

Photoplethysmography for non-invasive diagnosis of cold urticaria

Daria Fomina¹, Sofia Serdotetskova¹, Alexander Machikhin², Mikhail Volkov², Anastasia Guryleva², Mojca Bizjak³, Valeriya Bukova², Marina S. Lebedkina¹, Gerelma Andrenova¹, Olga Mukhina¹, Mukatova Irina⁴, Inna Danilycheva⁵, and Marcus Maurer⁶

¹GBUZ Gorodskaa kliniceskaa bo'lnica No 52 Departamenta zdravooohranenia goroda Moskvyy

²FGBUN Naucno-tehnologiceskij centr unikal'nogo priborostroenia Rossijskoj akademii nauk

³Klinika Golnik

⁴Astana Medical University

⁵NRC Institute of Immunology FMBA of Russia

⁶Charite Universitatsmedizin Berlin

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Abstract

Background: Cold urticaria (ColdU) is a common type of chronic inducible urticaria. Patients with typical ColdU develop wheals in response to standard cold stimulation tests (CSTs), an ice cube (ICT) or TempTest[®]. As of now, the evaluation of CST response is visual and subjective. Validated, robust, and objective test readouts lacking today are needed. **Methods:** We subjected 63 patients (39 with typical ColdU and 24 with atypical ColdU) and 15 healthy controls (HCs) to TempTest[®] CSTs and critical temperature threshold assessments. Blood microcirculation photoplethysmography (PPG) measurements were performed 5 min before and 10 min after the ICT on the volar forearm. **Results:** PPG amplitudes reflected normal baseline skin blood perfusion in patients with typical or atypical ColdU. Ice cube CSTs induced a marked increase in blood perfusion and PPG amplitudes in typical but not atypical ColdU, with distinct pre-post CST changes in PPG amplitudes in the former. The ratio of post-provocation and baseline PPG amplitudes (R_{PPG}) in typical ColdU patients exceeded that in atypical ColdU patients and HCs more than 3-fold. Almost all typical ColdU patients (98%), but only 13% of atypical ColdU patients and 7% of HCs had $R_{PPG} > 3$. PPG results matched those of CSTs in 94% of all tested individuals. **Conclusion:** Photoplethysmographic assessments of CST responses appear accurate and provide objective readouts. PPG may be of use in diagnosing ColdU, distinguishing typical and atypical ColdU, and more precise threshold testing.

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Short title: Photoplethysmography in cold urticaria diagnosis

⁺Sofia Serdotetskova¹, Alexander Machikhin², Daria Fomina^{1,3,4}, Mikhail Volkov^{2,5}, Anastasia Guryleva², Mojca Bizjak⁶, Valeriya Bukova^{2,7}, Marina Lebedkina¹, Gerelma Andrenova¹, Olga Mukhina¹, Mukatova Irina⁴, Inna Danilycheva⁸, Marcus Maurer^{9,10}

¹Urticaria Center of Reference and Excellence (UCARE), Moscow Center of Allergy and Immunology, Clinical City Hospital No. 52, Ministry of Healthcare of Moscow, Russia

²Scientific and Technological Center of Unique Instrumentation, Russian Academy of Sciences, Moscow, Russia

³Sechenov University, Moscow, Russia

⁴ Astana Medical University, Astana, Kazakhstan

⁵ ITMO University, Saint-Petersburg, Russia

⁶ Urticaria Center of Reference and Excellence (UCARE), University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

⁷ Bauman Moscow State Technical University, Moscow, Russia

⁸ NRC Institute of Immunology FMBA of Russia, Moscow, Russia

⁹ Urticaria Center of Reference and Excellence (UCARE), Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Dermatological Allergology, Allergie-Centrum Charité, Department of Dermatology and Allergy, Berlin, Germany

¹⁰ Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany

Correspondence:

Daria Fomina

Urticaria Center of Reference and Excellence (UCARE), Moscow Center of Allergy and Immunology, City Clinical Hospital No. 52, Ministry of Healthcare of Moscow, Russia

3 Pekhotnaya Street, Moscow 123182

Tel: +7-916-597-18-06

E-mail: daria.s.fomina@gmail.com

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Author contribution:

Alexander Machikhin, Daria Fomina and Inna Danilycheva designed the study. Valeriya Bukova and Sofia Serdotetskova performed the experiments. Mikhail Volkov and Anastasia Guryleva processed the experimental data. Sofia Serdotetskova, Alexander Machikhin, Mikhail Volkov, Anastasia Guryleva, Marcus Maurer, Marina Lebedkina, Olga Mukhina, Gerelma Andrenova and Irina Mukatova contributed to data interpretation. Sofia Serdotetskova, Alexander Machikhin wrote the manuscript with critical input from Mojca Bizjak and Marcus Maurer. The project is managed by Daria Fomina. All authors reviewed the manuscript.

