Follow-up Tricuspid Annular Plane Systolic Excursion Predicts Survival in Pulmonary Arterial Hypertension

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Online Data Supplement
METHODS

Patient Population, Data Collection and Outcomes:

Patients were included if their RHC met PAH hemodynamic criteria (mPAP ≥ 25 mm Hg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) ≥ 3 WU) in the absence of other known causes of PH, had adequate windows on echocardiography, and had an available repeat echocardiogram, as described above. All patients with left heart disease-associated PH (defined by mPAP ≥ 25 mmHg and PCWP > 15 mmHg), significant lung disease (by review of pulmonary function tests and chest computed tomography as previously described), chronic thromboembolic PH (CTEPH) and congenital heart disease-associated PH with prior surgical correction (as those with prior cardiac surgery have diminished TAPSE irrespective of intrinsic RV function, as previously described), were excluded.

Patients were initiated on pulmonary hypertension (PH)-specific therapy including phosphodiesterase-5 inhibitors (PDE-5i; sildenafil or tadalafil), endothelin receptor antagonists (ERA; bosentan or ambrisentan), inhaled prostacyclins (treprostinil or iloprost), or parenteral prostacyclin therapy (treprostinil or epoprostenol), in isolation or in combination at the discretion of the physician. Patients were assessed by the type, number and time on therapy after baseline echocardiogram to serial follow-up study. Additionally, baseline demographic variables including age, sex and self-reported race, body mass index (BMI), along with clinical variables including cause of pulmonary arterial hypertension (PAH; classified as idiopathic, connective tissue disease, or other), and baseline and follow-up World Health Organization functional class (WHO FC) and 6-minute walk distance (6MWD), were collected.
**Hemodynamics**

All patients underwent standard hemodynamic assessment by RHC including mean (End-expiratory) right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), as well as cardiac output (CO) via the Fick method and expressed as L/min. Mixed venous oxygen saturation (MVO2) was determined while patients were breathing room air. Heart rate and noninvasive blood pressure were recorded during the procedure. Trans-pulmonary gradient (TPG) was calculated as mPAP-PAWP and pulmonary vascular resistance (PVR) was calculated from these measurements as TPG/CO and expressed in Wood Units (WU). Stroke volume (SV; CO/HR), cardiac index (CI; CO/body surface area [BSA]), stroke volume index (SVI; CI/HR) were calculated. Repeat hemodynamic data were available in 35 subjects.

**Echocardiography**

All echocardiograms were performed using either the Philips IE33 (Philips Healthcare, Andover, MA), or the GE Vingmed Vivid 7 Ultrasound (GE, Vingmed Ultrasound, Horten, Norway) ultrasound platforms.

The 2-D echo-Doppler examination protocol included standard echocardiographic assessments of the left and right-sided heart chambers and vascular structures per the American Society of Echocardiography guidelines along with other parameters to further interrogate right-sided structures. This included right (RA) atrial size and planimetered RA area (RAA) at end-systole (in the apical four-chamber view), right (RVIDd) and left (LVIDd) ventricular dimensions (obtained at end-diastole), RV end-diastolic area (RVAd) and RV end-systolic area
(RVAs), with right ventricular fractional area of change (RV FAC) calculated in the standard manner ([RVAd- RVAs]/RVAd x 100). Both RA area and RV end-diastolic area were indexed to patient height.4

The systolic eccentricity index was obtained from the parasternal short axis view, and calculated as the ratio of the minor axis parallel to the interventricular septum (D1) to the minor axis perpendicular to the interventricular septum (D2) at end-systole (D1/D2). Right ventricular outflow tract velocity time integral (RVOT VTI), acceleration time (AcT) and systolic notching pattern was obtained from the RVOT pulse wave Doppler profile in the parasternal short or long axis views, as previously described.4-6 The maximal trans-tricuspid flow velocity was obtained in the usual manner and used to quantify the RV-PA pressure gradient using the modified Bernoulli equation (4v²).7 Tricuspid regurgitation (TR) severity was assessed semi-quantitatively (graded 0-3). Diastolic function, was assessed by trans-mitral Doppler velocity and tissue Doppler using standard techniques, as previously described.4,8

All studies were analyzed off-line using ProSolv CardioVascular Client software (Fujifilm Medical Systems, Stamford, CT). Analyses were performed by two experienced cardiologists trained in the echo-Doppler assessment described above, and blinded to the study subjects’ clinical, hemodynamic and outcome status.

