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Additional prognostic value of echocardiographic follow-up in pulmonary hypertension - role of 3D right ventricular area strain

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ABSTRACT

Background: Outcomes in pulmonary hypertension (PH) are related to right ventricular (RV) function and remodeling. We hypothesized that changes in RV function and especially area strain (AS) could provide incremental prognostic information compared to the use of baseline data only. We therefore aimed to assess RV function changes between baseline and 6-month follow-up and evaluate their prognostic value for PH patients using 3D echocardiography.

Methods: 95 PH patients underwent a prospective longitudinal study including ESC/ERS guidelines prognostic assessment and 3D RV echocardiographic imaging at baseline and 6-month follow-up. Semi-automatic software tracked the RV along the cycle and its output was post-processed to extract 3D deformation patterns.

Results: Over a median follow-up of 24.8 [22.1-25.7] months, 21 patients died from PH or were transplanted. Improvements in RV global AS were associated with stable or improving clinical condition as well as survival free from transplant ($p < 0.001$). The 3D deformation patterns confirmed that the most significant regional changes occurred within the septum. RV global AS change over 6-month by +3.5% identifies patients with a 3.7-fold increased risk of death or transplant. On multivariate COX analysis, changes in WHO class, BNP and RV global AS were independent predictors of outcomes. Besides, the combination of these three parameters was of special interest to identify high risk patients (HR 11.5[1.55-86.06]).

Conclusion: Changes in RV function and especially changes in 3D RV AS are of prognostic importance. Our study underlines that assessing such changes from baseline to follow-up is of additional prognostic value for PH patients.

KEY WORDS: Pulmonary hypertension; right ventricular function; 3D echocardiography; myocardial deformation imaging.

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INTRODUCTION

Pulmonary hypertension (PH) is a severe cardiopulmonary disorder that gradually leads to symptoms and premature death. Outcomes are mostly related to right ventricular (RV) function and remodeling [1-6]. The analysis of volume and strain from 3D speckle-tracking is now feasible on the RV [7-10] and provides valuable information about its regional function and relation with the clinical condition and prognosis of PH patients [11-13].

Nonetheless, baseline information may still be limited for the patients' evaluation and risk stratification. Data that help refine the patients' risk between treatment-naive incident patients and prevalent PH patients are lacking. The European Society of Cardiology (ESC) / European Respiratory Society (ERS) guidelines for the management of PH [14] recommend the "goal-oriented therapy", which implies considering improvements in both clinical, echocardiographic parameters and BNP levels. They suggest a comprehensive assessment that classifies PH patients into low, intermediate or high risk groups, with estimated 1-year mortality of <5%, 5-10% and >10%, respectively. Patients with pulmonary arterial hypertension (PAH) or group 4 PH with at least one low-risk criteria or a low-risk stratum at follow-up had a significantly reduced risk of death and clinical worsening [15]. Despite this, only few studies [16,17] investigated patients' changes in relation with outcome. Instead of baseline only, follow-up parameters can reflect both PH evolution and therapy effect and offer a more reliable risk assessment [18-20]. However, studies assessing the prognostic role of

follow-up echocardiographic data and the value of finer descriptors of the 3D RV function are lacking.

In this study, we hypothesized that changes in 3D RV function from baseline to follow-up and especially area strain (AS) could provide incremental insights into the prognosis of PH patients. For this purpose, we performed a comprehensive examination of changes in 3D RV deformation between baseline and follow-up, including global and regional values and the examination of 3D deformation patterns, and evaluated their added value to characterize the patients' outcome.

METHODS

Study design and patients

The study was prospective and longitudinal. We included consecutive clinically stable adult PH patients followed up at our center between October 2014 and March 2018 who were enrolled into a standardized echocardiographic protocol. All participants consented and provided written informed consent. The study was approved by the research Ethics committees at our institution, and complied with the ethical guidelines of the Helsinki Declaration (NCT02799979).

Pre-capillary PH was considered when mean pulmonary artery pressure at rest was ≥ 25 mmHg with pulmonary capillary wedge pressure ≤ 15 mmHg (using right heart catheterization data). We only included PH patients from group 1 (pulmonary arterial hypertension) and group 4 (if they

were not eligible to either pulmonary endarterectomy or pulmonary angioplasty). We excluded patients with significant left heart disease (systolic or diastolic dysfunction, left ventricular (LV) dilatation or hypertrophy, mitral or aortic valvar disease), atrial fibrillation or other sustained arrhythmias at the time of inclusion, poor acoustic windows, and patients with chronic thromboembolic pulmonary hypertension if they were eligible for either endarterectomy or pulmonary angioplasty. We also excluded patients with severe tricuspid regurgitation, as it can lead to RV volume overload in patients already suffering from RV pressure overload, thus aggravating their condition and often leading to an increase in diuretics; the change in diuretics was critical in our study as it could have led to changes in RV function with changes in RV load.

Demographics and clinical evaluation (age, gender, diagnosis, baseline WHO class, PH-targeted advanced therapy), determination of BNP plasma levels (Beckman Access 2, Triage BNP assay (Biosite Diagnostics Inc, San Diego, CA)) and 6-minute walk test were performed at baseline and follow-up. Prognostic assessment was performed per the ESC/ERS guidelines [14], using the following parameters: signs of right heart failure, progression of symptoms, syncope, WHO functional class, 6-minute walking distance, BNP plasma levels, imaging, and right heart catheterization data when available.

