

CPD

A novel, simple, validated and reproducible instrument for assessing provocation threshold levels in patients with symptomatic dermographism

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Summary

Background. Symptomatic dermographism is a common urticarial condition. There is a need for an objective method to determine the provocation threshold for patients, in order to facilitate individualized diagnosis and treatment.

Aim. To compare the dermal responses evoked by a new type of dermographometer (FricTest) with those evoked by a spring-loaded dermographometer (the Dermographic tester).

Methods. Dermal provocation was performed in 30 patients with symptomatic dermographism and 30 healthy controls. The FricTest consists of six tips of varying length, which are stroked over the skin, while the Dermographic tester has a single tip. The widths and volumes of the resulting weals were measured.

Results. Both instruments were similar in their ability to produce dermal responses. The weal widths of 1 and 3 mm induced by the FricTest were used as the provocation thresholds to distinguish between patients and controls, and to indicate the different levels of severity within the patient group.

Conclusions. The FricTest was easy to use and produced an objective response. This simple and inexpensive instrument could be used to individualize diagnosis and treatment of patients with symptomatic dermographism, allowing for better personalized management.

Introduction

Symptomatic dermographism (also known as dermographic urticaria or urticaria factitia) is the most common type of physical urticaria, and is present in 1.5–5% of the population.¹ The condition is characterized by the development of weals and itching after

mild stroking of the skin, and is distinguished from simple dermographism, in which transient wealing, but not pruritus, may result from the same stimulus. In symptomatic dermographism, wealing develops within seconds to minutes after provocation, and typically persists for 1–2 h.^{2,3}

The usual method of confirming the diagnosis is to stroke the skin with a wooden tongue depressor or a closed ballpoint pen to produce a palpable weal.^{4,5} A consensus meeting in 1996 published a definition of physical urticarias and urticarial vasculitis,⁶ recommending that a positive diagnosis is made if a wealing reaction of the skin occurs within 10 min in response to a moderate stroking stimulus of $< 36 \text{ g/mm}^2$ ($3\text{--}5 \times 10^5 \text{ Pa}$). Itching is almost invariable, and lesions last up to 1 h. Furthermore, the report suggested

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that the test may be performed by stroking the skin with a dermatographometer, a handheld device with a spring-loaded tip, originally designed by Bettley in 1962.⁷

Although this consensus laid the basis for a positive or negative diagnosis of symptomatic dermographism,^{2,3,8–10} the symptoms of the condition are not uniform, but differ widely in severity, as does the response to treatment. Consequently, it would be desirable to obtain sensitive and reproducible estimates of wealing thresholds for individual patients in order to individualize management and treatment. Such an attempt was initially reported in 2008 by Borzova and colleagues,¹¹ who used a dermatographometer at three different settings (20, 36 and 60 g/mm²) to obtain a quantitative response to ultraviolet B phototherapy. In that study, a positive response was the lowest shear pressure to elicit a positive wealing response when measured at 10 min after provocation.

To simplify the assessment of provocation thresholds, we have developed a six-pronged dermatographometer that allows for simultaneous dermal stimulation with six different provocation levels: three above and three below 36 g/mm², and we describe its use in a case-control study against a single-pronged instrument.

Methods

Ethics approval

The study was approved by the Charité ethics committee, and was conducted according to the principles of the Declaration of Helsinki. All participants gave signed informed consent at the beginning of the study.

Patients

We recruited 30 patients (14 men, 16 women; mean $\pm$ SD age 39.8 ± 10.4 years, range 22–64) with a confirmed diagnosis of symptomatic dermographism² and 30 healthy volunteers (11 men, 19 women; mean $\pm$ SD 31.9 ± 7.5 years, range 19–49) from the Department of Dermatology and Allergy.

Patients were requested to refrain from taking systemic corticosteroids or applied topical antihistamines, corticosteroids or mast-cell stabilizers for 2 weeks before attending the clinic, and had stopped oral antihistamines at least 72 h before assessment. No participant had performed physical exercise, smoked, or ingested xanthines or alcohol for at least 4 h before the test. Participants were seated in a draught-free room at ambient temperature (20–22 °C), and were acclimatized for 20 min before the tests were performed.

