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EDITORIAL

Micro Computed Tomography in Experimental Pulmonary Arterial Hypertension

Do Good Things Come in Small Packages?

See Article by Kojonazarov et al

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Right ventricular (RV) function is now recognized as one of the most important predictors of prognosis in many cardiovascular disease states, including pulmonary hypertension and left heart failure with reduced and persevered ejection fraction.[1,2] This is particularly important for patients with pulmonary arterial hypertension (PAH) where RV failure not only drives symptomology but is also the leading cause of death.[3,4] In prospective cohorts, the response of the RV to PAH-therapy is a critical prognostic marker with decreasing function portending a worsening prognosis, irrespective of any changes in pulmonary vascular resistance.[5] The importance of assessing RV function is thus evident, yet detailed assessment of RV function remains difficult—even with contemporary imaging modalities—given the complex 3-dimensional geometric shape, bellows-like motion, and load dependence of RV function.

Small animals are frequently used in the evaluation of experimental PAH and right heart failure; their similarities to humans in cardiovascular physiology, relatively fast reproductive rate, and ease of animal handling make them ideal models for research. However, their small size and fast heart rates can limit in-vivo imaging and phenotyping of the RV. Echocardiography, magnetic resonance imaging (MRI), and microPET are established tools for the evaluation of RV function and physiology in small animal research. Although each imaging modality can be readily adapted from bench to bedside in translational research, the challenges of RV imaging in humans remain evident in small animal models. In clinical practice, powerful noninvasive imaging tools have emerged with capabilities extending beyond global RV assessment to now include regional and even molecular information. MRI is considered the 'gold-standard' for the noninvasive assessment of RV function, volumes, and mass, but imaging costs and accessibility continue to limit widespread clinical application.[6] At most institutions, 2-dimensional echocardiography constitutes first-line imaging for patients with suspected right heart failure and pulmonary hypertension; limitations in qualitative assessment of function may be overcome with recent advancements in 3-dimensional echocardiography and speckle tracking/train imaging, yielding more reliable estimates of right ventricular ejection fraction with less operator dependence.[7] Computed tomography (CT) has superior spatial resolution but inferior contrast resolution as compared to MRI. Indeed, this is particularly relevant for assessing ventricular volumes in rodents whose heart rates range from 300 to 600 bpm. The use of a contrast agent and fast gantry rotation times may help improve contrast and temporal resolution, respectively, to allow for a detailed assessment of ventricular volumes.[8] It is important to note that all of these noninvasive assessments of RV function are dependent on RV preload and afterload and, therefore, do not fully characterize the intricacies of

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RV function. RV function must, therefore, be expressed relative to its load, referred to as ventriculoarterial coupling. Coupling is a measure of energy transfer and can be assessed from the ratio of end-systolic elastance (E_{es}) and arterial elastance (E_a), variables both derived from pressure-volume loop analysis.[9] E_{es} is a load-independent measure of RV contractility, whereas E_a is a ventricular-independent measure of the load on the RV.[9] Load-independent diastolic indices of RV function can similarly be derived.[10] Currently, accurate assessment of ventriculoarterial coupling requires invasive hemodynamics in both humans and small animal models.

In the current issue of *Circulation: Cardiovascular Imaging*, Kojonazarov et al[11] report on the first quantitative assessment of RV and left ventricular systolic and diastolic volumes and function using micro computed tomography (microCT) in an experimental model of PAH. They used the SU54126 and chronic hypoxia model (SU54126/CH) model, which is currently the gold-standard preclinical model for PAH research.[12–14] Using a Quantum GX microCT in conjunction with a blood-pool iodinated contrast agent, this group recapitulates the RV phenotype commonly observed in the human condition, that is, RV enlargement, dilation of the pulmonary artery, and a flat interventricular septum. The investigators obtained volumes and functional parameters for RV/left ventricular systolic and diastolic function. As expected, RV end-diastolic and systolic volumes were markedly elevated in PAH rats, with an impaired RV ejection fraction. RV systolic function was also impaired, as described by a decreased peak ejection rate and longer total ejection time. In contrast, left ventricular filling volumes were decreased with preserved left ventricular ejection fraction. This study is unique in that they also quantified RV diastolic function in PAH rats, which was also impaired (↓peak filling rate) compared with healthy controls. Diastolic indices measured by microCT also seemed to correlate with invasively derived RV end-diastolic pressure. Importantly, this study provides a comprehensive analysis of both RV systolic and diastolic function, which is largely lacking from the preclinical literature. However, these results need to be tempered with the limited sample size (4 PAH and control rats) and the lack of any comparison to either the gold-standard MRI or load-independent measures of ventricular function (ie, coupling via pressure-volume loop analysis). These important steps will be critical to validate microCT in this preclinical model.