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ABSTRACT (233/250)

Background: Cold urticaria (ColdU) is a common type of chronic inducible urticaria. Patients with typical ColdU develop wheals in response to standard cold stimulation tests (CSTs), an ice cube (ICT) or TempTest[®]. As of now, the evaluation of CST response is visual and subjective. Validated, robust, and objective test readouts lacking today are needed.

Methods: We subjected 63 patients (39 with typical ColdU and 24 with atypical ColdU) and 15 healthy controls (HCs) to TempTest[®] CSTs and critical temperature threshold assessments. Blood microcirculation photoplethysmography (PPG) measurements were performed 5 min before and 10 min after the ICT on the volar forearm.

Results: PPG amplitudes reflected normal baseline skin blood perfusion in patients with typical or atypical ColdU. Ice cube CSTs induced a marked increase in blood perfusion and PPG amplitudes in typical but not atypical ColdU, with distinct pre-post CST changes in PPG amplitudes in the former. The ratio of post-provocation and baseline PPG amplitudes (R_{PPG}) in typical ColdU patients exceeded that in atypical ColdU patients and HCs more than 3-fold. Almost all typical ColdU patients (98%), but only 13% of atypical ColdU patients and 7% of HCs had $R_{PPG} > 3$. PPG results matched those of CSTs in 94% of all tested individuals.

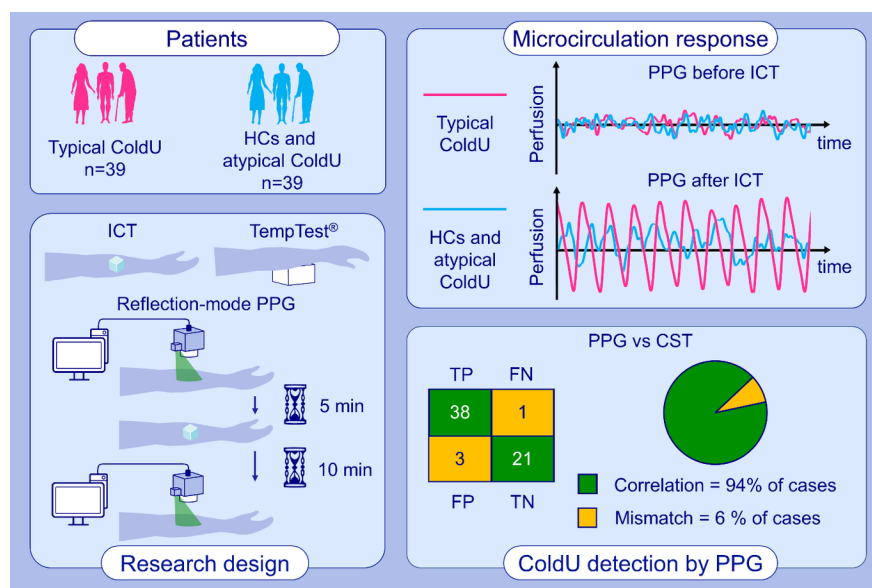
Conclusion: Photoplethysmographic assessments of CST responses appear accurate and provide objective readouts. PPG may be of use in diagnosing ColdU, distinguishing typical and atypical ColdU, and more precise threshold testing.

Keywords: cold urticaria, image processing, non-invasive diagnostics, photoplethysmography, skin inspection

Abbreviations

AU	Arbitrary units	
CInd:	Chronic inducible urticaria	
ColdU:	Cold urticaria	
CST:	Cold stimulation test	
CTT:	Critical temperature threshold	
DLQI:	Dermatology Life Quality Index	
ICT:	Ice cube test	
HC:	Healthy control	
PPG:	Photoplethysmography	
R_{PPG} :	Ratio of post-provocation and baseline PPG amplitudes	Ratio of post-provocation and baseline PPG amplitudes
UCT:	Urticaria Control Test	Urticaria Control Test

GRAPHICAL ABSTRACT:



ColdU , cold urticaria, *CST* , cold stimulation test, *FN* , false negative, *FP* , false positive, *HCs* , healthy controls, *ICT* , ice cube test, *PPG* , photoplethysmogram, *TN* , true negative, *TP* , true positive.

GRAPHICAL ABSTRACT HIGHLIGHTS:

Microcirculation response to cold triggers varies between typical ColdU patients and atypical ColdU patients / HCs.

Reflection-mode PPG enables non-contact quantitative estimate of the perfusion.

Changes in perfusion can detect typical ColdU and indicate the disease activity.

PPG-based measurements correlate with CSTs (ICT or TempTest®) in 94% of cases.

INTRODUCTION

Cold urticaria (ColdU) is the second most common subtype of chronic inducible urticaria (CindU) after symptomatic dermatographism. ColdU is characterized by wheals and/or angioedema following skin contact with various cold triggers (air, liquids, surfaces, objects). The main hazard of ColdU is the development of potentially life-threatening cold-induced anaphylaxis occurring in approximately one third of patients.

