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Effects of Right Ventricular Ejection Fraction on Outcomes in Chronic Systolic Heart Failure

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Background—Studies of the effect of right ventricular ejection fraction (RVEF) on outcomes in heart failure (HF) are limited by small sample size and short follow-up.

Methods and Results—We examined the effect of baseline RVEF on outcomes in 2008 Beta-Blocker Evaluation of Survival Trial (BEST) participants with HF and left ventricular ejection fraction $\leq 35\%$ during 24 months of mean follow-up. RVEF, estimated by gated-equilibrium radionuclide ventriculography, was used to categorize patients into 4 RVEF groups: $\geq 40\%$ ($n=733$), 30% to 39% ($n=531$), 20% to 29% ($n=473$), and $<20\%$ ($n=271$). Unadjusted rates for all-cause mortality in patients with RVEF $\geq 40\%$, 30% to 39%, 20% to 29%, and $<20\%$ were 27%, 32%, 35%, and 47%, respectively. When compared with patients with RVEF $\geq 40\%$, unadjusted hazard ratios and 95% confidence intervals for all-cause mortality for those with RVEF 30% to 39%, 20% to 29%, and $<20\%$ were 1.19 (0.97 to 1.46; $P=0.087$), 1.45 (1.17 to 1.78; $P=0.001$), and 1.98 (1.59 to 2.47; $P<0.0001$), respectively. Respective multivariable-adjusted hazard ratios (95% confidence intervals) for all-cause mortality associated with RVEF 30% to 39%, 20% to 29%, and $<20\%$ were 1.07 (0.87 to 1.32; $P=0.518$), 1.12 (0.89 to 1.40; $P=0.328$), and 1.32 (1.02 to 1.71; $P=0.034$), respectively. Adjusted hazard ratios (95% confidence intervals) for other outcomes associated with RVEF $<20\%$ (compared with $\geq 40\%$) were as follows: cardiovascular mortality, 1.33 (1.01 to 1.76; $P=0.041$); HF mortality, 1.61 (1.03 to 2.52; $P=0.037$); sudden cardiac death, 1.29 (0.87 to 1.91; $P=0.212$); all-cause hospitalization, 1.21 (1.00 to 1.47; $P=0.056$); and HF hospitalization, 1.39 (1.10 to 1.77; $P=0.007$).

Conclusions—Baseline RVEF $<20\%$ is a significant independent predictor of mortality and HF hospitalization in systolic HF. (*Circulation*. 2010;121:252-258.)

Key Words: heart failure ■ hospitalization ■ mortality ■ right ventricular ejection fraction

The impact of a reduced left ventricular (LV) ejection fraction (EF) on outcomes in heart failure (HF) is well documented in the literature.¹⁻⁴ However, little is known about the impact of a reduced right ventricular (RV) EF on outcomes in chronic systolic HF.⁵⁻⁷ Most studies of RVEF in HF are limited by small sample size, short follow-up, or potential bias due to confounding variables.⁸⁻¹⁵ Of the 2708 patients with HF and LVEF $\leq 35\%$ in the Beta-Blocker Evaluation of Survival Trial (BEST), 2008 had data on baseline RVEF along with data on a large number of other baseline characteristics and long-term follow-up.¹⁶ Therefore, the objective of the present study was to examine the effect of baseline RVEF on outcomes in BEST patients.

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Methods

Study Design

We obtained a public-use copy of the BEST data set from the National Heart, Lung, and Blood Institute (NHLBI).¹⁷ The BEST

was sponsored by the NHLBI and the Department of Veterans Affairs Cooperative Studies Program. The rationale, design, and results of the BEST have been reported previously.^{16,18} Briefly, 2708 chronic HF patients were randomly assigned to bucindolol or placebo between May 1995 and December 1998 at 90 clinical sites in the United States and Canada and followed for a mean duration of 24 months. All but 1 participant consented to be included in the public-use copy of the database used for the present analysis.

Patients

At randomization, all HF patients in the BEST study had LVEF $\leq 35\%$, had a mean duration of 49 months of HF, and had New York Heart Association functional class III (92%) or IV (8%) symptoms. Most patients were receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers ($>90\%$), diuretics ($>90\%$), and digoxin ($>90\%$). The protocol was approved by the institutional review board of each participating site, and all patients gave written informed consent.