**Data Analysis**

The cohort was dichotomized by serial TAPSE value as follows: Group 1: follow-up TAPSE ≥ 2 cm and Group 2: follow-up TAPSE < 2 cm. This cutpoint was chosen based on
normative data of TAPSE from prior studies\textsuperscript{9,10} and as proposed by the current European Society of Cardiology treatment guidelines for PH\textsuperscript{11}.

Univariable and bivariable Cox proportional hazards models were constructed using TAPSE as a continuous or dichotomous variable and included variables found to be significant in univariable analyses (p value < 0.20) and variables previously shown to have prognostic significance in order to adjust for potential confounding factors. A landmark analysis was also performed to assess survival by TAPSE threshold (TAPSE \geq 2 \text{ cm}), with entry at 1 year from initial cohort enrollment, and survival time assessed from landmark entry\textsuperscript{12}. The echocardiogram obtained closest to this landmark was used as the follow up study that was compared to the baseline echocardiogram. Variables that were found to be collinear by variance inflation factor testing in multiple linear regression were excluded from Cox multivariable analyses. The proportional hazards assumption was examined for all covariates using a continuous time-varying predictor and generalized linear regression of scaled Schoenfeld residuals on functions of time.

Intra- and inter-observer agreement was expressed by using intraclass correlation coefficients (ICCs) with 95\% confidence intervals. Analyses were performed using Stata version 13.1 (StataCorp., College Station, TX), as well as GRAPHPAD Prism version 6.07 (GraphPad Software Inc; La Jolla, CA).

\textbf{Results}

\textit{Follow-up TAPSE, 6MWD, and RV:LV ratio}

We assessed the prognostic value of follow-up 6MWD > 400 m as compared to follow-up TAPSE \geq 2 \text{ cm}. In both univariable and bivariable models, follow-up 6MWD > 400 m was
highly predictive of survival (HR 0.26 (95% CI (0.09-0.82), p=0.02). However, follow-up TAPSE ≥ 2 cm remained highly significant when adjusting for follow-up 6MWD > 400 m.

Supplemental figure 1A demonstrates a scatter plot analysis of follow-up 6MWD over the range of TAPSE measurements. The combination of a low follow-up 6MWD (< 400 m) and low follow-up TAPSE (< 2 cm) was associated with increased mortality whereas a normal follow-up TAPSE (≥ 2 cm) despite a low follow-up 6MWD was associated with lower mortality. More specifically, of the 27 patients with follow-up 6MWD < 400 m and TAPSE < 2 cm, 13 died (48%), compared to 3 of 18 patients (17%) with 6MWD < 400 m but a follow-up TAPSE ≥ 2 cm, yielding an odds ratio of 4.64 (95% CI 1.08-19.8) and a difference that trended toward significance (p=0.055), highlighting the importance of preserved TAPSE with regard to survival even in the setting of reduced 6MWD.

We also assessed the prognostic importance of follow-up RV size, as assessed by RV:LV ratio in addition to RV function as assessed by TAPSE. As seen in supplemental figure 1B, 14 of the 45 patients with follow-up RV:LV > 1 cm (31%) died while 5 of the 24 patients with RV:LV ≤ 1 cm died (21%; p=ns). However, when assessing those with follow-up RV:LV > 1 cm by TAPSE group, more patients died who had a follow-up TAPSE < 2 cm as compared to those with a TAPSE ≥ 2 cm (11/25 patients (44%) vs. 3/20 (15%), respectively, p=0.05). Thus, the presence of an enlarged and dysfunctional RV on repeat assessment was associated with higher mortality, as compared to those with an enlarged RV and normal function, with the lowest mortality (2 out of 17 subjects, 12%) noted in those with both relatively normal RV size and normal RV function.
## Supplemental Table 1. Changes in Echocardiographic Within the Total Cohort and Follow-up TAPSE Groups

