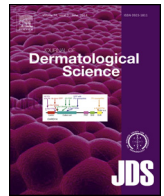




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Development of a standardized pulse-controlled ergometry test for diagnosing and investigating cholinergic urticaria

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ABSTRACT

Background: Cholinergic urticaria (CholU) is a common condition in which active or passive warming leads to development of pinpoint wheals, flares and itch.

Objective: To develop a standardized protocol for diagnosing CholU and measuring trigger thresholds, independent of patients' fitness levels.

Method: Ten CholU patients and matched healthy controls underwent pulse-controlled incremental ergometry for 30 min (stationary bicycle) increasing their pulse rate by 15 beats every 5 min. Non-invasive, heat-flux double-sensor and conventional electronic thermometers measured core and skin surface temperatures from which mean body temperature (MBT) was calculated. The time of onset of sweating (starch-iodine test) and symptoms (whealing) were recorded.

Results: All individuals completed the ergometry protocol without difficulty. All CholU patients but no controls developed wheals. The time to whealing correlated inversely with disease severity. In four patients MBT increased $<0.5^{\circ}\text{C}$ and in two whealing occurred at a temperature lower than at the start of exercise. Onset of symptoms correlated with the time of sweating.

Conclusion: Pulse-controlled ergometry is sensitive and specific for diagnosing CholU and investigating trigger thresholds and disease mechanisms. Our results refute the hypothesis that a rise in MBT is the critical trigger for CholU while sweating appears to have the central role.

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1. Introduction

Cholinergic urticaria (CholU), originally described by Duke in 1924 [1], is characterized by itchy pin point sized short lived wheals with pronounced surrounding flare reactions, which occur in response to physical exercise, passive warming, emotional stress or hot food and beverages [2,3]. Young adults are affected most frequently with a peak onset between 10 and 30 years of age [4–7].

While it is well established that the symptoms of cholinergic urticaria are precipitated by exercise or passive heating of the

body, for example, in a sauna, the underlying mechanism(s) of this condition are unclear. Several theories have been proposed. Perhaps the earliest theory was that the cause is a rise in the weighted mean body temperature (MBT), which is derived from measurements of skin and esophageal temperatures [8]. The second theory stems from the observation by Hausteiner et al. [9] that there was a 44% reduction in muscarinic acetylcholine receptors in patients with CholU compared with healthy controls. Sawada et al. [10] extended these observations and proposed that acetylcholine released from nerves upon exercise cannot be completely 'trapped' by the cholinergic receptors of eccrine glands and, therefore, overflows to cause degranulation of adjacent mast cells to cause wheal formation. This is supported by reports that intracutaneous injections of cholinergic agents induce wheal formation in patients with CholU [11,12]. The third theory is the presence of a 'sweat antigen' that induces localized allergic responses [6,13,14] and the fourth is acquired hypohidrosis due to occlusion of the superficial portion of the sweat glands which leads to leakage of sweat into the dermis with consequential development of wheals [15,16].

Abbreviations: CholU, cholinergic urticaria; MBT, mean body temperature; IGA, Investigator Global Assessment.

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Provocation tests for the diagnosis of CholU have been based on increasing body temperature either by exercise (e.g. on a treadmill or stationary bicycle) or use of a hot bath or sauna [3,8,12]. The study of Illig et al. [8] determined a medium rise in MBT of 0.7 °C was necessary to cause whealing. Furthermore, The EAACI/GA²LEN/EDF/UNEV consensus panel recommendation for confirming the diagnosis of CholU is to achieve a rise of ≥ 1.0 °C of 'body core temperature' by a passive warming test consisting of sitting for up to 15 min in a bath full of water at 42 °C [3]. The major problem with such tests is the measurement of body temperature. The most acceptable to the patient is to use an oral thermometer. However, this is inaccurate as increased breathing, particularly during exercise, results in cooling of the oral mucosa. A more accurate method to measure core temperature is the use of an oesophageal or rectal thermometer. However, their use is invasive and not readily applicable to provocation in an outpatient urticaria clinic. To overcome these problems, a new non-invasive thermometer has been developed which combines two sensors separated by a known thermal resistance, a so-called 'double-sensor' thermometer [17,18], which can measure core temperature when taped to the skin of the forehead. Knowledge of core temperature and skin temperature then allows the calculation of mean body temperature [8].

