Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis

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Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S, Temporelli PL, Arena R. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. Am J Physiol Heart Circ Physiol 305: H1373–H1381, 2013. First published August 30, 2013; doi:10.1152/ajpheart.00157.2013.—Echo-derived pulmonary arterial systolic pressure (PASP) and right ventricular (RV) tricuspid annular plane systolic excursion (TAPSE; from the end of diastole to end-systole) are of basic relevance in the clinical follow-up of heart failure (HF) patients, carrying two- to threefold increase in cardiac risk when increased and reduced, respectively. We hypothesized that the relationship between TAPSE (longitudinal RV fiber shortening) and PASP (force generated by the RV) provides an index of in vivo RV length-force relationship, with their ratio better disclosing prognosis. Two hundred ninety-three HF patients with reduced (HFrEF, LV dysfunction) and preserved left ventricular (LV) ejection fraction (HFpEF, preserved LV diastolic function) were frequently presenting with higher PASP and lower TAPSE. HFrEF and HFpEF patients exhibited a similar distribution along the regression line. The median follow-up duration was 20.8 mo. TAPSE vs. PASP relationship showed a downward regression line shift in nonsurvivors who were more frequently presenting with higher PASP and lower TAPSE. HFpEF and HFrEF patients exhibited a similar distribution along the regression line. Given the TAPSE, PASP, and TAPSE-to-PASP ratio (TAPSE/PASP) collinearity, separate Cox regression and Kaplan-Meier analyses were performed: one with TAPSE and PASP as individual measures, and the other combining them in ratio form. Hazard ratios for variables retained in the multivariate regression were as follows: TAPSE/PASP $\leq$ 0.36 mm/mmHg [hazard ratio (HR): 10.4, $P < 0.001$]; TAPSE $\leq$ 16 mm (HR: 5.1, $P < 0.01$); New York Heart Association functional class $\leq$ 3 (HR: 4.4, $P < 0.001$); E/e’ (HR: 4.1, $P < 0.001$). This study shows that the TAPSE vs. PASP relationship is shifted downward in nonsurvivors with a similar distribution in HFpEF and HFrEF, and their ratio improves prognostic resolution. The TAPSE vs. PASP relationship as a possible index of the length-force relationship may be a step forward for a more efficient RV function evaluation and is not affected by the quality of LV function.

Disease progression that carry a two- to threefold increase in risk of cardiac death, irrespective of degree of left ventricular (LV) dysfunction (6–8, 14, 15, 29).

Reasons for RVF in HF patients are ischemic heart disease, unfavorable left to RV interdependence, and pulmonary hypertension (PH). PH is the primary mechanism of RVF with a variable magnitude according to interindividual susceptibility and different case-series (21). Both PH (2, 4, 18) and RVF (7, 8, 10, 14, 15, 29) are independently related to clinical worsening, and a cumulative risk prediction exists for RVF and excessive levels of pulmonary arterial systolic pressure (PASP) (15, 17).

Assessment of RV dimensions, geometry, and function is affected by the complex chamber shape requiring assumptions by noninvasive techniques. Notwithstanding, there is agreement in considering echocardiography as the most immediate and simple approach to obtain reliable markers of RV systolic function in cardiopulmonary disorders (32). Among the echo-derived variables used for RV systolic function assessment, tricuspid annular plane systolic excursion (TAPSE) is easily obtainable, reproducible, and highly predictive of poor outcome in a wide spectrum of HF cohorts (6, 10, 11, 26).

The direct measure of PASP is the gold standard for securing PH diagnosis, especially in cases of uncertain interpretation (20), but right heart catheterization may not be seen as the initial approach to pulmonary pressure assessment (21). Conversely, Doppler estimation of PASP is feasible, measurable in a high rate of cases (16, 31), and clinically relevant in community and population-based studies (4, 27).

