Assessment of right ventricular-arterial coupling by echocardiography in older HF patients with reduced to mid-range ejection fraction: Impact on survival

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Abstract

Echocardiography of right ventricular (RV)-arterial coupling obtained by the estimation of the ratio of the longitudinal annular systolic excursion of the tricuspid annular plane and pulmonary artery systolic pressure (TAPSE/PASP) has been found to be a remarkable prognostic indicator in patients with HF. Our aim was to evaluate the impact of TAPSE, PASP and their ratio in the prognostic stratification of outpatients with HF aged ≥70 years and reduced to mid-range ejection fraction (EF).

A complete echocardiographic examination was performed in 400 outpatients with chronic HF and left ventricular (LV) EF ≤ 50% who averaged 77 years in age. During a median follow-up period of 25 months (interquartile range: 8-46), there were 135 cardiovascular deaths. Two different Cox regression models were evaluated, one including TAPSE and PASP, separately, and the other with TAPSE/PASP. In the first model, LV end-systolic volume index, age, no angiotensin converting enzyme (ACE) inhibitor use, TAPSE, PASP and gender were found to be independently associated with the outcome after adjustment for demographics, clinical, biochemical, echocardiographic data. In the second model, TAPSE/PASP resulted the most important independent predictor of outcome (hazard ratio [HR]:0.07, p<0.0001) followed by LV end-systolic volume index, no ACE inhibitor use, age and gender. The use of the variable TASPE/PASP improved the predictive value of the new multivariable model (area under the curve [AUC] of 0.74 *vs* AUC of 0.71; p<0.05). TASPE/PASP improved the net reclassification (NRI = 14.7%; p<0.01) and the integrated discrimination (IDI = 0.04; p<0.01). In conclusion, the study findings showed that assessment of RV-arterial coupling by TAPSE/PASP was of major importance to assess the prognosis of patients with chronic HF and LV EF ≤50% aged ≥70 years.

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Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Authors' contribution: GMR, ADA, study design and data collection; SG, GLM, data collection; PF, supervision; MM, statistical analysis; FLD, study design and supervision. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Availability of data and materials: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Patient consent for publication: Not applicable.

Ethics approval: This retrospective, observational study was conducted in accordance with all relevant guidelines and procedures.

Funding: This study was not funded.

Key words: Echocardiography; heart failure; right ventricle.

Received for publication: 10 March 2020.
Accepted for publication: 9 April 2020.

Monaldi Archives for Chest Disease 2020; 90:1269
doi: 10.4081/monaldi.2020.1269

Introduction

Heart failure (HF) is highly prevalent in the elderly [1], with a one-year mortality rate of 35%, far higher than in the younger patients [2]. Several hemodynamic and echo-Doppler parameters have been found to be related to prognosis of elderly patients with chronic systolic HF, including lower left ventricular (LV) end-systolic volume index [3] and increased left atrium dimensions [4]. Pulmonary artery hypertension (PH) is a frequent finding with advancing age in the general population [5], and in HF patients [6,7], with evidence of a negative impact over clinical outcomes in the latter patients' population [8-12]. Moreover, the chronic overload of the right ventricle leads to right ventricular (RV) systolic dysfunction with negative prognostic implications [13]. As such, it would be interesting to further investigate the prognostic role of PH and RV dysfunction in elderly patients with HF. The assessment of RV function and pulmonary hemodynamics by measuring the longitudinal annular systolic excursion of the tricuspid annular plane (TAPSE) and pulmonary artery systolic pressure (PASP) is simple, feasible and clinically valuable [14]. Echocardiography of RV-arterial coupling obtained by the estimation of the ratio of the longitudinal annular systolic excursion of the tricuspid annular plane and pulmonary artery systolic pressure (TAPSE/PASP) has been found to be a remarkable prognostic indicator in patients with HF [15]. Based on these premises, the present study was designed to evaluate the impact of TAPSE, PASP and their ratio in the prognostic stratification of outpatients with HF aged ≥70 years and reduced to mid-range ejection fraction (EF).

