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● *Original Contribution*

HISTOLOGIC AND HEMODYNAMIC CORRELATES OF RIGHT VENTRICULAR FUNCTION IN A PRESSURE OVERLOAD MODEL: A STUDY USING THREE-DIMENSIONAL SPECKLE TRACKING ECHOCARDIOGRAPHY

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Abstract—The aim of our study was to assess the characterization of right ventricular (RV) deformation using three-dimensional (3D) speckle tracking echocardiography (STE) and association of 3D-STE indices with histologic and hemodynamic parameters in a chronic RV pressure overload animal model. Pulmonary artery banding (PAB) was used to induce RV pressure overload in seven beagles. 3D-STE, histologic and hemodynamic measurements were performed in PAB and sham-operated beagles 3 mo after PAB. RV longitudinal, radial and circumferential strain was measured from 3D-STE. Three mo after PAB, RV longitudinal strain was decreased; whereas radial and circumferential strain remained unchanged in PAB group. RV longitudinal strain was associated with interstitial fibrosis ($r = -0.733$) in the endocardial layer of the RV free wall. RV circumferential strain was related to dp/dt_{max} ($r = 0.718$). The significant correlations of RV 3D-STE indices with histologic and hemodynamic parameters indicate that 3D-STE may be a valuable tool for assessment of ventricular function in RV pressure overload. (E-mail: xiemx64@126.com) © 2018 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology.

Key Words: **Three-dimensional, Speckle tracking echocardiography, Right ventricular pressure overload, Hemodynamic, Myocardial remodeling.**

INTRODUCTION

Right ventricular (RV) dysfunction is a major determinant of outcome in patients with RV pressure overload (RVPO) (Ghio et al. 2010). Echocardiography as a non-invasive tool is widely used to evaluate RV function. However, accurate assessment of RV function using conventional echocardiography remains a challenge, owing to RV complex structure and contraction (Haddad et al. 2008).

In the recent years, two-dimensional (2D) speckle tracking echocardiography (STE) has been demonstrated to be a feasible and sensitive quantitative technique of assessing ventricular function and has been increasingly used for the functional assessment of the right ventricle in a variety of cardiovascular diseases (Fukuda et al. 2011; Li et al. 2015). Although 2D-STE is considered more beneficial than the conventional echocardiography, it is limited by the out-of-plane motion of speckles and the difficulty of assessing deformation in other dimensions (Cheung 2012). The newly developed three-dimensional (3D) STE enables tracking of out-of-plane speckle motion and simultaneous imaging of various ventricular segments on the basis of the full-volume data set (Cheung 2012). 3D-STE has been used extensively to quantify left ventricular function, but its value for RV assessment has not been well established.

Exposure of the right ventricle to chronic pressure overload also promotes myocardial remodeling, which may underlie the early changes in RV function. Pathologic cardiomyocyte growth, variable degrees of fibrosis and decreased RV capillary density have been identified as mechanisms that promote RV remodeling (Bogaard et al. 2009). However, to the best of our knowledge, no study provides a comprehensive histologic and hemodynamic

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profile and their associations with RV deformation using 3D-STE in a chronic RVPO model.

Accordingly, the purposes of our study were to assess the characteristics of RV global and regional deformation using 3D-STE and to explore the correlations of 3D-STE–determined indices with histologic and invasive hemodynamic mechanisms of the right ventricle in a chronic RVPO animal model.

MATERIALS AND METHODS

Twelve 14-mo-old male beagles with a mean weight of 11.2 ± 0.5 kg were used in our experiments. Beagles were randomized to a sham operation (control group, n = 5) or to a pulmonary artery banding (PAB) group (n = 7). One animal died one mo after PAB. Three mo after PAB, the beagles underwent an echocardiographic investigation and invasive hemodynamic measurements. Subsequently, the animals were euthanized using a lethal intravenous potassium infusion. The heart tissue samples were collected for histologic analysis. The research protocol was approved by the Institutional Care and Animal Use Committee, Tongji Medical College, Huazhong University of Science and Technology, Wuhan.