Whereas the pathophysiological, clinical, and prognostic significance of each of these two common practice measured variables is well established, they are generally seen as single numbers practically overlooking the basic concept that the RV is highly sensitive to the imposed pressure load. A combined assessment would provide more physiology-based information (1). Primarily, relating the shortening relative to the force developed may translate into an estimation of RV performance status that leads to a more refined approach in the clinical decision-making process and prognosis assessment in daily clinical practice.

Accordingly, we hypothesized that the relationship between TAPSE (length) and PASP (developed pressure) may be used and proposed as an in vivo expression of the cardiac length-force relationship, and that combining these variables under a
ratio may better disclose prognosis compared with either variable in isolation.

METHODS

Patients. From March 2005 to September 2010, 348 consecutive patients with known HF were screened for study enrollment at the time of referral for a clinically indicated hemodynamic and functional assessment. Patients underwent a two-dimensional echocardiographic-Doppler evaluation. Inclusion criteria were as follows: 1) history, signs, symptoms, and treatment of HF associated with either reduced LV ejection fraction (HFrEF) or preserved ejection fraction (HFpEF); and 2) levels of NH3-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) > 220 pg/ml. A total of 14 patients were excluded for technically inadequate echocardiographic windows. Included patients were monitored in this prospective observational study. Overall, 185 of patients presented with ischemic, and 96 with idiopathic, etiology. In the HFpEF group, six patients had Fabry disease, and six had postmyocarditis. The study was approved by the local Ethical Institutional Review Board, and informed consent was obtained from all subjects before enrollment.

Echocardiography and TAPSE measurement. Echocardiographic imaging was performed using a Philips IE33 and a 5.2-MHz transducer (Philips Medical Systems, Andover, MA). A two-dimensional Doppler examination was performed using a prespecified echocardiographic protocol using views specifically designed to optimize RV imaging. To obtain TAPSE, the apical four-chamber view was used, and an M-mode cursor was placed through the lateral tricuspid annulus in real time. Offline, the brightness was adjusted to maximize the contrast between the M-mode signal arising from the tricuspid annulus and the background. TAPSE was measured as the peak excursion of the tricuspid annulus (millimeters) from the end of diastole to end systole, with values representing TAPSE being averaged over three to five beats (13).

Conventional Doppler and tissue Doppler imaging measurements. The tissue Doppler imaging (TDI) of the mitral annulus movement was obtained from the apical four-chamber view. A 1.5-mm sample volume was placed sequentially at the lateral and septal annular sites, and the derived variables were averaged (22). Analysis was performed for the systolic (S’) and the early (e’ and late (a’) diastolic peak velocities. Pulsed-wave Doppler echocardiography was used to assess mitral peak early (E) and late (A) wave flow velocity. The ratio of early transmitial flow velocity to annular velocity (E/e’) was considered as an index of mean LV filling pressure (19). Adequate mitral and tissue Doppler signals were recorded in all patients.

RV systolic pressure was determined from the tricuspid regurgitation (TR) jet velocity using the simplified Bernulli equation, and combining this value with an estimate of the right atrial pressure by the diameter and collapsibility of the inferior vena cava that was added to the calculated gradient to yield PASP (25, 30). Because subjects had no significant RV outflow tract or pulmonic valve obstruction, RV systolic pressure was considered equal to PASP.

TR was evaluated in the apical four-chamber view, the parasternal short-axis view at the level of the aortic valve, and the RV inflow view, and its severity, using the jet area/right atrial area method, was graded as follows (mild if the regurgitant jet area/right atrial area was <19%; moderate if 20–40%; severe if >41%) (30). All measurements were performed by two senior researchers who read the recordings in a blinded manner and without knowledge of the clinical diagnosis.

Blood sampling procedures and hormonal assays. All patients had a measurement of plasma NT-pro-BNP. Venous blood samples were obtained after at least 30 min of rest and collected in tubes containing an ethylenediamine tetraacetic acid buffer. They were immediately placed on ice and centrifuged at 4°C. Plasma samples were stored at -20°C until assay. The time between NT-pro-BNP and echo measurements was 4 ± 3 days.