Methods

Study patients

Four hundred consecutive outpatients referred to our echocardiographic laboratory between April 2006 and June 2016 were evaluated. Eligible patients had to have age ≥70 years, HF and LV EF ≤ 50%. The exclusion criteria were: myocardial infarction or unstable angina or coronary artery bypass graft or percutaneous coronary angioplasty in the previous 30 days, significant organic valvular diseases, congenital heart diseases and any life-threatening conditions with adverse prognosis other than cardiovascular disease. Forty-five patients were also excluded because of poor image quality that prevented the acquisition of adequate tricuspid regurgitation signals.

Echocardiography

In this retrospective, observational study, transthoracic two-dimensional and Doppler echocardiographic examination was carried out with an Acuson Sequoia C256 ultrasound instrument (Mountain View, CA, USA) and an iE33 X5-matrix Ultrasound instrument (Philips, Andover, MA, USA) with 2nd-harmonic imaging and a 3.5-MHz transducer. A complete M-mode, two-dimensional and Doppler echocardiogram was carried out in all study patients according to the recommendations of the European Association of Echocardiography/American Association of Echocardiography [16]. As surrogate marker of LV filling pressure, E wave deceleration time (EDT) was measured. Mitral regurgitation severity was graded according to the vena contracta method. Patients were considered to have moderate-to-severe mitral regurgitation if they had a vena contracta width ≥0.5 cm in the parasternal long-axis view. RV systolic function was evaluated by M-mode echocardiography using TAPSE. Retrograde jets from tricuspid regurgitation were recorded by continuous wave Doppler for the measurement of the regurgitant jet peak velocity. The peak velocity was assigned as the average among five tricuspid regurgitant envelopes of greatest maximal velocities and spectral density. The pressure gradient across the tricuspid valve was measured using the simplified Bernoulli equation. The estimated PASP was calculated as the sum of the tricuspid gradient and the estimated right atrial pressure derived on the basis of the inspiratory collapse of the inferior vena cava.

Study groups

First, patients were subdivided into four groups: TAPSE >14 mm and PASP <40 mmHg (group A), TAPSE >14 mmHg and PASP ≥40 mmHg (group B), TAPSE ≤14 mmHg and PASP <40 mmHg (group C) and TAPSE ≤14 mmHg and PAPS ≥40 mmHg (group D) [17,18]. Then, they were classified into two groups according to the ratio of TAPSE and PASP [19].

Follow-up data

The study end point was cardiovascular mortality. Survival data were obtained through follow-up of patients and telephone contacts and verified through local authority registry and hospital records.

Statistical analysis

Data were described as mean and standard deviation (SD) if continuous and as counts and percent if categorical. Differences were assessed by analysis of variance and Mann-Whitney test. They were compared between subgroups with Bonferroni *post-hoc* test and chi square test.

Receiver-operating characteristic (ROC) curves were generated to define cut-off values for dividing patients according to survival status and the Area under the Curve (AUC) was generated. DeLog test was utilized to compare ROC curves. Demographic, clinical, and echo variables were evaluated for the end point in a univariate Cox proportional hazard model. Variables showing a significant association with survival (p<0.1) were included in the multivariate Cox models to determine which of them was independently related to the prognosis. Non missing, non collinear, a priori defined patients characteristics were included in the Cox models. Data were analyzed using the Statistical Package for the Social Sciences version 10.0 for Windows statistical software program (SPSS, Chicago, IL, USA) and Statview 5.0 (Abacus Concepts, SAS Institute, Cary, NC, USA).

Results

Table 1 outlines demographics, clinical and echocardiographic characteristics of patients categorized according to TAPSE and PASP. Patients with TAPSE ≤14 mmHg and PAPS ≥40 mmHg had lower LV EF, higher LV volumes, shorter EDT, higher E/e', had a greater prevalence of moderate-to-severe mitral regurgitation, chronic kidney disease and were more often in atrial fibrillation. Table 2 describes the characteristics of patients classified according to their LV EF. In patients divided according to TAPSE/PASP (Table 3), lower LV EF, higher LV volumes, shorter EDT, higher E/e' and presence of atrial fibrillation and moderate-to-severe mitral regurgitation were more often associated with reduced TAPSE/PASP.