ColdU often starts in early adulthood (18–27 years) and lasts on average for 4–5 years, with spontaneous remission or relief of symptoms in 50% of cases within 5 years. The incidence of ColdU in Central Europe is estimated at 0.05%. ColdU is more frequent in women.

ColdU is diagnosed based upon patient history and cold stimulation tests (CSTs). For CSTs, cold is applied to the volar forearm for 5 min, and the response is evaluated 10 min after the end of stimulation. Appearance of whealing at the site of exposure represents a positive test result (**Figure 1A and 1B**). About 75% of all patients with ColdU with positive responses to standard CSTs have typical ColdU. In atypical ColdU, CSTs are negative or induce atypical responses, such as delayed whealing. About 25% of all ColdU patients have atypical ColdU, and CSTs other than the standard ones are needed to elicit whealing and confirm the diagnosis⁴. Due to its easy accessibility, the most widely used CST is a melting ice cube test (ICT) with an ice cube in a water-filled plastic bag. However, testing with TempTest®, a Peltier element producing a 4–44°C temperature gradient, is preferred over ICT, because it can be used to assess disease activity, i.e. the critical temperature threshold (CTT).

The evaluation of CST responses in routine clinical practice is done by macroscopic inspection and is therefore subjective. In other words, CST sites are visually evaluated for whealing by the testing physician. This may lead to inter- and intra-observer variability, false positive and false negative CST results, and unreliable CTT measurements. For CTT determination with TempTest[®], the length of the wheal, starting at the 4°C contact site, reflects the wheal-inducing temperature range in individual patients; the longer the wheal, the higher the CTT. Where the wheal ends is therefore of key importance for informing patients about their CTTs and their risk of reacting to cold. Since the end of TempTest[®] induced wheals often only measures 1 mm in width, it can be challenging to determine visually where that end is and what the CTT is. These and other issues with reading CSTs need to be addressed. Validated, robust, and objective test readouts lacking today are needed. In the future, better methods for CST response assessment in patients with typical ColdU should be easy to use, reliable, cost-effective, and objective.

Upon skin exposure to cold, patients with ColdU develop wheal- and flare-type skin reactions explained respectively by increased extravasation and vasodilation. These processes are brought about by the degranulation of mast cells. Mast cell mediators, including histamine, induce vasodilation and extravasation, and they also activate sensory skin nerves, which contributes to vasodilation and flare responses. This response to cold is unique to ColdU and does not occur in people without ColdU, in whom cold exposure first induces vasoconstriction and then, upon rewarming, vasodilation. The differences in skin responses to the cold between healthy subjects and ColdU patients are linked to certain changes in skin microvasculature. Based on this, we hypothesized that the assessment of ColdU patients and healthy subjects permits detection of distinct microvasculature responses and their differentiation.

In vivo microvasculature responses can be assessed, mapped, quantified, and monitored by several methods and techniques, including laser Doppler perfusion and laser contrast speckle imaging, as well as photoplethysmography (PPG). The latter makes use of a light source and a photodetector to measure volumetric variations of cutaneous blood circulation. PPG provides reliable, low-cost, and easy to perform readings of local blood volume changes in the microvasculature of the inspected skin area. By contrast to other techniques, PPG is less sensitive to the patient's motion, more cost-effective, and easier to implement.

Microcirculation imaging techniques are most commonly targeted at the nailfold area, but for ColdU, the most representative data is acquired by imaging affected skin. CSTs are known to produce ColdU-specific skin circulatory responses. Meyer et al. studied vascular reactions caused by mast cell degranulation after exposure to a cold stimulus and showed that vascular reactions change under the influence of antihistamines.

Here, we used PPG to test our hypothesis that the development of cold-induced skin lesions in patients with typical ColdU is linked to distinct and detectable changes in skin microvasculature. Our long-term aim is to improve ColdU diagnosis and management by providing an objective, easy, reliable, and low-cost measure of typical ColdU CST.

METHODS

Study subjects and conduct

The study was performed at the Center of Allergy and Immunology, City Clinical Hospital No. 52 of the Ministry of Healthcare of Moscow (Moscow, Russia) between May 2021 and February 2023 after approval by the independent local ethics committee (protocol #06/0621). All study participants provided prior written informed consent.

We analyzed 63 patients with expert-confirmed ColdU. Of these, 39 patients had typical ColdU confirmed by positive ICT and TempTest[®] CSTs. The other 24 patients had atypical ColdU with negative ICT and TempTest[®] CSTs. In both groups, we recorded gender, age, the incidence of life-threatening reactions like angioedema and hypotensive reactions (weakness, dizziness, loss of consciousness), comorbid CSU, and other types of CIndUs, frequency of allergic, autoimmune and oncological diseases, duration of ColdU, treatment, and results of standardized validated questionnaires (Urticaria Control Test, UCT; Dermatology Life Quality Index, DLQI). Patients with typical and atypical ColdU were similar in their demographic and clinical

features, except for the duration of disease, which was 24 months (range 11 to 71 months) in typical ColdU and 212 months (range 60 to 360 months) in atypical ColdU (Table 1). We also investigated 15 healthy controls (HCs) who had no history of pathological reactions associated with cold exposure, and all of them had negative CSTs.