Event tracking and endpoints. Patients were tracked for cardiac mortality via hospital and outpatient medical chart review and were followed by the HF program at San Paolo Hospital, Milano, providing a high likelihood that all events were captured. Any death with a cardiac-related diagnosis was considered an event. Cardiac-related mortality was defined as death directly resulting from failure of the cardiac system. An example fitting this definition is myocardial infarction followed by cardiac arrest. Clinicians were not involved in decisions regarding cause of death. Subjects having a noncardiac death or undergoing a heart transplant/LV assist device implantation were treated as censored cases at the time of the event.

Statistical analysis. Statistical software packages (SPSS 19.0, Chicago, IL, and R, http://www.r-project.org/) was used to perform all analyses. Continuous and categorical data are reported as means ± SD and as percentages, respectively. Independent t-tests assessed differences in clinical, tissue Doppler echocardiography, and neurohormonal variables between subgroups of patients, according to event status. Linear regression analysis was used to assess the relationship between PASP (independent variable) and TAPSE (dependent variable) according to survivors vs. nonsurvivors, HFrEF vs. HFpEF, and a TAPSE threshold of <16 mm. One-way analysis of covariance was used to determine homogeneity-of-regression according to the aforementioned linear regression subgrouping. Univariate and multivariate (forward stepwise method; entry and removal value 0.05 and 0.10, respectively) Cox regression analysis was used to assess the prognostic value of key clinical, tissue Doppler echocardiography, and neurohormonal variables. For variables retained in the multivariate regression, hazard ratios were generated using optimal dichotomous threshold values. Previously established dichotomous threshold values for TAPSE, PASP, and E/e’ measurements were used for survival analysis in the present study (22). Since TAPSE-to-PASP ratio (TAPSE/PASP) has not previously been assessed for prognostic value, a receiver operating characteristic (ROC) curve analysis was used to identify the optimal dichotomous threshold value. Moreover, given the variability in NT-pro-BNP ranges among different HF cohorts, a ROC curve analysis was again used to identify the optimal dichotomous threshold value. Kaplan-Meier analysis was used to assess the differences in survival among subjects according to dichotomous classification of variables retained in the Cox multivariate regression analysis. The strength of univariate and multivariate predictors was compared using the concordance index. The log-rank test determined statistical significance among the risk categories for all Kaplan-Meier analyses. Given the collinearity issues between both TAPSE and PASP and the TAPSE/PASP, separate Cox regression models and Kaplan-Meier analyses were performed: the first with TAPSE and PASP as individual measures, and the second combining them as a single value in ratio form. A P value < 0.05 was considered statistically significant for all tests. One-way ANOVA assessed differences in TAPSE/PASP according to NT-pro-BNP quartiles. Tukey’s honestly significant difference was used to determine differences in subgroups when the one-way ANOVA P value was < 0.05. The evaluation of prognostic end points was blind to the TAPSE and PASP relationship. The end points were evaluated by an adjudication committee of two persons.

RESULTS

Patient population. Table 1 lists the demographic and hemodynamic variables according to major cardiac event status. With the exception of New York Heart Association (NYHA) class, which was significantly higher in subjects who died during the tracking period, demographic characteristics were similar among subgroups. However, Doppler and TDI echocardiography measures, TR, NT-pro-BNP, and TAPSE were significantly worse in subjects who died compared with those who survived during the tracking period. Table 2 reports the
demographic and hemodynamic variables of patients classified as either HFrEF or HFpEF. HFrEF patients were slightly, albeit significantly, younger, predominantly male, with ischemic etiology. TAPSE, NT-pro-BNP, Doppler, and TDI echocardiography measures were similar in both groups.