During a median follow-up period of 25.5 months (IQR: 8-46), 147 patients died. Among patients who died, there were 135 cardiovascular deaths. To assess predictors of cardiovascular mortality, two different Cox regression models were evaluated, one including TAPSE and PASP, separately, and the other with TAPSE/PASP. In the first model, LV end-systolic volume index, age, no angiotensin converting enzyme (ACE) inhibitor use, TAPSE, PASP and gender were found to be independently associated with the outcome after adjustment for demographics, clinical, biochemical, echocardiographic data. In the second model, TAPSE/PASP resulted the most important independent predictor of outcome followed by LV end-systolic volume index, age, no ACE inhibitor use and gender (Table 4).

The comparison of ROC (AUC) of TAPSE, PASP, LV EF and TAPSE/PASP is shown in Figure 1. A statistical significant difference was apparent between the AUCs of TAPSE/PASP and LVEF (p=0.022).

The use of the variable TAPSE/PASP improved the predictive value of the new multivariable model (area under the curve [AUC]

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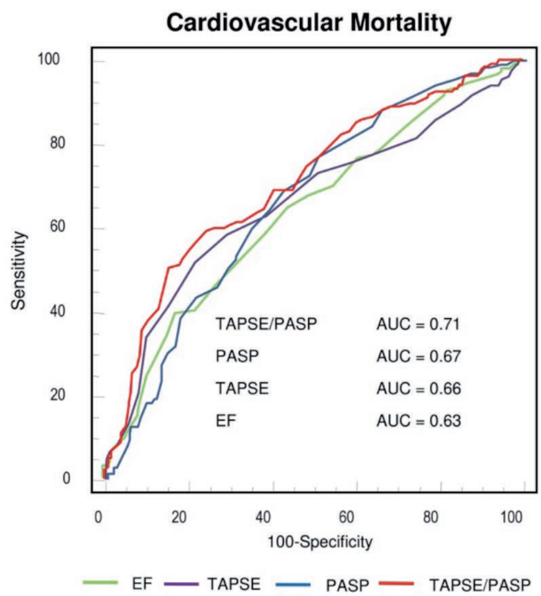

Figure 1. Comparison of Area Under Curves (AUC) of ROC analyses of LV EF, TAPSE, PASP and TAPSE/PASP. PASP, pulmonary artery systolic pressure; ROC, receiver operating characteristics; TAPSE, tricuspid annular systolic excursion.

of 0.74 *vs* AUC of 0.71; p<0.05). TAPSE/PASP improved the net reclassification (NRI = 14.7%; p<0.01) and the integrated discrimination (IDI = 0.04; p<0.01). The NRI of the model including TAPSE/PASP was 14.7% (p<0.01) higher than that of the model carrying TAPSE and PASP separately. IDI was 0.04 (p<0.01).

Kaplan-Meier survival plots in patients categorized according to TAPSE and PASP measures are shown in Figure 2A. When evaluating the combination of TAPSE and PASP, patients with normal RV function without PH had the lowest mortality. Patients with TAPSE ≤14mm and PASP <40 mmHg as well as those with increased PASP ≥40 mmHg and TAPSE >14mm had an intermediate prognosis. Low TAPSE and high PASP identified a population of patients with particularly poor survival. Figure 2B shows Kaplan-Meier survival plots of elderly patients classified according to TAPSE/PASP. Survival free from all-cause mortality in patients with reduced TAPSE/PASP was worse as compared to that of patients with a higher TAPSE/PASP.

Discussion

The results of this retrospective study indicate that right heart hemodynamics and function are of major importance to assess the prognosis of patients with chronic HF with reduced to mid-range

Table 1. Demographic, clinical and Doppler echocardiographic variables in patients with TAPSE >14 mm and PASP <40 mmHg (group A), patients with TAPSE >14 mmHg and PASP ≥40 mmHg (group B), patients with TAPSE ≤14 mmHg and PASP <40 mmHg (group C) and patients with TAPSE ≤14 mmHg and PAPS ≥40 mmHg (group D).