In this manuscript we describe a newly developed standardized pulse-controlled ergometry test for diagnosing and investigating CholU. In addition, we have used the double-sensor thermometer in attempt to learn more about the pathophysiological principles in CholU and, in particular, the relationship of changes in body temperatures to symptom development and disease severity.

2. Methods and materials

This was a study in which 10 patients with a confirmed diagnosis of CholU [3] and 10 healthy volunteers were recruited from the Department of Dermatology and Allergy, Charité – Universitätsmedizin, Berlin. Patient details are given in Table 1.

The study was approved by the Ethics Committee of Charité – Universitätsmedizin, Berlin (approval # EA4/124/10), registered with German Clinical Trials Register (DRKS-ID: DRKS00004277) and was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, national laws and regulations as well as to the Standard Operating Procedures (SOPs) of the Allergie-Centrum of the Charité – Universitätsmedizin, Berlin. All participants gave signed informed consent at the beginning of the study.

None of the participants had taken systemic corticosteroids or applied topical antihistamines, corticosteroids or mast-cell stabilizers for 2 weeks and had stopped oral antihistamines at least 72 h prior to assessment. No participant had performed physical exercise, had smoked, or ingested xanthines or alcohol for at least 4 h prior to the test.

Table 1
Patient demographics and results summary.

Parameter	Healthy controls	CholU patients
Number	10	10
Sex (m/f)	5/5	6/4
Age (years)	31.5 (24–38)	29.5 (19–44)
Body mass index (kg/m ²)	23.0 (19.8–29)	23.5 (20.5–27.8)
Erlangen atopy score	2 (0–9)	6 (2–14) [*]
Investigator Global Assessment	–	15 (12–17)

Data are presented as median with range.

^{*} $P=0.04$ difference between CholU patients and healthy controls.

To assess the severity of disease of a patient's CholU from their history, we developed an Investigator Global Assessment (IGA) which was calculated as follows:

- 1) Frequency of events (0–maximum 6 points): less than once a month = 0; once a month = 1; more than once a month = 2; once a week = 3; more than once a week = 4; daily = 5; more than once daily = 6 points.
- 2) Eliciting factors (one point for each, maximum 7 points): physical exercise, hot bath, hot shower, emotional stress, hot food, sauna, other: _____.
- 3) Duration of skin lesions (0–maximum 5 points): less than 5 min = 0; 5–10 min = 1; 10–20 min = 2; 20–30 min = 3; 30–60 min = 4; longer than 1 h = 5 points.
- 4) Itch during the events (0–maximum 3 points): none = 0; low = 1; medium = 2; severe = 3 points.

Using this scheme, disease severity was ranked between 0 and 21 IGA points.

The ergometry test, a 30 min static bicycle ride, was performed in a draft free room with an ambient temperature of 20–22 °C. Twenty minutes acclimatization time was allowed before tests during which time participants were fitted with a Double Sensor device attached to the forehead [18–20] (Double Sensor, T_{DS}, Draegerwerk AG, Luebeck, Germany). The Double Sensor was attached to the patients using a two-sided adhesive ring tape that left the sensor area open to contact the skin. Another piece of adhesive tape fixed the sensor securely to the subjects. In addition, conventional thermometers (NTC temperature sensors, Draegerwerk AG, Luebeck, Germany) were attached to both temples, the back and the upper arm with normal adhesive tape to measure skin temperature. A chest strap pulse monitor (Polar Electro GmbH, Büttelborn, Germany) was also fitted to monitor heart rate. All sensors were operated by Health Lab System (Koralewski Ind., Hambuehren, Germany). Starch-iodine powder (according to Minor' sweat test) [21] was applied to the lower back to detect sweating. A practical clinician's protocol for performing the provocation test is presented as an online appendix.

