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Abstract

Severe AS is the second most common reason for open heart surgery in the United States and one of the most frequently encountered cardiovascular diseases with great socioeconomic burden. Paradoxical low flow (PLF) is an emerging phenotype present in up to 30% of patients with severe AS (AVA <0.6 cm/m2, MG <40 mmHg) and is defined by preserved LVEF (>50%) and paradoxically low flow by stroke volume index <35 mL/m2 (Circulation. 2007;115:2856–2864). These patients have the highest risk of adverse cardiac events and mortality whether their disease is managed medically or surgically, yet their underlying pathophysiology remains unexplained (J Am Coll Cardiol. 2009;53:1865–1873). Several mechanisms have been proposed and collectively point towards restrictive cardiomyopathy (RCM). Transthyretin cardiac amyloidosis (ATTR) is the most common cause of RCM in older adults. Similarities between PLF and ATTR are striking and have led us to hypothesize that ATTR is a plausible mechanism for the genesis of RCM in PLF severe AS. Recently, our group demonstrated that technetium pyrophosphate (99mTc-PYP) imaging can be utilized to diagnose ATTR noninvasively with 97% sensitivity and 100% specificity (Circulation CV Imaging 2013 Mar 1;6(2):195-201). We now aim to use technetium pyrophosphate (^{99m}Tc-PYP) imaging to evaluate whether ATTR cardiac amyloid is associated with the RCM phenotype due to PLF in older adults with severe AS. In a case-control design, we propose to use noninvasive cardiac imaging, ^{99m}Tc-PYP to diagnose ATTR in 100 subjects with PLF and 100 control subjects with severe AS but no PLF. This cardiac imaging technique is specific,non-invasive, with relatively little risk and could facilitate screening for ATTR. On a broader scale, this study's results could provide the evidence needed to design a randomized multicenter trial aimed at evaluating clinical outcomes in PLF+/ATTR+ patients who undergo treatment with novel ATTR medications emerging from clinical trials. Finally, the ^{99m}Tc-PYP scanning protocol used in this study could be adapted for evaluation of ATTR in other vulnerable populations, e.g. patients with heart failure preserved ejection fraction (HFpEF) for whom large scale clinical trials have failed and emerging data from the Mayo Clinic suggests up to 30% have ATTR amyloid, presumed hypertensive cardiomyopathy with low voltage electrocardiograms, and in elderly patients with hypertrophic obstructive cardiomyopathy.