Variable	Group A (n=176)	Group B (n=128)	Group C (n=35)	Group D (n=61)	P value
Age (yrs)	77±5	78±5	77±5	78±4	NS
% of women	25	34	20	20	NS
Heart rate (beats/min)	70±12$^{++,\circ\circ}$	77±13	75±15	78±14	<0.0001
Atrial fibrillation, %	14$^{++,\circ\circ,\wedge\wedge}$	27$^{\pounds\pounds}$	31	48	<0.0001
Coronary artery disease (%)	56	61	54	62	NS
Diabetes (%)	17$^{\circ\circ}$	26	23	34	0.035
History of hypertension (%)	52	50	60	67	NS
eGFR <60 ml/min (%)	35$^{\circ\circ}$	41$^{\pounds}$	43	57	0.004
Systolic blood pressure (mmHg)	129±16	127±15	121±22	126±22	NS
Diastolic blood pressure (mmHg)	75±9	73±9	71±10	73±13	NS
Loop diuretics (%)	85	94	97	95	NS
Anti-aldosterone drugs (%)	40	42	38	34	NS
ACE inhibitors*(%)	88$^{\circ\circ,\wedge\wedge}$	81§	63	70	0.0005
Beta-blockers (%)	61	63	69	66	NS
NYHA class 3-4 (%)	14$^{++,\circ\circ,\wedge\wedge}$	37	40	49	0.0001
LV end-diastolic volume index (ml/m^2)	103±28$^{\circ\circ}$	110±36	105±38	118±39	0.016
LV end-systolic volume index (ml/m^2)	69±25$^{+,\circ\circ}$	76±29$^{\pounds}$	75±33	87±34	0.0006
LV ejection fraction (%)	35±8$^{+,\circ\circ,\wedge\wedge}$	33±7	30±10	28±8	<0.0001
Left atrial size (mm)	47±6$^{++,\wedge}$	49±6$^{\pounds\pounds}$	50±5$^{\&\&}$	54±7	<0.0001
Mitral regurgitation**(%)	10$^{++,\circ\circ,\wedge\wedge}$	40	43	54	<0.0001
E wave deceleration time (ms)	195±51$^{++,\circ\circ,\wedge\wedge}$	143±46§	167±60$^{\&\&}$	125±42	<0.0001
TAPSE (mm)	20±4$^{+,\circ\circ,\wedge\wedge}$	19±4$^{\pounds\pounds}$	12±2	12±2	<0.0001
PASP (mmHg)	32±5$^{\circ\circ,\wedge\wedge}$	47±7$^{\S\S,\pounds\pounds}$	34±5$^{\&\&}$	53±10	<0.0001

eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; NYHA, New York Heart Association; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure; E/e', mitral E peak velocity and averaged ratio of mitral to myocardial early velocities; NS, not significant; *including angiotensin receptors blockers; **moderate-to-severe; $^{+}$p<0.05 and $^{++}$p<0.01 Group A *vs* Group B; $^{\wedge}$p<0.05 and $^{\wedge\wedge}$p<0.01 Group A *vs* Group C; $^{\circ\circ}$p<0.01 Group A *vs* Group D; §p<0.05 and §§p<0.01 Group B *vs* Group C; $^{\pounds}$p<0.05 and $^{\pounds\pounds}$p<0.01 Group B *vs* Group D; $^{\&}$p<0.05 and $^{\&\&}$p<0.01 Group C *vs* Group D.

EF aged ≥70 years. The coexistence of PH and RV dysfunction was associated with a more advanced NYHA class, a more compromised LV EF, signs of elevated LV filling pressures, a greater prevalence of moderate-to-severe mitral regurgitation, chronic renal insufficiency, and atrial fibrillation. The ratio of TAPSE and PASP was the most important independent predictor of outcome at Cox regression analysis.