Mean body temperature was calculated using a formula based on that described by Illig et al. [8]:

$$\text{MBT} = (\text{CT} \times 0.87) + (\text{MST} \times 0.13)$$

where MBT = mean body temperature, CT = core temperature, and MST is the mean skin temperature averaged from the thermometers on the temples, back and upper arms. In their publication, Illig et al. [8] measured the temperatures of both the upper body and the legs which were weighted 60% and 40% respectively. Because our volunteers were exercising on a bicycle, we did not collect skin temperature values of the legs. However, we believe that our mean skin temperature measurement is a close enough approximation to make our calculations acceptable.

For the provocation test, the individual was seated on the bicycle (Fig. 1A) and remained stationary until the sensors measured stable results for at least 1 min. Cycling then commenced in pulse controlled manner by instructing individuals to speed up or slow down their pedalling speed to achieve an increase in pulse rate of 15 beats per minute every 5 min to a final maximum increase of 90 beats per minute above the starting level at 30 min (Fig. 1B). During exercise, core and skin temperature and heart rate were recorded every second. The times of the start of the sweating, defined as the appearance of the first blue dots in the starch-iodine powder, and the start of whealing were recorded. Observations were continued during a 10 min recovery period at the end of the 30 min of exercise.

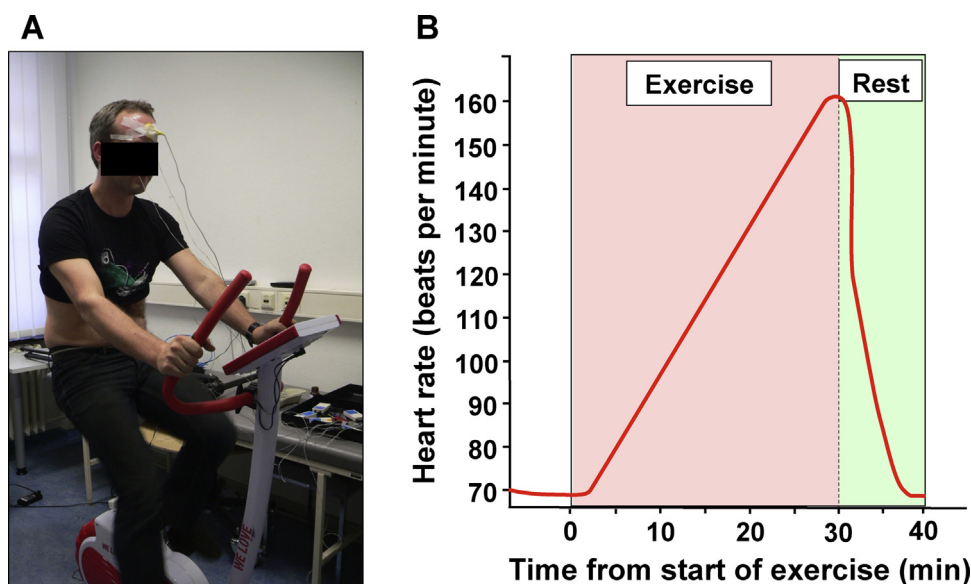


Fig. 1. (A) A patient seated on exercise bicycle. Note the core temperature thermometer taped to his forehead and skin thermometers attached to his temples. (B) Theoretical trace of incremental increase in heart rate of 90 beats per minute over the 30 min exercise period and subsequent fall during the subsequent recovery period. The 30 min exercise period is shown in red and the following 10 min recovery or rest period is shown in green.

2.1. Statistical analyses

As not all the data were normally distributed they are presented as median (with range) and the statistical significance of differences between patients and controls calculated using the Mann–Whitney *U*-test and between results in patients using the Wilcoxon signed-rank test for paired data. Correlations were calculated using the Pearson correlation test. $P < 0.05$ was considered to indicate a significant difference.

3. Results

As seen in Table 1, the ten patients and healthy controls were comparable regarding their sex, age and body mass index. However, the CholU patients had a significantly ($P = 0.04$) higher Erlangen atopy score [22] suggesting them to be more allergic. The Investigator Global Assessment (IGA) scores show that all the patients had moderate to severe cholinergic urticaria.

There were no significant differences between patients and healthy controls with respect to skin temperatures, core temperature and MBT at baseline or during the ergometry (Fig. 2). All healthy controls and 9 of the 10 patients showed a positive starch-iodine powder test for sweating. The recording of sweating could not be performed in the remaining patient due to a known allergy against iodine. There were no significant differences between patients and controls in these parameters at the time of the onset of sweating (Table 2).