The first echocardiography qualified the patient for inclusion and defined the starting date enrollment into the study, although the patient may have been diagnosed earlier. Follow-up was considered from this date until the patient's death or the end of the study (October 2018). Clinical

outcome was binary and defined by either mortality related to PH or lung transplantation.

In complement, we considered the clinical *evolution* at follow-up, which was separated into three categories. Patients were labeled as “*worsening*” if they presented one of the following outcomes: need to start advanced therapy targeting the prostacyclin pathway, hospitalization related to PH complication during follow-up, lung transplant or death. They were labeled as “*improving*” if they experienced at the last follow-up visit a decrease in the WHO class and either showed a >10% increase of their 6-minute walking distance or a >10% decrease in their BNP levels [21,22]. Other patients were labeled as “*stable*”.

Medications of our patients were adjusted before the first echocardiography. Indeed, if patients needed an uptitration or a therapy escalation between the two assessments, it was considered as a clinical outcome and patient data were not analyzed in this case (censored before the follow-up echocardiography). Thus, no changes in advanced therapy occurred between baseline and follow-up.

Patient follow-up and evolution

Patient follow-up consisted of consecutive evaluations on a regular time basis of at least 6 months as usually done for PH patients at our institution. At every visit, clinical and biochemical characteristics were evaluated. Echocardiographic follow-up with transthoracic 2D and 3D echocardiography was scheduled after 6 months. The most recent

evaluation was taken as the final visit. It was only analyzed if performed between 3 and 9 months after the first echocardiographic examination, provided the patient had the same diuretic dosage (assuming the volume status barely changed between the two examinations).

2D-echocardiographic acquisitions and measurements

We performed a 2D echocardiographic examination using an EPIQ-7 ultrasound system (Philips Medical Systems, Andover, MA). It included Doppler echocardiography complying with the recommendations of the American Society of Echocardiography (ASE) / European Association for Cardiovascular Imaging [23-25]. The following parameters were measured by a single operator and averaged over three consecutive cycles: LV ejection fraction (LV EF, using the Simpson biplane rule), end-diastolic LV diameter, systolic pulmonary artery pressure (derived from the tricuspid valve regurgitation), right ventricular outflow tract (RVOT) velocity-time integral (VTI), RA pressure (using the modified ASE rule according to *Brennan et al.* [23,26]), RA area (contoured in the 4-chamber view), tricuspid annular plane systolic excursion (TAPSE), tricuspid annular peak systolic velocity (S') and RV myocardial acceleration during isovolumic contraction (IVA) [27] measured by Tissue Doppler imaging at the lateral tricuspid annulus.

3D trans-thoracic echocardiography

We also performed 3D full-volume acquisitions using the matrix-array X5-1 transducer (Philips Medical Systems). At least four 3D cine-loops were acquired from an apical 4-chamber view focused on the RV. This focused view was not a classic 4-chamber view as the probe was tilted anteriorly to focus on the entire RV. Loops were stored from full-volume acquisition over two heart beats, which required ECG gating over four cardiac cycles during a quiet breath-hold. To allow post-processing with dedicated software, care was taken to maximize the volume rate (≥ 20 volumes per second) and to include the entire RV within the images.

3D deformation analysis

Offline analysis was performed by a single operator via commercial software dedicated to the RV (4D RV Function 2.0, TomTec Imaging Systems GmbH, DE), on the data acquired at baseline and 6-month follow-up. This software tracked the RV endocardial surface along the cardiac cycle using 3D speckle-tracking, which can be exported for post-processing as a set of 3D meshes made of triangular elements/cells. It also directly estimated the RV end-diastolic, end-systolic volumes and EF [28,29]. Trabeculations and papillary muscles were included as part of the RV cavity, as recommended [24].

The exported meshes were analyzed using VTK (v7.10, Kitware, New York, US), and Matlab (v.R2011a, MathWorks, Natick, US). Circumferential and longitudinal strain computations were based on the engineering strain, namely the relative change of length along these directions compared to

end-diastole, within a 5mm neighborhood. Due to the availability of endocardial surfaces only, radial strain was not computed. Area strain, which measures the local deformation of the 3D mesh elements, was computed as the relative change in the area of each triangular element with respect to end-diastole. Thus, it did not require the definition of radial-circumferential-longitudinal direction vectors, contrary to circumferential and longitudinal strains [30]. All the strain patterns were available at each point of the RV endocardium and at each instant of the cycle.

The commercial software labels the elements of the 3D meshes consistently across subjects. These labels were used to compare the strain patterns at similar locations across subjects and acquisitions. Strain patterns were displayed on the average mesh of each subgroup, obtained by standard computational anatomy tools (generalized Procrustes analysis). We examined baseline and follow-up values, as well as changes between these two instants. Global and regional strain values were respectively defined as the average strain over the whole RV and over each region, according to conventional RV regions definition [31].

Statistical analysis

Continuous variables are presented as mean \pm standard deviation in case of normal distribution, or median and 95% confidence interval if not. Categorical variables are presented as percentages. Both absolute and relative changes between baseline and follow-up are presented. Inter-group differences (paired data) between continuous variables were assessed by

the Student's t-test or the Wilcoxon test depending if the variables were / were not normally distributed, and the Fisher's exact test for categorical variables. Bonferroni correction was used for multiple comparisons. Multiple regression and the associated variance inflation factor were used to test multicollinearity between several variables. The relationship between echocardiographic parameters and clinical outcome was assessed through univariate and multivariate Cox proportional hazard regression, starting at the date of the first echocardiography. Multivariate survival analysis included all variables with a p-value <0.10 in the univariate analysis and the previously described prognostic parameters (WHO functional class, BNP, 6-minute walking distance and PH-targeted advanced therapy) and all the 3D echocardiography parameters.

