JACC: CARDIOVASCULAR IMAGING
VOL. 8, NO. 6, 2015

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2015.02.009

Right Intraventricular Dyssynchrony in Idiopathic, Heritable, and Anorexigen-Induced Pulmonary Arterial Hypertension

Clinical Impact and Reversibility

Roberto Badagliacca, MD, PhD,* Manuela Reali, MD, PhD,* Roberto Poscia, MD, PhD,* Beatrice Pezzuto, MD,* Silvia Papa, MD,* Mario Mezzapesa, MD,* Martina Nocioni, MD,* Gabriele Valli, MD, PhD,* Elisa Giannetta, MD, PhD,† Susanna Sciomer, MD,* Carlo Iacoboni, MD,* Francesco Fedele, MD,* Carmine Dario Vizza, MD*

ABSTRACT

OBJECTIVES The aim of this study was to determine the prevalence of right intraventricular dyssynchrony, its determinants and prognostic impact in idiopathic, heritable, and anorexigen-induced pulmonary arterial hypertension.

BACKGROUND Right ventricular dyssynchrony has been described in pulmonary arterial hypertension, but no evidence is available on its prognostic impact and evolution after therapy.

METHODS In 83 consecutive therapy-naïve patients, right ventricular dyssynchrony was evaluated by 2-dimensional speckle-tracking echocardiography calculating the standard deviation of the times to peak-systolic strain for the 4 mid-basal right ventricular segments (RV-SD4). After baseline (World Health Organization [WHO] class, pulmonary hemodynamics, 6-min walk test [6MWT]), a second assessment was performed after 12 months or when clinical worsening occurred.

RESULTS Patients with right ventricular dyssynchrony (RV-SD4 >18 ms) had advanced WHO class, worse 6MWT, right ventricular remodeling, and hemodynamic profile compared with patients ≤18 ms. Determinants of dyssynchrony included pulmonary vascular resistance, QRS duration, and right ventricular end-diastolic area ($r^2 = 0.38$; $p < 0.000001$). At 12 months, 32.5% of patients presented clinical worsening (actuarial rates: 19% at 6 months, 31% at 1 year). Multivariable models for clinical worsening prediction showed that the addition of RV-SD4 to clinical and hemodynamic variables (WHO IV, 6MWT, and cardiac index) significantly increased the prognostic power of the model (0.74 vs. 0.81; $p = 0.005$, 95% confidence interval [CI]: 0.02 to 0.11). Receiver operating characteristic analysis identified RV-SD4 ≥ 23 ms as the best cutoff value for clinical worsening prediction (95% negative predictive value). At 12 months, normalization of dyssynchrony was achieved in patients with a large reduction of pulmonary vascular resistance (-42 ± 4%).

CONCLUSIONS Right ventricular dyssynchrony is frequent in pulmonary arterial hypertension, is an independent predictor of clinical worsening, and might regress during effective treatments. (J Am Coll Cardiol Img 2015;8:642–52)

Pulmonary arterial hypertension (PAH) is a severe disease characterized by a progressive elevation of pulmonary vascular resistance (PVR), ultimately resulting in right ventricular (RV) dysfunction leading to heart failure and death (1). Prognosis depends on the ability of the RV to maintain its function in the face of increased afterload (2). Ventricular mechanical dyssynchrony has been well described in left ventricular (LV) failure as an important component of LV systolic performance and has formed the basis of cardiac resynchronization therapy, leading to significant improvements in

From the *Department of Cardiovascular and Respiratory Science, Sapienza University of Rome, Rome, Italy; and the †Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Fedele and Vizza are joint last authors.

Manuscript received November 26, 2014; revised manuscript received February 6, 2015, accepted February 12, 2015.

patient functional capacity and survival (3). Although RV mechanical dyssynchrony (RVD) has recently been described in pulmonary hypertension (4–6), currently we do not have evidence on its prognostic relevance. To address this issue, RV mechanics should be evaluated taking into account several methodological considerations such as a larger and more homogeneous PAH population than previous studies, absence of confounding factors, adequate management and follow-up of patients, and application of new echocardiographic techniques for mechanical delay evaluation.