Estimation of LVEF and RVEF

Data on baseline LVEF and RVEF were collected before randomization by gated-equilibrium radionuclide ventriculography with the

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use of standard techniques at each of the sites. If a patient did not have a LVEF and RVEF by radionuclide ventriculography at a BEST site during the 60 days before randomization, a study was performed at the time of randomization. For quality control purposes, the first 2 examinations at each site were sent for rereading at a core laboratory. Thereafter, a random sample of 5% of all the examinations was sent to the core laboratory for quality control.¹⁹ Valid measurements of RVEF were available for 2008 patients. The lower limit of normal RVEF by gated-equilibrium radionuclide ventriculography is 40%.^{20,21} For the present analysis, we categorized patients into 4 RVEF groups: $\geq 40\%$ ($n=733$ or 37%), 30% to 39% ($n=531$ or 26%), 20% to 29% ($n=473$ or 24%), and $<20\%$ ($n=271$ or 13%).

Study Outcomes

In the present study, primary outcomes were all-cause mortality (the BEST primary outcome) and HF hospitalization (a BEST secondary outcome). Our secondary outcomes were cardiovascular and HF mortality, sudden cardiac death, and all-cause hospitalization.

Statistical Analysis

We used χ^2 tests and ANOVA tests, as appropriate, for descriptive analyses to compare baseline characteristics between the 4 RVEF groups. Kaplan–Meier plots were constructed to determine associations of RVEF groups with all-cause mortality and HF hospitalization. Associations of various RVEF categories with outcomes were determined by Kaplan–Meier survival analysis and Cox proportional hazard models. RVEF category $\geq 40\%$ was used as the reference category, and dummy variables were used for RVEF categories 30% to 39%, 20% to 29%, and $<20\%$. Variables were entered into the model in multiple steps in the following order: step 1 (unadjusted: dummy variables for RVEF 30% to 39%, 20% to 29%, and $<20\%$), step 2 (step 1 plus LVEF), step 3 (step 2 plus demographics), step 4 (step 3 plus medical history), step 5 (step 4 plus medications), step 6 (step 5 plus clinical findings), and step 7 (step 6 plus laboratory findings). The same model was used for all of the outcomes. We confirmed the assumption of proportional hazards by a visual examination of the log (minus log) curves. All statistical tests were evaluated with the use of 2-tailed 95% confidence levels, and tests with $P<0.05$ were considered significant. Data analyses were performed with the use of SPSS for Windows, release 15, 2006 (SPSS Inc, Chicago, Ill).

Results

Baseline Characteristics

Patients had a mean age of 60 (± 12) years, 21% were women, and 21% were black. Compared with patients with normal RVEF, those in the lower RVEF categories had lower mean age, fewer women, and more blacks (Table 1). They also had lower mean LVEF, longer HF duration, and a higher prevalence of New York Heart Association functional class IV (Table 1). The distribution of RVEF among the study participants is displayed in Figure 1.

Association Between RVEF and Mortality

All-cause mortality occurred in 27%, 32%, 35%, and 47% of patients with RVEF $\geq 40\%$, 30% to 39%, 20% to 29%, and $<20\%$, respectively (Table 2 and Figure 2A). When compared with patients with RVEF $\geq 40\%$, unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality for those with RVEF 30% to 39%, 20% to 29%, and $<20\%$ were 1.19 (0.97 to 1.46; $P=0.087$), 1.45 (1.17 to 1.78; $P=0.001$), and 1.98 (1.59 to 2.47; $P<0.0001$), respectively. Respective adjusted HRs for all-cause mortality for those with RVEF 30% to 39%, 20% to 29%, and $<20\%$ were 1.07

(95% CI, 0.87 to 1.32; $P=0.518$), 1.12 (95% CI, 0.89 to 1.40; $P=0.328$), and 1.32 (95% CI, 1.02 to 1.71; $P=0.034$), respectively. Unadjusted and adjusted HRs (95% CIs) for cause-specific mortalities are displayed in Table 3.

Association Between RVEF and Hospitalization

HF hospitalization occurred in 33%, 37%, 41%, and 55% of patients with RVEF $\geq 40\%$, 30% to 39%, 20% to 29%, and $<20\%$, respectively (Table 3 and Figure 2B). Compared with patients with RVEF $\geq 40\%$, unadjusted HR for HF hospitalization for those with RVEF $<20\%$ was 2.25 (95% CI, 1.84 to 2.82; $P<0.0001$), which remained significant despite multivariable adjustment (HR, 1.39; 95% CI, 1.10 to 1.77; $P=0.007$). Unadjusted and adjusted HRs (95% CIs) for all-cause hospitalization are displayed in Table 3.

Effect of LVEF on Outcomes by RVEF

All-cause mortality occurred in 40% and 29% of patients with LVEF $<20\%$ and $\geq 20\%$, respectively (unadjusted HR for LVEF $<20\%$, 1.61; 95% CI, 1.38 to 1.87; $P<0.0001$). When adjusted for RVEF $<20\%$, this association was attenuated but remained significant (HR, 1.48; 95% CI, 1.26 to 1.74; $P<0.0001$).