| Echo Parameter | Total Cohort Baseline | Total Cohort Follow-up | p-value | Δ Total Cohort | Group 1 Baseline | Group 1 Follow-up | p-value | Δ Group 1 | Group 2 Baseline | Group 2 Follow-up | p-value | Δ Group 1 vs. Δ Group 2 |
|----------------|-----------------------|------------------------|---------|----------------|----------------|----------------|---------|-----------|----------------|----------------|---------|-----------------------|
| TAPSE, (cm)    | 1.6±0.5               | 2.0±0.4                | <0.0001 | 0.4±0.5        | 1.7±0.5        | 2.3±0.2        | <0.0001 | 0.5±0.5   | 1.5±0.5        | 1.7±0.3        | 0.07    | 0.2±0.4 <0.014 |
| RV fractional area change, % | 26±10 | 26±11 | 0.51 | 25±9.0 | 28±10 | 0.16 | 3.0±10 | 27±12 | 25±12 | 0.7 | -2.0±10 | 0.17 |
| RA, cm | 4.8±1.0 | 4.5±1.1 | 0.04 | -0.4±0.9 | 4.8±0.9 | 4.3±0.9 | 0.03 | -0.5±0.9 | 4.9±1.2 | 4.7±1.2 | 0.43 | -0.2±1.0 | 0.29 |
| LA, cm | 3.4±0.6 | 3.7±0.6 | 0.007 | 0.3±0.6 | 3.4±0.6 | 3.8±0.6 | 0.012 | 0.4±0.6 | 3.4±0.6 | 3.6±0.6 | 0.21 | 0.2±0.6 | 0.19 |
| RVIDd, cm | 5.0±0.9 | 4.8±0.9 | 0.25 | -0.2±0.9 | 4.8±0.8 | 4.6±0.8 | 0.36 | -0.2±1.0 | 5.2±0.9 | 5.0±1.0 | 0.45 | -0.2±0.6 | 0.99 |
| LVIDd, cm | 3.8±0.6 | 4.2±0.7 | <0.0001 | 0.4±0.8 | 3.8±0.6 | 4.4±0.6 | <0.0001 | 0.6±0.7 | 3.8±0.6 | 4.0±0.7 | 0.18 | 0.2±0.9 | 0.07 |
| RVIDd:LVIDd | 1.3±0.4 | 1.2±0.4 | <0.001 | -0.16±0.4 | 1.3±0.3 | 1.1±0.2 | <0.0001 | -0.2±0.4 | 1.4±0.4 | 1.3±0.5 | 0.22 | -0.2±0.5 | 0.53 |
| RAA index, cm²/m² | 13.0±4.4 | 12.1±4.2 | 0.19 | -0.9±4.3 | 12.8±3.8 | 11.6±3.3 | 0.12 | -1.3±3.4 | 13.1±5.1 | 12.7±5.1 | 0.74 | -0.3±3.8 | 0.25 |
| RVAd index, cm²/m² | 14.8±4.4 | 13.6±4.5 | 0.13 | -1.2±3.6 | 14.2±3.4 | 12.7±3.9 | **0.04** | -1.5±4.1 | 15.5±5.3 | 14.7±4.9 | 0.55 | -0.8±3.0 | 0.16 |
|--------------------|----------|----------|------|----------|----------|----------|---------|----------|----------|----------|------|----------|-----|
| Systolic eccentricity index | 1.4±0.7 | 1.1±0.4 | **<0.001** | 0.3±0.9 | 1.3±0.6 | 1.1±0.4 | 0.13 | 0.2±0.9 | 1.5±0.7 | 1.0±0.5 | **0.002** | -0.5±1.0 | **0.005** |
| RV-PA gradient, mm Hg | 65±29 | 53±23 | **0.008** | -12±29 | 68±35 | 48±26 | **0.013** | -18±35 | 62±21 | 58±17 | 0.4 | -1.69±22.8 | **0.044** |
| TR severity (grade ≥3+), n (%) | 19 (27) | 20 (29) | 0.89 | 10 (27) | 7 (19) | 0.70 | 9 (27) | 13 (39) |  |  |  |  |  |
| RVOT VTI, cm | 11±3.2 | 15±4.5 | **<0.0001** | 4.1±4.5 | 12±2.7 | 17±4.1 | **<0.0001** | 5.1±4.6 | 10±3.4 | 13±3.9 | **0.002** | 2.8±4.1 | 0.06 |
| Notch, n (%) | None: 3 (4) LSN: 27 (39) MSN: 39 (57) | None: 14 (27) LSN: 27 (39) MSN: 28 (41) | **0.001** | None: 10 (27) LSN: 15 (41) MSN: 12 (32) | None: 2 (6.3) LSN: 11 (34) MSN: 19 (59) | None: 4 (13) LSN: 12 (38) MSN: 16 (50) | **<0.001** |  |  |  |  |  |
| AcT, ms | 69±18 | 85±19 | **<0.0001** | 16±25 | 69±19 | 90±19 | **<0.0001** | 21±28 | 69±18 | 79±18 | **0.04** | 9.2±18 | 0.06 |
| LVEF, % | 67±7.9 | 68±7.1 | 0.91 | -0.1±9.0 | 68±7.6 | 68±4.9 | 0.87 | 0.4±8.0 | 67±8.2 | 67±8.9 | 0.98 | -0.7±10 | 0.63 |

