

Letter to the Editor

Specificity of conventional and Ves v 5-spiked venom decreases with increasing total IgE*To the Editor:*

Skin testing and specific IgE (sIgE) determination in the serum are the mainstays in the diagnosis of Hymenoptera venom allergy. The relatively low sensitivity of the vespid venom (i3) of the CAP system (Thermo Fisher Scientific, Waltham, Mass) was a well-known phenomenon, ranging from 83.4% to 88.2% compared with 95.7% to 96.1% of the bee venom.¹⁻³

In the last few years, component-resolved diagnosis led to a marked improvement in the diagnosis of vespid venom allergy. First, it has been demonstrated that sIgE determination against the major vespid allergen Ves v 5 alone showed a higher sensitivity than against the venom extract⁴ and patients who initially had negative test results could be diagnosed with Ves v 5.⁵ When Ves v 1 was additionally available for diagnosis, the combination of both allergens further increased sensitivity to 94% to 96%.^{3,6} Then, the venom extract was spiked with Ves v 5, and sensitivity was reported to be improved from 83.4% to 96.8%.³ Consequently, the new test was introduced in summer 2012.

That prompted us to look at sensitivity and specificity of the conventional and spiked venom in our patients. Initially, we checked the sensitivity of the conventional extract in 113 patients of our database. After availability of the spiked venom, we were able to reanalyze 91 of those sera to determine its sensitivity. For the calculation of specificity, 111 controls without a history of a systemic sting reaction or large local reaction were randomly recruited. Fifty-seven (51.4%) controls had detectable sIgE to at least 1 allergen in a test panel of common aeroallergens and were therefore considered to be atopic. We also aimed to investigate the effect of tIgE on specificity, and whether spiking of the venom resulted in higher sIgE levels.

Surprisingly, although the sensitivity of the spiked venom was slightly higher, we were not able to confirm that sensitivity increased significantly: 106 of 113 (93.8%) patients allergic to

vespid venom were positive to the conventional venom, and 87 of 91 (95.6%) could be diagnosed with the spiked venom ($P = .572$).

Many efforts were made to increase sensitivity, but the matter of specificity was never addressed. In Hymenoptera venom allergy, high specificity is usually observed in highly selected, nonatopic, skin test-negative controls.⁷ However, real-life situation individuals with atopy and high total IgE (tIgE) levels cannot be excluded, and specificity typically decreases with increasing tIgE.⁸ This issue concerns both the conventional and the spiked venom.

Overall, specificity was 61% (68 of 111) for the conventional venom and 56% (62 of 111) for the spiked venom ($P = .07$), and there was an almost perfect agreement between the tests (κ , 0.852). Similar to sensitivity, we did not observe a statistical difference in specificity between both venoms, but we found a tIgE-dependent decrease in specificity. To evaluate the effect of tIgE, controls were grouped according to their tIgE levels: "low" tIgE, less than 50 kU/L; "moderate," 50 to 250 kU/L; and "high," more than 250 kU/L. With increasing levels of tIgE, specificity of the conventional venom decreased from 80% (low tIgE, 40 of 50 negative) to 52% (moderate tIgE, 24 of 46) and 27% (high tIgE, 4 of 15), respectively. The decrease in specificity of the spiked venom was similar, with 72% (36 of 50), 50% (23 of 46), and 20% (3 of 15), respectively. Although specificity differed significantly between the tIgE groups ($P < .001$), it was comparable between the conventional and the spiked venom within tIgE groups (Fig 1). This low specificity is in good agreement with previous reports, in which a specificity of 63.3%¹ and 72.0%,⁹ respectively, has been reported. Accordingly, tIgE levels were significantly lower in controls who were negative to the conventional and spiked venom, with 34.3 (13.7; 107.0) and 31.5 (13.0; 108.0) kU/L, than in controls with positive results, with 110.0 (51.1; 290.0) and 100.0 (43.8; 223.0) kU/L ($P < .001$).