Effect of Bucindolol on Outcomes by RVEF

Among patients with RVEF $\geq 40\%$, all-cause mortality occurred in 24% and 30% of patients randomized to receive bucindolol and placebo, respectively (HR for bucindolol, 0.73; 95% CI, 0.55 to 0.97; $P=0.031$). All-cause mortality for patients in the bucindolol versus placebo groups were 30% versus 33% for those with RVEF 30% to 39% ($P=0.477$), 32% versus 38% for those with RVEF 20% to 29% ($P=0.162$), and 49% versus 43% for those with RVEF $<20\%$ ($P=0.314$).

Discussion

The findings of the present comprehensive report, based on the largest study of RVEF in HF to date, confirm previous reports describing the importance of RV failure on outcomes in patients with chronic systolic HF and identify RVEF $<20\%$ as having an independent effect on mortality. Although RVEF $<40\%$ was associated with progressive increase in the risk of mortality and hospitalization, only RVEF $<20\%$ had an intrinsic association with increased mortality and HF hospitalization that was independent of all measured baseline characteristics that included many potential confounders such as age, LVEF, and cardiovascular comorbidities. These findings suggest that RVEF may be useful as both a marker and mechanism of poor prognosis in systolic HF and that the estimation of RVEF should be considered as part of a comprehensive assessment of these patients.

LVEF impairment is believed to be the most common cause of RVEF impairment.^{4,6} An increase in RV afterload through the development of pulmonary arterial hypertension secondary to chronic pulmonary venous hypertension has long been considered the main underlying mechanism of RV failure.²² However, recent findings from animal models of pulmonary hypertension suggest that degree or duration of RV pressure overload may not fully explain RV failure and

Table 1. Baseline Patient Characteristics by RVEF

	RVEF \geq 40% (n=733)	RVEF 30–39% (n=531)	RVEF 20–29% (n=473)	RVEF <20% (n=271)	P
Age, y	61 (\pm 12)	60 (\pm 12)	61 (\pm 12)	58 (\pm 13)	0.010
Female	184 (25)	108 (20)	84 (18)	38 (14)	<0.0001
Black	119 (16)	109 (20)	112 (24)	88 (32)	<0.0001
Current smoker	127 (17)	91 (17)	85 (18)	37 (14)	0.470
New York Heart Association class III	687 (94)	488 (92)	424 (90)	229 (84)	<0.001
Body mass index, kg/m ²	36 (\pm 8)	37 (\pm 9)	36 (\pm 8)	36 (\pm 8)	0.018
Heart rate, bpm	81 (\pm 13)	81 (\pm 13)	82 (\pm 13)	87 (\pm 14)	<0.0001
Systolic blood pressure, mm Hg	121 (\pm 18)	116 (\pm 18)	114 (\pm 18)	112 (\pm 17)	<0.0001
Diastolic blood pressure, mm Hg	71 (\pm 11)	71 (\pm 11)	70 (\pm 11)	72 (\pm 11)	0.050
LVEF, %	26 (\pm 6.6)	23 (\pm 6.8)	21 (\pm 6.7)	17 (\pm 6.1)	<0.0001
RVEF, %	49 (\pm 7.3)	34 (\pm 3.0)	25 (\pm 2.9)	14 (\pm 3.3)	<0.0001
Past medical history					
Duration of HF, mo	47 (\pm 45)	48 (\pm 46)	56 (\pm 56)	50 (\pm 49)	0.012
Idiopathic dilated cardiomyopathy	220 (30)	148 (28)	113 (24)	83 (31)	0.096
Coronary artery disease	428 (58)	310 (58)	299 (63)	161 (59)	0.342
Evidence of prior inferior/posterior myocardial infarction	110 (15)	77 (15)	62 (13)	41 (15)	0.807
Coronary artery bypass surgery	205 (28)	161 (30)	164 (35)	74 (27)	0.063
Percutaneous coronary intervention	116 (16)	81 (15)	73 (15)	38 (14)	0.919
Hypertension	419 (57)	313 (59)	261 (55)	165 (61)	0.427
Diabetes mellitus	246 (34)	189 (36)	163 (34)	103 (38)	0.597
Hyperlipidemia	343 (47)	241 (45)	176 (37)	109 (40)	0.005
Atrial fibrillation	153 (21)	145 (27)	134 (28)	57 (21)	0.005
Chronic kidney disease*	281 (38)	186 (35)	189 (40)	107 (39)	0.384
Medications					
Bucindolol	362 (49)	276 (52)	233 (49)	146 (54)	0.506
Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers	705 (96)	513 (97)	455 (96)	258 (95)	0.809
Digitalis	668 (91)	491 (92)	447 (94)	458 (95)	0.056
Diuretics	668 (91)	496 (93)	451 (95)	262 (97)	0.003
Vasodilators	340 (46)	255 (48)	200 (42)	127 (47)	0.305
Anticoagulants	400 (55)	337 (63)	286 (60)	163 (60)	0.012

Values are n (%) or mean (\pm SD).