Assessment of disease control and impact

The UCT was used to assess disease control during the past month. The maximum UCT score, 16 points, reflects completely controlled disease, and scores from 0 (the lowest score) to 11 points indicate poorly controlled disease. The DLQI permits clinicians to assess the impact of skin disease on the quality of life of patients over the past week. The minimum score (0 points) corresponds to the absence of a negative effect of urticaria symptoms on the patient's quality of life. The higher the score, the more severely the quality of life is affected (the maximum result is 30 points).

Cold stimulation testing and critical temperature measurements

ICT was performed following a standard protocol. Briefly, a melting ice cube in thin plastic bag was placed on the volar surface of the patient forearm for 5 min, with macroscopic assessment of the test site 10 min later. TempTest[®] CSTs were done with TempTest[®] 4.0 (Courage & Khazaka, Cologne, Germany), which has a single Peltier element (length: 350 mm, width: 2 mm) that provides a continuous temperature gradient from 4°C to 44°C. The use of TempTest[®] allows for reproducible and standardized cold (and heat) provocation tests and the identification of CTTs. TempTest[®] CST results were also assessed 10 min after the end of cold exposure.

Experimental setup for PPG measurements

We developed a setup for high-magnification and high-resolution imaging of the forearm area where ICTs were performed (**Figure 2**). To achieve a uniform glare-free illumination, we installed two 5 W LED-based light sources with green (central wavelength $\lambda = 520$ nm, FWHM 30 nm) illumination that corresponded to the hemoglobin absorption, thus enabling the high contrast of blood vessels against the blood-free imaging field. Our imaging system included a long-working-distance (70 mm) microscope tube with continuously adjustable 1.5–2.5 $\times$ zoom and a monochrome CMOS camera (IDS uEye UI-3060CP-M-GL Rev.2, 1/1.2", 1936 $\times$ 1216 pixels, frame rate up to 166 fps). For uniformly sharp imaging, we flattened the skin surface with a 2.5 mm thick glass plate located on a separate stand. To minimize residual distortions in the image edges, we limited the resolution to 1000 $\times$ 1000 pixels. Thus, our setup allowed imaging of skin areas in the range of 1.5 $\times$ 1.5 mm² to 2.5 $\times$ 2.5 mm² with resolution high enough to detect single capillaries of 5–10 μ m in diameter.

PPG data acquisition and processing

To obtain photoplethysmographic data, we acquired 12-bit skin images within 40 s at a 50 Hz frame rate and then processed the whole stack of 2000 frames in MATLAB. The key stages of the data processing pipeline have previously been described and are shown in **Figure 3**. Briefly, we eliminated uneven illumination and sensor non-uniformity and then enhanced the contrast of all images and carried out frame-to-frame matching using the GeFolki algorithm to exclude image shifts caused by the patient's movements. The change of pixel intensity in the areas associated with the blood flow in the resulting image stack is a pulsatile signal. For other regions, this change is insignificant and aperiodic. To compute the blood flow signal, we subtracted slowly time-varying background and frequency components out of the cardiovascular-related range of 0.3–7 Hz. The resulting well-matched, noise-free and intensity-corrected blood flow images were made suitable for PPG calculation by averaging the intensity pixel values of each frame. The PPG amplitude was proportional to the amount of arterial blood that reaches the visualized skin area and thus characterized its blood perfusion. It was measured in arbitrary units (AU). We performed photoplethysmographic assessments of the volar forearm of all patients 5 min before and 10 min after the ice cube application.

Statistical analyses

PPG values are presented as the mean $\pm$ standard error of mean (SEM). The criterion of statistical signifi-

cance was $p < 0.05$ for all PPG characteristics. We applied Origin (OriginLab Corp.) for the ROC-analysis and for the two-way ANOVA at the $\alpha=0.05$ to test for differences between PPG amplitudes and the age and sex of study subjects. Statistical characteristics including correlation coefficient, sensitivity, specificity, positive and negative predictive value (PPV and NPV, respectively), and accuracy were calculated using MATLAB.

RESULTS

Patients with ColdU exhibit normal baseline skin blood perfusion

Before ICTs, at baseline, patients with typical ColdU, patients with atypical ColdU, and HCs exhibited similar skin blood perfusion with an average PPG amplitude of $6.2 \cdot 10^{-4} \pm 5.7 \cdot 10^{-6}$ AU, $6.3 \cdot 10^{-4} \pm 4.6 \cdot 10^{-5}$ AU, and $5.4 \cdot 10^{-4} \pm 3.6 \cdot 10^{-5}$ AU, respectively. Across all study subjects and groups, age and sex were not linked to differences in PPG amplitudes.

