Structural Heart

The Journal of the Heart Team

ISSN: 2474-8706 (Print) 2474-8714 (Online) Journal homepage: https://www.tandfonline.com/loi/ushj20

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To cite this article: Victoria Delgado (2017) Right Ventricular Dyssynchrony to Measure the Effects of Pulmonary Endarterectomy in Chronic Thromboembolic Pulmonary Hypertension, Structural Heart, 1:3-4, 160-161, DOI: 10.1080/24748706.2017.1356492

To link to this article: https://doi.org/10.1080/24748706.2017.1356492

Accepted author version posted online: 17 Jul 2017.
Published online: 27 Jul 2017.

STRUCTURAL HEART
2017, VOL. 1, NOS. 3–4, 160–161
https://doi.org/10.1080/24748706.2017.1356492

EDITORIAL

Right Ventricular Dyssynchrony to Measure the Effects of Pulmonary Endarterectomy in Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the leading causes of precapillary pulmonary arterial hypertension.[1] The exact prevalence and incidence of CTEPH remain difficult to determine since pulmonary embolism may be silent in two thirds of the patients and some of the patients presenting with acute pulmonary embolism may have pre-existing undiagnosed CTPEH. The estimated cumulative incidence of CTEPH within 2 years after symptomatic pulmonary embolism ranges from 0.1% to 9%.[2] In the United States, the estimated prevalence of CTEPH among the population younger than 65 years is 63 per million individuals and increases to 1007 per million individuals among those aged 65 years or older.[1]

A diagnosis of CTEPH with a mean pulmonary arterial pressure >30 mmHg treated with anticoagulation portends poor prognosis (3-year mortality rate of 90%). Pulmonary thromboendarterectomy (PEA) is the treatment of choice and it has demonstrated significant improvements in clinical symptoms, normalization of hemodynamics and reductions in mortality with low operative risk (in-hospital mortality rate of 4.7%).[3] The mechanical obstruction caused by the thromboembolic material and the development of secondary vasculopathy due to chronic inflammation and increased shear stress are the underlying pathophysiological mechanisms of pulmonary hypertension in CTEPH. Secondary vasculopathy is responsible for the disease worsening despite optimal anticoagulation treatment and the presence of residual pulmonary hypertension after PEA. Therefore, early referral of patients with CTEPH to PEA before secondary vasculopathy develops may result in superior outcomes. Nearly 80% of patients with CTEPH are suitable for PEA. World Health Organization functional class II–IV symptoms and surgical accessibility of thrombi in the main, lobar or segmental pulmonary arteries are the general criteria to define patient suitability for this treatment.[3] In contrast, pulmonary vascular resistance or measures of right ventricular function are not considered in the selection of patients for PEA. However, in evaluating the efficacy of a therapy, improvement in cardiac performance is an important endpoint along with improvement in clinical symptoms and survival.

The right ventricle responds to chronic pressure overload with hypertrophy, dilation, and eventually systolic dysfunction. At the cellular level, changes in cardiac myosin composition, down-regulation of various potassium channels contributing to prolongation of the action potential duration and changes in metabolism with an increased uptake of glucose have been described and associated with right ventricular (RV) dysfunction.[4] Many of these changes may be present years before overt RV dilation and dysfunction are detected with non-invasive cardiac imaging. Recent advances in tissue Doppler and strain imaging have permitted the assessment of active myocardial deformation and its characterization along the cardiac cycle as a surrogate of the electrophysiological and mechanical changes occurring in the RV remodelling process. Several measurements of intra- and interventricular (RV-left ventricular [LV]) dyssnchrony have been derived and correlated with conduction velocities, action potential duration and systolic function of the right ventricle in patients with pulmonary hypertension.[5–8] The standard deviation of time to peak longitudinal strain of 6 RV segments measured with speckle tracking echocardiography on the apical 4-chamber view is one of the parameters most frequently used to characterize RV dyssynchrony. Using this parameter, Kalogeropoulos and colleagues showed that RV dyssynchrony was significantly larger among patients with pulmonary hypertension compared with controls (63 ± 21 ms vs. 25 ± 15 ms, $p < 0.001$).[7] RV dyssynchrony was independently correlated with RV fractional area change and RV global longitudinal strain.[7] In addition, Hardziyenka and colleagues have shown that patients with CTEPH exhibit delayed RV electrical activation and epicardial action potential duration on epicardial mapping compared to the left ventricle as well as delayed onset of diastolic relaxation of the RV wall with respect to the LV wall on tissue Doppler imaging.[8] These findings suggest that the electrical remodelling is not only confined to the RV but also the LV.

How treatment of pulmonary hypertension may influence on RV dyssynchrony remains largely unknown and was the hypothesis of the article by Wong and colleagues published in this issue of *Structural Heart*.[9] A total of 127 consecutive CTEPH patients (mean age 51 ± 14 years, 59% female) were evaluated with right heart catheterization and speckle tracking echocardiography before and after PEA. RV dyssynchrony was measured as the standard deviation of peak-systolic strain between three free wall segments (RVDP) and corrected to the R-R interval according to Bazett's formula (RVDT). Baseline

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mean tricuspid annulus plane systolic excursion (TAPSE), RV fractional area change and RV longitudinal strain were 15 mm, 17% and −11%, respectively, indicating severely impaired RV systolic function. Baseline mean RVDP and RVDT were 9.4% and 103 ms, respectively. After PEA, significant reductions in mean pulmonary arterial pressure (from 46 ± 12 to 23 ± 7 mmHg, $p < 0.001$) and pulmonary vascular resistance (from 723 ± 358 to 238 ± 133 [dynes-sec] /cm^5, $p < 0.001$) were noted along with significant increases in cardiac output (from 4.4 ± 1.3 to 5.6 ± 1.2 L/min, $p < 0.001$). Interestingly, global RV longitudinal strain did not change and TAPSE decreased (from 1.5 ± 0.6 to 0.7 ± 0.4 cm, $p < 0.001$) after PEA. However, measures of RV dyssynchrony significantly improved after PEA as indicated by significant decreases in RVDP (from 9.4 ± 6.2 to 5.4 ± 3.8%, $p < 0.001$) and RVDT (from 103 ± 65 to 56 ± 65 ms, $p < 0.0001$). These changes in RV dssynchrony were correlated with preoperative RV systolic function but not with changes in pulmonary hemodynamics. Patients with better TAPSE tended to have larger improvement in RVDT after PEA.

These findings have important clinical implications since the presence of RV dyssynchrony in CTEPH seems to be an earlier marker of RV remodeling than measures of RV systolic dysfunction. In addition, restoration of RV synchronicity (larger improvement in RV dyssynchrony) could be a surrogate of sustained efficacy of PEA. It is well known that the presence of secondary vasculopathy may cause residual pulmonary hypertension after successful PEA. The present study by Wong and co-workers[9] did not correlate the presence of residual pulmonary hypertension with RV dyssynchrony measures at follow-up and did not extend the study with RV-LV interdependence measures (interventricular dyssynchrony). However, it would be interesting to investigate whether patients with technically successful PEA but residual pulmonary hypertension had less acute improvement in RV dyssynchrony and if significant interventricular dyssynchrony was still present at long-term follow-up. If this hypothesis is confirmed, additional analyses including measures of RV-LV interdependence would be of interest to understand which patients could be candidates for bail-out therapies such as RV pacing to resynchronize both ventricles.[10] There is no doubt that PEA has been a therapeutic breakthrough for patients with CTEPH but there remain additional unresolved issues that need ongoing research.

Disclosure statement

The author reports no conflicts of interest.

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