Induction of skin responses

In this proof-of-concept study, we compared the newly developed dermatographometer (FricTest; Biomedizinische Werkstätte der Charité, Berlin, Germany) and a calibrated spring-loaded dermatographometer (Dermographic tester; HTZ Ltd, Vulcan Way, New Addington, Croydon, Surrey, UK) in inducing dermographism. Although either the back or the forearm may be used for diagnostic provocation,² we chose the forearm because it is simpler to test in daily practice.

The FricTest consists of a plastic comb with six smooth steel tips (which are 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 mm in length, respectively) in two horizontal rows, with each of the prongs being 20 mm apart (Fig. 1a). Each tip is 3 mm in diameter and has a slightly rounded end to avoid scratching the skin. To obtain a response, the instrument is placed vertically so that the steel tips are touching the skin through a clear plastic template 2 mm thick (Fig. 1b), and then stroked once from left to right across the width of the volar surface of the forearm for a distance of approximately 60 mm.

The Dermographic tester is a pen-sized instrument (Fig. 1a) with a spring-loaded round-ended steel tip 4.5 mm long and with a diameter of 2.3 mm, which is used to apply controlled and localized static or shear force to the skin. In this study, the instrument was stroked across the skin three times, once for each level of force applied. The pressure can be varied by turning a dial on the instrument; the scale settings measured in this study were 0, 5, or 10 (equivalent to 28, 70 and 108 g/mm², respectively).

Two investigators (RVdS and EA) used the devices to induce dermographic responses on both patients and healthy controls. The first investigator applied the FricTest to the right forearm and the calibrated Dermographic tester to the left forearm, while the second investigator applied the FricTest only to the right forearm, at least 30 mm from the previous application.

Assessment of response

The values for the force that FricTest tips exerted were calculated from the forces determined for the Dermographic tester, using the equation:

$$F_f = (F_d \times V_f) / V_d,$$

where F_f is the FricTest tip force to be calculated, F_d the mean force exerted by the Dermographic tester (from the manufacturer's information), V_f the mean volume of the weal provoked by the FricTest tip, and V_d the mean volume of the weal provoked by the Dermographic tester. The overall mean values of weal

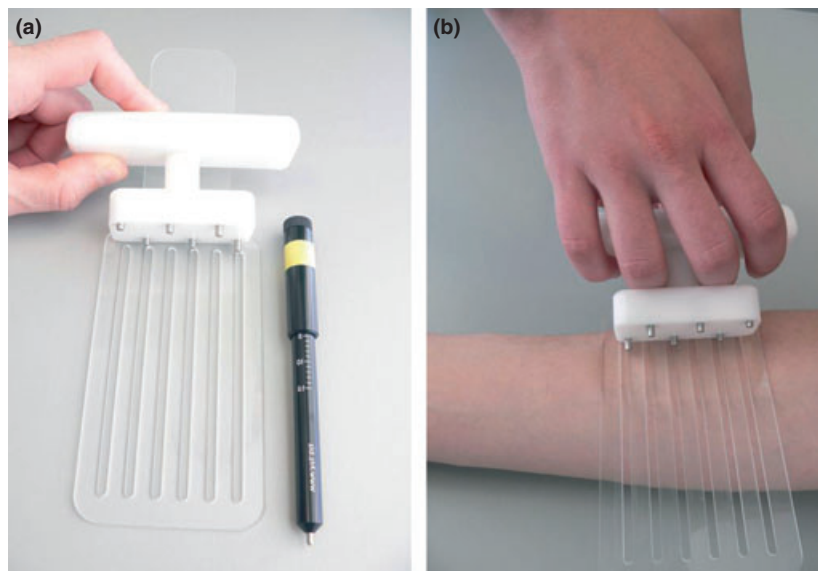


Figure 1 (a) The FricTest (left) and the Dermographic tester (right); (b) FricTest being used to assess dermographism on the volar surface of the forearm.

volume from the two investigators ($n = 60$) were used for these calculations. The forces exerted by the 3.5, 4.0, 4.5 and 5.0 mm FricTest tips were calculated to be 28, 45, 66 and 93 g/mm², respectively. The forces exerted by the 2.5 and 3.0 mm tips could not be calculated because they produced negligible wealing.

