDV<sub>20</sub></b>	<b>RV Wall Thickness</b>
Age	0.86	0.74
Sex	0.71	0.50
Body mass index	0.68	0.84
Coronary artery disease	0.53	0.16
Diabetes mellitus	0.52	0.71
Atrial Fibrillation	0.67	0.80
Chronic obstructive pulmonary disease	0.82	0.99
Hypertension	0.68	0.40
Obstructive sleep apnea	0.71	0.19
New York Heart Association class	0.11	0.80
Glomerular filtration rate	0.93	0.84
<b>Hemoglobin</b>	<b>0.02</b>	0.61
Degree of mitral regurgitation	0.23	0.86
<b>Left ventricular mass index</b>	0.11	<b>0.03</b>

\*P-values are for interaction term in a Cox-proportional hazard model comprised of the predictor, the covariate, and an interaction term between the two.

EDV<sub>20</sub>=left ventricular end-diastolic volume at an idealized end-diastolic pressure of 20 mmHg;

RV=right ventricular

**Supplementary Table S4. Association of Pathophysiologic Markers with Cardiovascular Hospitalization or Death in Heart Failure with Preserved Ejection Fraction (Cardiac Amyloid Patients [N=15] Excluded)**

Predictor Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
	Unadjusted (Model 1)		Adjusted (Model 2*)	
<b>Hemodynamic Markers</b>				
Estimated PASP (mmHg) (N=289)	1.30 (1.09-1.55)	0.003	1.01 (0.83-1.23)	0.93
Estimated RAP (mmHg) (N=358)	1.40 (1.20-1.63)	<0.001	1.22 (1.02-1.46)	0.03
Log BNP (pg/ml)	1.69 (1.42-2.00)	<0.001	1.39 (1.08-1.80)	0.01
E/e' ratio	1.27 (1.11-1.44)	<0.001	1.07 (0.92-1.26)	0.38
LA volume index (ml/m <sup>2</sup> )	1.16 (1.02-1.33)	0.03	1.02 (0.85-1.21)	0.85
<b>LV Diastolic Function</b>				
Lateral e' velocity (cm/s)†	1.12 (0.94-1.33)	0.21	0.90 (0.73-1.12)	0.34
EDV <sub>20</sub> (ml)†	1.27 (1.06-1.52)	0.009	1.32 (1.04-1.67)	0.024
<b>LV Systolic Function</b>				
Lateral s' velocity (cm/s)†	1.24 (1.03-1.48)	0.02	1.04 (0.85-1.26)	0.73
E <sub>es</sub> (mmHg/ml)	1.08 (0.92-1.26)	0.34	1.07 (0.90-1.28)	0.43
ESV <sub>120</sub> (ml)	0.83 (0.70-0.99)	0.04	0.84 (0.68-1.02)	0.08
<b>Ventricular-Arterial Coupling</b>				
E <sub>a</sub> /E <sub>es</sub>	1.09 (0.92-1.28)	0.32	1.06 (0.89-1.26)	0.53
<b>RV Structure and Function</b>				
RV wall thickness (mm) (N=347)	1.51 (1.32-1.72)	<0.001	1.38 (1.17-1.63)	<0.001
RV basal diameter (cm)	1.15 (0.99-1.34)	0.06	1.02 (0.85-1.21)	0.87
RV/LV diameter ratio	1.18 (1.01-1.38)	0.04	1.08 (0.90-1.30)	0.39
RVEDAI (cm <sup>2</sup> /m <sup>2</sup> )	1.33 (1.13-1.57)	0.001	1.18 (0.98-1.42)	0.09
RVESAI (cm <sup>2</sup> /m <sup>2</sup> )	1.26 (1.10-1.45)	0.001	1.28 (1.04-1.58)	0.02
RVFAC (%)†	1.24 (1.09-1.42)	0.001	1.21 (0.99-1.48)	0.06

N=404 unless otherwise specified

\*Adjusted for age, sex, and clinical comorbidities, which included body-mass index, coronary artery disease, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disorder, obstructive sleep apnea, hypertension, glomerular filtration rate, hemoglobin concentration, degree of mitral regurgitation, LV mass index, and New York Heart Association functional class. †Hazard ratios are reported as per-standard deviation increase in predictor variable except when noted by (†) in which case hazard ratios are reported per standard deviation decrease in predictor variable.