The optimal cut-off values to predict survival were obtained from receiver operating characteristics (ROC) curves. ROC curves were compared using the *DeLong et al.* [32] method. Test-retest variability consisted of intra- and inter-operator comparisons as well as inter-loop strain comparisons, and included intra-class correlation coefficients.

For all analyses, a p-value <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc 19.1.7 (MedCalc Software, Mariakerke, BE).

RESULTS

Baseline characteristics

Overall, 156 patients with pulmonary hypertension were screened. We excluded 34 patients for which the evaluation of their clinical outcome occurred before the second assessment, 14 because their second 3D echocardiography fell outside the allowed study period (from 3 to 9 months), 11 because of poor acoustic window, and 2 because of missed follow-up. Thus, 95 patients with pulmonary hypertension (mean age 60 ± 18 years; 58% female) were included in our study and followed over a median of 24.8 [22.1-25.7] months, whose main characteristics are presented in Table 1.

Of these, 80 patients (84%) were from group 1: 15 had PAH associated with connective tissue disease, 32 had idiopathic PAH, 1 had BMPR2-related PAH, 11 had PAH associated with congenital heart disease, 10 had PAH associated with portal hypertension, 6 had drug-induced PAH, 5 had HIV-associated PAH. The remaining 15 patients (16%) were from group 4 and had chronic thrombo-embolic PH under medical therapy (contraindication to either pulmonary endarterectomy or angioplasty). Besides, 86 patients (91%) were treated with advanced PH therapy at baseline: 10 with triple combination therapy (endothelin receptor antagonist + PDE5 inhibitor + prostacyclin), 27 with dual combination therapy (endothelin receptor antagonist + PDE5 inhibitor or riociguat) and 49 with single oral PH therapy (of these, 23 patients were treated with endothelin receptor antagonists, 19 with PDE5 inhibitors and 7 patients with riociguat).

Evolution at follow-up

At follow-up, 20 patients died from PH and 1 patient underwent lung transplant. Another patient died from septic shock related to angiocholitis. Compared to baseline and according to the definition given in the Methods section, 36 patients (38%) were labeled as stable, 22 patients (23%) as improving, and 37 patients (39%) as worsening and were hospitalized because of right heart failure or needed to start therapies targeting the prostacyclin pathway. An uptitration or escalation of their oral advanced therapy was required for 31 patients. The median delay between the two echocardiographic assessments (baseline and follow-up) was 5.8 [5.3-6.1] months.

At 6-month follow-up, patients labeled as stable or improving had significantly higher 3D RV EF ($p < 0.001$) and improved RV global AS, circumferential and longitudinal strain ($p < 0.001$ for all). Two-dimensional RV function was only slightly improved, as observed for the TAPSE ($p = 0.03$) and peak tricuspid s' ($p = 0.002$), while changes in the RA area were not significant ($p = 0.21$).

3D deformation patterns

Improvements in the RV global AS (meaning more negative strain at follow-up) were associated with stable or improving clinical condition as well as survival ($p < 0.001$).

RV global AS did not significantly differ between subgroups at baseline ($p = 0.23$), although slight differences in the AS pattern were observed in the lateral wall (left part of Figure 1). Larger differences in the

AS patterns were visible at follow-up (central part of Figure 1). Such differences were enhanced by the patterns evolution from baseline to follow-up (right part of Figure 1), with marked worsening of poor outcome patients. This was quantitatively confirmed by significant differences in the relative changes in global strain ($p < 0.001$), the largest differences between subgroups being observed within the septum ($p < 0.001$) (Table 2).

The comparison of deformation patterns according to clinical evolution led to similar observations (Figure 2), with rather similar RV AS patterns at baseline despite slight differences in the lateral wall, and marked worsening in patients with poor clinical evolution.

These trends were confirmed by looking at the individual evolution of each patient from baseline to follow-up, summarized in Figure 3 for each prognostic and clinical evolution subgroup.

Variability analysis

Variability was assessed in 30 patients using intra-class correlation coefficients: inter-observer variability was 0.92 [0.78-0.96] for RV EF; intra-observer variability was 0.95 [0.88-0.98] for RV EF and 0.94 [0.85-0.98] for RV global AS; inter-loop variability was 0.94 [0.87-0.98] for RV EF and 0.93 [0.86-0.96] for RV global AS.

Outcome analysis: baseline and follow-up

At baseline, the WHO class, 6-minute walking distance, RA area, RA pressure, TAPSE, LV EF, RV end-diastolic volume, and RV lateral AS were univariate predictors of survival free from transplant.

At follow-up, the WHO class, 6-minute walking distance, BNP, presence of pericardial effusion, RA area, RA pressure, TAPSE, LV EF, RV EF, RV end-diastolic volume, RV global and lateral AS, RV global longitudinal strain, and RV global circumferential strain were univariate predictors of survival free from transplant.

At follow-up, on multivariate Cox analysis, the WHO class, 6-minute walking distance, presence of pericardial effusion, RA area, RA pressure, RV end-diastolic volume, RV global AS, RV global longitudinal strain, and RV global circumferential strain were independent predictors of clinical outcome.

