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Assessment of right ventricular adaptability to loading conditions can improve the timing of listing to transplantation in patients with pulmonary arterial hypertension

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BACKGROUND: Right ventricle (RV) performance is load dependent, and right-sided heart failure (RHF) is the main cause of death in pulmonary arterial hypertension (PAH). Prediction of RV worsening for timely identification of patients needing transplantation (Tx) is paramount. Assessment of RV adaptability to load has proved useful in certain clinical circumstances. This study assessed its predictive value for RHF-free and Tx-free outcome with PAH.

METHODS: Between 2006 and 2012, all potential Tx candidates with PAH, without RHF at the first evaluation, were selected for follow-up (except congenital heart diseases). At selection and at each follow-up, N-terminal prohormone brain natriuretic peptide (NT-proBNP) and the 6-minute walk distance were measured, and RV adaptability to load was assessed by echocardiography. Collected data were tested for the ability to predict RV stability and Tx-free survival.

RESULTS: During a 12-month to 92-month follow-up, RHF developed in 23 of 79 evaluated patients, despite similar medication and no differences in initial RV size and ejection fraction compared with the patients who remained stable. However, unstable patients had an initially lower RV load-adaptation index and afterload-corrected peak global systolic longitudinal strain-rate values as well as higher RV dyssynchrony, tricuspid regurgitation, and NT-proBNP levels ($p \leq 0.01$). At certain cutoff values, these variables appeared predictive for 1-year and 3-year freedom from RHF and 3-year Tx-free survival. An RV load-adaptation index reduction of $\geq 20\%$ showed the highest predictive value (90.0%) for short-term (≤ 1 year) RV decompensation.

CONCLUSIONS: Assessment of RV adaptability to load allows prediction of RV function and Tx-free survival with severe PAH during the next 1 to 3 years. This can improve the timing of listing for Tx. J Heart Lung Transplant ■■■■;■:■■■–■■■

Pulmonary arterial hypertension (PAH) is a severe progressive disorder with poor outcome where the initial insult involves the pulmonary vasculature.[1] Pressure overload-induced right ventricular (RV) failure (RVF) leads to right heart (RH) failure (RHF), which is the main cause of death in PAH.[2] Short-term mortality in PAH patients with acute RHF can reach 40%.[1,3–6] With transplant (Tx) waiting time prolongation, early prediction of irreversible RVF is of paramount importance.

RV performance is highly load dependent, and a reduction in systolic function and ventricular enlargement occur much earlier in the pressure-overloaded RV (e.g., in

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PAH) than in the pressure-overloaded left ventricle (LV).[1,2] Therefore, pulmonary load is an important determinant of RV function in PAH, but there is high variability in RV adaptation to pressure overload.[1] RV adaptability to load as assessed by 2 composite echocardiography (echo) variables – 1) RV size, geometry, and load, taking into account the right atrial (RA) pressure or 2) velocity of myocardial shortening and load – appeared able to predict RV function during loading changes such as pulmonary vascular resistance reduction after LV assist device (LVAD) implantation.[7]

Likewise, it might be presumed that a reduction of RV adaptability to load might predict RHF and survival also in patients with PAH. The aim of our study was therefore to assess the predictive value of RV adaptability to load for short-term and medium-term stability of RV function and Tx-free outcome in potential Tx candidates with PAH, with the final goal of finding new tools to optimize the timing for Tx listing.

Methods

Patients, data collection, and study design

We evaluated all consecutive potential Tx candidates with PAH referred but not yet listed for Tx who were aged ≥18 years, had no RHF, and were clinically stable during the last 3 months before their first evaluation, which took place between January 2006 and September 2012. Before selection, all patients underwent RH catheterization (RHC) for pulmonary hemodynamic measurements. Patients were included in the analysis if they met the modified definition of World Health Organization Group 1 pulmonary hypertension and hemodynamic criteria by RHC (mean pulmonary arterial pressure ≥25 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance >3 WU). Patients with congenital systemic-to-pulmonary shunts were not included in the study because the RV adaptation to loading conditions in these patients, and especially the assessment of that adaptation, can all substantially differ from that in the other PAH forms. Also not included were PAH patients with atrial fibrillation at the time of possible selection because RV adaptation to loading and assessment of that adaptation in these patients can also differ from that of patients without atrial fibrillation.