Cold-induced whealing in patients with typical ColdU is linked to markedly increased blood perfusion and PPG amplitudes

Patients with typical ColdU had high blood perfusion at skin sites that developed wheals in response to ICT, with an average PPG amplitude of $41.4 \cdot 10^{-4} \pm 5.8 \cdot 10^{-5}$ AU. This was markedly higher than their blood perfusion at baseline (PPG amplitude: $6.2 \cdot 10^{-4} \pm 5.7 \cdot 10^{-6}$ AU) as well as that of cold-exposed skin sites in patients with atypical ColdU (PPG amplitude: $9.9 \cdot 10^{-4} \pm 1.4 \cdot 10^{-4}$ AU) and HCs (PPG amplitude: $9.5 \cdot 10^{-4} \pm 1.5 \cdot 10^{-4}$ AU). Patients with atypical ColdU and HCs did not develop wheals at CST skin sites.

Patients with typical ColdU exhibit distinct pre-post CST changes in PPG amplitudes The ratio of post-provocation and baseline PPG amplitudes (R_{PPG}) was markedly higher in typical ColdU patients (6.7 ± 0.3) than in atypical ColdU patients (1.9 ± 0.4) and HCs (1.9 ± 0.5). Of 39 typical ColdU patients, 38 (97.4%) had an $R_{PPG} > 3$, but only 3 of 24 patients with atypical ColdU (12.5%) and one of 15 (6.7%) HCs (**Figure 4**).

Tripling of PPG amplitude predicts positive CST response

In 93.6% of all tested individuals, CST results matched those of PPG, categorized as negative and positive based on R_{PPG} [?]3 and >3 , respectively. With this cutoff, PPG correctly predicted 93.7% of typical and atypical ColdU patients (**Table 2**). As for the HCs, 93.3% demonstrated negative PPG responses, i.e. insignificant microcirculation change due to the exposure to cold, and were thus correctly identified in line with their CST results.

4 DISCUSSION

Our study demonstrates that the results of cold provocation testing in patients with typical ColdU can be accurately and objectively assessed by PPG. This suggests that the implementation of photoplethysmographic measurements in everyday clinical practice may improve the diagnostic work-up of patients with ColdU. PPG may be especially helpful for differentiating typical and atypical ColdU and for testing patients with typical ColdU for their temperature thresholds. Unlike the current practice of visual evaluation, PPG makes it possible to perform a quantitative and objective assessment of the skin response of ColdU patients to cold exposure.

PPG measurements before and after ICT showed that microcirculation responses to ICT are different in typical ColdU patients and HCs. After exposure to cold, the relative increase in PPG amplitude was significantly higher in ColdU patients than in HCs. These results indicate a high sensitivity of PPG-based measurements in detecting perfusion changes in patients with a positive CST, as well as a high negative prognostic accuracy. Our proposed non-invasive and easy-to-implement approach may thus become the basis for new technologies and devices for ColdU diagnosis, complementing current ICTs and improving the assessment of ColdU disease activity and treatment effectiveness.²³ The identified R_{PPG} threshold value may further be used in clinical practice to distinguish typical ColdU from atypical ColdU. The ability of PPG to detect and quantify even small increases in skin blood flow is underscored by the distinct pre-post CST

changes in PPG amplitudes, where tripling of PPG amplitudes is predictive of positive CST responses, in patients with typical ColdU.

Our finding that patients with ColdU demonstrate normal baseline skin blood perfusion is not surprising. In ColdU, urticarial lesions appear only when the skin is exposed to sub-threshold temperatures. It was therefore expected that the PPG-based assessment of skin blood flow at baseline would not show differences in blood perfusion between ColdU patients and HCs. This also supports the notion that there are no major long-term changes in the skin microvasculature of patients with ColdU. It would be interesting to compare baseline PPG signatures of ColdU patients and patients with CSU, where chronic inflammatory changes such as increased mast cell numbers and neovascularization have been described.

The most important finding of our study is that cold-induced whealing in patients with typical ColdU is linked to markedly increased blood perfusion and PPG amplitudes. This demonstrates that whealing comes with distinct and detectable changes in skin microvasculature and PPG metrics that permit objective skin readings of provocation test responses. This finding may be relevant beyond ColdU, for example, for the assessment of skin responses to provocation testing in symptomatic dermographism and solar urticaria.

How can PPG-based measurements improve CTT readings in ColdU? Our findings suggest that PPG can precisely determine the edge of a cold-induced wheal, which is critical for assessing the CTTs of individual ColdU patients, i.e. the highest temperature that suffices to produce a wheal. TempTest^(r)-based CSTs in patients with typical ColdU produce linear wheals that start and end where the skin is exposed to 4degC and the CTT, respectively. PPG objectively identifies the end of a TempTest^(r)-induced wheal unlike how the CTT is currently determined, i.e. by inspection, which is subjective and subject to intraoperator and interoperator variability of measurements. Accurate PPG-based CTT measurements may, thus, benefit the monitoring of treatment responses in routine practice and clinical trials.