Accordingly, the aims of this study were to determine the prevalence of RVD in a large cohort of idiopathic, heritable, and anorexigen-induced pulmonary arterial hypertension (IPAH, HPAH, APAH), therapy-naïve patients, to better elucidate the factors influencing RVD, to evaluate the prognostic impact of RVD and its evolution on long-term follow-up.

METHODS

POPULATION AND STUDY PROTOCOL. The study population included 83 consecutive therapy-naïve patients with IPAH, HPAH, and APAH, without severe tricuspid regurgitation or electrocardiographic signs of intraventricular conduction delay to avoid other confounding factors for RVD evaluation. Patients were referred to our center from January 1, 2010 to December 31, 2011, and diagnosis of PAH had been made according to European guidelines (7). Three patients with suboptimal echocardiographic images were excluded from all subsequent analyses. Thus, the patient study group consisted of 80 patients.

SEE PAGE 653

Patients with IPAH, HPAH, and APAH should be considered a homogeneous population with common pathophysiological pathways and histologic findings (8).

Baseline evaluation included medical history, physical examination, a nonencouraged 6-min walk test (6MWT), right heart catheterization (RHC), and echocardiographic assessment. Thereafter, patients started a specific PAH treatment, according to European guidelines (7).

All patients were prospectively followed-up for 12 months with phone calls (every month) and clinical examinations (every 1 to 3 months) for the presence of clinical worsening (CW), defined as a reduction in exercise capacity (-15% compared with baseline 6MWT), worsening in World Health Organization (WHO) functional class, or clinical deterioration requiring hospital admission (need for intravenous diuretic or inotropic drugs, need for new PAH therapies, lung transplantation, or death) (9). The CW was evaluated by 2 physicians (V.C.D., P.R.) blinded on the echocardiographic results.

A second assessment (WHO class, 6MWT, RHC, echocardiography) was performed after 12 months or when CW occurred. 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 n. 42412).

RIGHT HEART CATHETERIZATION. Hemodynamic evaluation was made with standard technique, as previously described (10).

STANDARD ECHOCARDIOGRAPHY. Echocardiographic studies were performed using commercially available equipment (Vivid S6, GE Medical Systems, Milan, Italy) and acquired within 24 hours from RHC. Standard M-mode, 2-dimensional (2D) and Doppler images were obtained during breath hold and stored in cine-loop format from 3 consecutive beats. Measurements were performed in accordance with the American Society of Echocardiography Guidelines (11).

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

Pulsed-wave tissue Doppler imaging (PW-TDI) was used for the following measures: isovolumic contraction velocity (S1), isovolumic acceleration (IVA), and peak systolic velocity (S2). All reported measurements are the averages derived from 3 consecutive cardiac cycles.

2D SPECKLE-TRACKING ECHOCARDIOGRAPHY. Acquisition. For speckle tracking analysis (EchoPAC workstation 7.0.1, GE Medical Systems), standard grayscale 2D images in the 4-chamber apical view were acquired and digitally stored in 3 beats cine-loop format.

Analysis. To assess the segmental characteristics of the RV, we adopted the 6-segment model, excluding the apical segments for the analysis because of the

ABBREVIATIONS AND ACRONYMS

IVA = isovolumic acceleration

IVS = interventricular septum

LVEId = left ventricular diastolic eccentricity index

LVEIs = left ventricular systolic eccentricity index

PW-TDI = pulsed waved tissue Doppler imaging

RV = right ventricular

RVEDA = right ventricular end-diastolic area

RVESA = right ventricular end-systolic area

RVFAC = right ventricular fractional area change

RVFW = right ventricular free wall

RV-SD4 = standard deviation of the times to peak-systolic strain for the 4 mid-basal right ventricular segments

S1 = isovolumic contraction velocity

S2 = peak systolic velocity

STE = speckle-tracking echocardiography