Follow-up on survival. Among the 334 patients initially enrolled, 25 did not fulfill the eligibility criteria, 9 did not provide their consent to be included in the study follow-up, and 7 were excluded because they were lost at follow-up. The median follow-up duration was 20.8 mo. There were 47 deaths during the 4-yr tracking period. The average yearly event rate was 8.1%.

TAPSE vs. PASP relationship and ratio. Figure 1 reports the TAPSE vs. PASP relationship and shows a downshift of the regression line for nonsurvivors vs. survivors (A), although the slope of the regression line was similar (P = 0.367). Nonsurvivors exhibited a more unfavorable relationship, having higher PASP and lower TAPSE values, respectively. Figure 1 also shows the regression line for HFrEF and HFpEF (B) that was significantly different (P = 0.009), despite a similar distribution across the respective TAPSE and PASP. When patients were separated according to TAPSE <16 mm, a downward shift occurred for TAPSE <16 mm group, with the slope of the regression significantly different (P = 0.048) (Fig. 1C). No correlation was found between TAPSE and LV ejection fraction (LVEF) (r² = 0.096, P value = 0.8). Figure 2 presents the average TAPSE/PASP distribution according to NYHA functional class. The Kaplan Meier survival curves according to TAPSE/PASP quartiles distribution are reported in Fig. 3.

TAPSE and PASP coefficient of variation. The intraobserver coefficient of variation (comparing paired readings obtained by the same observer on two separate occasions) was 3% and 4% for TAPSE and PASP measures, respectively. The interobserver coefficient of variation (comparing results obtained and analyzed by two observers for the same subject) was 3.5% for TAPSE and 4.7% for PASP variables.

Univariate and multivariate analysis. Table 3 lists the univariate and multivariate Cox regression analyses. When measures were assessed as continuous variables, age, NYHA class,
all tissue Doppler echocardiography measures, and NT-pro-BNP were significant univariate predictors. TAPSE/PASP appeared to improve univariate prediction. In the first multivariate regressions, TAPSE demonstrated the highest $R^2$, whereas NYHA class and E/e' were retained in the regressions. In the second multivariate regression, TAPSE/PASP demonstrated the highest $R^2$, whereas only NYHA class was retained in the regression as a secondary prognostic marker. The concordance index demonstrated slight improvement in the predictive model for the second multivariate regression.

ROC curve analysis revealed that the optimal dichotomous threshold for TAPSE/PASP was $<= 0.36$ mm/mmHg (area under the curve: 0.78, 95% confidence interval: 0.75–0.86, sensitivity 83%, specificity 72%, $P < 0.001$). Moreover, for this HF cohort, the optimal dichotomous threshold for NT-pro-BNP was $<= 1.060$ pg/ml (area under the curve: 0.75, 95% confidence interval: 0.67–0.82, sensitivity 68%, specificity 91%, $P < 0.001$).

Table 4 lists the hazard ratios for dichotomous expressions of all variables retained in the multivariate Cox regression analyses. While all were highly significant, TAPSE/PASP expressed dichotomously was slightly stronger compared with other variables.

Figure 4 illustrates the Kaplan-Meier analysis using TAPSE/PASP and NYHA class. Survival became progressively worse as the number of unfavorable responses increased.

**DISCUSSION**

Present findings provide some new insights into RV function evaluation in HF with both pathophysiological and clinical implications. Overall, the information attained seems to be valuable in the daily practice when assessing the right heart in HF syndrome by echocardiography. According to the hypothesis tested, we propose that the relationship TAPSE vs. PASP, taken as an index of in vivo RV length vs. developed force, provides a more comprehensive noninvasive assay of RV contractile state that adds to the information offered by either variable considered separately.

The proposed approach for assessing RV contractile performance separates different relationships across mortality rate (survivors vs. nonsurvivors) and broadly applies to cardiac failure, irrespective of its predominant systolic or diastolic origin (HFrEF and HFpEF). In addition, the combination of both variables under a ratio emerged as a strong and independent predictive variable [hazard ratio (HR) 10.3] among those retained in the multivariate regression model.