The ROC analysis confirmed the added-value of AS over other criteria (Figure 4, left): adding RV global AS at follow-up ($>-18\%$; cut-off determined from the ROC curve) on top of the low risk ESC criteria significantly improved the risk stratification (AUC 0.848 [0.760-0.913] vs. 0.923 [0.850-0.968]; $p=0.02$).

Outcome analysis: changes from baseline to follow-up

Changes from baseline to follow-up in the WHO class (HR 3.2 [1.6-6.3], $p<0.001$), BNP (HR 1.002 [1.001-1.003], $p<0.001$), RV global AS (HR 1.14 [1.07-1.20], $p<0.001$) were independent predictors of clinical outcome, contrary to the TAPSE, RA area, and RA pressure. The optimal cut-off for

changes in RV global AS was +3.5% (cut-off determined from the ROC curve), meaning worsening i.e. less negative values (AUC 0.812 [0.610-0.892]); this cut-off identifies patients with a 3.7-fold increased risk of death or transplant (HR 3.74 [1.54-9.06]).

The ROC analysis also helped comparing the value of adding AS on top other criteria (Figure 4, right). Changes in RV global AS were more predictive than changes in WHO (AUC 0.695 [0.579-0.795], $p=0.10$), but comparable to changes in BNP (AUC 0.724 [0.610-0.821], $p=0.25$). Patients who had at least one of these three characteristics (worsening RV global AS by more than the identified cut-off, and/or worsening WHO class by at least 1 unit, and/or any increase in BNP plasma levels) were identified at very high-risk (HR 11.5 [1.55-86.06]) of death or transplantation.

On another hand, using clinical improvement as the endpoint (at the last follow-up visit : either decrease in the WHO class, >10% increase in 6-minute walking distance or >10% decrease in BNP levels), we found that change in RV global AS ≤ -6 (improvement of RV global AS by 6 or more) also predicted clinical improvement (HR 4.25 [1.76-10.26]).

DISCUSSION

To our knowledge, this is the first study designed to interpret the prognostic value of changes in RV function with respect to the current prognostic stratification of PH patients, and up to the 3D analysis of RV deformation. Strain had already been identified as predictor of outcome in this population. On top of this, this prospective study demonstrates that (i)

individual and regional changes in RV deformation are highly related with clinical outcome, and (ii) they provide independent prognostic information with a significant positive value to the current risk stratification.

Follow-up versus baseline assessment

We included both incident and prevalent patients, which is one the main interests of this study. Looking at follow-up values and changes from baseline to follow-up allows pooling the effect of treatment and mixing these two types of patients. Besides, the change in RV function with therapy (for the treatment-naïve at baseline) was observed as it was for prevalent patients.

Baseline RV deformation and function in our cohort were not significant predictors of outcome, unlike changes in AS. This result underlines the importance of dynamic assessment combined with baseline data, as previously demonstrated with the ESC risk stratification [18]. In our opinion, assessing the evolution of RV function should be preferred over a single assessment, to facilitate comparisons in a population mixing incident and prevalent patients. We previously identified RV AS as predictor of outcome, in a larger population of both mixed incident and prevalent PH patients [12]. Here, we demonstrate that RV AS changes also provide additional prognosis information for PH patients.

Previous studies already expressed similar recommendations. A decreased saturation predicted clinical deterioration in Eisenmenger syndrome [16]. Recently, a post-hoc analysis of PATENT-2 found that

changes in WHO functional class and NT-pro BNP at 12 weeks were associated with clinical worsening-free survival, but not with survival [33]; our study differs in terms of rate of events (25%) and population, as patients with various PH etiologies without any age limitation were included. An increase in pulmonary arterial capacitance over time (assessed by right heart catheterization) was associated with decreased mortality [34]. Changes in RV deformation could represent, in association with changes in WHO and BNP, a more advanced evaluation strategy for advanced PH therapies. This view is also supported by a recent echocardiographic study using 2D RV free wall strain [35].

Risk assessment

Current guidelines recommend the “goal-oriented therapy” approach to assess patients for the presence of pericardial effusion and to monitor the RA area. In our study, we found that follow-up RA area and pressure were predictors of outcome, contrary to the changes in these parameters. The RA size could evolve more slowly compared to the evolution of RV deformation, which might explain this. This faster rate of changes in RV deformation may itself come from the higher RV sensitivity to advanced PH therapy-induced modifications.

Beyond highlighting the importance of RV functional assessment in PH patients, our study also suggests the importance of an integrated approach that considers imaging, biomarkers and clinical evaluation. Despite the prognostic value of baseline and changes in WHO class, their predictive

value is significantly improved by adding changes in BNP plasma levels and in RV AS. Simple cut-offs have been used: RV global AS worsening by more than 3.5%, and BNP increase. Such factors could help physicians improve the classification of disease severity and identify whether a patient is worsening on treatment and escalate therapy if needed.

Three-dimensional RV assessment

RV global AS change over 6-month by +3.5% identifies patients with a 3.7-fold increased risk of death or transplant. This is a confirmation of the importance of studying 3D RV function in pulmonary hypertension, allowing a better risk stratification. Given the RV deformation pattern, including both longitudinal and circumferential components, Area strain, that sums all deformation, makes studying RV strain simpler. The analysis of deformation patterns, in 3D, brought finer insights into the changes in relation to outcome. In particular, substantial worsening was observed within the septum in patients with poor outcomes, contrary to the other subgroup. This region is more sensitive to pressure overload and its deformation is affected by RV-LV interactions. We already know that LV parameters such as the eccentricity index and LV strain [1,36,37] are of prognostic importance in PAH, which supports our observations within the septum, underlining the importance of LV-RV interactions. A recent study investigating rat models of RV pressure overload concluded that altered geometry and wall stress lead to adverse RV-LV interactions through the septal hinge-points, and to

fibrosis [38]. This fibrosis might explain that high-risk patients are more prone to RV AS changes in the septal region.