Several hemodynamic and echo-Doppler measures have been

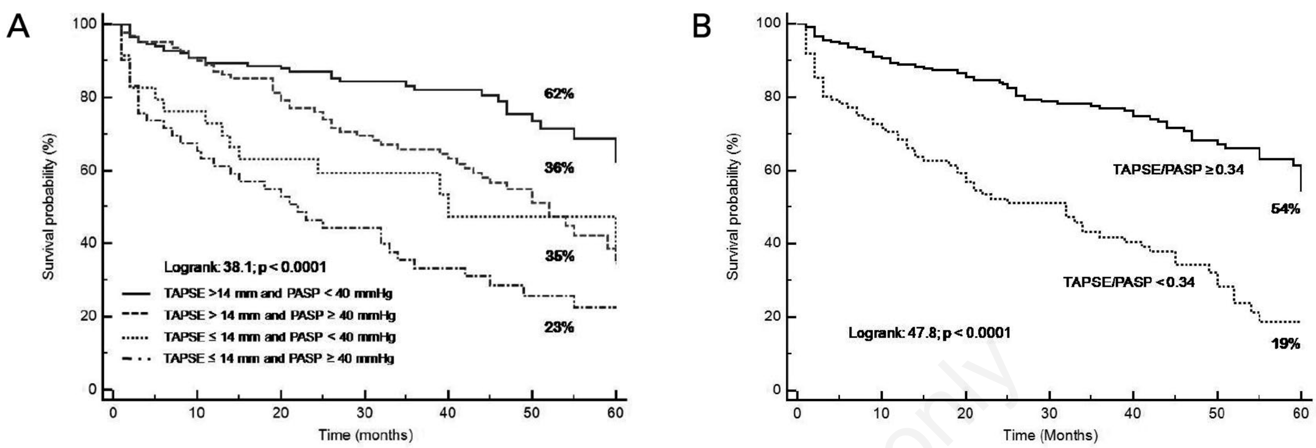

Figure 2. A) Kaplan-Meier plots showing survival free from all-cause mortality in the elderly cohort with heart failure and left ventricular ejection fraction ≤50% divided according to TAPSE >14 mm and PASP <40 mmHg (group A), TAPSE >14 mmHg and PASP ≥40 mmHg (group B), TAPSE ≤14 mmHg and PASP <40 mmHg (group C) and TAPSE ≤14 mmHg and PAPS ≥40 mmHg (group D). B) Kaplan-Meier plots showing survival fr ee from all-cause mortality in the elderly cohort with heart failure and left ventricular ejection fraction ≤50% divided according to the ratio of tricuspid annular plane systolic excursion and estimated pulmonary artery systolic pressure (TAPSE/PASP).

Table 2. Demographic, clinical and Doppler echocardiographic variables in patients divided according to reduced to mid-range ejection fraction.

Variable	LV EF <40 (n=315)	EF ≥40% (n=85)	p value
Age (yrs)	77±5	78±5	NS
% of women	24	29	NS
Heart rate (beats/min)	75±13	69±13	0.0002
Atrial fibrillation, %	23	31	NS
Coronary artery disease (%)	64	54	NS
Diabetes (%)	25	1/	NS
History of hypertension (%)	54	37	0.005
eGFR <60 ml/min (%)	45	32	0.027
Systolic blood pressure (mmHg)	126±18	131±16	0.035
Diastolic blood pressure (mmHg)	74±10	76±10	NS
Loop diuretics (%)	92	78	0.0002
Anti-aldosterone drugs (%)	40	39	NS
ACE inhibitors* (%)	79	88	NS
Beta-blockers (%)	62	68	NS
NYHA class 3-4 (%)	31	20	0.039
LV end-diastolic volume index (ml/m^2)	115±33	82±22	<0.0001
LV end-systolic volume index (ml/m^2)	82±28	47±14	<0.0001
LV ejection fraction (%)	30±6	44±3	<0.0001
Left atrial size (mm)	50±6	49±10	NS
Mitral regurgitation** (%)	34	13	0.0002
E wave deceleration time (ms)	163±56	140±56	0.0007
TAPSE (mm)	17±5	19±5	0.0067
PASP (mmHg)	41±11	37±11	0.0032

*Including angiotensin receptors blockers; **moderate-to-severe; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; NYHA, New York Heart Association; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure.