At selection and thereafter at each follow-up, in addition to routine laboratory analyses and N-terminal prohormone brain natriuretic peptide (NT-ProBNP) plasma level measurements, electrocardiogram recordings, measurements of the 6-minute walk distance (6MWD), partial pressure of arterial oxygen (P_{O_2}), and oxygen saturation (using free-flowing ear capillary blood), all patients also underwent comprehensive echo, including tissue Doppler and strain imaging.

Collected data were tested for ability to predict RV stability and Tx-free survival. The main goals of the final evaluation of prospectively gathered information on RV size, geometry and function (including tricuspid valve function) in potential Tx candidates with PAH were:

1. assessment of the predictive value of RV adaptability to load for Tx-free patient outcome and for the time-course of RV function during the next 1 to 3 years;
2. identification of non-invasively measurable variables with the highest predictive value for stability of RV function and Tx-free patient outcome with severe PAH; and
3. optimization of RV assessment by echo.

Main outcome measures were RV function and RHF-free patient survival.

To attain our goals, all data were prospectively collected according to a well-established protocol in all patients who fulfilled the criteria for inclusion in this study.

The clinical syndrome of RHF with RVF as its main cause was diagnosed in the presence of systemic venous congestion (hepatomegaly with venous distension, peripheral edema, enlarged pulsatile jugular veins, inferior vena cava dilation >2 cm) associated with progressive RV and RA dilation, tricuspid regurgitation (TR) grade ≥III, and worsening of symptoms (dyspnea, weakness, fatigue).

Echo assessment of RH function

Transthoracic echo (TTE) was used for assessment of right heart function, including RV adaptability to increased load and assessment of intraventricular synchronicity of myocardial shortening. An overview of TTE parameters and parameter-derived indexes, which were prospectively collected in all patients according to a standard protocol, is reported in Table 1. TTE was performed according to the guidelines of the American Society of Echocardiography by using GE VIVID 7 and VIVID E9 (General Electric, Fairfield, CT) ultrasound machines. Strain analysis of the 2-dimensional (2D) echo images was performed off-line with the aid of customized EchoPAC software (General Electric).

To assess RV adaptability to load, we also used the same load adaptation index (LAI_{RV}) that has already been found useful for pre-operative distinction between impaired RVs with and without the potential for recovery during RV afterload reduction by a LVAD in patients with end-stage left heart failure.[7] The LAI_{RV} is based on the relationship between RV load and RV dilation, taking also the RA pressure into account: $LAI_{RV} = [\Delta P_{RV-RA}]/[EDV/L_{ED}] \approx VTI_{TR}/(A_{ED}/L_{ED}) = [VTI_{TR}\ (cm) \bullet L_{ED}\ (cm)]/A_{ED}\ (cm^2)$.

As shown, RV load adaptation is reflected by the ratio between the systolic pressure gradient between the RV and right atrium (ΔP_{RV-RA}) and the RV end-diastolic volume/long-axis length (EDV/L_{ED}). Using the TR velocity time integral (VTI_{TR}) instead of ΔP_{RV-RA} (which is calculated from VTI_{TR}) and replacing RV EDV by the easily measurable RV end-diastolic area (A_{ED}), which correlates with the EDV, an easily calculable index of similar value for RV evaluation can be obtained.[7] As shown in Figure 1 (A and B), a small RV area relative to long-axis length (size and geometry unaltered) in a patient with high VTI_{TR} (i.e., high RV systolic pressure and relatively low RA pressure) yields a high LAI_{RV}, which indicates good adaptation to load (i.e., no relevant RV dilation and consequently no relevant TR despite high RV pressure load indicating good right-sided heart function). However, a large area relative to the long-axis length (spherical dilation), despite a low VTI_{TR} (i.e., relatively low RV systolic pressure and relatively high RA pressure), yields a low LAI_{RV}, indicating poor adaptation to load (i.e., excessive RV dilation and high RA pressure despite low RV pressure load indicating impaired right sided heart function).

The RV load-corrected peak global systolic longitudinal strain rate ($PSSrL \bullet \Delta P_{RV-RA}$), another combined variable for assessment of RV adaptability to load, was also used in this study (Figure 1D). This easily and reproducibly obtainable variable, based on the relationship between the velocity of RV myocardial shortening and RV load, has also proved useful for pre-operative distinction between impaired RVs with and without the potential for recovery during RV afterload reduction by an LVAD in patients with end-stage left heart failure.[7] Because the velocity of myocardial