Limitations

This was a single center prospective study with a limited number of patients. Most patients (85%) were from group 1 PAH but the others (15%) were from group 4 PH. Thus, our results require further validation in a larger cohort of PAH patients. Patients were enrolled at different points during the time course of their disease, and the prognostic value of the studied parameters was not evaluated against this disease stage. The mortality related to PH or transplant rate was quite high in our study (22%), which could be explained by the mean age and severity of our population.

Right heart catheterization only served for PH diagnosis and was not necessarily performed at baseline in our study, but may have been done months earlier in some patients. Thus, we did not assess the relationship between echo severity and right heart catheterization within the baseline to follow-up interval.

CONCLUSION

In summary, our study demonstrates the prognostic value of changes in RV function, here assessed through 3D RV strain and overall the importance of follow-up data. The most significant changes in RV strain occurred within the septum. Additionally, the combination of changes in WHO function class, BNP and 3D RV AS demonstrated its value for the

identification of high-risk patients, compared to the use of prognostic parameters independently.

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CONFLICTS OF INTEREST: Nothing to Disclose

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TABLES

Table 1. Main characteristics of our population at baseline and at 6-month follow-up (second assessment)

| | Baseline | Follow-up | 6-month change (% of initial value) | p-value |
|--|-----------------------|-----------------------|--|----------------|
| WHO class \geq III, n(%) | 59 (62%) | 47 (49%) | | <0.01 |
| BNP, pg/mL | 219.0 [119.0-291.0] | 102.0 [85.4-147.9] | -25.5[-43.0-0.0] | 0.03 * |
| 6MWD, m | 364.6 \pm 122.3 | 361.6 \pm 138.4 | 5.5 \pm 18 | 0.87 |
| Echocardiographic parameters | | | | |
| 3D RV EF, % | 34.8 [32.2-38.0] | 39.0 [35.9-43.0] | 11.1[5.4-14.7] | 0.001 |
| RV EDV, mL | 100.5 [85.9-109.1] | 98.2 [86.0-109.0] | 2.5[-4.9-13.4] | 0.53 |
| Global RV area strain, % | -19.7 \pm 6.5 | -21.9 \pm 8.0 | 9.7[4.0-17.4] | 0.005 |
| Global RV circumferential strain, % | -11.4 [-12.6 - -10.5] | -12.6 [-13.7 - -11.4] | 7.4[1.2-16.9] | 0.03* |
| Global RV longitudinal strain, % | -7.2 [-8.1 - -6.9] | -8.9 [-10.5 - -8.2] | 11.1[5.4-14.7] | 0.007* |
| TAPSE, mm | 19.9 \pm 5.5 | 19.8 \pm 5.4 | 1.97 \pm 31.2 | 0.89 |
| S', cm/s | 11.2 \pm 2.8 | 11.7 \pm 3.0 | 3.7[-3.29-6.73] | 0.04 |
| IVA, m/s² | 2.0 [1.7-2.3] | 2.1 [1.8-2.3] | 2.19 \pm 39 | 0.67* |
| RA pressure, mmHg | 10.5 \pm 4.0 | 10.1 \pm 4.8 | -4.5 \pm 41.4 | 0.37 |
| RA area, cm² | 24.0 [22.0-25.0] | 23.3 [21.3-25.3] | 9.19 \pm 22.2 | 0.86 * |
| RVOT VTI, cm | 14.7 \pm 4.8 | 15.6 \pm 5.1 | 3.9 [1.8-9.2] | 0.03 |
| LV EF, % | 66.7 \pm 7.8 | 66.2 \pm 7.1 | 0.14[-3.7-2.2] | 0.59 |
| LV EDD, mm | 45.6 \pm 4.0 | 45.7 \pm 3.9 | 0.19[-5.3-6.8] | 0.48 |
| Systolic PA pressure, mmHg | 76.0 [70.9-89.7] | 70.5 [64.9-78.1] | -8.51[-13.3-2.8] | 0.008* |
| Pericardial effusion, n(%) | 12 (13%) | 12 (13%) | - | 1 |
| Volume rate, Hz | 20 [20-25] | 23 [20-24] | | 0.81* |

* Indicates p-value using Mann-Whitney comparison whereas other values were compared using Student t-test; 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; IVA, myocardial acceleration during isovolumic contraction; LV, left ventricular; PA, pulmonary arterial; RA, right atrial; RV, right ventricular; RVOT, right ventricular outflow tract; S', Doppler tissue imaging tricuspid lateral annular systolic velocity; TV, tricuspid valve; VTI, velocity-time integral; WHO, world health organization.

