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Effect of electrical dyssynchrony on left and right ventricular mechanics in children with pulmonary arterial hypertension

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BACKGROUND: Electrical and right ventricular (RV) mechanical dyssynchrony has been previously described in pediatric pulmonary arterial hypertension (PAH), but less is known about the relationship between electrical dyssynchrony and biventricular function. In this study we applied cardiac magnetic resonance (CMR) imaging to evaluate biventricular size and function with a focus on left ventricular (LV) strain mechanics in pediatric PAH patients with and without electrical dyssynchrony.

METHODS: Fifty-six children with PAH and comprehensive CMR evaluation were stratified based on QRS duration *z*-score, with electrical dyssynchrony defined as *z*-score ≥2. Comprehensive biventricular volumetric, dyssynchrony, and strain analysis was performed.

RESULTS: Nineteen PAH patients had or developed electrical dyssynchrony. Patients with electrical dyssynchrony had significantly reduced RV ejection fraction (35% vs 50%, $p = 0.003$) and greater end-diastolic (168 vs 112 ml/m^2, $p = 0.041$) and end-systolic (119 vs 57, ml/m^2, $p = 0.026$) volumes. Patients with electrical dyssynchrony had reduced RV longitudinal strain (–14% vs –19%, $p = 0.007$), LV circumferential strain measured at the free wall (–19% vs –22%, $p = 0.047$), and the LV longitudinal strain in the septal region (–10% vs –15%, $p = 0.0268$). LV mechanical intraventricular dyssynchrony was reduced in patients with electrical dyssynchrony at the LV free wall (43 vs 19 ms, $p = 0.019$).

CONCLUSIONS: The electrical dyssynchrony is associated with the reduced LV strain, enlarged RV volumes, and reduced biventricular function in children with PAH. CMR assessment of biventricular mechanical function with respect to QRS duration may help to detect pathophysiologic processes associated with progressed PAH.

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Although pulmonary arterial hypertension (PAH) increases right ventricular (RV) after-load and reduces function, left ventricular (LV) systolic and diastolic

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performance is being increasingly recognized as a prominent comorbidity of PAH, with major implications regarding clinically outcomes in both adult and pediatric populations.[1–3] In particular, the ventricular mechanical interdependence in pediatric PAH patients has been thoroughly described by echocardiography, which has demonstrated compromised LV function through assessment of strain.[4,5] The relatively novel concept of intraventricular mechanical dyssynchrony has been introduced in PAH patients in descriptions of the non-uniform contractile function of the RV.[6,7] Both RV intraventricular mechanical dyssynchrony and electrical dyssynchrony have been described in children with PAH, yet the direct association between the mechanical and electrical components remains poorly understood.[8] A better understanding of the relationship between electrical and mechanical dyssynchrony in children with PAH may be of importance, given the known negative impact of electrical dyssynchrony on LV mechanics in patients with systolic and diastolic heart failure.[9,10]

Cardiac magnetic resonance (CMR) serves as the "gold standard" approach for evaluation of ventricular size and function, and is becoming more frequently applied for strain functional evaluation using feature tracking methods.[11–13] Consequently, in this study we aimed to: (1) evaluate CMR-derived strain metrics in children with PAH with or without electrical dyssynchrony; (2) characterize the inter- and intraventricular mechanical dyssynchrony along with respect to the severity of electrical dyssynchrony; and (3) evaluate standard ventricular volumetric and functional metrics with regard to electrical dyssynchrony. We hypothesized that CMR-derived RV and LV strain indices along with standard ventricular volumetric and functional metrics will differ in PAH with electrical dyssynchrony, and that association will exist between LV intraventricular mechanical and electrical dyssynchrony.

Methods

This study was a retrospective observational investigation of all PAH patients seen at the Pulmonary Hypertension Clinic of the Children's Hospital Colorado who underwent comprehensive CMR evaluation. The initial diagnosis was established according to accepted pediatric PAH guidelines by means of previous right heart catheterization and echocardiography.[1] PAH-specific markers, including World Health Organization (WHO) functional class (FC), 6-minute walk distance, brain natriuretic peptide (BNP), and N-terminal pro-BNP, were sampled at the time of catheterization. This study was part of a Colorado multi-institutional review board–approved imaging protocol.

Electrical dyssynchrony was assessed from interpreted 12-lead electrocardiograms (ECGs) that were collected within 1 week of CMR acquisition during usual clinical follow-up. The QRS duration was sampled from multiple leads independently by 2 electrophysiology specialists blinded to severity of the PAH disease. The QRS duration–specific z-scores were calculated with respect to specific age category based on historical control data collected by Davignon et al,[14] with QRS duration means and standard deviations specific for each age category as described by Hill et al.[8] Electrical dyssynchrony was then uniformly defined by z-score ≥ 2 for each age group. Interobserver variability of electrical dyssynchrony (QRS duration) revealed minimal percent bias of 1.1 ms with 95% limits of agreement from –0.4 to 2.4 ms, with a correlation coefficient of 0.94.

CMR acquisition protocol

The CMR protocol was conducted as described previously.[15] A gradient–echo sequence with ECG gating was applied with 12- to 32-channel phased coils using a 1.5- or 3.0-Tesla magnet system (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany, and Ingenia, Philips Medical Systems, Best, The Netherlands, respectively). Standard cine long-axis, short-axis, and 4-chamber-axis images were obtained using steady state free precession (SSFP) during end-expiratory breath-holds.

Depending on patient size and field of view, the typical the parameters ranged from slice thickness of 4 to 10 mm, TE 1.1 to 1.5, TR 2.8 to 3.5, and in-plane resolution 1.2 to 1.4 mm, with temporal resolution between 14 and 28 ms, resulting from 30 to 40 cardiac phases. Ventricular end-systolic and end-diastolic contours for volumetric and functional assessment were calculated using QMASS (Medis Medical Imaging Systems, Inc., Raleigh, NC). Sampled indices included end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and ejection fraction (EF). For purposes of intergroup analysis, CMR-derived size measurements were normalized to body size area due to the age-related variations in our pediatric population.

Strain and mechanical dyssynchrony analysis

All strain and mechanical analyses were performed using a CVI42 platform version 5.6.6 (Circle Cardiovascular Imaging, Calgary, AB, Canada). The collected RV strain indices included peak global radial and circumferential strain measured at the mid-level using short-axis images along with respective time-to-peak metrics (Figure 1A). The LV radial and circumferential analysis used the mid-level of the American Heart Association 16-segment model, with 4 segments delineating the free wall and 2 segments corresponding to the interventricular septum (Figure 1B). In addition, we evaluated both RV global longitudinal strain and LV global longitudinal strain, where 3 segments were specifically indicative of the free wall and 3 segments were representative of septum (Figure 2). The LV intraventricular dyssynchrony was analyzed by computing the standard deviation (SD) of time-to-peak longitudinal strain measures generated for each segment considering particular LV compartments (global, free-wall, and septum), as described elsewhere.[7,8] The interventricular dyssynchrony was calculated by comparing the difference between LV- and RV-specific time to peak from longitudinal strain spectra. Figure 3 depicts the mechanical dyssynchrony evaluation algorithm for intra- and interventricular analysis.

Statistical analysis

Analyses were performed using JMP version 13.1 (or higher) statistical software (SAS Institute, Inc, Cary, NC).