All patients, but none of the controls, developed characteristic CholU wheal and flare-type skin reactions. While the median time to onset of symptoms was 27 min (Table 2), it should be noted that four of the ten patients developed their symptoms during the recovery period, i.e. after the end of exercise (Fig. 3A). The time to whealing was negatively correlated with the IGA score for CholU severity ($r = -0.70$, $P = 0.025$) (Fig. 4), i.e. the more severe the patients' CholU the less exercise is needed to make them wheal.

The median skin, core and mean body temperatures achieved after 30 min exercise, at the start of sweating and the time of whealing are shown in Table 2 and their development during exercise and recovery are shown in Fig. 2. Fig. 5 shows that all patients had a rise in MBT as a result of the 30 min exercise with four having a maximum rise of less than 0.5 °C. Fig. 5 also shows

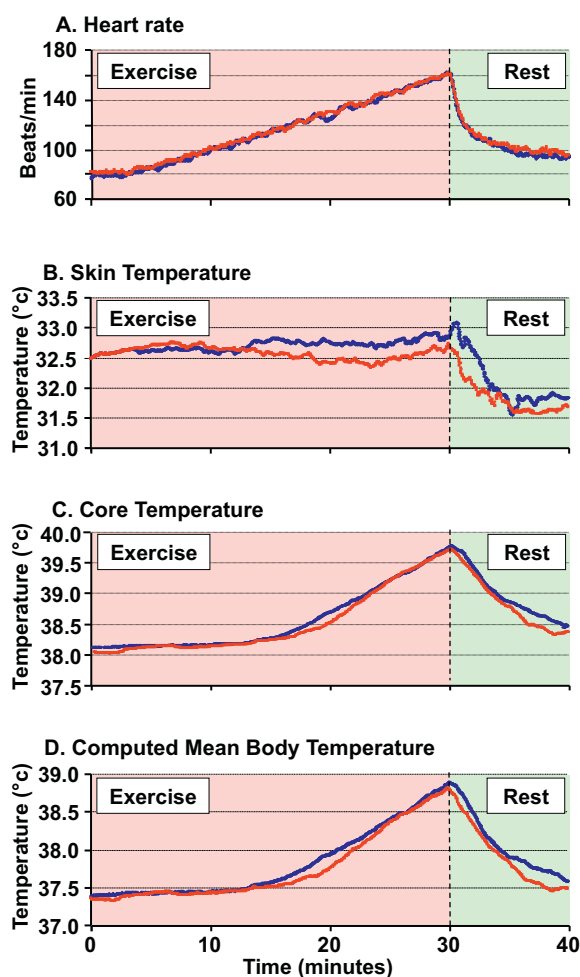


Fig. 2. Traces of means of 10 cholinergic urticaria patients (red) and 10 healthy volunteers (blue) for (A) heart rate, (B) skin temperature, (C) Core temperature, and (D) computed MBT. There were no statistically significant differences between patients and healthy volunteers.

Table 2

Results summary.