Our study has several limitations. These include the small sample size and the lack of diversity of patients in terms of age and skin type. Further studies are needed to confirm and extend our results.

Taken together, our findings suggest that photoplethysmographic assessments of ColdU CST responses appear to be accurate and can provide objective verification of positive and negative test results. Thus, PPG may assist in diagnosing ColdU, distinguishing typical and atypical ColdU, and making threshold testing more precise.

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Figure legends

Figure 1. Images of the skin of patients with typical ColdU and a positive response to cold stimulation testing with an ice cube (A) and TempTest[®] (B).

Figure 2. Experimental setup: scheme (A), appearance (B) and running state (C).

Figure 3. Data processing pipeline.

PPG, photoplethysmogram

Figure 4A. Change in skin perfusion at sites of cold exposure is significantly higher in patients with typical ColdU as compared to patients with atypical ColdU and HCs

PPG, photoplethysmogram, CTT, critical temperature threshold, Standard CST, standard cold stimulation test, ColdU, cold urticaria, TempTest[®], R_{PPG} , ratio of post-provocation and baseline PPG amplitudes

Vertical bars indicate CTT values for patients with a positive ICT and TempTest[®] (pink) and with negative standard CSTs (cyan). For participants with a negative TempTest[®], the bar height is shown as 1°C. Circles stand for the measured value R_{PPG} . R_{PPG} varies between typical ColdU patients and HCs. By introducing a proper R_{PPG} threshold of 3 (black line) we may clearly distinguish participants with (red circles) and without (blue circles) positive reactions to standard CSTs.

Figure 4B illustrates the similarities (green) and differences (black) between our PPG-based technique and CST with and an ICT or TempTest[®], in the same order.

Figure 5. ROC-curve of R_{PPG} and CST

FN , false negative, *FP* , false positive, *TN* , true negative, *TP*, true positive.

Table 1

	Total n=63	Typical ColdU n=39	Atypical ColdU n=24	p-value
Gender: Female	50 (79%)	31 (80%)	19 (79%)	0.976
Male	13 (21%)	8 (20%)	5 (21%)	
Age (years) (min-max)	42 (18-69)	42 (18-69)	42 (19-66)	0.804
CSU	8 (13%)	5 (13%)	3 (13%)	0.970
Comorbid CIndU:	18 (29%)	9 (23%)	9 (38%)	0.218
- symptomatic	12 (19%)	6 (15%)	6 (25%)	0.345
dermographism,				
- cholinergic	7 (11%)	5 (13%)	2 (8%)	0.582
urticaria				
- heat urticaria	1 (2%)	0	1 (4%)	0.199
- delayed pressure	4 (6%)	2 (5%)	2 (8%)	0.612
urticaria				
- vibratory	1 (2%)	0	1 (4%)	0.199
urticaria				
- solar urticaria	2 (3%)	0	2 (8%)	0.067
- contact urticaria	1 (2%)	1 (3%)	0	0.429
- aquagenic	0	0	0	-
urticaria				
- 2 types or more	13 (21%)	8 (21%)	5 (21%)	0.976
Angioedema	33 (52%)	22 (56%)	11 (46%)	0.414
Hypotensive	4 (6%)	1 (3%)	3 (13%)	0.116
episodes				
Allergic rhinitis	20 (32%)	10 (26%)	10 (42%)	0.185
Asthma	14 (22%)	8 (21%)	6 (25%)	0.677
Atopic dermatitis	2 (3%)	2 (5%)	0	0.423
Autoimmune	15 (24%)	10 (26%)	5 (21%)	0.663
disorders				
Oncology	2 (3%)	2 (5%)	0	0.260
Family history of	6 (10%)	3 (8%)	3 (13%)	0.528
ColdU				
H1-	50 (79%)	31 (79%)	19 (79%)	0.976
Antihistamines				
licensed doses				
H1-	9 (14%)	6 (15%)	3 (13%)	0.751
Antihistamines				
escalated doses				
Omalizumab	2 (3%)	2 (5%)	0	0.260
Duration of	60 (11-360)	24 (11-71)	212 (60-360)	<0.001
ColdU (months)				
UCT	11 (6-16)	10 (6-13)	13 (9-16)	0.028
DLQI	4 (0-10)	6 (2-10)	0 (0-4)	0.006

Table 1. Demographic and clinical features of patients with typical and atypical ColdU.

ColdU , cold urticaria, *CSU* , chronic spontaneous urticaria, *CIndU* , chronic inducible urticaria, *UCT* , Urticaria Control Test, *DLQI* , Dermatology Life Quality Index

Metric	Typical ColdU	Atypical ColdU and HCs	All study subjects
Sensitivity	0.974	-	0.875
Specificity	-	0.875	0.974
PPV	1.000	-	0.927
NPV	-	1.000	0.955
Accuracy	0.974	0.875	0.936

Table 2. Statistical metrics of R_{PPG} predictive capability

ColdU , cold urticaria, *HCs* , healthy controls, *NPV* , negative predictive *PPV* , positive predictive value, PPG amplitudes, *PPG* , photoplethysmography value, R_{PPG} , ratio of post-provocation and baseline

Supplemental material

Figure 1. Scatterplot of R_{PPG} and CTT.