*Estimated glomerular filtration rate <60 mL/min per 1.73 m² of body surface area.

that complex heart-lung interactions at cellular and molecular levels resulting in angioproliferative pulmonary vascular disease and myocardial fibrosis underlie RV failure.²³ RVEF may also be impaired because of other mechanisms, including

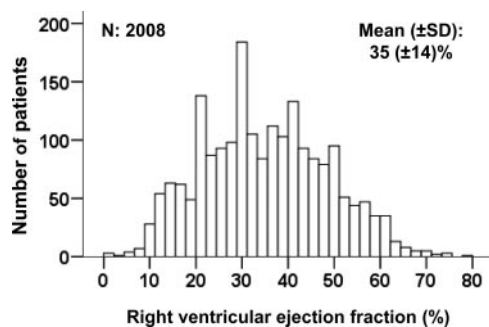


Figure 1. Histogram displaying frequency distribution of RVEF (%).

ventricular interdependence associated with septal dysfunction and limited pericardial flexibility, neurohormonal interactions, and reduced RV coronary perfusion secondary to decreased systolic driving pressure.^{6,7} Low RVEF, in turn, may further reduce LV output by impairing adequate LV preload, thereby enhancing neurohormonal activation.⁷ This may precipitate end-organ hypoperfusion and progressive clinical deterioration, leading to eventual poor outcomes. Therefore, low RVEF, although primarily a consequence of a low LVEF, may also be a cause of further LVEF impairment, disease progression, and poor outcomes.

RVEF and LVEF may also be impaired simultaneously, as in patients with idiopathic dilated cardiomyopathy. However, the prevalence of idiopathic dilated cardiomyopathy was low and was balanced across all 4 RVEF groups. These findings suggest that a reduced RVEF may not be a useful marker for idiopathic dilated cardiomyopathy in advanced chronic sys-

Table 2. Associations of RVEF With All-Cause Mortality

	HR (95% CI); <i>P</i>			
	RVEF ≥40% (n=733)	RVEF 30–39% (n=531)	RVEF 20–29% (n=473)	RVEF <20% (n=271)
All-cause mortality, %	27	32	35	47
Step 1: Unadjusted	1.00 (Reference)	1.19 (0.97–1.46); <i>P</i> =0.087	1.45 (1.17–1.78) <i>P</i> =0.001	1.98 (1.59–2.47) <i>P</i> <0.0001
Step 2: Step 1 +LVEF	1.00 (Reference)	1.12 (0.91–1.37); <i>P</i> =0.295	1.27 (1.02–1.57) <i>P</i> =0.031	1.52 (1.20–1.94) <i>P</i> =0.001
Step 3: Step 2 +demographics*	1.00 (Reference)	1.14 (0.93–1.40); <i>P</i> =0.217	1.26 (1.02–1.56) <i>P</i> =0.036	1.62 (1.27–2.06) <i>P</i> <0.0001
Step 4: Step 3 +medical history†	1.00 (Reference)	1.06 (0.86–1.31); <i>P</i> =0.563	1.18 (0.95–1.47) <i>P</i> =0.139	1.52 (1.19–1.95) <i>P</i> =0.001
Step 5: Step 4 +medications‡	1.00 (Reference)	1.06 (0.86–1.30); <i>P</i> =0.597	1.17 (0.94–1.45) <i>P</i> =0.169	1.49 (1.16–1.91) <i>P</i> =0.002
Step 6: Step 5 +clinical findings§	1.00 (Reference)	1.05 (0.85–1.30); <i>P</i> =0.640	1.07 (0.86–1.34) <i>P</i> =0.542	1.37 (1.06–1.76) <i>P</i> =0.015
Step 7: Step 6 +laboratory findings	1.00 (Reference)	1.07 (0.87–1.32); <i>P</i> =0.518	1.12 (0.89–1.40) <i>P</i> =0.328	1.32 (1.02–1.71) <i>P</i> =0.034

*Demographics: age, sex, and race.

†Medical history: duration of smoking, duration of HF, New York Heart Association class, coronary artery disease, angina pectoris, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, atrial fibrillation, >70% coronary artery stenosis, positive stress perfusion test, and ECG evidence of anterior, lateral, and inferior-posterior myocardial infarction.

‡Medications: bucindolol, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, digitalis, diuretics, and anticoagulants.