Parameter	CholU patients (n = 10)	Healthy controls (n = 10)
Initial temperatures		
Skin temperature (°C)	32.7 (31.8–33.5)	32.7 (30.0–34.1)
Core temperature (°C)	37.9 (37.1–39.2)	38.1 (37.4–38.9)
Mean body temperature (°C)	37.2 (36.5–38.4)	37.4 (36.8–38.0)
Maximum temperatures		
Skin temperature (°C)	32.4 (32.0–33.9)	32.8 (31.2–34.5)
ΔSkin temperature (°C)	−0.4 (−1.45–0.92)	0.17 (−1.14–2.44)
Core temperature (°C)	39.4 (37.8–40.6)	40.0 (38.7–40.7)
ΔCore temperature (°C)	1.53 (0.26–2.76)	1.69 (0.29–2.54)
Mean body temperature (°C)	38.5 (37.1–39.6)	39.0 (37.8–39.9)
ΔMean body temperature (°C)	1.36 (0.16–2.52)	1.50 (0.10–2.31)
Start of sweating		
Time (min)	18 (12–31)	21 (9–26)
Skin temperature (°C)	32.5 (32.0–33.5)	32.5 (30.1–33.7)
ΔSkin temperature (°C)	−0.3 (−0.63–0.49)	−0.07 (−0.54–1.59)
Core temperature (°C)	38.4 (36.7–39.4)	38.6 (37.8–40.2)
ΔCore temperature (°C)	0.27 (−0.41–1.15)	0.27 (−0.07–1.75)
Mean body temperature (°C)	37.7 (36.1–38.4)	37.9 ± (37.1–39.3)
ΔMean body temperature (°C)	0.22 (−0.37–0.96)	0.22 (−0.13–1.73)
Start of whealing		
Time (min)	27 (19–38)	–
Skin temperature (°C)	32.3 (31.6–33.7)	–
ΔSkin temperature (°C)	−0.56 (−1.86–0.73)	–
Core temperature (°C)	39.0 (36.6–40.2)	–
ΔCore temperature (°C)	0.84 (−1.42–2.34)	–
Mean body temperature (°C)	38.1 (36.0–39.2)	–
ΔMean body temperature (°C)	0.71 (−1.32–2.13)	–

Data are presented median with range. There were no statistically significant differences between results for CholU patients and healthy controls.

that wheals began to be observed before the maximum temperature rise in six of the patients and in one of these, whealing commenced 0.45 °C below the initial temperature before exercise. In the other four patients, wheals appeared during the rest period when the temperature had fallen from maximum. There were no significant changes in skin temperature from starting level at any time during ergometry. There was no correlation between the time to wheal and the time to increase of either core or mean body temperature.

The start of onset of demonstrable sweating preceded wheal development in all patients except one who developed wheals 3 min before sweating was demonstrable (Fig. 3A). There was a

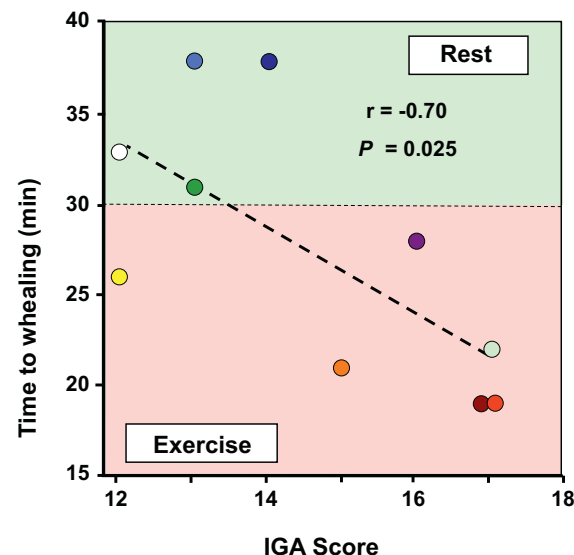


Fig. 4. The Pearson correlation between the time of the start of whealing and the Investigator Global Assessment (IGA) score. The 30 min exercise period is shown in red and the following 10 min 'cool-down' rest period is shown in green. Individual patients are indicated by different coloured circles which are consistent throughout the figures.

significant Pearson correlation between the times of the start of sweating and whealing ($r = -0.67$, $P = 0.49$, Fig. 3B).

4. Discussion

Pulse controlled exercise provocation testing is both highly sensitive and specific for diagnosing CholU. Wheals were produced in all CholU patients but not in healthy controls. Additionally, it is the first protocol that allows an assessment of disease severity, which is significantly correlated with the threshold time to whealing.

Because it is pulse-controlled, the exercise is relatively gentle and easy to perform from the viewpoints of both the clinician and the patient. Even though most CholU patients avoid strenuous physical exercise in everyday life, fitness did not appear to be a problem as all individuals were able to complete the ergometry protocol without undue hardship.