found to be related to the outcome of elderly patients with chronic systolic HF, but little is known regarding the prognostic role of combination of pulmonary hypertension and RV dysfunction [20]. To date, the determination of PASP has become a routine part of an echo-Doppler examination since PASP can be estimated by adding right atrial pressure to the tricuspid pressure gradient derived from the tricuspid regurgitation velocity [21]. Tricuspid regurgitation is very common and increases in prevalence and severity as PH increases. However, echo-Doppler tends to overestimate PASP, especially when pressures are normal or only mildly elevated. Hence, Doppler-derived PASP between 35 mmHg and 45 mmHg should be interpreted with caution [22]. On the other hand, echo-Doppler can rule out PH. A recent study demonstrated that PASP <45 mmHg confidently excludes PH in heart transplant candidates [23].

TAPSE is the most extensively used parameter for evaluation of RV function. This parameter is simple, accurate and reproducible and its prognostic value has been verified. The prognostic significance of TAPSE in patients with systolic HF and dilated cardiomyopathy has been demonstrated by Ghio *et al.*, who found that TAPSE ≤14 mm identified patients with the worst outcome [17]. Recently, a compromised RV-arterial coupling, as defined by a TAPSE/PASP ratio <0.36, was found to be a remarkable prognostic indicator superior than assessing RV function and PASP separately [19]. These findings were substantially confirmed by our results, where a TAPSE/PASP ratio of 0.34 was found to be the best threshold to discriminate survival among elderly patients with chronic HF with reduced to mid-range EF. It is apparent thought that a compromised RV-arterial coupling can better stratify patients than PAPS and TAPSE alone, because it depends not only on a lower TAPSE for a given RV pressure load, but also on reduced contractile function of the right ventricle. At Cox regression analyses, it emerged that TAPSE/PASP outperformed parameters of LV function for predicting the outcome of HF patients aged ≥70 years.

Although the finding of an association of PH and RV dysfunction with the outcome of HF patients is not new [18], the results of this study show that a reduced TAPSE/PASP in chronic HF with reduced to mid-range EF is especially important in elderly patients with chronic HF with reduced to mid-range EF. In most of patients with LV systolic dysfunction and HF, the development of PH is related to the degree of mitral regurgitation and to the presence of LV diastolic dysfunction and restrictive LV filling [24-27]. Medial hypertrophy of muscular pulmonary arteries and arterial intimal fibrosis secondary to congestive vasculopathy may contribute to exacerbate PH and RV overload [28]. This is often followed by the occurrence of RV dysfunction and the increase in central venous pressure. The compromised RV performance can raise renal venous pressure that drives the filtration through kidneys and this might impair renal function [29]. The prognostic importance of RV overload and dysfunction in patients with chronic HF aged ≥70 years and the finding of an association with advanced LV diastolic dysfunction and more than mild mitral regurgitation suggests that the exposure to a chronic burden of retrograde transmission of elevated left sided filling pressures is of

Table 3. Demographic, clinical and Doppler echocardiographic variables in patients divided according to TAPSE/PASP.

Variable	TAPSE/PASP ≥0.34 (n=290)	TAPSE/PASP <0.34 (n=110)	p-value
Age (yrs)	77±5	78±5	NS
% of women	27	20	NS
Heart rate (beats/min)	72±12	79±13	<0.0001
Atrial fibrillation, %	18	44	<0.0001
Coronary artery disease (%)	57	66	NS
Diabetes (%)	20	31	0.021
History of hypertension (%)	51	64	0.026
eGFR <60 ml/min (%)	39	49	0.031
Systolic blood pressure (mmHg)	128±16	124±20	0.024
Diastolic blood pressure (mmHg)	74±9	73±11	NS
Loop diuretics (%)	88	97	0.006
Anti-aldosterone drugs (%)	40	37	NS
ACE inhibitors* (%)	82	77	NS
Beta-blockers (%)	61	67	NS
NYHA class 3-4 (%)	18	23	0.0001
LV end-diastolic volume index (ml/m^2)	105±31	115±39	0.012
LV end-systolic volume index (ml/m^2)	71±27	83±34	NS
LV ejection fraction (%)	34±7	29±9	<0.0001
Left atrial size (mm)	48±6	51±10	NS
Mitral regurgitation** (%)	23	46	<0.0001
E wave deceleration time (msec)	180±55	130±45	<0.0001
TAPSE (mm)	20±4	13±3	<0.0001
PASP (mmHg)	36±8	51±10	<0.0001

*Including angiotensin receptors blockers; **moderate-to-severe; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; NYHA, New York Heart Association; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure.