§Clinical findings: body mass index, heart rate, systolic and diastolic blood pressure, S3 gallop, pulmonary rales, and x-ray findings of cardiothoracic ratio and pulmonary edema.

||Laboratory findings: creatinine, potassium, sodium, magnesium, blood urea nitrogen, glucose, uric acid, total cholesterol, albumin, hemoglobin, white blood cells, and platelets.

tolic HF. Low RVEF was also not associated with prior inferior-posterior myocardial infarction, which may involve the RV. Taken together, these data suggest that in patients with advanced chronic systolic HF, RVEF impairment may primarily be a consequence of LVEF impairment.

Interestingly, nearly 37% of patients in our study maintained a normal RVEF. This is intriguing and emphasizes the complex interdependent relationship between the LV and the RV. Patients with preserved RVEF in our study had higher mean LVEF and shorter duration of HF (Table 1), which may

have played a role in the preservation of the RV systolic function. RV function may also be preserved because of a lower RV systolic load and unique RV hemodynamics that provide inherent protective mechanisms against permanent ischemic damage.²⁴ There may also be individual susceptibilities to RVEF impairment, as suggested by data from the pulmonary arterial hypertension literature.^{7,25} Mechanisms by which some patients with pulmonary hypertension develop RV failure and others do not are not clearly understood. Altered gene expression and variations in neurohormonal activation have been proposed to partially account for these differences.^{5,6,23,25} Further research is needed to understand the development of RVEF impairment in systolic HF.

The role of the RV in chronic HF was overlooked for many years, partly because it was considered to be merely a passive chamber.²⁶ Several prior studies have reported an association between RVEF and poor outcomes in different HF populations with the use of various methods of RVEF assessment.^{8–15} In 1 study of 34 patients with systolic HF, low RVEF (<35%) was associated with increased mortality.⁸ In the largest known study of RVEF to date, in 377 patients with systolic HF, RVEF <35% was similarly associated with increased mortality.¹⁴ Several echocardiographic indices of RV impairment have also been associated with poor outcomes.^{27–30} Compared with these previous studies, our study is distinguished by its large sample size, longer person-years of follow-up, adjustment for a large number of prognostically important covariates, and various cause-specific outcomes.

The overall prognosis for patients with advanced systolic HF is poor. RVEF may serve as a useful tool to identify patients at high risk for poor prognosis. Any decline in RVEF between 20% and 39% may be used as a marker of poor prognosis. However, RVEF <20% has a significant intrinsic association with an increased risk of death and HF hospitalization that appears to be independent of other risk factors. Unadjusted all-cause mortality rates in patients with RVEF

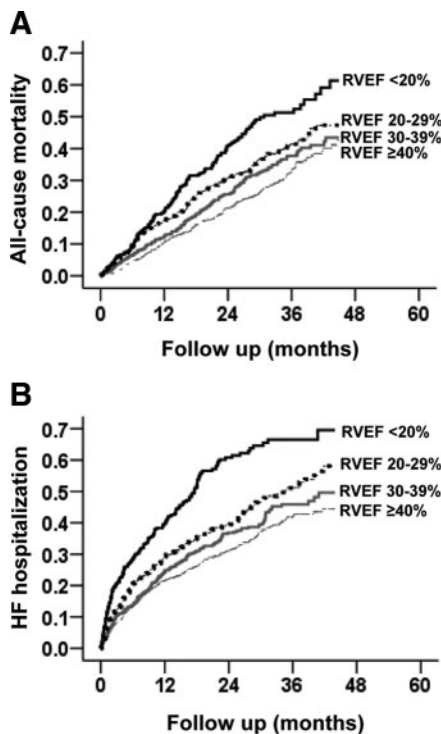


Figure 2. Kaplan–Meier plots for all-cause mortality (A) and HF hospitalization (B) by RVEF categories.