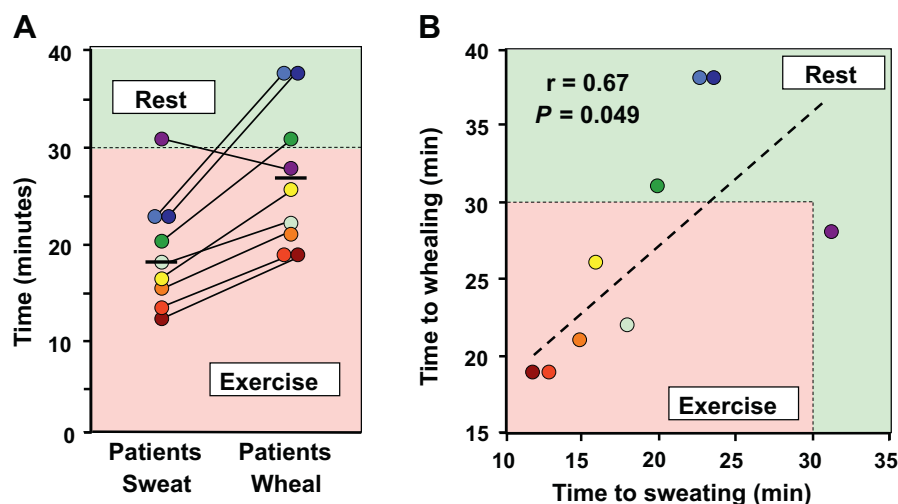


Fig. 3. (A) Time between the beginning of exercise and the start of sweating and whealing in CholU patients. (B) The Pearson correlation between the times of the start of sweating and whealing. The 30 min exercise period is shown in red and the following 10 min 'cool-down' rest period is shown in green. Individual patients are indicated by different coloured circles which are consistent throughout the figures.

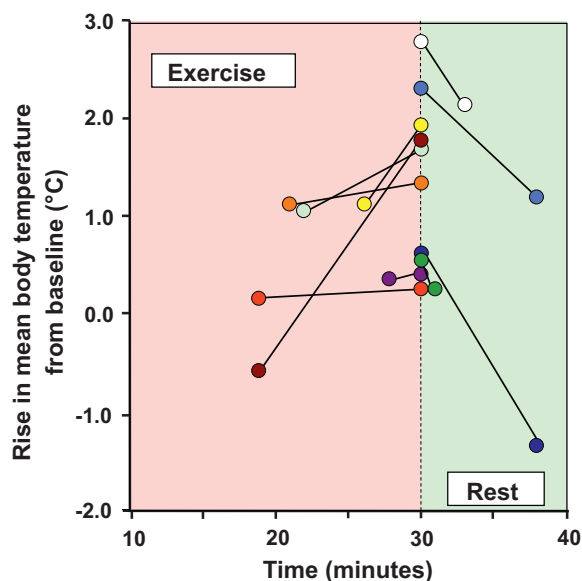


Fig. 5. The maximum changes in MBT from baseline at the end of 30 min exercise and at the time of whealing. The 30 min exercise period is shown in red and the following 10 min 'cool-down' rest period is shown in green. Individual patients are indicated by different coloured circles which are consistent throughout the figures.

All subjects showed sweating before the end of exercise provocation and the time to the beginning of sweating did not differ between CholU patients and healthy controls. Also, there was no difference between patients and controls in the core temperature and MBT at which sweating began, indicating that in our patients the ability to start sweating was not compromised. Because we used the starch-iodine powder method for assessing sweat production, no conclusions may be drawn about the volume of sweat produced by the two groups of individuals. Thus, anhidrosis would have been detected, hypohidrosis, which is one of the postulated mechanisms of CholU [23] would probably not have been detected.

In their classical 1980 paper, Illig et al. [8] used a sauna to achieve 'outside-in' body heating and physical exercise to induce an 'inside-out' increase in body temperature.

Both resulted in wheals in CholU patients. From their data they concluded that the physical trigger mechanism seems to be related to thermoregulatory processes and that the crucial point is neither the skin temperature nor the body 'core' temperature but a rise in the weighted average body temperature. In their physical exercise test, the median rise MBT at the onset of skin lesions was 0.42 °C (range 0.28–0.65 °C). In our less strenuous exercise test, whealing occurred in two patients at temperatures below their initial starting levels (Fig. 4). Also, in three patients whealing occurred when the MBT was falling after the completion of exercise. Finally, there was no correlation between the IGA score for the severity of CholU and either the maximum MBT or the MBT at the time of whealing. Taken together, these observations refute the hypothesis of a rise in the MBT being the critical trigger for CholU.