Table 2. Absolute and relative changes in patients' characteristics at 6-month follow-up according to the vital status of the patient

| 6-month changes in | Survivors | Death or | p-value |
|-------------------------------------|-----------------------------------|------------------------|---------|
| | without transplant n=74 | Transplant n=21 | |
| BNP, pg/mL | -118.1±232.9 | +231.2±485.7 | 0.004 |
| 3D RV EF, % | +5.6±9.4 | -3.8±10.4 | 0.0004 |
| <i>Relative change (%E1)</i> | +20.8±37.9 | -7.5±28.0 | 0.001 |
| 3D RV EDV, mL | -3.4±35.0 | +23.7±46.1 | 0.02 |
| <i>Relative change (%E1)</i> | +6.6±37.6 | +29.2±51.0 | 0.03 |
| Global RV area strain, % | -3.8±6.7 | +3.6±6.7 | 0.0001 |
| <i>Relative change (%E1)</i> | +10.4±35.6 | -45.1±75.9 | 0.0001 |
| Global RV circumferential strain, % | -1.9±4.3 | +2.4±4.5 | 0.0005 |
| <i>Relative change (%E1)</i> | +23.4±47.6 | -15.6±32.9 | 0.0006 |
| Global RV longitudinal strain, % | -2.2±4.5 | +1.4±3.6 | 0.001 |
| <i>Relative change (%E1)</i> | +61.5±174.7 | -15.0±50.6 | 0.001 |
| TAPSE, mm | +0.0±6.9 | -0.2±6.3 | 0.52 |
| <i>Relative change (%E1)</i> | +5.7±29.6 | -6.2±26.5 | 0.11 |
| S', cm/s | +0.7±2.0 | -0.3±2.5 | 0.08 |
| <i>Relative change (%E1)</i> | +8.0±17.8 | -0.01±26.1 | 0.14 |
| RA area, cm ² | -1.4±6.7 | +3.4±9.4 | 0.05 |
| <i>Relative change (%E1)</i> | -2.0±23.6 | +9.0±19.2 | 0.07 |
| LV EF, % | -0.62±17.3 | -0.26±23.8 | 0.94 |
| <i>Relative change (%E1)</i> | -2.8±20.7 | -4±27.5 | 0.88 |
| LV EDD, mm | +0.2±1.3 | -0.2±1.5 | 0.26 |
| <i>Relative change (%E1)</i> | +0.5±2.9 | -0.4±3.4 | 0.25 |

BNP, brain natriuretic peptide; EDV, end-diastolic volume; EF, ejection fraction; LV, left ventricular; RA, right atrial; RV, right ventricular. P-value was obtained using Student t-test.

Table 3: Outcome analysis – Predictors of death or lung transplant

| | Univariate analysis | | Multivariate analysis | |
|--|---------------------|---------|-----------------------|---------|
| | HR [95% CI] | p-value | HR [95% CI] | p-value |
| <i>Baseline parameters</i> | | | | |
| WHO Class \geq III | 2.26 [1.26-4.03] | 0.006 | * | |
| 6MWD | 0.99 [0.99-1.00] | 0.02 | 0.99 [0.98-1.00] | 0.02 |
| BNP | 1.00 [0.99-1.00] | 0.53 | * | |
| RA area | 1.05 [1.02-1.08] | 0.002 | * | |
| RA pressure | 1.24 [1.11-1.38] | <0.001 | 1.27 [1.01-1.59] | 0.04 |
| TAPSE | 0.91 [0.83-1.00] | 0.04 | 0.85 [0.73-0.98] | 0.03 |
| LVEF | 1.05 [1.00-1.12] | 0.04 | 1.18 [1.05-1.32] | 0.006 |
| LVEDD | 0.96 [0.86-1.07] | 0.47 | * | |
| RV EF | 0.96 [0.91-1.01] | 0.08 | 0.93 [0.86-1.01] | 0.09 |
| RV EDV | 1.01 [1.00-1.02] | 0.003 | * | |
| RV global area strain | 1.05 [0.96-1.14] | 0.29 | 1.21 [0.99-1.47] | 0.06 |
| RV lateral area strain | 1.05 [1.01-1.12] | 0.03 | 1.18 [1.05-1.32] | 0.005 |
| RV global circumferential strain | 1.07 [0.93-1.23] | 0.33 | 1.36 [1.01-1.84] | 0.04 |
| RV global longitudinal strain | 1.06 [0.92-1.22] | 0.40 | * | |
| Pericardial effusion | 1.89 [0.69-5.16] | 0.21 | 11.26 [2.72-46.55] | <0.001 |
| <i>Follow-up parameters</i> | | | | |
| WHO class III \geq III | 26.9 [3.6-201.2] | 0.001 | * | |
| 6MWD | 0.99 [0.98-0.99] | 0.005 | 0.99 [0.98-1.00] | 0.02 |
| BNP | 1.00 [1.00-1.00] | 0.003 | 1.00 [1.00-1.00] | 0.11 |
| RA area | 1.10 [1.06-1.14] | <0.001 | 1.18 [1.00-1.40] | 0.04 |
| RA pressure | 1.29 [1.17-1.42] | <0.001 | 1.48 [1.03-2.12] | 0.03 |
| TAPSE | 0.89 [0.81-0.97] | 0.007 | 0.72 [0.50-1.04] | 0.08 |
| LV EF | 1.07 [1.01-1.14] | 0.02 | * | |
| LV EDD | 0.93 [0.83-1.04] | 0.93 | * | |
| RV EF | 0.91 [0.88-0.95] | <0.001 | 0.38 [0.11-1.38] | 0.14 |
| RV EDV | 1.02 [1.01-1.03] | <0.001 | 1.03 [1.00-1.05] | 0.01 |
| RV global area strain | 1.16 [1.09-1.24] | <0.001 | 1.53 [1.13-2.07] | 0.006 |
| RV lateral area strain | 1.15 [1.09-1.22] | <0.001 | 1.10 [1.04-1.17] | <0.001 |
| RV global circumferential strain | 1.25 [1.13-1.38] | <0.001 | 2.15 [0.998-4.628] | 0.051 |
| RV global longitudinal strain | 1.31 [1.15-1.48] | <0.001 | 1.50 [1.06-2.14] | 0.02 |

| | | | | |
|-----------------------------|-----------------|-------|--------------------|-------|
| Pericardial effusion | 3.4 [1.38-8.49] | 0.008 | 34.8 [3.76-320.93] | 0.002 |
|-----------------------------|-----------------|-------|--------------------|-------|

*variables not included in the multivariate stepwise COX analysis (p-value >0.1)

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; LV, left ventricular; RA, right atrial; RV, right ventricular; WHO, world health organization.

