Association Between Thrombolytic Treatment and the Prognosis of Hemodynamically Stable Patients With Major Pulmonary Embolism

To the Editor:

Konstantinides et al \(^1\) recently reported the results of a major multicenter registry involving more than 700 patients with severe pulmonary embolism (PE) but no clinical instability. They deserve to be congratulated for their interesting data. However, we would like to comment on these data.

We believe that it is particularly difficult to assess PE gravity using only clinical criteria. When patients are prescribed bed rest for a few hours, we have often encountered significant discrepancy between “clinical status” and echocardiography, pulmonary angiography, or right-side catheterization results.\(^2\) After a few hours’ bed rest, patients who have suffered from syncope or transient collapse before hospitalization are often quiet in their beds. Probably the slightest exertion or stress (or the slightest recurrence of PE) would lead to severe clinical signs.

As a result, we believe that in some cases, the lack of hypotension may lead to misdiagnosing the seriousness of PE. In particular, in young patients with no concomitant diseases, blood pressure may be maintained in normal ranges by several compensatory mechanisms. The fact that 70% of the patients reported with tachycardia and with a mean oxygen partial pressure of 56 mm Hg strengthens this observation. Consequently, hypotension should not be used as the only clinical criterion to justify thrombolytic treatment. In this regard, we totally agree with the results of Konstantinides et al.

Another important point is the interpretation of the results of this study. As the authors themselves clearly state, “even multivariate analysis cannot be expected to eliminate the biasing effect of all confounding factors.”\(^1\) In particular, it may be that because the treatment was not randomly assigned, practitioners would have chosen thrombolysis in those patients with low risk of bleeding (ie, younger age, less major surgery, less history of stroke). As a result, thrombolytic treatment may not represent the only independent predictor of outcome but an “artificial” way in which patients with lower risk of mortality and major complications have been selected. Finally, the criterion chosen for identifying the thrombolytic group was the use of thrombolytic treatment in the first 24 hours after PE diagnosis. However, in 125 patients (23%), the attending physicians proceeded to provide thrombolytic treatment later. On the one hand, the time lag between diagnosis and treatment seems less interesting than the exact determination, although often very difficult to state precisely, of the interval between the onset of PE and the start of the treatment. The latter should be the actual interval to be considered. On the other hand, it would have been interesting to know whether results concerning thrombolytic treatment would have changed if this subgroup of patients thrombolized later were taken into account. Did patients with a severe PE diagnosis assessed 36 hours previously derive benefit from thrombolytic treatment?

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Response

It is by no means suggested in our article\(^1\) that the clinical findings alone can be sufficient for severity assessment or for the choice of treatment in patients with pulmonary embolism. On the contrary, the interactions of the pathophysiologic factors leading to hemodynamic compromise after an acute thromboembolic event are known to be very complex.\(^2\) In our registry, the vast majority of the patients had echocardiographic or, to a lesser extent, invasive (catheter-derived) evidence of pulmonary hypertension and/or right ventricular dysfunction. We have previously reported on the importance of echocardiography for risk stratification of patients with clinically suspected acute pulmonary embolism.\(^4\) In fact, the results of the present registry support the thesis that patients with echocardiographic (or clinical) evidence of acute right ventricular failure might benefit from thrombolytic treatment even in the absence of arterial hypotension at presentation. However, we totally agree with Ferrari et al that these results should be confirmed by a prospective, randomized trial.

We chose the time of diagnosis of pulmonary embolism to define thrombolytic treatment as early or late. This is a time point that can be most reliably and precisely identified in the patient’s records. On the other hand, patients with pulmonary embolism are often unable to determine the exact time of symptom onset because symptoms can develop gradually over a period of hours or even days.

Finally, the assignment of patients to the two treatment arms (thrombolysis or heparin alone) was based, as stated in our article, on the intention-to-treat principle. Considering patients who were given thrombolytic agents later during the hospital stay would substantially increase the likelihood of selection bias. The reason is that the indication for thrombolysis in this patient group is usually mandated by failure of the initially chosen heparin treatment, which is manifested as clinical or hemodynamic deterioration.

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