HR=hazard ratio, CI=confidence interval, PASP=pulmonary artery systolic pressure, RAP= right atrial pressure, BNP=B-type natriuretic peptide, LA=left atrial, EDV=end-diastolic volume, Ees=end-systolic elastance, ESV=end-systolic volume, RV=right ventricle, LV=left ventricle, RVFAC = right ventricular fractional area change, TAPSE=tricuspid annular plane systolic excursion, RVEDAI=right ventricular end-diastolic area index, RVESAI=right ventricular end-systolic area index

**Supplementary Table S5. Association of Pathophysiologic Markers with Cardiovascular Hospitalization or Death After Adjustment for Hemodynamic Markers of Heart Failure Severity (Cardiac Amyloid Patients [N=15] Excluded)**

Predictor Variable	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
	Model 2* + PASP		Model 2+ RAP		Model 2 + LogBNP		Model 2 + E/e'		Model 2 + LAVI	
EDV <sub>20</sub> (ml)†	1.53 (1.11-2.10)	0.009	1.29 (0.99-1.66)	0.06	1.31 (1.04-1.66)	0.024	1.30 (1.02-1.67)	0.04	1.32 (1.04-1.68)	0.02
RV wall thickness (mm)	1.55 (1.25-1.91)	<0.001	1.36 (1.12-1.64)	0.001	1.37 (1.16-1.62)	<0.001	1.37 (1.16-1.63)	<0.001	1.39 (1.17-1.64)	<0.001
RV basal diameter (cm)	1.30 (1.02-1.66)	0.04	1.26 (1.00-1.59)	0.05	1.18 (0.95-1.46)	0.13	1.28 (1.03-1.58)	0.02	1.26 (1.03-1.53)	0.02
RVEDAI (cm <sup>2</sup> /m <sup>2</sup> )	1.29 (1.01-1.64)	0.04	1.17 (0.92-1.47)	0.20	1.12 (0.91-1.38)	0.30	1.20 (0.98-1.48)	0.08	1.25 (1.02-1.52)	0.03
RVESAI (cm <sup>2</sup> /m <sup>2</sup> )	1.21 (0.97-1.50)	0.09	1.13 (0.91-1.40)	0.29	1.10 (0.91-1.35)	0.33	1.17 (0.96-1.42)	0.11	1.18 (0.97-1.42)	0.09

\*Adjusted for age, sex, and clinical comorbidities, which included BMI, coronary artery disease, DM, atrial fibrillation, chronic obstructive pulmonary disorder, obstructive sleep apnea, hypertension, glomerular filtration rate, hemoglobin concentration, degree of mitral regurgitation, LV mass index, and New York Heart Association functional class.

†Hazard ratios are reported as per-standard deviation increase in predictor variable except when noted by (†) in which case hazard ratios are reported per standard deviation decrease in predictor variable.

HR=hazard ratio, CI=confidence interval, PASP=pulmonary artery systolic pressure, RAP= right atrial pressure, BNP=B-type natriuretic peptide, LAVI=left atrial volume index, EDV=end-diastolic volume, Ees=end-systolic elastance, ESV=end-systolic volume, RV=right ventricle, TAPSE=tricuspid annular plane systolic excursion, RVEDAI=right ventricular end-diastolic area index, RVESAI=right ventricular end-systolic area index

**Supplementary Figure S1. Locally weighted smooth scatter plots demonstrating the association between EDV<sub>20</sub>, RV wall thickness, and the combined outcome of cardiovascular hospitalization or death.**