Assessment of skin responses

Weal width and volume were recorded before and at 5, 10, 15, 20, 25 and 30 min after dermographic provocation. Responses were considered positive if a palpable weal was present 10 min after provocation, and cut-off values for weal widths of ≥ 1 , ≥ 2 and ≥ 3 mm were assessed for their specificity and sensitivity in confirming symptomatic dermographism and distinguishing between patients and healthy controls. Weal width was measured at the site of maximum width using a transparent ruler. The volume of a standard 50 mm length of weal was measured using a volumetric optical scanning system¹² (Primos 5.075 D; GMF, Teltow, Germany).

Statistical analysis

The required group size was estimated using a power of 80% (t -test) with a two-sided significance level of 5% and a medium effect of 1.2 standard deviations.

Because the results data were normally distributed, the statistical significance of the differences in responses to defined provocation levels at different times within groups was calculated using the Student t -test for paired data, and the differences between

groups were calculated using the Student t -test for unpaired data. $P < 0.05$ was considered significant.

Results

Response to dermal provocation

Skin provocation of patients with symptomatic dermographism using both the FricTest and the Dermographic tester resulted in weal responses that lasted for the entire duration of the 30-min observation period (Fig. 2).

The FricTest produced graded responses depending on the length of the tip, with significant mean weal width and volume responses being seen at all times using the 3.5, 4, 4.5 and 5 mm tips (equivalent to 28, 45, 66 and 93 g/mm², respectively), but not with the 2.5 and 3 mm tips.

Provocation with the Dermographic tester also produced significant graded weal responses with the instrument settings of 0, 5 and 10 (equivalent to 28, 70 and 108 g/mm², respectively).

In healthy volunteers, the mean values at all times were < 1 mm for weal widths and < 2 mm³ for weal volumes in all responses induced by the FricTest or the Dermographic tester.

Investigator differences in FricTest-induced weal response measurements

The use of the FricTest by two independent investigators during the same consultation allowed for comparison between their results (Fig. 3). For weal

