Presence or Absence of Elevated Acute Total Serum Tryptase by Itself Is Not a Definitive Marker for an Allergic Reaction

To the Editor:

We read with interest the study by Laroche *et al.*[1] who examined the value of plasma histamine and serum or plasma tryptase in evaluating severe perioperative anaphylaxis. We would like to add some thoughts to further explore and clarify the significance of tryptase as a "predictable marker of allergic reaction." Indeed, elevated serum total tryptase associated with typical symptomatology (urticaria, bronchospasm) may be, in the majority of cases, sufficient for diagnosis of an allergic reaction with high probability. At the same time, perioperative cardiovascular collapse may be associated with nonallergic causes and still have an elevated acute level serum tryptase and the absence of diagnostic symptomatology (*e.g.*, urticaria), suggesting a nonallergic cause. For example, we encountered a patient with hypertension and renal insufficiency who developed lisinopril-associated cardiovascular collapse immediately after anesthetic induction. The patient had a high acute serum tryptase level (16 μg/l) without bronchospasm or urticaria. Surprisingly, 72 h after recovery from the event, serum tryptase remained elevated (>16 μg/l); allergologic evaluation ruled out anaphylaxis and mastocytosis, and the incidental finding of elevated tryptase was attributed to his chronic kidney insufficiency. Decreased glomerular filtration slows elimination of the stem cell factor,[2,3] which may induce mast cell hyperplasia, causing an increased level of tryptase.[4]

Tryptase is continually secreted by mast cells in tissues, and then diffuses into the circulation, where it can be measured as protryptase. Protryptases can undergo additional processing *within the cell* to become mature tryptase, which is stored in mast cell granules and secreted *only during mast cell activation*. In the absence of mast cell activation, nearly all of the serum tryptase represents the immature proform. During mast cell–mediated anaphylaxis, total serum tryptase levels (pro + mature) may exceed 11.5 μg/l; however, the pathognomonic laboratory finding indicative of mast cell degranulation is the presence of mature tryptase with serum levels exceeding 1 μg/l.[5] Because testing for mature tryptase is not widely available, another approach is to compare *acute* (within 4 h of event) and *baseline* total tryptase levels (at least 24 h after all signs and symptoms of the event have subsided) to distinguish between an increased mast cell burden (*e.g.*, mastocytosis where baseline tryptase levels remain elevated) and mast cell degranulation (where only acute tryptase levels are elevated). The minimal elevation of acute over baseline tryptase levels suggested to be clinically significant is calculated as at least 2 + 1.2 × baseline tryptase level. Unfortunately, baseline samples in the anaphylaxis group were not collected in this retrospective study. Besides mastocytosis, persistently elevated serum tryptase is found in patients with acute myelocytic leukemia, myelodysplastic syndromes, hypereosinophilic syndrome, therapy with recombinant stem cell factor, and chronic renal insufficiency. In one study of obese adults (body mass index of 44 ± 6.5 kg/m^2), serum tryptase levels were greater than 15.7 μg/l.[6] Any patient may develop cardiovascular collapse, and if their baseline tryptase level is elevated, concluding that mast cell degranulation occurred because of an elevated acute level alone may be wrong. And *vice versa*, true basophil-mediated anaphylactic reactions may occur without increase in serum tryptase. Although acute histamine levels can be helpful in establishing basophil-induced anaphylaxis, they are rarely captured due to the short (minutes) histamine half-life (and low priority for obtaining this testing during resuscitation). Providing a patient survives the event, histamine metabolite from 24-h urine, *N*-methylhistamine, might better reflect previous histamine release.

Therefore, in some patients with severe perioperative reactions, a diagnosis of an allergic reaction (mast cell degranulation) cannot be conclusively made from a single acute total tryptase level even if elevated; nor can an allergic reaction be excluded from a single measurement, even if within the normal range. A more complex assessment is needed, which should include consideration of nonallergic conditions associated with increased burden of mast cells as well as a mild allergic reaction that may not manifest as a tryptase level outside the normal range. Tests such as urinary prostaglandin D2 metabolite, 11-β prostaglandin F2α, and urinary histamine metabolite, *N*-methylhistamine, may be valuable adjuncts to confirm or exclude the allergic etiology of patients who develop perioperative cardiovascular collapse.[7] However, these tests are typically obtained from the 24-h urine, so they are not available in most forensic cases. The exception is a postmortem measurement of mature tryptase, which strongly indicates premortem mast cell activation (testing baseline tryptase levels is not an option in postmortem investigations). Unfortunately, only one center currently conducts the mature tryptase assay (Virginia Commonwealth University, Richmond, VA).

In conclusion, there are clinical situations where cardiovascular collapse with a high serum total tryptase level in the acute blood sample may not indicate this to be a mast cell activation event. Therefore, the statement that "allergy mediators exceeding the threshold are evidence of allergic events" is not universally correct, even though this conclusion fit the data in the study by Laroche *et al.*,[1] because of their study design: all patients in their "group ALLERGY" were selected based on positive symptomatology and positive allergy tests,

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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.