Table 3. Associations of RVEF With Cause-Specific Outcomes

	Events, %	Unadjusted HR (95% CI); <i>P</i>	Adjusted HR* (95% CI); <i>P</i>
Cardiovascular mortality			
RVEF \geq 40%	23	1.00 (Reference)	1.00 (Reference)
RVEF 30% to 39%	25	1.13 (0.90–1.41); <i>P</i> =0.299	0.98 (0.78–1.24); <i>P</i> =0.885
RVEF 20% to 29%	30	1.46 (1.17–1.83); <i>P</i> =0.001	1.09 (0.86–1.39); <i>P</i> =0.487
RVEF <20%	41	2.07 (1.64–2.63); <i>P</i> <0.0001	1.33 (1.01–1.76); <i>P</i> =0.041
HF mortality			
RVEF \geq 40%	8	1.00 (Reference)	1.00 (Reference)
RVEF 30% to 39%	9	1.05 (0.72–1.53); <i>P</i> =0.814	0.89 (0.60–1.32); <i>P</i> =0.549
RVEF 20% to 29%	11	1.49 (1.03–2.16); <i>P</i> =0.036	1.03 (0.69–1.54); <i>P</i> =0.890
RVEF <20%	18	2.47 (1.70–3.58); <i>P</i> <0.0001	1.61 (1.03–2.52); <i>P</i> =0.037
Sudden cardiac death			
RVEF \geq 40%	11	1.00 (Reference)	1.00 (Reference)
RVEF 30% to 39%	15	1.35 (0.99–1.84); <i>P</i> =0.056	1.22 (0.89–1.67); <i>P</i> =0.221
RVEF 20–29%	15	1.55 (1.13–2.14); <i>P</i> =0.007	1.23 (0.88–1.72); <i>P</i> =0.228
RVEF <20%	20	2.01 (1.43–2.83); <i>P</i> <0.0001	1.29 (0.87–1.91); <i>P</i> =0.212
All-cause hospitalization			
RVEF \geq 40%	60	1.00 (Reference)	1.00 (Reference)
RVEF 30% to 39%	64	1.10 (0.96–1.90); <i>P</i> =0.168	1.03 (0.89–1.19); <i>P</i> =0.665
RVEF 20–29%	65	1.24 (1.07–1.44); <i>P</i> =0.005	1.09 (0.93–1.27); <i>P</i> =0.312
RVEF <20%	73	1.61 (1.36–1.90); <i>P</i> <0.0001	1.21 (1.00–1.47); <i>P</i> =0.056
HF hospitalization			
RVEF \geq 40%	33	1.00 (Reference)	1.00 (Reference)
RVEF 30% to 39%	37	1.16 (0.96–1.39); <i>P</i> =0.126	1.00 (0.83–1.21); <i>P</i> =0.984
RVEF 20–29%	41	1.45 (1.20–1.75); <i>P</i> <0.0001	1.09 (0.89–1.34); <i>P</i> =0.395
RVEF <20%	55	2.25 (1.84–2.82); <i>P</i> <0.0001	1.39 (1.10–1.77); <i>P</i> =0.007

*Multivariable model based on model 7 from Table 2.

\geq 40% and <20% were 27% and 47%, respectively, over a mean of 24 months of follow-up. This represents a 20% absolute difference in mortality rates between the highest and lowest category of RVEF, representing 20 excess deaths for every 100 patients followed over a 2-year period. The magnitude of absolute increased risk associated with low RVEF is thus substantial. Therefore, measurement of RVEF should be integrated into the global clinical evaluation of HF patients. Radionuclide imaging currently constitutes a well-validated quantitative estimate of RVEF, and our data suggest that RVEF measured by this technique can be used to assess prognosis in these patients. However, echocardiographic assessment of the RV from multiple views including the apical 4-chamber view can give overall qualitative assessments of RV size and function that may be prognostically useful. HF patients with RVEF <20% may benefit from referral to a specialized HF clinic.

Little is known about evidence-based therapy for HF with low RVEF because very few studies in chronic HF have evaluated the impact of therapies specifically on the RV or in patients with low RVEF.^{1,4,31} In 1 small study of 14 stable HF patients, captopril use was associated with reduction in both LV and RV end-diastolic volumes and improvement of LVEF and RVEF.³² Recently, sildenafil, a phosphodiesterase 5 inhibitor, has been shown to improve exercise capacity and quality of life in systolic HF patients (n=34) with a mean

RVEF of 34% and secondary pulmonary hypertension.³³ In that study, patients randomized to sildenafil (versus placebo) had improvement of both resting and exercise RVEF.³³ In a small study of 22 patients with HF, therapy with carvedilol improved LVEF and RVEF.³⁴ However, findings from the present study suggest that bucindolol had no effect on mortality in HF patients with low RVEF. Further data are needed to better understand the impact of existing and new HF therapies on HF patients with low RVEF.

Several limitations of our study need to be considered. RVEF in our study was estimated with the use of gated-equilibrium radionuclide ventriculography, which has since been replaced by first-pass radionuclide ventriculography.²¹ However, it has been validated extensively and has the advantage of being independent of geometric assumptions in contrast to conventional echocardiography.³⁵ RVEF is highly dependent on loading conditions and may not adequately reflect intrinsic RV contractility.⁵ We also had no data on RV end-systolic and end-diastolic volumes. However, to the best of our knowledge, no study to date has examined the association of RV volume or dimension with outcomes in chronic systolic HF. Because a change in RV volume may be the first sign of RV dysfunction, future studies need to examine whether it might be a better marker of prognosis than RVEF in these patients. Finally, BEST participants were not receiving

β -blockers approved for HF, which may limit generalizability of these findings.

