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EDITORIAL

Distensibility, an Early Disease Marker of Pulmonary Vascular Health: Ready for Clinical Application

Farhan Raza, MD; Naomi C. Chesler, PhD

A man is as old as his arteries.[1]

–Thomas Syndenham

Similar to Thomas Syndenham linking (systemic) arteries with an individual's health in 1600s,[1] pulmonary vascular health has been linked to exercise intolerance and clinical outcomes in recent years.[2,3] These reports include rare diseases such as pulmonary arterial hypertension (PAH) and common diseases such as heart failure with preserved ejection fraction.[3,4] Pulmonary vascular health can be quantified by hemodynamic afterload faced by the right ventricle (RV afterload), which comprises steady and pulsatile components.[5,6] Although the steady load is captured by clinical metrics of pulmonary vascular resistance (PVR), the pulsatile load can be assessed with variable precision by different metrics: the simplified metric of pulmonary arterial compliance computed as stroke volume/pulmonary pulse pressure,[7] bioengineering metrics of pulmonary vascular impedance,[8,9] and pulmonary vascular distensibility with exercise[10,11] (Figure).

See Article by Elliott et al.

Abnormalities in pulsatile RV afterload and their impact on RV failure, specifically in pulmonary hypertension (PH) related to left heart disease, are uniquely defined by impedance analysis,[8,9,12] albeit these are beyond the scope of this editorial. Although more simplistic, pulmonary vascular distensibility, which captures the vasodilation of pulmonary vasculature with exercise,[10,11,13] also affects the pulsatile component of the RV afterload. Distensibility is defined as the percent increase in diameter (or area) of the smallest pulmonary arteries per mm Hg increase in pressure.[10,11] To quantify distensibility coefficient (α), different programing languages can be used (eg, Matlab, R) to fit pressure-flow data in multiple loading conditions (eg, rest, passive leg raise, exercise stages) with a nonlinear equation using the Linehan model of pulmonary vascular distensibility.[10,11,13,14] In healthy individuals, the increase in diameter is 1.5% to 2% per mm Hg. Reduced distensibility (α <0.7% per mm Hg), indicative of poor pulmonary vascular health, is linked to RV failure and adverse clinical outcomes in PAH, heart failure with preserved ejection fraction, and heart failure with reduced ejection fraction.[3,10,15] Although the physiological and prognostic values of distensibility are well demonstrated, implementation remains a challenge in the clinical care of patients with PH and heart failure.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Elliot et al[16] have addressed the need for widespread implementation by creating a

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Correspondence to: Farhan Raza, MD, Division of Cardiovascular Medicine, University of Wisconsin-Madison, 600 Highland Avenue, CSS, E5/582 Madison, WI 53792. Email: fraza@medicine.wisc.edu

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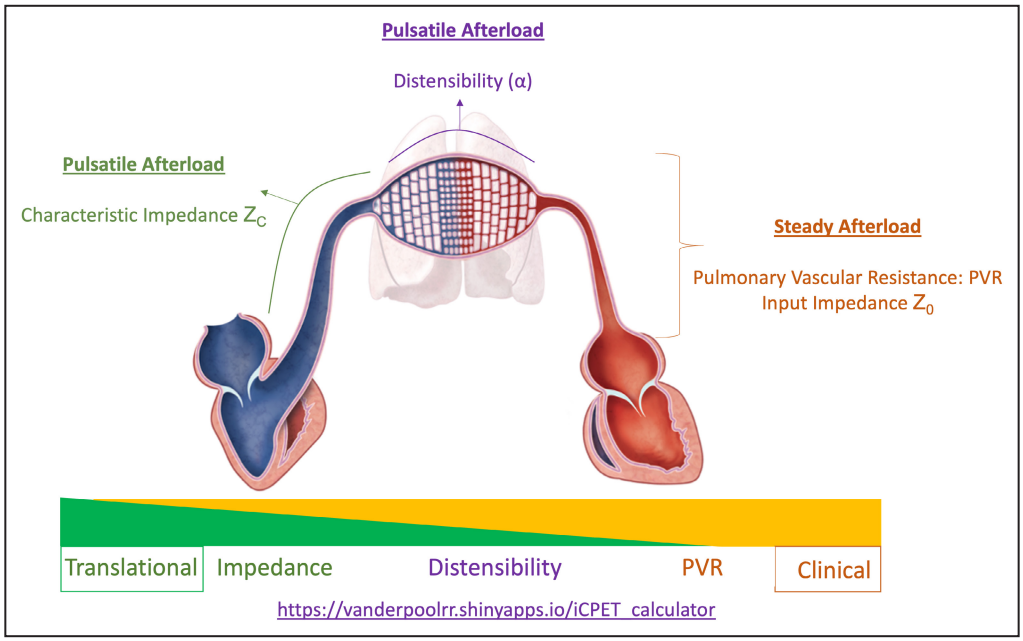

Figure. Methods of assessing pulmonary vascular afterload.
α indicates distensibility; PVR, pulmonary vascular resistance; Z_0, input impedance; and Z_C, characteristic impedance.

web-based tool to calculate distensibility: https://vanderpoolrr.shinyapps.io/iCPET_calculator. The interactive platform, based on RShiny, is user friendly for clinicians and requires 3 stages of pressure-flow data (mean pulmonary artery pressure [mPAP], pulmonary artery wedge pressure, cardiac output), for example, at rest and 2 stages of exercise. However, Kozitza et al[11] reported that a passive-leg-raise stage can be used as an additional loading condition for distensibility quantification and showed a similar trend to distensibility assessed with multistage exercise. Hence, a different loading condition, for example, passive leg raise, can be used in this 3-stage invasive cardiopulmonary exercise test (iCPET) calculator. Elliot et al[16] created this iCPET calculator in 4 commonly used programming languages: Excel, Matlab, Python, and R/Rshiny (shared publicly at https://github.com/vanderpoolrr/iCPET_calculator). The publicly available iCPET calculator, based on RShiny, is interactive and allows users to save the analysis along with plots.