ICT , ice cube test, *TT* , TempTest[®], *CTT* , critical temperature threshold

The correlation coefficient (CC) of R_{PPG} of ICT/TT-positive patients and the CTT is 0.12, at once the CC of R_{PPG} of all study objects and the CTT is 0.70, the CC of post CST PPG amplitudes for typical ColdU and CTTs is 0.15.

Figure 2. Typical PPGs before (A, C) and after ICT (B, D) for a healthy person (A, B) and a ColdU patient (C, D).

Figure illustrates PPGs in one of the ColdU patients with positive SPT and one of the HCs. The frequency of the pulses indicates the heartbeat. The pulse shape may be associated with the state of tissue and its pathologies. Before ICT, PPG amplitudes for ColdU and healthy volunteers have similar values but after cold exposure they grow in a different way. The relative increase of PPG amplitude is much higher for ColdU patients than for healthy ones. To quantify the effect of exposure to cold on microcirculation, we introduced the value R_{PPG} as a ratio of PPG amplitudes after and before the ICT.

ColdU, cold urticaria, ICT, ice cube test, *PPG* , photoplethysmography

Orcid

Sofia Serdotetskova <https://orcid.org/0000-0001-8472-1115>

Alexander Machikhin <https://orcid.org/0000-0002-2864-3214>

Daria Fomina <https://orcid.org/0000-0002-5083-6637>

Mikhail Volkov <https://orcid.org/0000-0002-9658-9467>

Anastasia Guryleva <https://orcid.org/0000-0003-2239-3725>

Mojca Bizjak <https://orcid.org/0000-0003-2595-468X>

Valeriya Bukova <https://orcid.org/0000-0001-9564-4308>

Marina Lebedkina <https://orcid.org/0000-0002-9545-4720>

Olga Mukhina <https://orcid.org/0000-0002-3794-4991>

Gerelma Andrenova <https://orcid.org/0000-0001-7053-3900>

Irina Mukatova <https://orcid.org/0000-0002-5804-8643>

Inna Danilycheva <https://orcid.org/0000-0002-8279-2173>

Marcus Maurer <https://orcid.org/0000-0002-4121-481X>

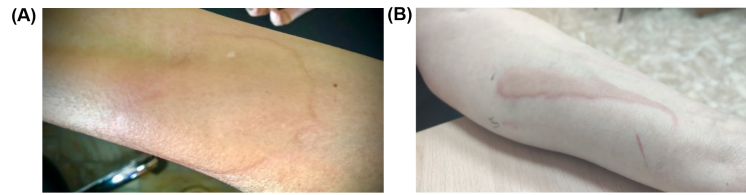


Figure 1_Serdotskova et al.

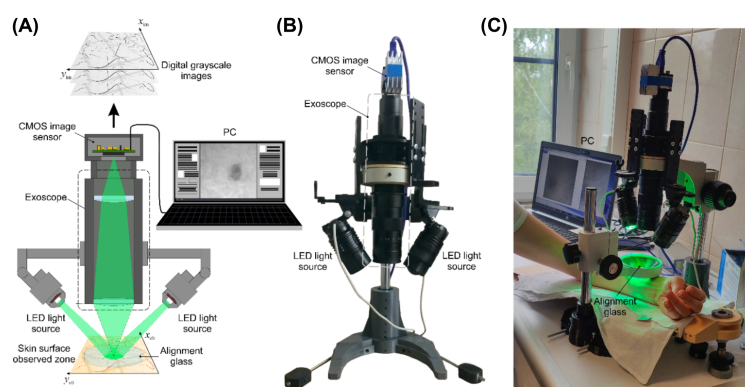


Figure 2_Serdotskova et al.

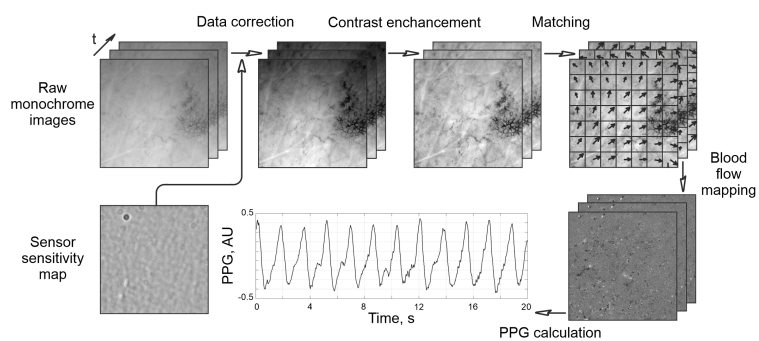


Figure 3_Serdotskova et al.