Definition of abbreviations: AcT = acceleration time; LA = left atrial; LVIDd = left ventricular diastolic dimension; LVEF = left ventricular ejection fraction; PA = pulmonary arterial; RA = right atrial; RAAi = right atrial area indexed to patient height; RV = right ventricular; RVAd = right ventricular area indexed to patient height; RVIDd = right ventricular diastolic dimension; RVOT VTI = right ventricular outflow tract velocity time integral; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.
Supplemental Table 2. Follow-up Hemodynamic Data

| Follow-Up Hemodynamics | Total Cohort (n=35) | TAPSE ≥ 2 cm (n=20) | TAPSE < 2 cm (n=15) | p-value |
|------------------------|---------------------|---------------------|---------------------|---------|
| HR, beats/min          | 75±15               | 71±13               | 79±17               | 0.12    |
| Systolic BP, mm Hg     | 122±18              | 118±16              | 128±20              | 0.14    |
| RAP, mm Hg             | 8.4±3.9             | 7.7±3.5             | 9.3±4.4             | 0.23    |
| PASP, mm Hg            | 78±17               | 78±18               | 79±16               | 0.84    |
| mPAP, mm Hg            | 46±11               | 45±12               | 47±9.6              | 0.73    |
| PAWP, mm Hg            | 12±3.7              | 12±3.2              | 13±4.2              | 0.42    |
| PVR, Wood Units        | 6.7±3.3             | 6.2±3.3             | 7.3±3.3             | 0.31    |
| CO, L/min              | 5.5±1.7             | 6.0±1.7             | 4.8±1.4             | 0.03    |
| CI, L/min/m²           | 3.1±1.1             | 3.3±1.1             | 2.8±1.0             | 0.15    |
| SVI, ml/m²             | 42±15               | 47±15               | 37±13               | 0.05    |
| MVO2, %                | 69±6.5              | 72±6.9              | 65±3.3              | 0.07    |

Definition of abbreviations: BP = blood pressure; CI = cardiac index; CO = cardiac output; HR = heart rate; mPAP = mean pulmonary arterial pressure; MVO2 = mixed venous oxygen saturation; PAWP = pulmonary artery wedge pressure; PASP = pulmonary artery systolic pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVI = stroke volume index.

Supplemental Figure Legend:

Supplemental Figure 1: Scatterplot analysis (A) Comparing 6MWD, TAPSE and survival at one year and (B) RV:LV ratio, TAPSE and survival at one year. 6MWD = 6-minute walk distance; RV = right ventricle, LV = left ventricle.
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