FIGURE LEGENDS

Figure 1: Mean pattern of RV area strain at baseline (left) and 6-month follow-up (center), displayed over the average RV shape for each prognosis subgroup. Changes from baseline to follow-up are also displayed over the average RV shapes at follow-up (right), and colored from red (increase, meaning deterioration in area strain) to blue (decrease, meaning improvement in area strain). Both septal and lateral wall faces of the RV are displayed in each subplot. Strain worsening is observed in deceased patients, with the main changes observed in the septal region.

Figure 2: Mean pattern of RV area strain at baseline (left) and 6-month follow-up (center), displayed over the average RV shape for each clinical evolution subgroup. Display similar to Figure 1. Strain worsening is only observed in clinically worsening patients.

Figure 3: Boxplots illustrating individual changes in RV global area strain from baseline to follow-up, for each prognostic and each clinical evolution subgroup.

Figure 4: ROC curves for clinical outcome. Left: adding RV global area strain ($>-18\%$ at follow-up) to the number of ESC low risk criteria at follow-up increases the AUC. Right: adding changes in BNP plasma levels and

changes in RV global area strain (worsening by more than 3.5%) to the changes in the WHO class also increases the AUC.

Figure 1

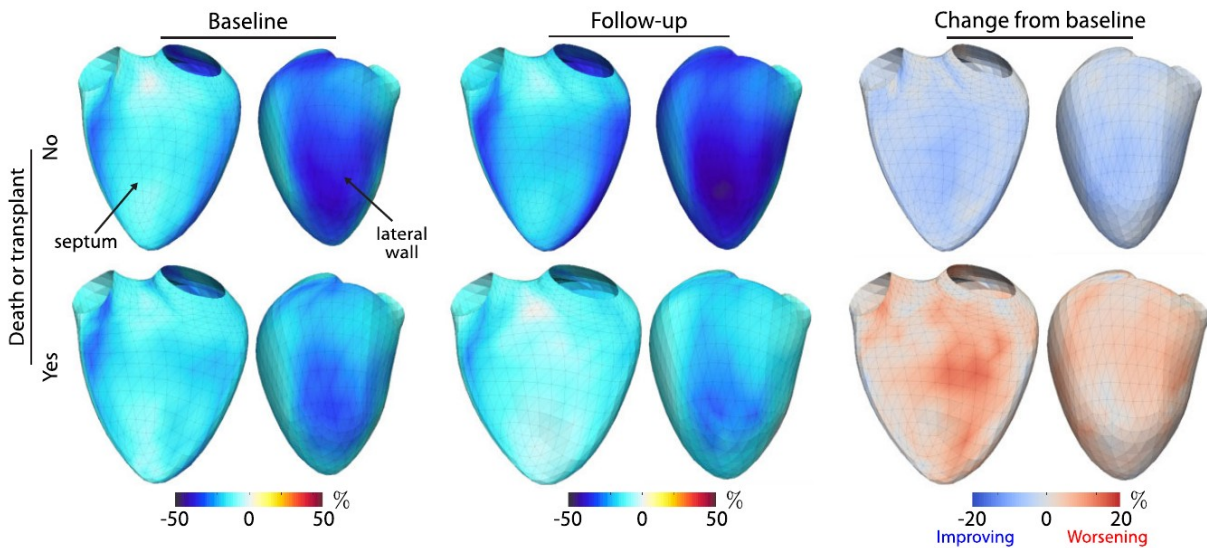


Figure 2

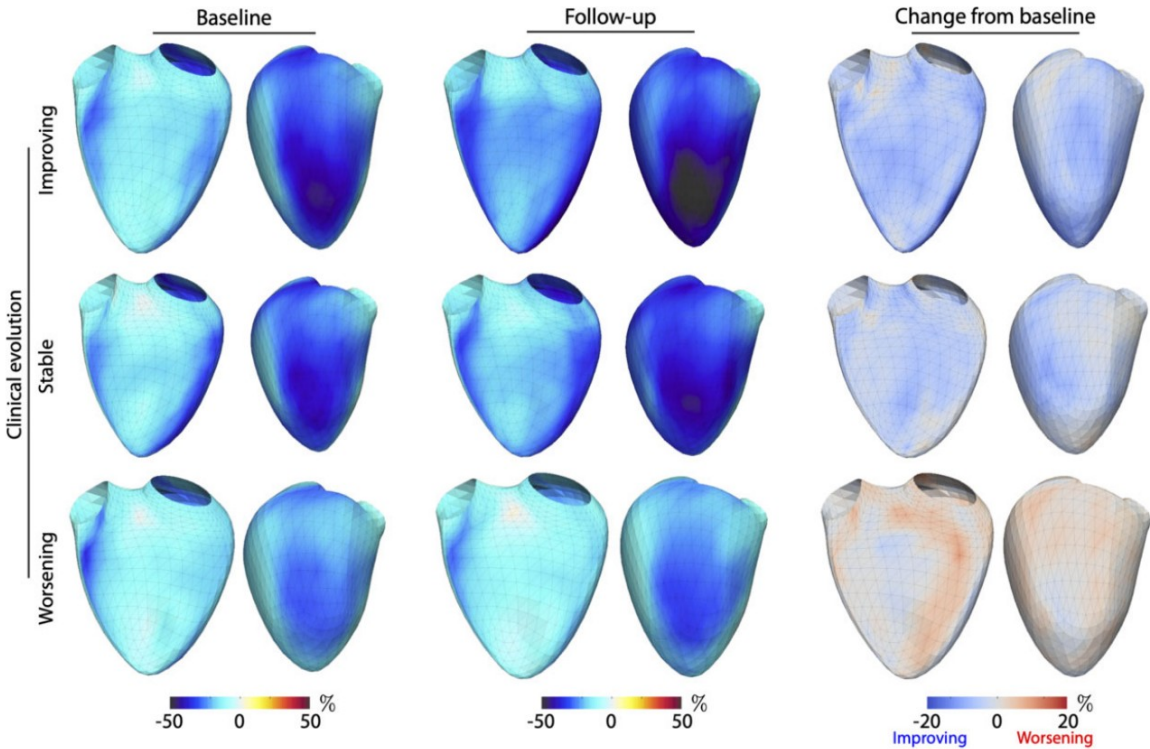


Figure 3

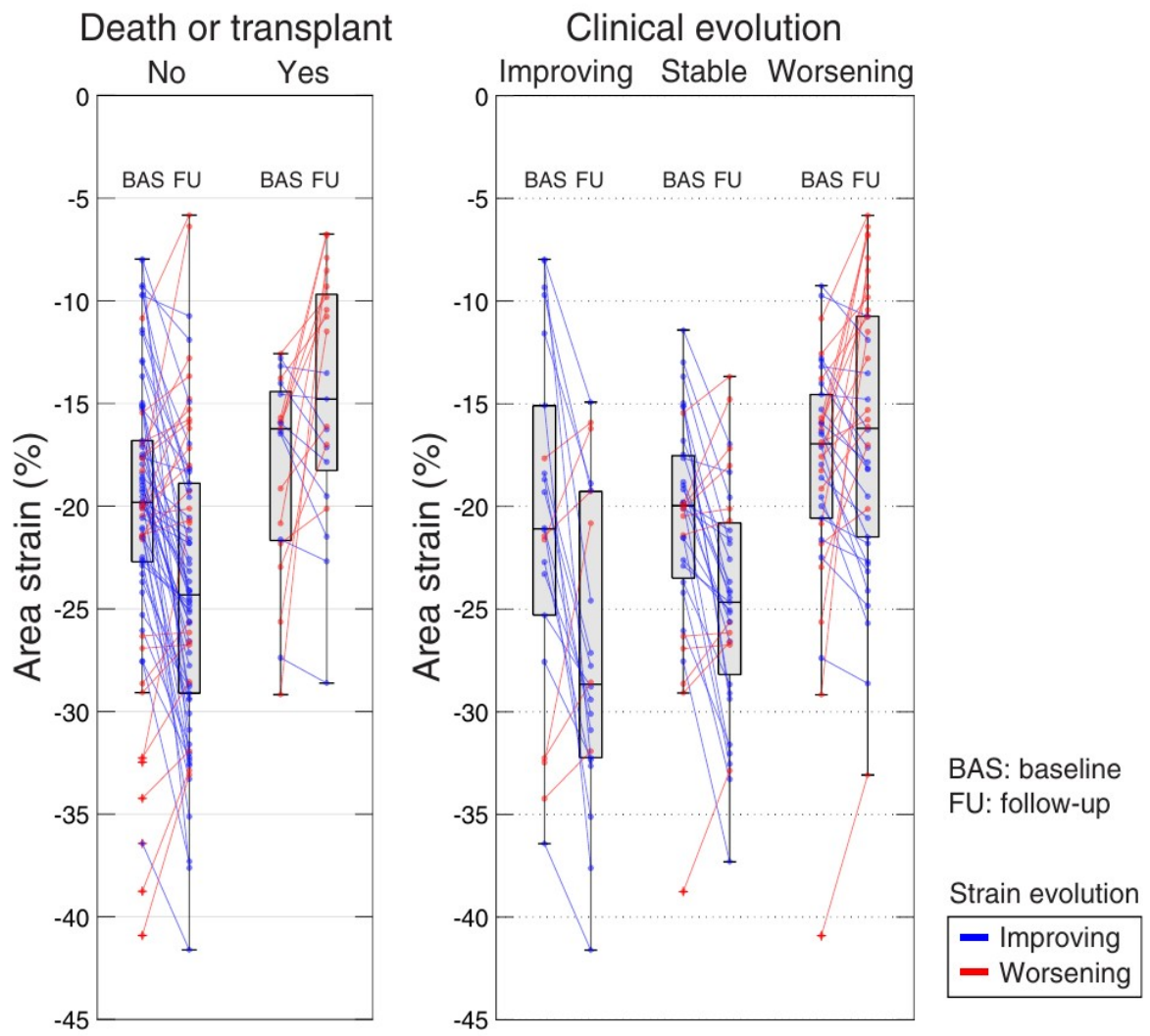


Figure 4

