Received: 30 October 2022 | Revised: 22 November 2022 | Accepted: 7 December 2022

DOI: 10.1111/all.15619

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTER

Reduced intra-subject variability of an automated skin prick test device compared to a manual test

To the editor,

Respiratory allergies affect 30%–40% of individuals worldwide and represent a major health-economic problem.[1] Identification of the triggering or causative allergens in symptomatic patients is based on skin prick test or serum-specific IgE analysis in addition to a detailed medical history by the physician.[2,3] Skin prick test (SPT) is the first choice diagnostic instrument according to international guidelines because of reduced cost, faster results, less invasiveness and a better sensitivity-specificity profile compared to extract-based specific IgE analysis.[4,5] However, there is a need for standardized automation of the entire SPT procedure given that SPT exhibits both operator and device-dependent variability.[6,7]

A monocentric, prospective diagnostic test accuracy study (ISRCTN14098475) was performed at the University Hospitals of Leuven (UZ Leuven, Belgium) to compare reproducibility, tolerability and safety of a newly developed Skin Prick Automated Test or SPAT (Figure S1A–C) to the Skin Prick Manual Test or SPMT (Figure S1D–F). The full methodology can be found in the Appendix S1. In brief, SPAT was performed on the right arm and SPMT was performed on the left arm. On both arms, pricks were applied with 10 mg/ml histamine ($N = 9$) and glycerol-saline ($N = 1$) as respectively positive and negative control (HAL Allergy) in line with previous device validation studies (also Appendix S1).

In total, 118 healthy volunteers (49 males – 69 females; mean ± standard deviation age: 40.1 ± 13.3) were enrolled in the study (Figure S2). SPAT showed significantly lower coefficient of variation of the histamine wheal sizes (SPAT median (IQR): 13.6% (10.4%–17.7%)) compared to SPMT (SPMT median: 17.6% (13.6%–22.9%); $p < 0.0001$; Figure 1). Similar findings were obtained in all but one of the pre-defined age decades (Figure S3). Wheal sizes were significantly larger in SPAT compared to SPMT for both control ($p = 0.002$) and histamine prick ($p < 0.0001$; Figure 2A). The wheal size difference between histamine and control wheals was equal between SPAT and SPMT ($p = 0.13$; Figure 2B). The 97.5% percentile (=4.5 mm) in controls was used to determine the cut-off that defines a positive wheal with SPAT. Sensitivity and specificity profiles of SPAT (respectively 1.00 (0.96–1.00); 0.99 (0.95–1.00)) and SPMT (respectively 0.93 (0.86–0.96); 1.00 (0.96–1.00)) were comparable (Table S1).

Subjective scoring of discomfort as assessed by VAS was significantly lower in the SPAT (median (IQR): 2 cm (1–2 cm)) compared to the SPMT (2 cm (1–4 cm)) group ($p = 0.0009$; Figure S4). No adverse events were reported during the study for either test.

Prick failures were analysed on a total number of 1180 pricks (Table S2). Overall, prick failures occurred significantly less frequently during SPAT compared to SPMT ($p < 0.0001$). The time needed to execute the SPAT pricks per participant (20 s) was markedly less compared to the time needed to execute the SPMT pricks per participant (on average 144 s). The amount of histamine required to carry out the pricks of the entire study with SPAT (4.5 ml) was 2.7 times less compared with SPMT (12.0 ml).

Even though the SPAT produces larger histamine wheal sizes, it exhibits lower intra-subject wheal variability compared to SPMT. Larger histamine wheal sizes could be attributed to the combination of vertical pressure and 90° clockwise rotation of the lancet.[8] Lower intra-subject test variability represents a major advancement in the field of allergy diagnostics because skin-prick test

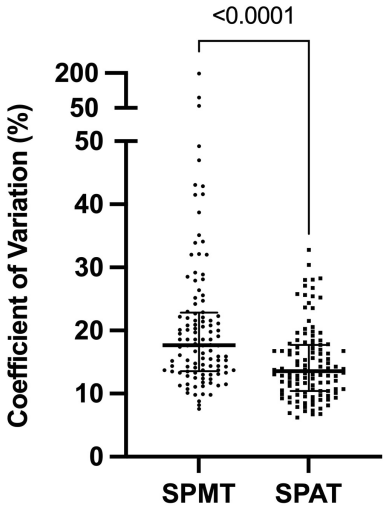

FIGURE 1 Intra-subject variability of histamine pricks between manual (SPMT) and automated (SPAT) skin prick test. Coefficient of variation was calculated and compared between SPMT and SPAT by Mann–Whitney test. Data are represented as scatter dot plot with median and interquartile range.

