and all cases in the "group CONTROL" had cardiovascular collapse clinically unrelated to allergy or anesthesia. And finally, the absence of a tryptase within the normal range in patients with cardiovascular collapse does not exclude an allergic reaction because an acute level of 8 μg/l might be considered significantly elevated if the baseline level was only 1. Therefore, both the clinical presentation and the baseline tryptase level remain very important elements for the diagnostic probability regarding whether a clinical event can be attributed to anaphylaxis or other etiologies.

Competing Interests

Drs. Sprung and Weingarten have nothing to disclose. Virginia Commonwealth University receives royalties from ThermoFisher for their tryptase assay, which are shared with Dr. Schwartz as its inventor.

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In Reply:

We read with great interest the valuable comments of Sprung *et al.* on the diagnostic value of total tryptase in allergic events. This group, which has been a pioneer in tryptase discovery and evaluation, points out that the comparison of acute tryptase concentrations with basal values 24 h afterword is more reliable than a single measurement at the time of the reaction.

Indeed, several factors discussed by Sprung *et al.*, as well as in our article,[1] may be responsible for elevated basal tryptase concentrations. Mastocytosis, when severe, can be responsible for immediate hypersensitivity reaction but is rare and usually already diagnosed in patients referred to the operating room. This is also the case for acute myelocytic leukemia, myelodysplastic syndromes, hypereosinophilic syndrome, and therapy with recombinant stem cell factor. Finally, mildly increased tryptase concentrations have been reported in stages 4 and 5 chronic renal failure and in hemodialysis patients but not in stages 1 and 2.[2]

Although these clinical conditions are relatively uncommon, the interest of basal tryptase measurements at distance from the clinical reaction has long been recognized.[3,4] These limits of tryptase measurements have led our group, among others, to promote the development of systematic assessment of immediate perioperative hypersensitivity reactions based on clinical history, tryptase and histamine measurements, and delayed specific allergy investigation, notably skin tests.[5,6]

Although we largely agree with most remarks made by Sprung *et al.*, in most cases, patients will survive, allowing for a delayed allergy work-up. This gives an opportunity to perform basal tryptase measurements, thus increasing the diagnostic value of tryptase measurement performed during the reaction, and also to identify possible sensitization using skin testing, even in case of mild reactions in the absence of tryptase increase.

The situation appears completely different in case of unfavorable outcome, when neither delayed tryptase sample nor skin tests can be obtained. Therefore, we focused our study on fatal or life-threatening per-anesthetic anaphylactic reactions compared with other types of shock. We showed that resuscitation maneuvers and treatment of shock did not induce by themselves a significant increase in tryptase concentrations and determined thresholds allowing for a sensitivity exceeding 90%.[1]

In addition, as mentioned in our article, we suggested to look for a preanesthetic sample whenever possible to discard other possible causes of basal tryptase increase.

Finally, we agree with Sprung *et al.* that clinical history and symptoms are of critical importance for the diagnosis of anaphylaxis. However, the medical history of anesthetized patients is considered by anesthesiologists before anesthesia, allowing them to diagnose underlying pathologies potentially responsible for increased basal tryptase concentrations. Therefore, in cases of immediate hypersensitivity reaction occurring within 5 min following antibiotic or muscle relaxant administration, for example, in the absence of any other evident cause of death (*i.e.*, American Society of Anesthesiologists IV or V status, failure to intubate, malignant hyperthermia, succinylcholine-induced hyperkaliemia), our results indicate that an increased tryptase concentration is a strong support for the diagnosis of an allergic reaction.

Competing Interests

Dr. Laroche had congress fees paid by ThermoFisher for other studies presentation. The other authors declare no competing interests.

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More Attention to Respiration: A Simple but Effective Approach to Reduce Postoperative Mortality?

To the Editor:

Congratulations to Mazo *et al.*[1] for their elaborate and extensive work. They designed the Prospective Evaluation of a RIsk Score for postoperative pulmonary COmPlications in Europe (PERISCOPE) study to improve the external validity of the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score, which they describe as the only prospective internal validated score to predict postoperative pulmonary complications.[2] Therefore, they tested the generalizability of this score in a large European cohort and three subsamples: Spain, Western Europe, and Eastern Europe. They conclude that their risk score predicts three levels of postoperative pulmonary complications in an area outside the development setting.

Yet, to us the generalizability of the score seems doubtful, because the postoperative mortality reported in this study is inconsistent with the mortality reported in the European Surgical Outcomes Study (EUSOS).[3]

This inconsistency is conspicuous because the design, especially sampling strategies, of PERISCOPE resembles in many details the EUSOS study:

- Both groups performed a multicenter design including numerous European hospitals.
- Both groups defined continuous 7-day cohort periods to collect data of patients undergoing an in-hospital surgical procedure.
- Both studies excluded patients undergoing obstetric procedures.
- Both studies observed in-hospital mortality as an important outcome variable.

PERISCOPE (n = 5.099 patients) reports an overall in-hospital mortality of 0.9%, Spain (n = 2.000): 1.0%, Western Europe (n = 1.538): 0.8%, Eastern Europe (n = 1561): 0.9%. The crude mortality in the EUSOS study (n = 46.539 patients) was 4% ranging from 1.2% in the participating hospitals in Iceland (n = 162) to 21.5% in Latvia (n = 302). The United Kingdom provided the biggest sample of n = 10.630 patients, the mortality rate was 3.6%. In Spain (n = 5.433), 3.8% of surgical patients died.

This significant difference between both studies is especially remarkable due to the high-risk surgical procedures like cardiac or neurosurgery, which are included in the PERISCOPE but not in the EUSOS study. With respect to the aim of the PERISCOPE study, which is to improve generalizability, we consider it therefore indispensable to include this observation in the validation of the predictive score.

Two of the authors were involved in both publications. We wonder, why they did not discuss this important possible restriction of their validation study. Possibly the analysis of the ARISCAT study, in which the score to predict pulmonary complications was developed, gives an important clue to interpret the data.

Mazo *et al.*[1] refer to the excellent internal validity of the ARISCAT study. Internal validity means optimal control of study conditions to ensure that the covariation of predictive score and outcome is not biased (nonspuriousness). Nonetheless, the better the internal validity is, the more limited is the external validity, *i.e.*, the more elaborated the strategies are to control confounding influences, the more limited is the generalizability of a study.

The PERISCOPE study increases the external validity of the predictive score by a large degree of replication of the ARISCAT design in a new sample of patients. This strategy limits this generalizability to the special conditions as reported in the ARISCAT study. These conditions differ from the EUSOS investigation with high external and less controlled internal validity. Thus, the differences in mortality reported in the optimal controlled ARISCAT and PERISCAT studies compared with the EUSOS study may be explained simply by the effects induced into the participating hospitals by the studies itself. It is possible that the fact that respiration was studied directed the attention of hospital staff toward more careful observation of the respiration of postsurgical patients.

From our point of view, is it useful to consider this following aspect: if the authors conclude that increased attention to respiration (*e.g.*, simply measuring oxygen saturation) may have contributed to reduce mortality, we will obtain a very easy to handle but highly effective approach to significantly reduce mortality in our hospitals.