In conclusion, in patients with advanced systolic HF, RVEF impairment is common and is associated with poor outcomes. Whereas RVEF <40% is a marker of increased risk of death and hospitalization, RVEF <20% has a significant intrinsic association with increased risk of death and HF hospitalization. RVEF may be used to risk-stratify advanced systolic HF patients during initial and subsequent evaluations. Future studies need to determine risk factors for RVEF impairment and to develop and test interventions to prevent RVEF impairment and improve outcomes in those with low RVEF.

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Disclosures

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References

- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391–e479.
- Ahmed A, Perry GJ, Fleg JL, Love TE, Goff DC Jr, Kitzman DW. Outcomes in ambulatory chronic systolic and diastolic heart failure: a propensity score analysis. *Am Heart J*. 2006;152:956–966.
- Martinez-Selles M, Garcia Robles JA, Prieto L, Dominguez Munoa M, Frades E, Diaz-Castro O, Almendral J. Systolic dysfunction is a predictor of long term mortality in men but not in women with heart failure. *Eur Heart J*. 2003;24:2046–2053.
- Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;29:2388–2442.
- 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;117:1436–1448.
- 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;117:1717–1731.
- Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smart FW, Suzuki YJ, Gladwin M, Denholm EM, Gail DB. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. *Circulation*. 2006;114:1883–1891.
- Polak JF, Holman BL, Wynne J, Colucci WS. Right ventricular ejection fraction: an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. *J Am Coll Cardiol*. 1983;2:217–224.
- Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol*. 1995;25:1143–1153.
- Gavazzi A, Berzuini C, Campana C, Inserra C, Ponzetta M, Sebastiani R, Ghio S, Recusani F. Value of right ventricular ejection fraction in predicting short-term prognosis of patients with severe chronic heart failure. *J Heart Lung Transplant*. 1997;16:774–785.
- Juilliere Y, Barbier G, Feldmann L, Grentzinger A, Danchin N, Chierri F. Additional predictive value of both left and right ventricular ejection fractions on long-term survival in idiopathic dilated cardiomyopathy. *Eur Heart J*. 1997;18:276–280.
- de Groote P, Millaire A, Foucher-Hossein C, Nogue O, Marchandise X, Ducloux G, Lablanche JM. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol*. 1998;32:948–954.
- La Vecchia L, Paccanaro M, Bonanno C, Varotto L, Ometto R, Vincenzi M. Left ventricular versus biventricular dysfunction in idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1999;83:120–122, A129.
- Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol*. 2001;37:183–188.
- Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol*. 2007;49:2028–2034.
- The BEST Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659–1667.
- National Heart, Lung, and Blood Institute. The Beta-Blocker Evaluation of Survival Trial (BEST). Available at: <https://biolincc.nhlbi.nih.gov/studies/best/>. Accessed December 20th 2009.
- The BEST Steering Committee. Design of the Beta-Blocker Evaluation of Survival Trial (BEST). *Am J Cardiol*. 1995;75:1220–1223.
- The BEST Investigators. *Beta-Blocker Evaluation of Survival Trial (BEST) Protocol*. Bethesda, Md: National Heart, Lung, and Blood Institute and Department of Veterans Affairs Cooperative Studies Program; 1999. Available at: <https://biolincc.nhlbi.nih.gov/static/studies/best/Protocol.pdf/>. Accessed December 20th 2009.
- Manno BV, Iskandrian AS, Hakki AH. Right ventricular function: methodologic and clinical considerations in noninvasive scintigraphic assessment. *J Am Coll Cardiol*. 1984;3:1072–1081.
- Hesse B, Lindhardt TB, Acampa W, Anagnostopoulos C, Ballinger J, Bax JJ, Edenbrandt L, Flotats A, Germano G, Stopar TG, Franken P, Kelion A, Kjaer A, Le Guludec D, Ljungberg M, Maenhout AF, Marcassa C, Marving J, McKiddie F, Schaefer WM, Stegger L, Underwood R. EANM/ESC guidelines for radionuclide imaging of cardiac function. *Eur J Nucl Med Mol Imaging*. 2008;35:851–885.
- Setaro JF, Cleman MW, Remetz MS. The right ventricle in disorders causing pulmonary venous hypertension. *Cardiol Clin*. 1992;10:165–183.
- Bogaard HJ, Natarajan R, Henderson SC, Long CS, Kraskauskas D, Smithson L, Ockaili R, McCord JM, Voelkel NF. Chronic pulmonary artery pressure elevation is insufficient to explain right heart failure. *Circulation*. 2009;120:1951–1960.
- Dell'Italia LJ, Lembo NJ, Starling MR, Crawford MH, Simmons RS, Lasher JC, Blumhardt R, Lancaster J, O'Rourke RA. Hemodynamically important right ventricular infarction: follow-up evaluation of right ventricular systolic function at rest and during exercise with radionuclide ventriculography and respiratory gas exchange. *Circulation*. 1987;75:996–1003.
- Bogaard HJ, Abe K, Vonk Noordegraaf A, Voelkel NF. The right ventricle under pressure: cellular and molecular mechanisms of right-heart failure in pulmonary hypertension. *Chest*. 2009;135:794–804.
- Rigolin VH, Robiolio PA, Wilson JS, Harrison JK, Bashore TM. The forgotten chamber: the importance of the right ventricle. *Cathet Cardiovasc Diagn*. 1995;35:18–28.

