Utility of Brain Natriuretic Peptide to Predict Right Ventricular Dysfunction and Clinical Outcome in Patients With Acute Pulmonary Embolism

To the Editor:

We read the paper by Kucher et al.1 which demonstrated the association between high levels of pro-brain natriuretic peptide (BNP) and increased risk of adverse clinical outcome (death, resuscitation, mechanical ventilation, pressors, thrombolysis, catheter fragmentation, and surgical embolectomy) in patients with acute pulmonary embolism. The authors concluded that patients with acute pulmonary embolism and low pro-BNP levels have an uneventful course and good prognosis.

We studied 50 patients with confirmed acute pulmonary embolism prospectively and followed them up for their in-hospital course and complications.2 Echocardiography and BNP measurement were performed in all patients at admission. Thirty-one patients (62%) of our study population had right ventricular (RV) dysfunction (dilatation of the right ventricle with a diastolic diameter >30 mm, RV/left ventricular end-diastolic diameter ratio >1, or hypokinesis of the right ventricle). We found that patients without RV dysfunction had significantly lower BNP levels compared with patients with RV dysfunction. There was a significant correlation between RV end-diastolic diameter and BNP. In addition, BNP discriminated between patients with and those without RV dysfunction (area under the receiver operating characteristic, 0.78). A BNP >90 pg/mL was associated with a risk ratio of 28.4 for the diagnosis of RV dysfunction. However, all patients presenting with syncope necessitating cardiopulmonary resuscitation showed normal BNP levels. Thus, normal BNP levels do not exclude severe pulmonary embolism. This might be due to an insufficient time span for right ventricular BNP production and secretion as a consequence of sudden RV pressure overload resulting in syncope with cardiac arrest in these patients. All of the patients with syncope and normal BNP levels showed elevated troponin T levels, stressing the value of troponin T measurements in identifying patients with severe pulmonary embolism. Kucher et al3 mention that a possible limitation of their study lies in the absence of serial pro-BNP testing and thus in an underestimation of pro-BNP elevation given the possible transient nature of its release. Indeed, in our study, we found highly dynamic BNP release kinetics with rapidly falling BNP levels after initiation of therapy aimed at improving RV dysfunction, especially after thrombolysis. On the other hand, in patients admitted with subacute pulmonary embolism >2 days after onset of symptoms, we still found BNP levels significantly elevated.

Overall, we found BNP levels not to be predictive for mortality or in-hospital complications. Patients with RV dysfunction as determined by echocardiography had significantly more in-hospital complications, confirming that echocardiography remains the bedside gold standard for the detection of RV dysfunction. Further studies in larger patient populations possibly comparing pro-BNP and BNP kinetics and their respective predictive values appear warranted.

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To the Editor:

Kucher et al1 studied the prognostic information yielded by pro-brain natriuretic peptide (pro-BNP) levels for patients with acute pulmonary embolism and concluded that pro-BNP level <500 pg/mL can predict an uneventful hospital course. However, this study raises methodological issues that alter the soundness of the conclusions.

The first concern relates to the use of a composite end point, giving the same weight to death and to a criterion called “escalation therapy.” This latter criterion, already used in a previous study,2 is subjective and of doubtful significance, including criteria with very different life impacts: for example, indications for thrombolysis were not defined, but the thrombolysis requirement accounts for 10 of the 20 patients with adverse outcomes.

The second concern relates to the employed cutoff of pro-BNP level (500 pg/mL), which was identified by receiver operating characteristic curve analysis. Although largely used in the medical literature, these data-driven cutoffs lead to a considerable inflation in the type I error rate. We used Monte Carlo simulation to determine the type I error rate, based on a hypothetical cohort of 73 patients with similar proportion of events. For each patient, we drew a random value from a log-normal distribution (the distribution commonly observed for biochemical markers). In 10 000 samples, we were able to determine a cutoff of this randomly generated variable that significantly discriminates the outcome at the 0.05, 0.01, and 0.001 levels in 52%, 15%, and 3% of cases, respectively. In other words, when using a probability value <0.05 to indicate statistical significance, the true type I error is in fact 52%!

In summary, although BNP has strong biological plausibility to be an independent marker of clinical outcome for patients with pulmonary embolism, the results of the present study, and especially the proposed cutoff, should be interpreted cautiously.

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Response

We agree with the two concerns from Drs Thabut and Logeart. Unfortunately, most prospective pulmonary embolism (PE) trials have included only low numbers of patients. More studies are needed to confirm that the natriuretic peptides are useful tools for risk stratification and treatment guidance in patients with PE.

The use of thrombolysis as an end point for PE studies is controversial. The potential strength of the natriuretic peptides is in the identification of low-risk and intermediate-risk rather than high-risk patients. The negative predictive value is even higher...
for in-hospital death than for the composite end point, which includes thrombolysis. Indeed, 4 studies have shown that low levels of natriuretic peptides on admission predict a benign clinical course.\textsuperscript{1–4} The negative predictive value for in-hospital mortality ranged from 99\%\textsuperscript{5} to 100\%.\textsuperscript{1,2,4}

Dr Krüger et al describe several PE patients with syncope who had normal pro-brain natriuretic peptide (BNP) levels but elevated troponin T levels on admission, suggesting that BNP mRNA synthesis, prohormone synthesis, and prohormone secretion into the circulation may take several hours after the onset of myocardial stretch. We also described 3 patients with massive PE and low BNP levels who had a symptom duration <8 hours.\textsuperscript{2} Therefore, we urge caution in interpreting low natriuretic peptide levels in high-risk PE patients with a short symptom duration.

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