Are We Correctly Defining Intermediate-Risk Pulmonary Embolism?

To the Editor:
We read with interest the article in CHEST (October 2014) by Doyen et al regarding patent foramen ovale in pulmonary embolism (PE). The rationale for this article is the possible inclusion of transesophageal echocardiography into algorithms for the use of fibrinolytics in patients with intermediate-risk PE. The authors based their definition of intermediate-risk PE on the 2008 European Society of Cardiology guidelines, which approximate the early-mortality risk for this group at 3% to 15%. We question the current validity of that definition given the results of past meta-analyses and the recent Pulmonary Embolism Thrombolysis (PEITHO) trial.

Several meta-analyses have disputed the use of echocardiogram and cardiac biomarkers for risk stratification of normotensive patients. A 2004 meta-analysis of echocardiography in normotensive patients found the positive predictive value for PE-related in-hospital mortality to be only 4% and 5% in the two available studies. A 2007 meta-analysis showed that, indeed, an elevated troponin level was associated with increased mortality in normotensive patients with PE (OR, 5.90; 95% CI, 2.68-12.95), but given that the prevalence of death was 34 of 190 in patients with an elevated troponin level, the positive predictive value of an elevated troponin level for mortality was only 18%. A 2008 meta-analysis of brain natriuretic peptide in PE found that, in a subgroup of three studies that excluded unstable patients, an elevated brain natriuretic peptide level was associated with in-hospital mortality (pooled OR, 7.63; 95% CI, 2.08-28.07; P = .002), but the large CI suggests the need for further study.

A recently published study of fibrinolytics for intermediate-risk PE by the PEITHO investigators only served to confirm these concerns about the ability to risk stratify patients with PE based on right ventricular dysfunction and cardiac biomarkers. According to the e-Appendix, the study had been powered for a predicted early mortality of 7% in the intermediate-risk group; yet the early mortality in the intermediate-risk placebo group reached only 1.8%, well short of expected. Without knowing whether the cohort in the current study is actually at a higher risk of early mortality, it is difficult not only to interpret the findings and conclusions, but also to determine how transesophageal echocardiography may be included (if at all) in PE algorithms for patient care.

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References

Response
To the Editor:
We read with great interest the correspondence from Drs Bradford and Farber concerning our recent article in CHEST. They questioned the validity of the
intermediate-risk pulmonary embolism (PE) definition based on European Society of Cardiology (ESC) criteria. Indeed, the mortality observed in our study (2.4%), as in the recent Pulmonary Embolism Thrombolysis (PEITHO) trial, was lower than expected (3%-15%), suggesting that current intermediate-risk PE risk stratification is not accurate.

We agree that ESC risk stratification concerning intermediate-risk PE may be heterogeneous, because patients may have very different risks of mortality. Recently, Bova et al subdivided patients with intermediate-risk PE into three different groups of mortality. They computed a risk score using right ventricular dysfunction, elevated troponin level, heart rate ≥ 110 beats/min, and systolic BP between 90 and 100 mm Hg. Mortality was 1.7%, 5.0%, and 15.5% for stages I, II, and III, respectively. Inclusion of systolic BP and heart rate allowed more accurate risk stratification.

However, using this score, our population still remains at a high risk of mortality. Indeed, stages II and III concerned 48.8% and 24.4% of patients, respectively. The expected mortality should have been between approximately 5% and 15.5%. To explain the lower mortality observed (2.4%), we offer these hypotheses. In our city (about 532,000 people), a network has been built to recruit all cases of PE. This has allowed us to manage about 120 to 150 cases of PE every year. We believe that, as with many other diseases, the greater the number of cases treated, the better the prognosis; furthermore, all of these patients were hospitalized in the cardiac ICU for at least 1 or 2 days, with continuous monitoring and regular adaptation of treatment. We also suggest that PE management has improved worldwide after 2008 ESC guidelines publication. Analysis of the main studies involving intermediate-risk PE from 2009 to 2014 suggested that the global intermediate-risk PE mortality decreased by between 2% and 10%.

We, therefore, believe that these patients are representative of an intermediate-risk PE population, and our findings should be considered for intermediate-risk PE management: A large patent foramen ovale (PFO) correlated with a 43.8% risk of stroke. The presence of a PFO should explain the risk of hemorrhagic transformation with fibrinolysis. Intracranial bleeding is the main event that explains the lack of superiority in the fibrinolytic group of the PEITHO trial. We believe that PFO screening could help select the population that benefits most from fibrinolysis.

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