Clinical significance of noninvasive right heart disease evaluation. During recent years, the right heart systolic function has been repeatedly found as a crucial determinant of

![Fig. 1. Plot of tricuspid annular plane systolic excursion (TAPSE)/pulmonary arterial systolic pressure (PASP) relationship according to survivors vs. non-survivors (A), heart failure reduced ejection fraction (HFrEF) vs. heart failure preserved ejection fraction (HFpEF; B), and TAPSE (cutoff $\leq 16$ mm; C).](image)

![Fig. 2. Average TAPSE-to-PASP ratio (TAPSE/PASP) distribution according to New York Heart Association (NYHA) functional class. *$P < 0.05$.](image)
outcome in HF populations, irrespective of the imaging technique applied or the variables used for assessing RV function (6–8, 11, 14, 15, 23, 29).

In daily clinical practice, the assessment of RV function is essentially based on echocardiography, and most echo- and Doppler-derived variables related to systolic function provide clinical insights and relevant prognostic indications. Among others, TAPSE is increasingly utilized due to its ease of measurement, high reproducibility, and robust predictive power, which has been reported to be equal to or even superior to other echo-Doppler indexes of RV function (such as RV fractional area changes, TDI peak systolic velocity) (20–22, 32). In addition, TAPSE can be derived in the vast majority of patients, regardless of HR and rhythm, extending the advantages of its measurement to patients with elevated HR and atrial fibrillation. Interestingly, the most recent findings suggest that TAPSE is also predictive in patients with HFpEF with a 1-yr mortality rate of 9% for patients in the lower TAPSE quartile (6). Our data confirm the information that TAPSE has strong predictive value and expand the evidence by analyzing a heterogeneous population with different severity and both HFrEF and HFpEF. Whereas initial studies investigating the predictive value of TAPSE have identified a quite low cutoff as prognostic (>14 mm), recent evidence obtained in large populations of patients, analyzed also according to quartile subdivisions (6, 8), have suggested that TAPSE has the same ability even at a higher threshold (6). In agreement with these findings, in the first multivariate model, a cutoff of 16 mm emerged.

Legend for Figure 3

<table>
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<tr>
<th>Months</th>
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<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
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<td>124</td>
<td>98</td>
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<td>Group A</td>
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<td>Group B</td>
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<td>34</td>
<td>26</td>
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<td>Group C</td>
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<td>42</td>
<td>20</td>
<td>16</td>
<td>11</td>
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<tr>
<td>Group D</td>
<td>78</td>
<td>50</td>
<td>19</td>
<td>13</td>
<td>7</td>
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<tr>
<th>Subjects</th>
<th>Events</th>
<th>% Event-Free Survival</th>
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<tr>
<td>A TAPSE/PASP &gt;0.64 mm/mmHg</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>B TAPSE/PASP 0.50-0.64 mm/mmHg</td>
<td>75</td>
<td>6</td>
</tr>
<tr>
<td>C TAPSE/PASP 0.36-0.49 mm/mmHg</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>D TAPSE/PASP &lt;=0.35 mm/mmHg</td>
<td>78</td>
<td>34</td>
</tr>
</tbody>
</table>

Log-rank: 78.881 p<0.0001

Fig. 3. Kaplan Meier analysis according to TAPSE/PASP quartiles.
as the strongest, albeit slightly, multivariate predictor. Interestingly enough, TAPSE emerged as a better predictor compared with a series of well-recognized prognostic variables such as E/e', LVEF, and age, whereas it performed similarly compared with PASP, prospecting the utility of combining both variables for a more comprehensive clinical decision-making.

**TAPSE vs. PASP relationship.** Despite the fact that several invasive and noninvasive techniques have been used for assessing RV function, clinically applicable noninvasive measures of the RV contractile performance are lacking, and data are confined to isolated experimental settings by using pressure-volume loop analysis (3, 9, 12) or the single-beat technique (5).