Information on the modification and its implications on test results was scarce, and mainly laboratories but not clinicians were notified. In addition, only the order number changed, but the code i3 remained identical. Importantly, spiking of the venom extract

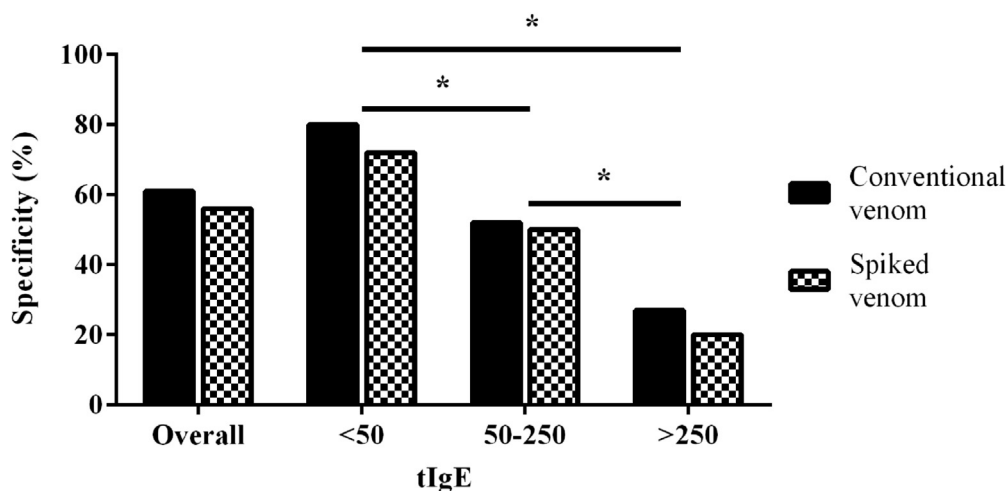


FIG 1. Specificity of rVes v 5-spiked and conventional venom decreases with increasing tIgE level. * $P < .001$.

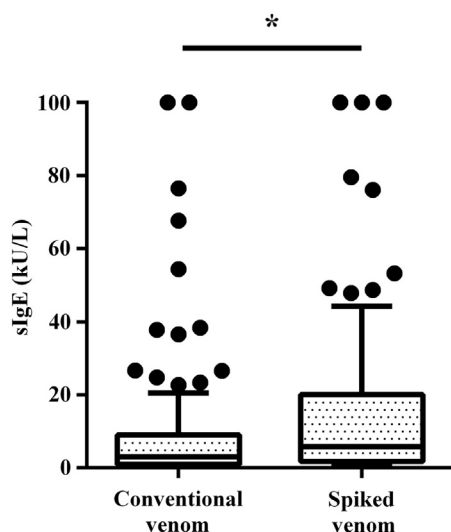


FIG 2. Increase in sIgE levels to the rVes v 5-spiked venom. sIgE levels to the spiked venom were 1.9-fold higher (* $P < .001$). For better clarity, 5 values greater than 100 are displayed as 100 kU/L. Actual values after dilution of the sera were 110 and 182 kU/L to the conventional venom and 248, 612, and 1393 kU/L to the spiked venom.

resulted in a higher IgE-binding capacity. Although there was no significant increase in sensitivity, sIgE levels were markedly increased. Median sIgE value increased 1.9-fold from 2.99 (0.97; 8.86) to 5.82 (1.79; 20.10) kU/L ($P < .001$; Fig 2). This is of particular importance for long-term projects. Observational studies monitoring sIgE levels after field stings or sting challenges, as well as during or after venom immunotherapy (VIT), will be completely distorted. Also, analyses of databases with patients allergic to vespid venom could be biased if information on the used test is not entered and the results of the conventional and spiked venom are evaluated together.

There is consensus that the decrease in sIgE and skin test reactivity is not able to predict the efficacy of VIT; however, the European guidelines still recommend stopping immunotherapy after 3 years if both skin test results and venom sIgE become negative.¹⁰ Therefore, it is still common to determine sIgE during and at the end of VIT. With the spiked venom it appears very unlikely that test results will become negative after 3 years. Although it may be of small clinical importance whether sIgE becomes negative or even increases during VIT, it can be perplexing if sIgE starts to rise during or after immunotherapy.

Taken together, although sensitivity of the spiked venom was reported to be higher than that of the conventional venom, we could not confirm a significant increase in sensitivity. Moreover, specificity of both tests is still an issue. Hymenoptera venom allergy takes a special position among immediate type allergies because IgE antibodies are frequently involved in large local reaction, which impairs specificity for systemic sting reactions.¹¹

Therefore, despite continuous improvement, it will probably never be possible to predict the outcome of the next sting by current means of sIgE determination. However, modifications of the diagnostic test had a significant effect on test results and should therefore have been sufficiently communicated.

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