EDITORIAL

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Thrombolysis in submassive pulmonary embolism: Finding the balance

In this issue of the *Journal*, Ataya et al[1] provide a comprehensive review of thrombolysis in submassive pulmonary embolism, a subject of much debate. In *massive* pulmonary embolism, thrombolytic therapy is usually indicated[2]; in *submassive* pulmonary embolism, the decision is not so clear. Which patients with submassive embolism would benefit from thrombolysis, and which patients require only anticoagulant therapy? The answer lies in finding the balance between the potential benefit of thrombolytic therapy—preventing death or hemodynamic collapse—and the numerically low but potentially catastrophic risk of intracranial bleeding.

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In general, submassive pulmonary embolism refers to an acute pulmonary embolus serious enough to cause evidence of right ventricular dysfunction or necrosis but not hemodynamic instability (ie, with systolic blood pressure > 90 mm Hg) on presentation.[3] It accounts for about 25% of cases of pulmonary embolism,[4,5] and perhaps 0.5 to 1% of patients admitted to intensive care units across the country.[6] The 30-day mortality rate can be as high as 30%, making it a condition that requires prompt identification and appropriate management.

But clinical trials have failed to demonstrate a substantial improvement in mortality rates with thrombolytic therapy in patients with submassive pulmonary embolism, and have shown improvement only in other clinical end points.[7] Part of the problem is that this is a heterogeneous condition, posing a challenge for the optimal design and interpretation of studies.

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TABLE 1

Predictors of death within 30 days in acute pulmonary embolism

Test	Cut-off value	Negative predictive value, %	Positive predictive value, %
Echocardiography	Various for right ventricular dysfunction	98	8
Computed tomographic pulmonary angiography	RV:LV diameter ratio ≥ 0.9	93	8
B-type natriuretic peptide (BNP)	75–100 pg/mL	98	14
NT-pro-BNP	600 pg/mL	99	7
Troponin T	14 pg/mL	98	9

NT-pro-BNP = N-terminal pro-BNP

WHO IS AT RISK OF DEATH OR DETERIORATION?

If clinicians could ascertain in each patient whether the risk-benefit ratio is favorable for thrombolytic therapy, it would be easier to provide optimal care. This is not a straightforward task, and it requires integration of clinical judgment, high index of suspicion for deterioration, and clinical tools.

One of the challenges is that it is difficult to identify normotensive patients at the high-

est risk of poor outcomes. Several factors are associated with a higher risk of death within 30 days (**Table 1**). While each of these has a negative predictive value of about 95% or even higher (meaning that it is very good at predicting who will *not* die), they all have very low positive predictive values (meaning that none of them, by itself, is very good at predicting who *will* die).

For this reason, a multimodal approach to risk stratification has emerged. For example, Jiménez et al[8] showed that normotensive patients with acute pulmonary embolism and a combination of abnormal Simplified Pulmonary Embolism Severity Index, elevated B-type natriuretic peptide level, elevated troponin level, and lower-extremity deep vein thrombosis had a 26% rate of complications (death, hemodynamic collapse, or recurrent pulmonary embolism) within 30 days.

Bova et al[9] showed that the combination of borderline low systolic blood pressure (90–100 mm Hg), tachycardia (heart rate ≥ 110 beats per minute), elevated troponin, and right ventricular dysfunction by echocardiography or computed tomography allowed for the separation of three groups with significantly different rates of poor outcomes.

Which patients would benefit from thrombolysis, and which need only anticoagulation?

WHO IS AT RISK OF BLEEDING?

Estimation of the risk of bleeding is currently less sophisticated, and we need a bleeding score to use in the setting of acute pulmonary embolism. A few studies have shed some light on this issue beyond the known absolute and relative contraindications to thrombolysis.

Ataya et al[1] note a meta-analysis[10] showing that systemic thrombolytic therapy was not associated with an increased risk of major bleeding in patients age 65 or younger. Similarly, a large observational study showed a strong association between the risk of intracerebral hemorrhage and increasing age[11] and also identified comorbidities such as kidney disease as risk factors. While the frequently cited Pulmonary Embolism Thrombolysis trial[12] showed a significantly higher risk of stroke with tenecteplase, careful review of its data reveals that all 10 of the 506 patients in the tenecteplase group who sustained a hemorrhagic stroke were age 65 or older.[12]

A TEAM APPROACH

Thus, in patients with acute pulmonary embolism, clinicians face the difficult task of assessing the patient's risk of death and clinical worsening and balancing that risk against the risk of bleeding, to identify those who may benefit from early reperfusion therapies, including systemic thrombolysis, catheter-directed thrombolysis, mechanical treatment, and surgical embolectomy.