We propose a counterintuitive and quite simple approach to assess in vivo RV contraction by plotting fiber longitudinal shortening (TAPSE) vs. the force generated for overcoming the imposed load (PASP). The proposed method seems easy and safe to apply, performing very well for disease severity separation without a significant confounding influence of HR and TR. Indeed, more severe patients and nonsurvivors were distributed along a downward shifted regression line compared with survivors. This pattern seems not to be simply due to a lower TAPSE for a given systolic load in nonsurvivors, but also to reduced contractile properties of the RV, as suggested by a steeper slope of the TAPSE vs. PASP relationship in cases with TAPSE < 16 mm. Remarkably, the overall performance relationship for RV function in the HFpEF subgroup was similar as in the HFrEF subgroup. Along with this similarity, HFpEF and HFrEF were homogenously distributed across the relationship, suggesting that a similar RV dysfunction may occur, irrespective of LV morphological characteristics and predominance of systolic or diastolic dysfunction. Even more, no correlation was found between TAPSE and LVEF, making it unlikely that LV systolic function had a major role in determining TAPSE changes. These observations are consistent with the emerging evidence that the prevalence of left-sided PH is similar (28) or even higher (23) in HFpEF. Furthermore, average PASP, TAPSE, and NT-pro-BNP levels were similar in the HFrEF and HFpEF subgroups.

**TAPSE/PASP and NYHA functional class.** An additional aim of our study was to test the prognostic accuracy of TAPSE/PASP with the assumption that the combination of the two variables may improve risk stratification. The TAPSE/PASP emerged as a strong and independent predictor of mortality.

Table 3. Survival analysis for key clinical, Doppler, and tissue Doppler echocardiography and neurohormonal variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>C-Index</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.00–1.07)</td>
<td>0.55</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sex</td>
<td>1.31 (0.63–2.71)</td>
<td>0.52</td>
<td>0.46</td>
</tr>
<tr>
<td>HF etiology</td>
<td>1.39 (0.77–2.53)</td>
<td>0.51</td>
<td>0.28</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.46 (2.28–5.26)</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR</td>
<td>1.01 (0.96–1.06)</td>
<td>0.51</td>
<td>0.64</td>
</tr>
<tr>
<td>TR</td>
<td>1.75 (1.24–2.48)</td>
<td>0.63</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.97 (0.94–1.00)</td>
<td>0.61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PASP</td>
<td>1.08 (1.05–1.10)</td>
<td>0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE</td>
<td>0.73 (0.66–0.80)</td>
<td>0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE/PASP</td>
<td>2.10 (1.70–2.58)</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e'</td>
<td>1.12 (1.08–1.16)</td>
<td>0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td>1.00 (1.00–1.00)</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

C-index, concordance index; HR, heart rate; TR, tricuspid regurgitation. *Retained in multivariate regression. †TAPSE and PASP separately entered into the multivariate analysis. ‡TAPSE/PASP entered as a derived ratio into the multivariate analysis.

Table 4. Hazard ratios for variables retained in the multivariate regression when expressed as optimal dichotomous threshold

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dichotomous Threshold</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>TAPSE/PASP</td>
<td>≤50.9 (χ^2)</td>
<td>5.4–19.8</td>
<td>&lt;0.001</td>
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<tr>
<td>TAPSE</td>
<td>≤49.2 (Residual χ^2)</td>
<td>10.3</td>
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<tr>
<td>NYHA class</td>
<td>≤12.1 (Residual χ^2)</td>
<td>0.83</td>
<td>&lt;0.001</td>
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<td>E/e'</td>
<td>≤1.1 (Residual χ^2)</td>
<td>0.30</td>
<td></td>
<td></td>
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<tr>
<td>NT-pro-BNP</td>
<td>≤0.58 (Residual χ^2)</td>
<td>0.45</td>
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</table>