To demonstrate the utility of this tool, their study population included 3 disease groups: (1) PAH (n=22, rest mPAP ≥25 mm Hg) and (2) a comparator (n=6, mixed group with rest mPAP <25 mm Hg) with baseline and follow-up studies (median follow-up=19 months) as well as (3) a control group (n=5, healthy participants) with 1-time study. The rest-to-exercise hemodynamic data were acquired on a supine stationary ergometer. In addition to rest hemodynamics, at least 2 stages of exercise hemodynamics were performed to acquire pressures (mPAP, pulmonary artery wedge pressure) and flow (cardiac output). Subsequently, they performed a nonlinear fit to these multipoint stages of pressure-flow plots (mPAP, pulmonary artery wedge pressure, cardiac output), as previously described.[10,11,14] To assess RV:pulmonary arterial (PA) coupling, the single-beat method was used on RV pressure waveforms to quantify the end-systolic:arterial elastance ratio (Ees/Ea) as approximated by [maximum isovolumetric pressure – (P_{max}) – end-systolic pressure (ESP)]/ESP.[17] RV stroke work index (RVSWI) was calculated as 0.0136×stroke volume index×(mPAP–right atrial pressure).[18]

The reported values of α in Elliot et al are consistent with prior literature: control group (mean)=1.55% per mm Hg, comparator=0.79% per mm Hg (pretreatment), and PAH=0.13% per mm Hg (pretreatment). Posttreatment, distensibility improved in the comparator group with early-stage disease (α=0.88% per mm Hg) but did not change significantly in the PAH group with advanced-stage disease (posttreatment α=0.17% per mm Hg). These observations are also consistent with prior literature as a loss of distensibility is reported as an early disease marker[15] and is only reversible if PH is identified and treated at an early stage as reported by Wallace et al (α=0.69% per mm Hg to 1.15% per mm Hg posttreatment).[19] Elliot et al also showed an inverse hyperbolic PVR≈α relationship, similar to the well-known PVR≈compliance relationship (figure 5A and figure S5 in Elliott et al[16]). That is, distensibility is less modifiable when PVR is high, and α may improve only when PVR approaches

a lower value (<3–4 Woods units). Overall, these findings suggest that resistive components of pulmonary circulation lose compliance early in disease in PAH, which can be captured with a loss of distensibility, and are less modifiable with advanced pulmonary vascular remodeling. However, with future antifibrotic therapies such as Sotatercept, reverse remodeling of pulmonary vascular disease in PAH may result in improved distensibility.

Moreover, to assess the impact of improved distensibility posttreatment on right heart function, the authors reported pre and posttreatment ventricular–vascular coupling. In the PAH group, a small increase in α after treatment was associated with a Ees/Ea and decreased RV workload (RVSWI was closer to normal: 8–12 g/m per beat×m^{-2}).[18] A similar trend was noted in the comparator group, with a higher Ees/Ea after treatment. These behaviors were driven mainly by a decrease in RV afterload (arterial elastance: Ea). These findings suggest that even a small increase in distensibility in advanced-stage PAH may contribute to significant improvement in RV:PA coupling and a reduction in RV workload.

Being early adopters, we tried the web-based distensibility calculator by Elliot et al with consecutive sampling of a cohort of 40 patients who underwent iCPET at our center for a clinical indication of suspected PH. These individuals included 25 patients with heart failure with preserved ejection fraction, 8 patients with PAH, and 7 healthy participants. The 3 stages included rest, passive leg raise, and a single stage of peak exercise. Based on prior literature of α <0.7% per mm Hg as higher risk for adverse outcomes,[10,11] we noted α <0.7% per mm Hg in 20 participants, whereas the other 20 participants had α ≥0.7% per mm Hg. The participants with lower distensibility (versus higher distensibility) had worse exercise PH (mPAP/cardiac output slope [mean]: 8.9 mm Hg/L×min^{-1} versus 4.2 mm Hg/L×min^{-1}) and exercise capacity (peak oxygen consumption [mean]: 9.4 mL/kg×min^{-1} versus 12.4 mL/kg×min^{-1}). Per echocardiogram, patients with lower distensibility (versus higher distensibility) had worse RV:PA coupling (tricuspid annular plane systolic excursion to pulmonary artery systolic pressure ratio [mean]: 0.33 mm/mm Hg versus 0.62 mm/mm Hg). The associations in our data agree with the findings of Elliot et al and prior literature. This demonstrates an easy application and prognostic relevance of iCPET calculator to quantify pulmonary vascular distensibility. Furthermore, we confirmed that this web-based implementation can be performed by a clinician without a bioengineering background, which should make it accessible to most PH pulmonologists or cardiologists and heart failure or interventional cardiologists.

In summary, the study by Elliott and colleagues makes a significant advancement to widespread implementation of distensibility as a metric of pulmonary vascular health in PH and heart failure. With the evidence of improved distensibility leading to higher RV:PA coupling and reduced RV workload, the iCPET calculator may serve as a useful tool in risk stratification and treatment decisions in PH of varying phenotypes. Using this tool, future work can report on differences in distensibility based on sex and different exercise modalities (supine versus upright ergometer).

ARTICLE INFORMATION

Affiliations

Department of Medicine-Cardiovascular Division, University of Wisconsin-Madison, Madison, WI (F.R.); and Edwards Lifesciences Foundation Cardiovascular Innovation and Research Center and Department of Biomedical Engineering, University of California, Irvine, Irvine, CA (N.C.C.).

Disclosures

None.

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