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Right ventricular dyssynchrony in idiopathic pulmonary arterial hypertension: Determinants and impact on pump function

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BACKGROUND: Right ventricular (RV) dyssynchrony has been described in pulmonary arterial hypertension (PAH), but no evidence is available on its morphologic determinants and its effect on systolic function. The aim of this study was to evaluate the morphologic determinants of RV dyssynchrony by echocardiographic and cardiac magnetic resonance imaging and its effect on systolic function.

METHODS: In 60 consecutive idiopathic PAH (IPAH) patients with narrow QRS, RV dyssynchrony was evaluated by 2D speckle-tracking echocardiography, calculating the standard deviation of the times to peak systolic strain for the four mid-basal RV segments (RV-SD4). Patients were grouped by the median value of RV-SD4 (19 milliseconds) and compared for RV remodeling and systolic function parameters, WHO class, pulmonary hemodynamics and 6-minute walk test (6MWT).

RESULTS: Despite similar pulmonary vascular resistance and mean pulmonary arterial pressure, patients with RV-SD4 at >19 milliseconds had advanced WHO class and worse 6MWT, RV hemodynamics, RV remodeling and systolic function parameters compared with patients at ≤ 19 milliseconds. The morphologic determinants of RV dyssynchrony resulted RV end-diastolic area, LV diastolic eccentricity index and RV mass volume ratio ($r = 0.69$, $r^2 = 0.47$, $p < 0.0001$). Finally, we found a significant inverse correlation between RV mid-basal segments post-systolic shortening time and cardiac index ($r = -0.64$, $r^2 = 0.41$, $p = 0.001$), accounting for the significant correlation between RV-SD4 and cardiac index ($r = 0.57$, $r^2 = 0.32$, $p = 0.003$).

CONCLUSIONS: In IPAH with narrow QRS, RV dyssynchrony is associated with RV dilation and eccentric hypertrophy pattern, suggesting a role of segmental wall stress heterogeneity as the major determinant of mechanical delay. Post-systolic shortening, as inefficient contraction, contributes to pump dysfunction.

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Idiopathic pulmonary arterial hypertension (IPAH) is characterized by a progressive increase in pulmonary vascular resistance (PVR), leading to right ventricular

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(RV) overload. Prognosis depends on the ability of the RV to maintain efficiency in face of increased after-load, underscoring the fundamental role of RV adaptation mechanisms to guarantee cardiac output.[1] Left ventricular dyssynchrony has been identified as a major prognostic factor in left side chronic heart failure due to systolic left ventricular dysfunction[2] and it has been targeted using a non-pharmacologic approach.[3] Recently, RV mechanical dyssynchrony has been described in pulmonary arterial hypertension (PAH),[4–7] but limited data are available regarding its effects on cardiac output, as a result of adaptive or maladaptive compensatory mechanisms. Moreover, the morphologic determinants associated with mechanical dyssynchrony have not yet been evaluated in the setting of severe increased pulmonary pressure. Thus, the aim of this study was to evaluate the morphologic determinants of RV dyssynchrony using a comprehensive echocardiographic and cardiac magnetic resonance (CMR) imaging method, and to assess its effect on systolic function and cardiac output.

Methods

Population and study protocol

The study population included consecutive therapy-naive patients with IPAH, World Health Organization (WHO) Functional Class II to IV status, and without severe tricuspid regurgitation or electrocardiographic signs of intraventricular conduction delay. We excluded patients with a QRS duration of $\geq$120 milliseconds, as this implies an electromechanical delay. QRS duration was measured on a digital electrocardiographic (ECG) tracing at a velocity of 20 mm/second to obtain a precise assessment. Patients were referred to our Pulmonary Hypertension Unit (Policlinico Umberto I, Sapienza University of Rome, Italy) from January 2011 to December 2012.

The diagnosis of PAH relied on right heart catheterization (RHC) showing pre-capillary pulmonary hypertension (mean pulmonary artery pressure [mPAP] $\geq$25 mm Hg, pulmonary wedge pressure [PWP] $\leq$15 mm Hg) and use of an algorithm that included respiratory function tests, perfusion lung scan, computed tomography scan and echocardiography to rule out secondary causes, in accordance with European guidelines.[8]

Baseline evaluation at the time of diagnosis included medical history, physical examination, a non-encouraged 6-minute walk test (6MWT), RHC and echocardiographic and CMR assessment.

All patients were included in the study protocol after informed consent. The protocol was approved by the institutional review board for human studies of the Policlinico Umberto I, Sapienza University of Rome (Protocol No. 42412).

Right heart catheterization

Hemodynamic evaluation was made with standard technique. Pressures were measured from the mid-chest position with a fluid-filled catheter and pressure transducer; the average values over three respiratory cycles were recorded. Cardiac output (CO) was measured by the thermodilution technique (American Edwards Laboratories, Santa Ana, CA). The value for pulmonary vascular resistance (PVR) was calculated with the formula: PVR = (mPAP – PWP) / CO.

Standard echocardiography

Baseline echocardiographic studies were performed with the patient in the left lateral decubitus position using commercially available equipment (Vivid S6; GE Medical Systems). All echocardiographic data were acquired within 24 hours from RHC.

Data acquisition was performed with a 3.5-MHz transducer at a depth of 16 cm in the standard parasternal and apical views. Standard M-mode, 2D and Doppler images were obtained during breath-hold and stored in cine-loop format from three consecutive beats. Measurements were performed in accordance with the guidelines of the American Society of Echocardiography.[9]

The following parameters and derived measures were considered in the analysis: right atrial area (RA area); RV end-diastolic area (RVEDA); RV end-systolic area (RVESA); RV fractional area change percent [RVFAC = (RVEDA – RVESA) / RVEDA × 100]; tricuspid annular plane systolic excursion (TAPSE); left ventricular systolic and diastolic eccentricity index (LV-EIs and LV-EId, respectively); and presence of pericardial effusion.

Pulsed waved tissue Doppler imaging (PW-TDI) was used to measure longitudinal myocardial tissue velocities. These velocities were obtained with the transducer in the apical 4-chamber view and the sampling volume (5 mm) positioned in the center of the basal RV free wall segment, parallel to the analyzed vector of regional motion. Sector width, gains and filters were adjusted to obtain the optimal tissue signal. Measurements included the isovolumic contraction velocity (S1), isovolumic acceleration (IVA) and peak systolic velocity (S2). All reported measurements represent averages derived from three consecutive cardiac cycles.

RV dyssynchrony assessment

RV dyssynchrony was assessed using 2D speckle-tracking echocardiography.

Acquisition

For speckle-tracking analysis, standard gray-scale 2-dimensional (2D) images, previously acquired in the 4-chamber apical view and digitally saved in cine-loop format, were analyzed. Three consecutive beats were recorded with a frame rate between 50 and 70 fps to allow for reliable analysis of the software (ECHOPAC workstation 7.0.1; GE Medical Systems). The RV endocardial border was manually traced and a fine-tuning of the region of interest was done to ensure that the segments were tracked appropriately. Finally, the software automatically divided the myocardium into six standard segments (basal, middle and apical for the RV free wall and the interventricular septum) and time–strain longitudinal curves were generated from each segment.

Analysis

Peak systolic strain amplitude and time intervals from QRS onset to peak systolic strain were calculated for all RV myocardial segments in the longitudinal direction. Time intervals were corrected for heart rate according to Bazett's formula.[10]

To assess the segmental characteristics of the RV, we initially adopted the six-segment RV model, but then shifted to a four-segment RV model, excluding apical segments from the analysis due to their high variability, even among normal subjects. This