Animal model

The beagles were anesthetized with intravenous injections of 3% pentobarbital sodium (1 mL/kg). After orotracheal intubation, the beagles were mechanically ventilated. A left thoracotomy through the 3rd intercostal space was performed to expose the pulmonary artery. A silk suture was tied tightly around an f8 stainless steel bougie (outer diameter of 5 mm) alongside the main pulmonary artery. After subsequent rapid removal of the bougie, a fixed constricted opening was created in the lumen equal to the diameter of the bougie. The degree of PAB was confirmed by epicardial echocardiography. The epicardial echocardiography revealed that the pulmonary artery was occluded to 5 mm, which corresponded to approximately 50% occlusion of the luminal diameter. The sham-treated beagles underwent the same thoracotomy without PAB. The beagles were then sutured and allowed to recover from anesthesia. Postoperative anti-infective therapy was achieved by an intramuscular injection of cefuroxime sodium 0.75 g every 24 h for 3 d.

Echocardiography study

We performed transthoracic echocardiography 3 mo after PAB, using a Philip IE33 ultrasound machine (Philips Medical Systems, Andover, MA, USA) on sham-operated and PAB beagles. The beagles were anesthetized with 3% pentobarbital sodium when echocardiographic investigations were performed. The beagles were fixed in position with the continuous monitoring of heart rates. Chest hair was depilated and a layer of sonographic coupling gel applied to the thorax. Measurements were performed according to the guidelines for echocardiographic assessment of the right heart (Rudski et al. 2010). Right atrial end-systolic diameter and RV end-diastolic diameter were assessed in the apical 4-chamber view. RV end-diastolic and end-systolic areas were also measured from the apical 4-chamber view to calculate RV fractional area change. RV fractional area change was defined as (RV end-diastolic area—RV end-systolic area)/RV end-diastolic area × 100 (Rudski et al. 2010). The tricuspid annular peak systolic excursion was obtained using M-mode echocardiography of the lateral annulus. The tricuspid annular peak systolic velocity, early-diastolic velocity and late-diastolic velocity were assessed by tissue Doppler imaging in the apical 4-chamber view. The tissue Doppler imaging-derived myocardial performance index was calculated. RV myocardial performance index was defined as the ratio of the sum of the RV isovolumic contraction time and the isovolumic relaxation time divided by the ejection time (Rudski et al. 2010). Acceleration of the myocardium during isovolumic contraction was assessed in the apical 4-chamber view by tissue Doppler imaging at the lateral tricuspid annulus. Pulmonary artery diameter and its pulmonary peak flow velocity at the location of PAB were also measured from the parasternal short axis view of the aortic root. Pulmonary acceleration time was measured as the interval between the onset of ejection and peak pulmonary flow velocity. Left ventricular (LV) end-diastolic volume, end-systolic volume and ejection fraction (EF) were measured by biplane Simpson's method (Lang et al. 2005). The principle of using this method is that the total LV volume was calculated from the summation of a stack of elliptical disks from the apical 2- and 4-chamber views.

3D echocardiographic imaging was performed at the cardiac apex, using a matrix-array transducer (X5-1). 3D full-volume data sets combining four sub-volumes were captured over four consecutive cardiac cycles (mean volume rate, 33 ± 6 volumes/s). All 3D echocardiographic images were stored for offline analysis by TomTec 4.0 software (TomTec Imaging Systems, Unterschleissheim, Germany). Because 3D-STE was designed for the left ventricle, a modified methodology was devised, as described in a previous report (Rajagopal et al. 2014; Smith et al. 2014). Using the 3D-STE software and with the cineloop frozen at the end-diastolic and end-systolic frames, the endocardial border was manually traced in the triplane views (the apical 4-chamber RV equivalent, 2-chamber RV equivalent and 3-chamber RV equivalent views) and adjusted in the 2 coronal planes (Fig. 1). The software then tracked the speckles from the 3D data set. RV end-diastolic volume, end-systolic volume and EF, and RV global and regional longitudinal, radial and circumferential strain were obtained from the software. RV free wall and interventricular