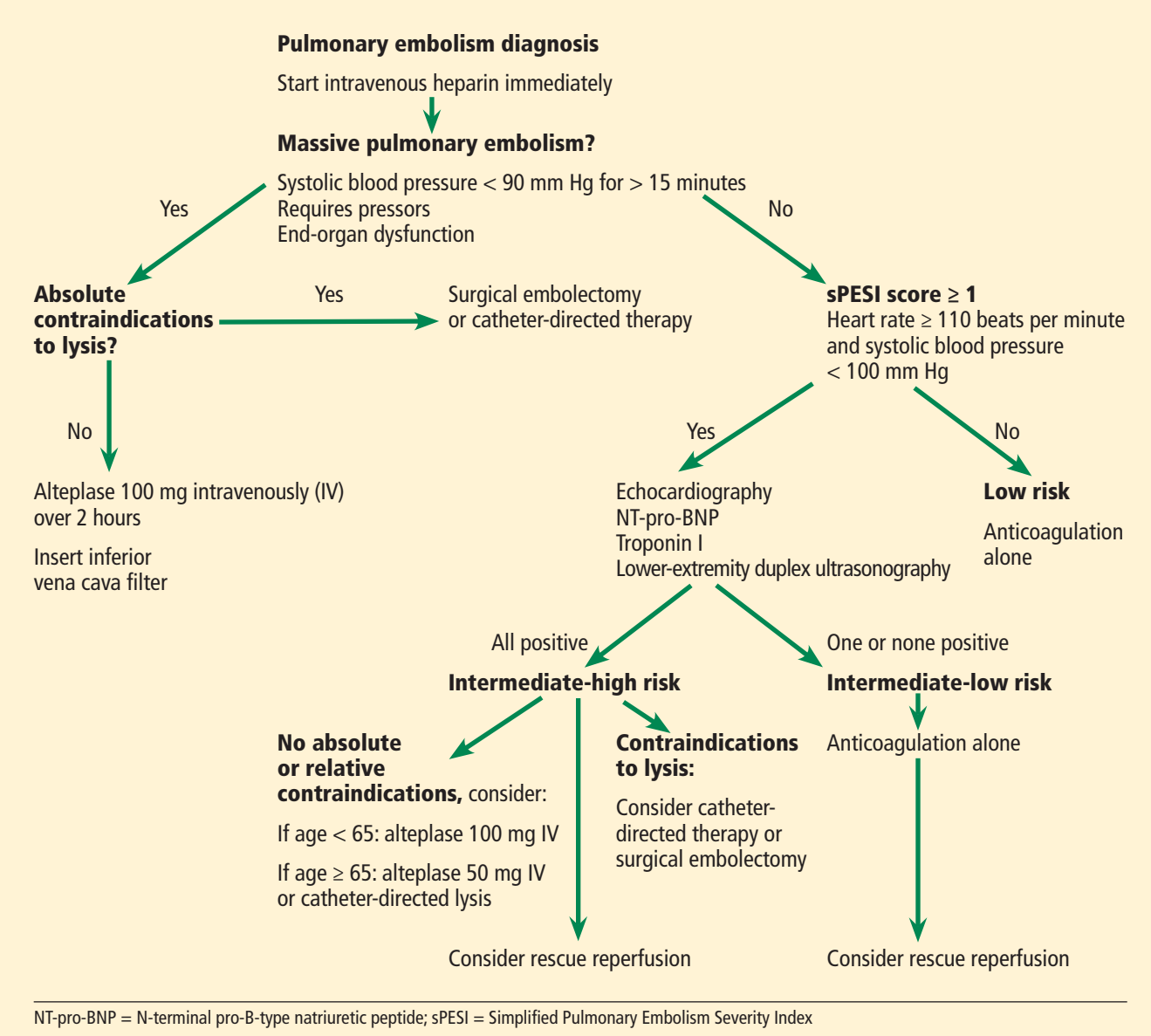
Given the absence of high-quality evidence to guide these decisions, several institutions have developed multidisciplinary pulmonary embolism response teams to provide rapid evaluation and risk stratification and to recommend and implement advanced therapies, as appropriate. This is a novel concept that is still evolving but holds promise, as it integrates the experience and expertise of physicians in multiple specialties, such as pulmonary and critical care medicine, vascular medicine, interventional radiology, interventional cardiology, emergency medicine, and cardiothoracic surgery, who can then fill the currently existing knowledge gaps for clinical care and, possibly, research.[13]

Early published experience has documented the feasibility of this multidisciplinary approach.[14] The first 95 patients treated at Cleveland Clinic had a 30-day mortality rate of 3.2%, which was lower than the expected 9% rate predicted by the Pulmonary Embolism Severity Index score (unpublished observation).

Figure 1 shows the algorithm currently used by Cleveland Clinic's pulmonary embolism response team, with the caveat that no algorithm can fully capture the extent of the complexities and discussions that each case triggers within the team.

TOWARD BETTER UNDERSTANDING

As Ataya et al point out,[1] the current state of the evidence does not allow a clear, simplistic, one-size-fits-all approach. A question that arises from this controversial topic is whether we should look for markers of right ventricular dysfunction in every patient admitted with a diagnosis of pulmonary embolism, or only in those with a significant anatomic burden of clot on imaging. Would testing everyone be an appropriate way to identify patients at risk



NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; sPESI = Simplified Pulmonary Embolism Severity Index

FIGURE 1. Cleveland Clinic pulmonary embolism response team algorithm.

of further deterioration early and therefore prevent adverse outcomes in a timely manner? Or would it not be cost-effective and translate into ordering more diagnostic testing, as well as an increase in downstream workup with higher healthcare costs?

Once we better understand this condition and the factors that predict a higher risk of deterioration, we should be able to design prospective studies that can help elucidate the most appropriate diagnostic and therapeutic approach for such challenging cases. In the meantime, it is important to appraise the evidence in a critical way, as Ataya et al have done in their review. ■

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