CI, confidence interval.
(hazard ratio 10.3), with a \( < \) 0.36 mmHg/mm threshold as the best identified cutoff for the entire population slightly better defining disease severity and prognosis, compared with TAPSE and PASP assessed individually. Although the improvement in prognosis using TAPSE/PASP was not dramatic compared with using TAPSE alone, the fact that both TAPSE and PASP are readily available variables and their ratio is easily calculated, justifies further exploration of this measurement as a prognostic marker. In this context, when variables are readily available, slight improvements in prognostic resolution, even when not statistically significant compared with previous models, may be justified from a clinical practice perspective. Additional research is needed to explore optimal prognostic modeling in this area. We hope the results of the present study facilitates future investigations into the prognostic implications of the TAPSE/PASP as an easy to obtain measure that may combine relevant information on RV-pulmonary circulation assessment.

Our findings show that TAPSE/PASP was inversely related to NYHA functional class and, when the two variables were combined, produced a slightly improved prognostic resolution. Accordingly, TAPSE/PASP is here viewed and proposed as a comprehensive modality for assessing the relationship between the right heart contractile performance and clinical functional status.

Interestingly, this approach may help to define earlier stages of symptoms that already reflect a condition of initial depression in RV functional reserve.

Study limitations. The study limitations are intrinsic in the measurement of PASP; correlations between echo and invasive data are reported with an \( r \) value that approximates 0.7 (24). The other well-known limitation to noninvasive assessment of
PASP is the lack of a satisfactory signal transduction in all subjects. Indeed, the only inclusion of patients with a discernible tricuspid regurgitant jet may be a bias. Despite these limitations, both PASP and TAPSE are standard measures in clinical practice and offer the opportunity to detect and monitor the RV consequences of left-sided PH in large HF populations. According to the landmark observations by Damy et al. (6), showing similar event rate in HFP EF vs. HfPEF for TAPSE quartile subdivision, it would be interesting to see the predictive accuracy of TAPSE/PASP in both HF populations. This has not been possible due to the low number of patients and cardiovascular events in the HfPEF population, but, intriguingly, it represents a direction for future studies. It remains unexplored whether other measurements of RV function currently under investigation, such as RV free wall global longitudinal strain and fractional area changes that incorporate both longitudinal and meridional RV function, would be additive or even superior to TAPSE evaluation.

TAPSE is a well-recognized preload-dependent measure, and this has not been accounted for in our model. Nonetheless, the estimated right atrial pressure was higher in nonsurvivors, which would, if anything, have tended to raise TAPSE. The average age of our HfPEF population, although significantly higher than that of the HfPEF patients, was lower than usually reported. This may be explained with the presence of some postmyocarditis and Fabry disease cases. We do not have any experimental correlate validating the proposed TAPSE vs. PASP as a reliable index of the length/force relationship.

Finally, the reproducibility analysis was performed on the same set of acquired images instead of different recordings of the same measures, and this may be considered a limitation.

Conclusions and perspectives. Results of the study strengthen the concept that noninvasive echo-derived variables related to RV systolic function are of basic clinical relevance in HF. The relationship of longitudinal RV fiber shortening (TAPSE) to developed pressure (PASP) may be viewed as a useful clinical index of the length/force relationship, and the ratio of the variables potentially possesses a more discerning ability to detect disease severity than each of the two variables separately. This approach seems to be worthy of consideration for HF patients presenting with either reduced or preserved LV systolic function, pending validation in larger samples and multiple echocardiographic laboratories.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.G. conception and design of research; M.G. performed experiments; M.G., S.C., and S.G. analyzed data; M.G., P.T., and R.A. interpreted results of experiments; M.G. and P.T. prepared figures; M.G. and R.A. drafted manuscript; M.G., F.B., G.P., L.M., and R.A. edited and revised manuscript; M.G., S.G., and R.A. approved final version of manuscript.

REFERENCES