Table 4. Prognostic determinants in the univariable and multivariable Cox regression analyses in patients with chronic HF with reduced to mid-range EF aged ≥70 years.

	Wald Chi-squared	p-value	Category	Hazard ratio	95% CI
Univariable					
TAPSE/PASP	34.9	<0.0001	Per unit	0.043	0.015-0.12
LV end-systolic volume index	25.8	<0.0001	-	1.01	1.01-1.02
LV ejection fraction	23.9	<0.0001	-	0.95	0.93-0.97
TAPSE	24.8	<0.0001	-	0.90	0.87-0.94
PASP	22.6	<0.0001	-	1.04	1.02-1.05
Mitral regurgitation	20.0	<0.0001	Yes *vs* no	2.00	1.55-3.01
LV end-diastolic volume index (ml/m^2)	20.0	<0.0001	Per unit	1.01	1.00-1.01
E/A ratio	18.8	<0.0001	-	1.02	1.01-1.02
No ACE inhibitors	17.1	<0.0001	-	2.17	1.51-3.12
NYHA	14.3	<0.0001	-	1.67	1.28-2.18
E wave deceleration time (ms)	13.9	<0.0001	-	0.99	0.98-0.99
Age	10.3	0.001	-	1.06	1.02-1.10
Left atrial size	9.5	0.002	-	1.04	102-1.07
eGFR	8.0	0.005	<60 ml/m^2 *vs* ≥60 ml/m^2	1.64	1.17-2.30
Diabetes	5.9	0.015	Yes *vs* no	1.59	1.09-2.31
Atrial fibrillation	5.6	0.018	-	1.57	1.08-2.27
Multivariable 1					
LV end-systolic volume index	11.7	0.001	Per unit	1.01	1.00-1.02
TAPSE	11.6	0.001	-	0.93	0.89-0.97
No ACE inhibitors	10.5	0.001	Yes *vs* no	1.85	1.28-2.68
Age	10.3	0.001	Per unit	1.06	1.02-1.10
Gender	3.4	0.064	-	1.50	1.00-2.31
PASP	5.4	0.02	-	1.02	1.00-1.03
Multivariable 2					
TAPSE/PASP	24.1	<0.0001	Per unit	0.07	0.024-2.02
LV end-systolic volume index	12.3	<0.0001	-	1.01	1.00-1.02
No ACE inhibitors	9.4	0.002	Yes *vs* no	1.79	1.24-2.60
Age	8.9	0.003	Per unit	1.06	1.02-1.10
Gender	4.31	0.038	Yes *vs* no	1.56	1.03-2.37

TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure; ACE, angiotensin converting enzyme; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; LV, left ventricular.

Limitations

The difference in number of patients in study groups is relevant. In contrast to PH, definitions of abnormal RV function are arbitrary and no consensus exists. The complex geometry of the right ventricle complicates the echo-Doppler assessment of RV performance. TAPSE has been shown to be affected by global heart motion and can be influenced by diastolic parameters and this may sometimes misguide clinicians. Therefore, other methods for assessing RV function have been proposed [30]. The quantitative assessment of RV function through fractional area change was also predictive of outcome in patients with left ventricular dysfunction [31]. Unfortunately this method is frequently affected by sampling errors (image quality, endocardium not clearly viewable, incorrect projection). Tissue Doppler evaluation (S') of RV is relatively simple, but limited to a small region of the free wall of the RV [32]. Three-dimensional evaluation of RV might be considered the most accurate technique however this new echocardiographic technique is not yet widespread [33].

Conclusions

Echocardiography of RV-arterial coupling seems valuable to risk stratify elderly patients with HF and reduced to mid-range LV EF.

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