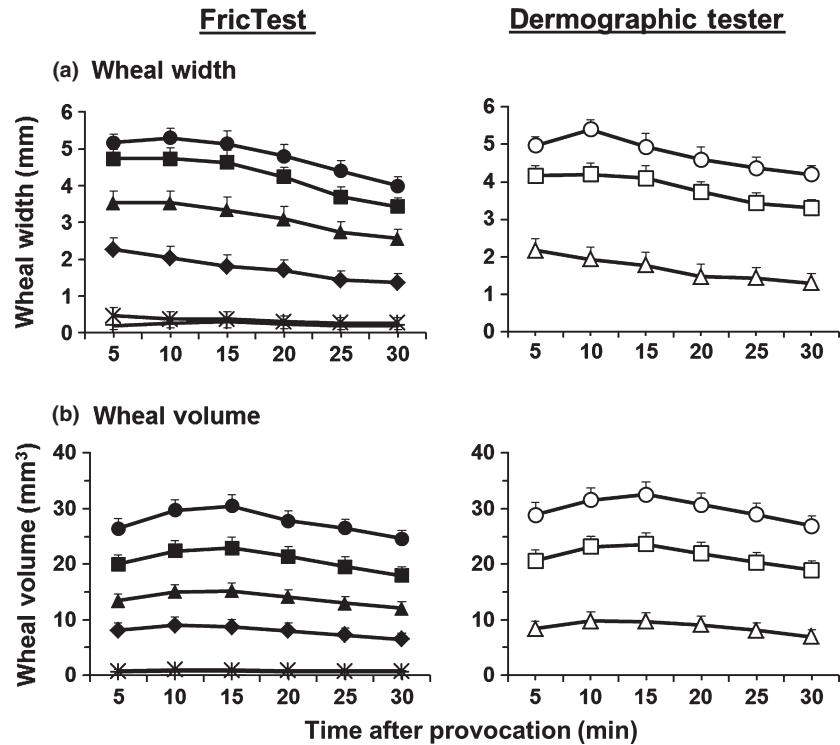


Figure 2 (a) Widths and (b) volumes of weals measured after provocation by the FricTest and the Dermographic tester. Each point is the mean $\pm$ SEM of measurements in 30 patients with symptomatic dermographism. Symbols for FricTest are: closed circle, 5 mm tip; closed square, 4.5 mm tip; closed triangle, 4 mm tip; closed diamond, 3.5 mm tip; x, 3 mm tip; +, 2.5 mm tip. Symbols for the Dermographic tester: open circle, instrument setting 10; open square, instrument setting 5; open triangle instrument setting 0.

width, the Pearson correlation for the investigators was $r^2 = 0.92$ ($P \leq 0.001$, $n = 180$) and for weal volume, it was $r^2 = 0.95$ ($P \leq 0.001$, $n = 180$).

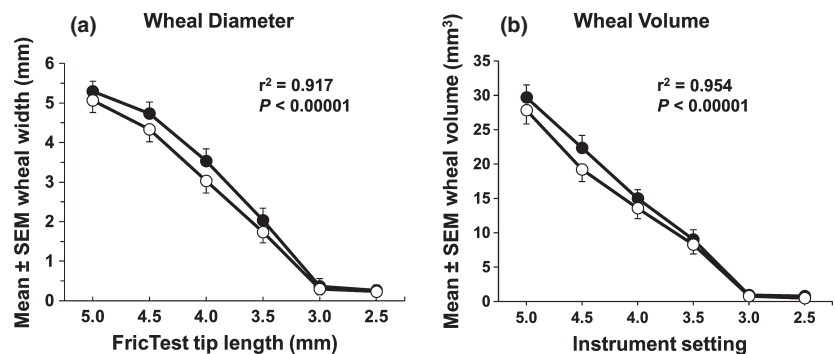
Detection of provocation thresholds

The numbers of people responding to provocation with weal widths of ≥ 1 , ≥ 2 or ≥ 3 mm at 10 min are shown in Fig. 4.

Using a provocation threshold sufficient to produce a weal width of ≥ 1 mm (Fig. 4a), all patients responded positively for weal width to the longest tip (5 mm) of the FricTest, and at least 28 of 30 to the next two tips (4 and 4.5 mm). Only 4/30 responded to the two shortest tips. With the Dermographic tester,

all patients responded positively to settings 5 and 10, and 23 of 30 responded positively to setting 0. Because setting 0 was the lowest setting on the Dermographic tester, it was therefore not possible to determine the actual provocation threshold for most of the patients. Tests with healthy volunteers found a large number of false positives at this setting, whereas with the FricTest, 6 and 10 of the 30 healthy controls responded positively for weal width to the 4.5 and 5 mm tips, respectively, whereas only 1 of the 30 patients responded to the shortest FricTest tip. With the Dermographic tester, 6 and 11, respectively, of the 30 healthy volunteers responded positively for weal width to the instrument settings of 5 and 10, but none responded to setting 0.

Figure 3 Investigator differences in measurement of (a) width and (b) volume of weals induced by the FricTest. Each point is the mean $\pm$ SEM of measurements made in 30 patients with symptomatic dermographism. The open and closed circles indicate the two different investigators. Pearson correlation values were calculated from a total of 180 measurements, 30 from each of the six FricTest tips.



