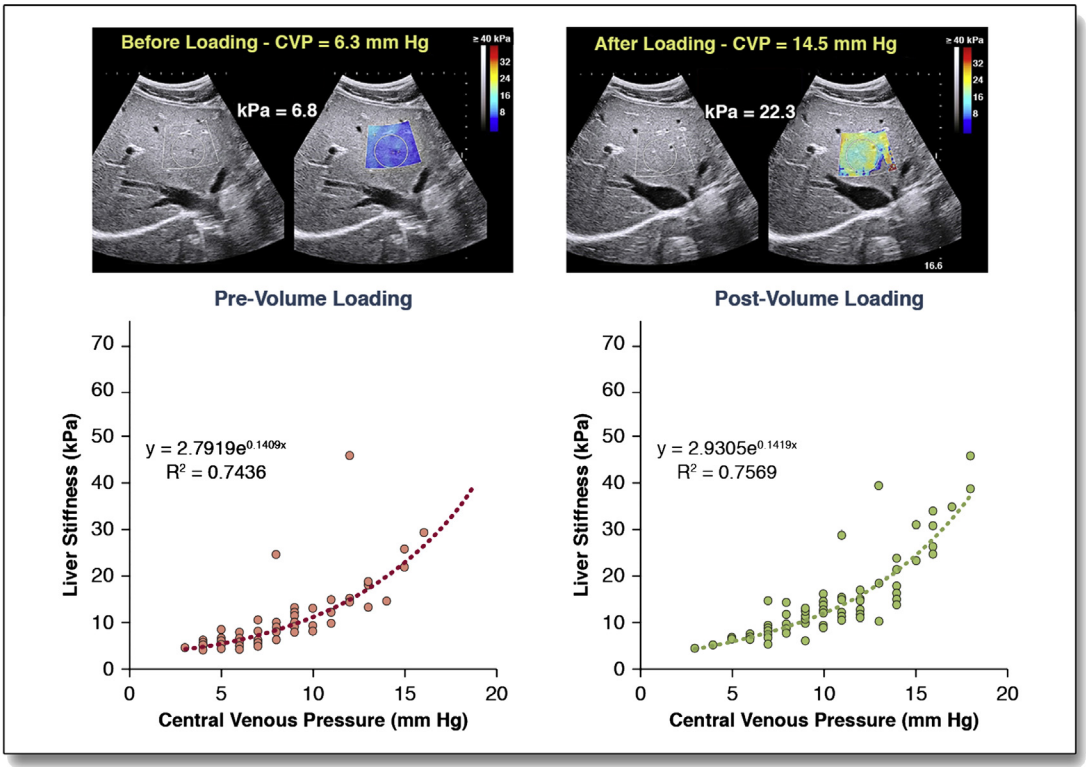
FIGURE 1 Results



Correlation between liver stiffness and central venous pressure (CVP), pre- and post-volume loading, with an example of evaluation of liver stiffness by shear wave elastography (kPa).

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Echocardiographic-Derived Strain-Area Loop of the Right Ventricle is Related to Pulmonary Vascular Resistance in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance (PVR) with right ventricular (RV) remodeling to normalize wall stress. Echocardiography is used in the assessment of RV function in PAH, however, the complex RV geometry and load dependency of traditional indices such as right ventricular fractional

area change (RVFAC) and tricuspid annular plane systolic excursion (TAPSE) limit its prognostic power. Recently, we introduced the assessment of the relation between RV longitudinal strain (ε) and RV area across the cardiac cycle, that is, ε-area loop, which provides new mechanical insight (1). In this study we assessed whether the RV ε-area loop: 1) differs between PAH patients versus control subjects; and 2) relates to PVR in PAH patients.

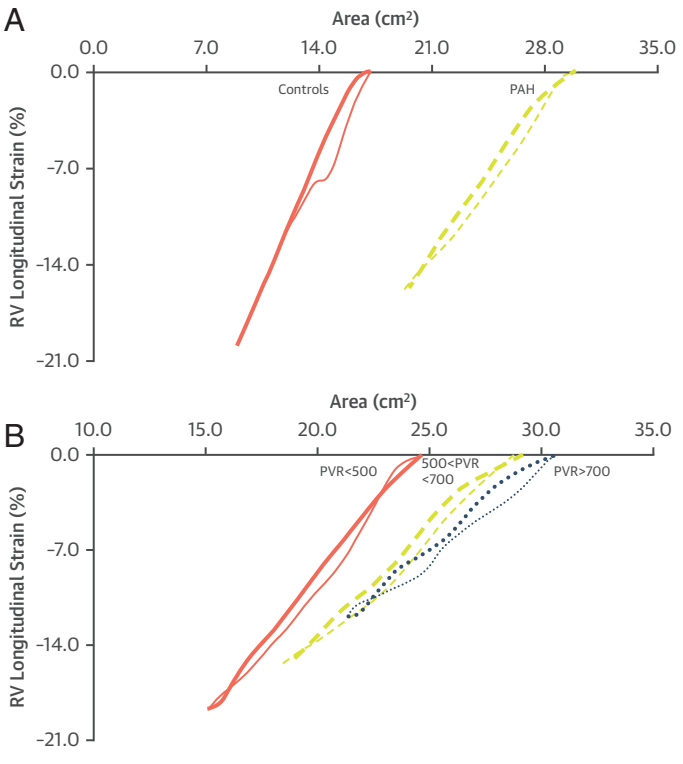
To address the first point, we included 42 "treatment naïve" PAH patients and 15 healthy control subjects. PAH patients were diagnosed through right heart catheterization. RV end-diastolic area, RV end-systolic area, RV diameters, RVFAC, and TAPSE were analyzed adhering to American Society of Echocardiography guidelines. RV ε-area loops were produced from the raw data and analyzed as previously described (2).

