CHEST

Refining Risk Stratification in Pulmonary Embolism

A Step Forward

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Acute pulmonary embolism (PE) is the third leading cause of death globally, yet the majority of patients have a low mortality rate and can be treated by anticoagulation alone.[1] Reperfusion therapy (thrombolysis or embolectomy) is indicated for high-risk PE, defined as hemodynamic instability from PE, and for certain intermediate-risk patients, particularly those who deteriorate while receiving anticoagulation alone.[2] Death from PE occurs as a consequence of right ventricular dysfunction (RVD). Because high-risk PE accounts for a minority of cases, and early PE-related mortality is relatively low (approximately 2%-5%) in intermediate-risk patients as a whole,[1,3-6] it is critical to identify those at increased risk of early death who may benefit from early reperfusion therapy.

Investigators have long sought to integrate echocardiographic findings into the assessment of acute PE.[7] Ostensibly, characterizing the degree of RVD should enhance our abilities to predict adverse PE outcomes and to choose appropriate therapies. Existing risk models, such as the Bova score[3] and European Society of Cardiology risk category,[5] however, suffer from binary classifications of RVD whereas most physicians recognize that RVD occurs on a spectrum.

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Myriad candidate markers that quantify RVD, such as tricuspid annular plane systolic excursion (TAPSE) and tricuspid S′ velocity, are independently associated with acute PE outcomes.[8,9] Previous studies of echocardiographic RVD have major limitations, however; these include their retrospective nature, likely selection bias (as not all patients with acute PE undergo echocardiography), and a failure to integrate the aforementioned risk stratification models.[10] Thus, although a litany of studies have explored RVD in acute PE, they may be of only marginal usefulness to the bedside physician.

In this issue of *CHEST*, Prosperi-Porta et al[11] have advanced the research agenda for echocardiographic assessment of intermediate-risk patients with acute PE. In their retrospective study of 665 intermediate-risk patients with a simplified Pulmonary Embolism Severity Index (sPESI) of 1 or greater, the authors found that the stroke volume index (SVI) as measured by echocardiography was strongly and independently associated with PE-related death or cardiopulmonary decompensation within 30 days. Most often, the authors derived SVI from the left ventricular outflow tract velocity-time integral (LVOT VTI), an echocardiographic surrogate of stroke volume that, as shown in this cohort, can be obtained in the overwhelming majority of patients. To clarify the usefulness of SVI, the authors calculated the *C*-statistic, or the area under the receiver operating curve. The *C*-statistic for SVI (0.87; 95% CI, 0.78-0.95) outperformed every other conceivable marker of RVD including the well-studied TAPSE and the Bova staging system. The ability of SVI to discriminate the prognosis of patients with acute PE was preserved even after comparisons against multiple other RVD markers and after sensitivity analyses.

The authors' findings could have major implications for fine-tuning the risk assessment in intermediate-risk PE, and their study has several major strengths. First, the authors introduce an enticing, intuitive marker of RVD that has not been previously reported to be prognostically significant. Second, the authors have incorporated one of the most robust risk prediction models (Bova score), controlled for this variable in their analyses, and still demonstrated an independent

association of SVI with adverse outcome. Similarly, the overwhelming majority of patients underwent troponin-T testing (582 of 665 patients, or 87.5%), a finding that strengthens the ability to control for confounders. Third, their use of SVI is justified by the physiology of impending cardiovascular collapse in acute PE. SVI serves as a rough marker of cardiac output among intermediate-risk patients whose low-flow state may not be appreciated at the bedside, such as when arterial BP is preserved through sympathetic tone. Fourth, the sample size in this study is among the largest in retrospective cohorts investigating echocardiographic markers of RVD. Finally, the authors used outstanding methodology by meticulously controlling for confounders and blindly adjudicating outcomes.

Like most studies in this space, the authors' conclusions must be tempered by an inherent selection bias in their cohort. From contemporary population-level data, we know that fewer than 50% of patients undergo echocardiography during hospitalization for acute PE.[12] Thus, these test performance characteristics may be biased by the distribution of disease severity in the cohort. Robust studies of prognosis require that all patients of interest (eg, all hospitalized patients with intermediate-risk acute PE) undergo the diagnostic test under investigation. If not, then the studied population is a nonrepresentative subset of the entire population of such patients, and the *C*-statistic will be inflated.

Further, we should recognize the poor positive predictive value of SVI, which was 20% in this study. This limitation should frame SVI as simply another tool to enhance risk prognostication, but physicians must continue to rely on multimodal testing of RVD to make informed therapeutic decisions. In comparing this cohort with the Pulmonary Embolism Thrombolysis (PEITHO) trial data, we can see that the populations and risk of adverse outcomes are very similar (26 of 665 patients, or 3.9%, in this cohort vs 41 of 1,004, or 4.1%, in PEITHO).[6] Thus, one must wonder if using SVI in clinical practice would improve decisions about fibrinolysis.

Nonetheless, this study should now incite researchers to move beyond using multivariate regression models to retrospectively evaluating markers of RVD in acute PE. Prosperi-Porta et al[11] have demonstrated that such markers are independently associated with adverse outcome of PE, but we still lack prospective observational studies that would validate an echocardiographic risk prediction model in intermediate-risk acute PE. A simplified model might include easily measurable and reproducible echocardiographic markers such as TAPSE and SVI (or even the RVOT or LVOT VTI for that matter). Further, data from studies like this one should inform the design of future therapeutic trials in acute PE. Decisions about fibrinolysis or other forms of reperfusion therapy might be more nuanced if specific echocardiographic indexes of RVD were incorporated.

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