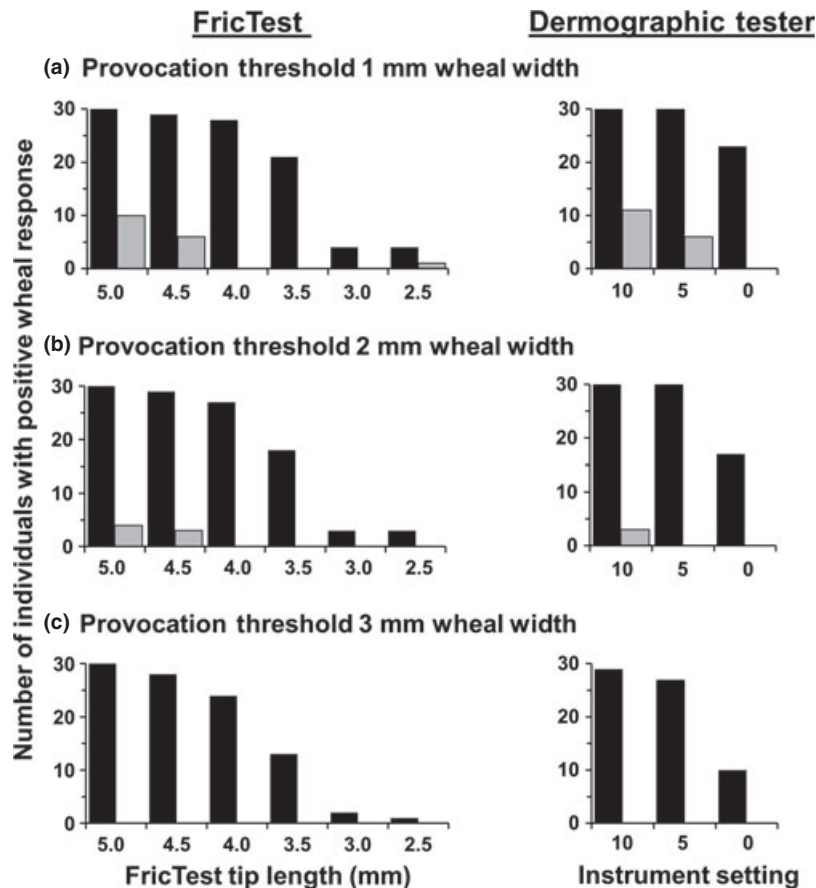


Figure 4 Provocation thresholds of patients with symptomatic dermographism and healthy controls, using cut-off values of ≥ 1 , ≥ 2 and ≥ 3 mm for wheal width at 10 min after provocation as positive response criteria. The black columns show the number of responders in a group of 30 patients with symptomatic dermographism, and the grey columns the number of responders in a group of 30 healthy controls.

Similar results were obtained with patients for both the FricTest and the Dermographic tester using a provocation threshold sufficient to produce a wheal width of ≥ 2 mm (Fig. 4b); however, the number of false positives with healthy volunteers was reduced. When the minimum response was set to ≥ 3 mm (Fig. 4c), there was a more graded response to provocation by the FricTest, with all patients responding to the longest tip and 13 of 30 to the 3.5 mm tip. With the Dermographic tester, 29 of 30 patients responded to the highest setting. There were no false positives with either instrument.

Discussion

In this proof-of-concept study, we found that the comb-like design of the FricTest allowed us to obtain a graded and reproducible provocation of wheals in patients with symptomatic dermographism, using a single stroke of the instrument over the skin. Furthermore, it enabled determination of provocation thresholds, defined as the lowest level of shear force needed to provoke a positive wheal response.

In this study, comparisons were made between the FricTest prototype and the spring-loaded Dermographic tester in provoking dermal responses in patients with symptomatic dermographism and in healthy controls. The FricTest was validated by comparison of wheal widths and volumes, which showed that the 3.5, 4, 4.5 and 5 mm tip lengths of the FricTest produced similar dermal responses in the patient group to those produced by the spring-loaded Dermographic tester at instrument settings of 0, 5 and 10. Furthermore, the comparison of dermal responses produced by application of the FricTest by two separate physicians showed the results to be reproducible.