27. Gorcsan J III, Murali S, Counihan PJ, Mandarino WA, Kormos RL. Right ventricular performance and contractile reserve in patients with severe heart failure: assessment by pressure-area relations and association with outcome. *Circulation*. 1996;94:3190–3197.
28. Zornoff LA, Skali H, Pfeffer MA, St John Sutton M, Rouleau JL, Lamas GA, Plappert T, Rouleau JR, Moye LA, Lewis SJ, Braunwald E, Solomon SD. Right ventricular dysfunction and risk of heart failure and mortality after myocardial infarction. *J Am Coll Cardiol*. 2002;39:1450–1455.
29. Dokainish H, Sengupta R, Patel R, Lakkis N. Usefulness of right ventricular tissue Doppler imaging to predict outcome in left ventricular heart failure independent of left ventricular diastolic function. *Am J Cardiol*. 2007;99:961–965.
30. Anavekar NS, Skali H, Bourgoun M, Ghali JK, Kober L, Maggioni AP, McMurray JJ, Velazquez E, Califf R, Pfeffer MA, Solomon SD. Usefulness of right ventricular fractional area change to predict death, heart failure, and stroke following myocardial infarction (from the VALIANT ECHO Study). *Am J Cardiol*. 2008;101:607–612.
31. Bristow MR, Zisman LS, Lowes BD, Abraham WT, Badesch DB, Groves BM, Voelkel NF, Lynch DM, Quaife RA. The pressure-overloaded right ventricle in pulmonary hypertension. *Chest*. 1998;114:101S–106S.
32. Massie B, Kramer BL, Topic N, Henderson SG. Hemodynamic and radionuclide effects of acute captopril therapy for heart failure: changes in left and right ventricular volumes and function at rest and during exercise. *Circulation*. 1982;65:1374–1381.
33. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, Tawakol A, Gerszten RE, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation*. 2007;116:1555–1562.
34. Quaife RA, Christian PE, Gilbert EM, Datz FL, Volkman K, Bristow MR. Effects of carvedilol on right ventricular function in chronic heart failure. *Am J Cardiol*. 1998;81:247–250.
35. Jain D, Zaret BL. Assessment of right ventricular function: role of nuclear imaging techniques. *Cardiol Clin*. 1992;10:23–39.

CLINICAL PERSPECTIVE

Right ventricular (RV) ejection fraction (EF) may often be low in patients with heart failure (HF) and reduced left ventricular (LV) EF. Studies of RVEF and outcomes in these patients are limited by small sample size and short follow-up. In the Beta-Blocker Evaluation of Survival Trial, 2708 HF patients with LVEF $\leq 35\%$ were followed for a mean of 2 years, and 2008 had data on baseline RVEF, estimated by gated-equilibrium radionuclide ventriculography. They had a mean RVEF of 35%, which was similar regardless of the cause of HF. Of these patients, 37% had normal RVEF ($\geq 40\%$), and 13% had RVEF $< 20\%$. Patients with reduced (versus normal) RVEF were more likely to be younger men with lower LVEF and longer duration of HF than those with higher RVEF. Compared with 27% death in those with RVEF $\geq 40\%$, 47% of those with RVEF $< 20\%$ died. In contrast, death rates for those with RVEF 20% to 29% and 30% to 39% were 32% and 35%, respectively. When we adjusted for age, LVEF, and other baseline characteristics, compared with RVEF $\geq 40\%$, only those with RVEF $< 20\%$ had a significant increased risk for all-cause mortality and HF hospitalization. These findings suggest that a decreasing RVEF is a marker of poor prognosis in HF patients with low LVEF. However, when RVEF is reduced to $< 20\%$, it may also have an intrinsic and independent effect on mortality. Future studies need to evaluate the underlying mechanism of RVEF impairment in systolic HF and therapies that can improve prognosis in those with low RVEF.