It is of note that the onset of sweating preceded wheal development in all patients except one who developed wheals 3 min before sweating was demonstrable. Even in this patient it is likely that sweat formation had begun intradermally at the time of wheal development. These data indicate that sweating is essential for the initiation of wheal formation in CholU and would lend would support to the hypothesis of a type I hypersensitivity against sweat antigens [24].

In conclusion, pulse-controlled ergometry is sensitive and specific for diagnosing CholU and investigating trigger thresholds and disease mechanisms. Our results refute the hypothesis that a rise in MBT is the critical trigger for CholU while sweating appears to have the central role in inducing wheal formation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jdermsci.2014.04.007>.

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Appendix A

Standardized pulse-controlled ergometry test for diagnosing and monitoring cholinergic urticaria

1. Before the test:

- General anamnesis, assess physical fitness and rule out cardiac diseases (e.g. by ECG).
- Inform patient that no systemic corticosteroids or applied topical antihistamines, corticosteroids or mast-cell stabilizers may be used 2 weeks before the test.
- Inform patient to stop oral antihistamines at least 72 hours prior to assessment.
- Inform patient to avoid wheal development by abstaining from physical exercise or passive warming for 24 hours before testing
- Inform patient not to smoke, drink coffee or alcohol for at least 4 hours prior to the test.
- Ask patients to bring sportswear/sportsbra, towel and change of clothes

2. Test protocol:

- Check that room has ambient temperature (between 20 and 22°C) and allow patients to acclimatise in the room for 20 minutes
- Check pulse and blood pressure
- Have patient take a seat on the bike
- Patient remains on the bike stationary until the pulse is stable for at least one minute.
- Ask patient to start cycling
- Ask patient to speed up or slow down pedalling to achieve an increase in pulse rate of 15 beats per minute every 5 minutes (NOTE: in the beginning very mild exercise!)
- Record the heart rate at least every second minute (use table)
- Stop at a final maximum increase of 90 beats per minute above the starting level at 30 minutes (see table) or at onset of whealing.
- Record the time of onset of sweating and whealing (in table)
NOTE: Whealing can start after the end of the ergometry test.
- Observe patient at least for 10 minutes after the end of exercise.
- Check pulse and blood pressure

5. Equipment needed:

- Stationary exercise bike
- Pulsemeter
- Stop watch
- Camera
- (Thermometers are not required unless for a special purpose)

Protocol: standardized pulse-controlled ergometry test for cholinergic urticaria

Patient:

Date:

target time (minutes)	target pulse rate (beats per minute)	actual time (minutes)	actual pulse rate (beats per minute)	Observations (S=Sweating; W=Whealing)
0	Baseline(e.g.70)	____:____	bpm	
1	+ 3 (e.g.73)			
2	+6 (e.g.76)			
3	+9 (e.g.79)			
4	+12 (e.g. 82)			
5	+15 (e.g. 85)			
6	+18 (e.g. 88)			
7	+21 (e.g. 91)			
8	+24 (e.g. 94)			
9	+27 (e.g. 97)			
10	+30 (e.g. 100)			
11	+33 (e.g. 103)			
12	+36 (e.g. 106)			
13	+39 (e.g. 109)			
14	+42 (e.g. 112)			
15	+45 (e.g. 115)			
16	+48 (e.g. 118)			
17	+51 (e.g. 121)			
18	+54 (e.g. 124)			
19	+57 (e.g. 127)			
20	+60 (e.g. 130)			
21	+63 (e.g. 133)			
22	+66 (e.g. 136)			
23	+69 (e.g. 139)			
24	+72 (e.g. 142)			
25	+75 (e.g. 145)			
26	+78 (e.g. 148)			
27	+81 (e.g. 151)			
28	+84 (e.g. 154)			
29	+87 (e.g. 157)			
30	+90 (e.g. 160)			Exercise Stop
31	Start Recovery			
32				
33				
34				
35				
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40				