A test to determine provocation thresholds should be simple and easy to perform. Consequently, only the measurement of wheal width was used, as this is the measure usually available in clinical practice. Ideally, the test should also discriminate between a truly clinical response, which may persist for 1–2 h, and a mild transient response, which may occur in some healthy people with sensitive skin (false positives). We found that a single measurement at 10 min was sufficient to do this.

Different ways of determining a positive response were examined. One method was the production of a palpable weal as recommended by Greaves.¹⁰ In practice, we defined a positive response as a palpable weal of ≥ 1 mm in width at 10 min after provocation. Using this criterion, all patients had a positive response at the severest level of provocation with both instruments, and a graded response at less severe levels. Using the more severe provocation levels, a significant number of the healthy controls produced palpable weals of 1 mm or greater in width. However, with the 4 mm tip, 28/30 patients but no healthy controls had a positive response. This tip was calculated to exert a force on the skin of 45 g/mm², just above the level of 36 g/mm² suggested by guidelines as an appropriate cut-off level for diagnosis of symptomatic dermographism.^{2,6} However, we found that the better option was to use a weal width of at least 3 mm to determine a positive response. This width, which is equal to the diameter of a FricTest tip, appeared to be the most appropriate threshold at which to distinguish between patients with symptomatic dermographism and healthy controls, as all of the tested patients but none of the healthy controls had a positive response. This definition of 'positive response' also allowed determination of severity levels within the patient group, and it therefore seems well suited for the use in routine clinical practice and in clinical trials.

Conclusion

We consider that the simple and inexpensive design of the FricTest should enable clinicians to make a more accurate diagnosis and therefore prescribe personalized management for patients with symptomatic dermographism. Furthermore, the close reproducibility of the results from the different investigators using the FricTest indicates that the instrument could be used in collaborative investigations with different researchers to assess the activity and natural course of symptomatic dermographism disease and to conduct therapeutic trials.

What is already known on this topic?

- Patients with symptomatic dermographism differ in the severity of their condition and in their local response to provocation testing.
- A dermographometer, is a manually adjustable, simple tool for the testing of dermographism.

What does this study add?

- We assessed the usefulness of a new dermographometer, the FricTest, which allows simultaneous testing of dermographism at six different levels without the need for manual adjustment, and compared this with an existing instrument.
- We found that the new instrument allows threshold testing in patients with symptomatic dermographism, which is helpful in the diagnosis and management of symptomatic urticaria.

Acknowledgements

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CPD questions

Learning objective

To provide up-to-date information on the features of symptomatic dermographism and the importance of threshold testing.

Question 1

Symptomatic dermographism belongs to which group of disorders?

- a) Spontaneous urticaria.
- b) Physical urticaria.
- c) Allergic urticaria.
- d) Autoimmune urticaria.
- e) Eczema.

Question 2

Symptomatic dermographism is diagnosed by which technique?

- a) Exposure of the skin to different temperatures.
- b) UV testing of the skin.
- c) Exercise provocation testing.
- d) Blood work for markers of systemic inflammation.
- e) Mild stroking of the skin.

Question 3

What is the key symptom of symptomatic dermographism?

- a) Pain.
- b) Dizziness.
- c) Nasal congestion.
- d) Pruritus.
- e) Loss of temperature sensation.

Question 4

Why is threshold testing important in symptomatic dermographism?

- a) To assess disease activity.
- b) To predict response to treatment.
- c) To estimate the time until remission.
- d) To detect comorbidities.
- e) To determine quality of life.

Question 5

Which of the following is the underlying cause of symptomatic dermographism?

- a) Genetic.
- b) Viral infection.
- c) Allergy.
- d) Bacterial infection.
- e) Unknown.

Instructions for answering questions

This learning activity is freely available online at <http://www.wileyhealthlearning.com/ced>.

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at <http://www.wileyhealthlearning.com/ced> and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.