An accurate functional assessment of the RV is crucial to determining the phenotype of adaptation. The RV hypertrophies in response to increased RV afterload, an initial adaptive response. However, there is heterogeneity in RV hypertrophy that is not explained by differences in RV mass or degree of afterload.[15] Adaptive and maladaptive phenotypes are well described, the latter being associated with reduced RV function, fibrosis, dilation, and poor outcomes (ie, decompensated RV remodeling).[16] In contrast, adaptive RV remodeling is often characterized by preserved RV systolic function, concentric hypertrophy with minimal dilatation and fibrosis.[15,17] There are currently no approved therapies that directly nor selectively target the RV, but there is tremendous interest in exploring therapies that prevent or reverse the transition from adaptive to maladaptive remodeling. Thus, there is a critical need to accurately characterize these diverse RV phenotypes. Whether microCT has a role in this regard remains to be determined, but the preliminary work by that Kojonazarov et al[11] provides rationale for further investigation.

Strain-dependent differences in survival have been reported in the SU54126/CH model of severe PAH.[12] Fischer rats exhibited mortality by 7 weeks (100%), whereas Sprague-Dawley rats from Harlan Laboratories showed 100% survival for over 14 weeks. These differences were observed despite comparable increases in pulmonary hemodynamics at 7 weeks.[12] This maladaptive remodeling observed in Fischer rats was associated with progressive RV dilation, impairment in RV angiogenesis, and differential expression in gene families related to vascular homeostasis, inflammation, and metabolism.[13] These findings demonstrate that the Fischer and Sprague-Dawley rat strains recapitulate the heterogeneity in RV remodeling phenotypes observed in humans. An important next step would be to elucidate whether microCT is able to accurately delineate these phenotypes. In our experience, mortality can increase with the use of imaging protocols that require lengthy anesthetic, particularly in animals with a proclivity for maladaptation (ie, Fischers). An advantage of CT over MR may be a faster acquisition time. This would be particularly relevant for researchers interested in studying end-organ manifestations of right heart failure or maladaptive phenotypes.

Studies have consistently demonstrated diastolic dysfunction in the context of PAH,[10,18,19] but relatively little is known about the significance as it relates to prognosis and therapy. Trip et al[10] used pressure-loop analysis to derive load-independent measures of RV diastolic function in a cohort of patients with PAH. Major findings reveal that RV diastolic stiffness (1) is associated with clinical progression, (2) is explained by RV wall thickness in patients with >5-year survival (ie, adaptive), (3) is out of proportion to increases in RV wall thickness in patients with <5-year survival (ie, maladaptive), and (4) is weakly associated with impaired RV systolic adaptation in treated PAH patients. This study further highlights the importance of future studies investigating diastolic dysfunction in both adaptive and maladaptive models. It is currently not known whether abnormalities in diastolic function are a harbinger of maladaptive remodeling and whether it precedes any systolic impairment.

In summary, this interesting study is an important first step in validating microCT for assessing both sys-

tolic and diastolic RV function. However, important questions remain: (1) are the CT diastolic–derived measurements prognostically important? (2) Can CT measures correlate with MRI and other invasive hemodynamic measurements? (3) Can these techniques be used to assess treatment response? The ideal noninvasive imaging modality for RV preclinical research is one that is well tolerated by animals, sensitive to changes in function, reliable/accurate, translatable to humans, and provides information that informs diagnosis, prognosis, and management. It remains to be determined whether micoCT will find its niche.

ARTICLE INFORMATION

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Disclosures

None

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