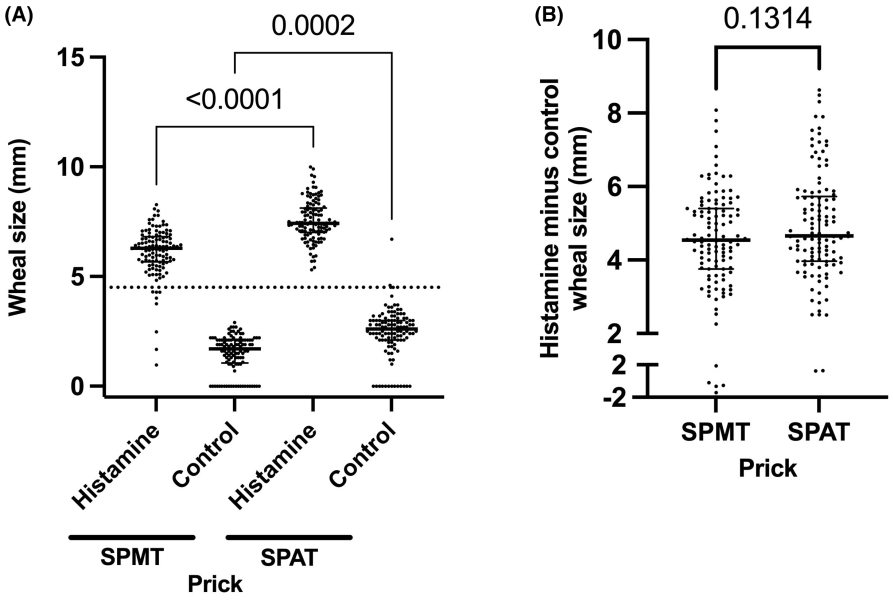

FIGURE 2 Readout via SPAT for SPMT and SPAT pricks. (A) Shows the average wheal sizes of histamine and control pricks by SPMT or SPAT after SPAT readout. Dunn's multiple comparison test was used for in between group comparisons. (B) Shows the histamine minus control wheal size comparison between SPMT and SPAT after SPAT readout.

reproducibility is one of the biggest issues in current clinical practice.[9] This study also demonstrated that the ability to discriminate a histamine from a control wheal is as good as with SPMT. In near future, new studies with SPAT in allergic and non-allergic individuals will shed a light on the precision of the device to detect allergy to inhalant allergens.

In conclusion, SPAT showed increased reproducibility and tolerability compared to SPMT. SPAT is able to limit the number of prick failures due to human errors during SPMT. The fact that SPAT is time saving and consumes less allergen solution when dropping glasses are used to run the SPT makes it an interesting cost-effective instrument for future allergy diagnostics.

ACKNOWLEDGMENTS

We would like to thank Leen Cools and Els Costermans for their coordination of the study on site. We would also like to thank all volunteers who participated in the study.

FUNDING INFORMATION

Hippo Dx; FWO, Grant/Award Number: 1805518N; SmartHub Vlaams Brabant

CONFLICT OF INTEREST

SG, SFS and LVG hold shares of Hippocreates who developed the SPAT device. MJT received consulting fees for statistical advice for the study. SG, DL and SFS are employees of Hippocreates. RS is supported by a FWO senior clinical investigator fellowship (1805518N). SU, WB, MJ, PWH have nothing to disclose. The study was supported by a grant from SmartHub Vlaams Brabant.

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REFERENCES

1. Zuberbier T, Lötvall J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. *Allergy*. 2014;69(10):1275-1279.
2. Bousquet J, Anto JM, Bachert C, et al. Allergic rhinitis. *Nat Rev Dis Primer*. 2020;6(1):95.

3. Sampath V, Abrams EM, Adlou B, et al. Food allergy across the globe. *J Allergy Clin Immunol*. 2021;148(6):1347-1364.
4. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test – European standards. *Clin Transl Allergy*. 2013;3:3.
5. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008;100(3 Suppl 3):S1-S148.
6. Werther RL, Choo S, Lee KJ, Poole D, Allen KJ, Tang MLK. Variability in skin prick test results performed by multiple operators depends on the device used. *World Allergy Organ J*. 2012;5(12):200-204.
7. Topal SG, Karaman BF, Aksungur VL. Variables affecting interpretation of skin prick test results. *Indian J Dermatol Venereol Leprol*. 2017;83(2):200-204.
8. Kahveci M, Karabulut E, Soyer O, Sahiner UM, Buyuktiryaki B, Sekerel BE. Fine-tuning the use of a skin prick test device. *World Allergy Organ J*. 2020;13(5):100122.
9. Bousquet J, Heinzerling L, Bachert C, et al. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy*. 2012;67(1):18-24.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.