We observed a rightward shift of the RV ε-area loop in PAH patients compared with control subjects (**Figure 1A**). PAH patients had lower peak ε (−15.6 ± 4.0 vs. −21.0 ± 4.0; $p < 0.01$), lower slope of the linear regression line in systole (S_{slope}: −1.6 ± 0.5 vs. −2.8 ± 0.7; $p < 0.01$), and lower dissociation between late systolic and diastolic ε (late diastolic uncoupling [UNCOUP_LD]: 1.0 ± 2.1 vs. 3.3 ± 3.2; $p < 0.01$) compared with control subjects. When changes in ε were presented against relative changes in area, we found no differences between groups suggesting that the smaller S_{slope} in PAH relates to an attenuated change in ε for every absolute change in ventricular size rather than changes in RV contractility. Finally, we observed a greater coupling in cardiac mechanics during late diastole in PAH patients. Because PAH patients present an increased RV diastolic stiffness (3), increased RV relaxation in the longitudinal plane may facilitate diastolic filling, suggesting an attempt to augment diastolic filling of a less compliant RV.

To address the second point, we divided the PAH patients into 3 groups based on PVR that was acquired during invasive right heart catheterization: 1) PVR < 500; 2) 500 < PVR < 700; and 3) PVR >700 dynes·s·cm^{-5}. Higher PVR was associated with a progressive rightward shift of the RV ε-area loop (**Figure 1B**), a lower peak ε (−18.9 ± 3.0 vs. −15.6 ± 2.4 vs. −12.3 ± 4.3; $p < 0.01$), and lower S_{slope} (−2.1 ± 0.4 vs. −1.6 ± 0.5 vs. −1.2 ± 0.4; $p < 0.01$). A higher PVR in PAH patients is associated with progressive changes in RV function, which may relate to progressive levels of myocardial stiffness in PAH patients (3). These observations demonstrate that increases in PVR are linked to the characteristic changes in the RV ε-area loop. This latter observation is relevant because PVR plays a central role in the etiology of PAH, which supports the idea that the RV ε-area loop provides information relevant to the development and/or progression of PAH.

To explore the potential clinical use of ε-area loops, we used receiver-operating characteristic (ROC) curves to determine whether traditional markers (i.e., RVFAC and TAPSE) and novel characteristics (i.e., peak ε and S_{slope}) could distinguish between control subjects and PAH as well as between PAH patients with lower PVR (<500 dynes·s·cm^{-5}) versus higher PVR (>500 dynes·s·cm^{-5}). Good discriminative capacity between control subjects versus PAH was present for ε-area loop characteristics (S_{slope}: area under the curve [AUC]-ROC: 0.89, 95% confidence interval [CI]: 0.972 to 0.807, $p < 0.01$; peak ε: AUC-ROC: 0.83, 95% CI: 0.939 to 0.728, $p < 0.01$) and traditional measures (RVFAC: AUC-ROC: 0.89, 95% CI: 0.975 to 0.797, $p < 0.01$; TAPSE: AUC-ROC: 0.77, 95% CI: 0.899 to 0.649, $p < 0.01$). Superior discriminative capacity to distinguish between patients with

FIGURE 1 RV ε-Area Loops in PAH Patients



Mean ε-area loops in **(A)** control subjects (Controls) and pulmonary arterial hypertension (PAH) patients and **(B)** PAH patients with pulmonary vascular resistance (PVR) < 500 (n = 13, **pink lines**), with 500 < PVR < 700 (n = 13, **yellow lines**), and with PVR > 700 (n = 11, **blue lines**). **Thick lines** represent the systolic and **thin lines** the diastolic parts of the ε-area relation, respectively. RV = right ventricular.

low versus higher PVR was present for ε-area loop characteristics (S_{slope}: AUC-ROC: 0.85, 95% CI: 0.978 to 0.724, $p < 0.01$; peak ε: AUC-ROC: 0.84, 95% CI: 0.975 to 0.707, $p < 0.01$) compared with traditional measures (RVFAC: AUC-ROC: 0.67, 95% CI: 0.843 to 0.487, p = NS; TAPSE-ROC: AUC: 0.73, 95% CI: 0.913 to 0.552, $p = 0.02$). This demonstrates the potential clinical use of the RV ε-area loops to distinguish between PAH groups.

In conclusion, our data demonstrate that PAH patients, especially those with higher PVR, demonstrate distinct RV ε-area loop characteristics compared with healthy control subjects. More importantly, adopting these RV ε-area characteristics improved classification of PAH and levels of PVR compared with traditional measures, highlighting the potential clinical relevance of the RV ε-area loop.

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