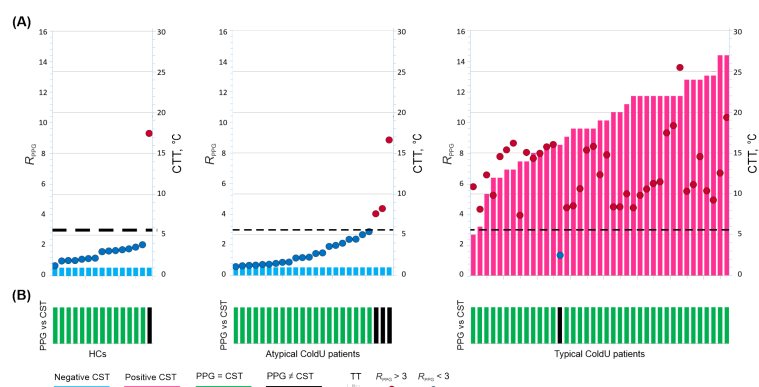


Figure 4_Serdotskova et al.

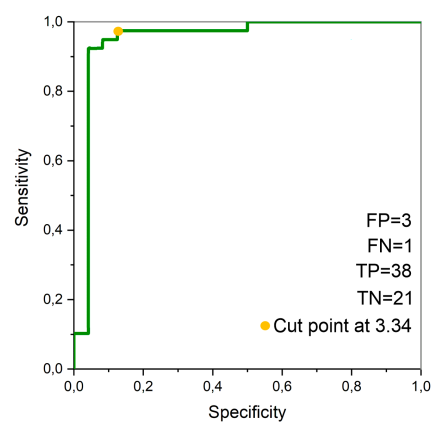
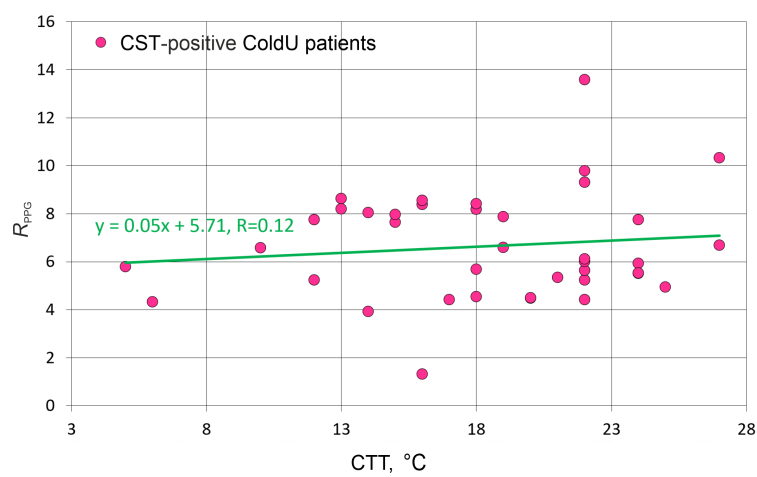
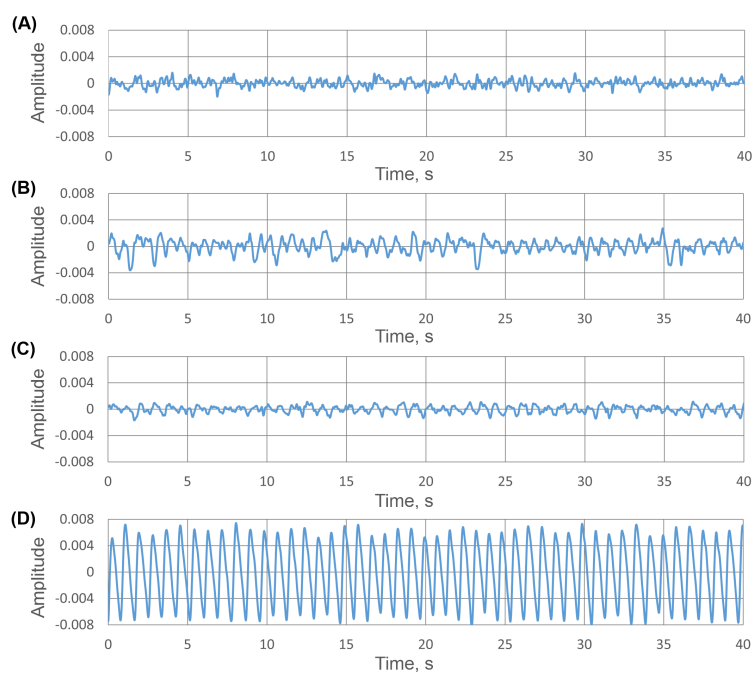


Figure 5_Serdotskova et al.



Supplemental material_Figure 1_Serdotskova et al.



Supplemental material_Figure 2_Serdotskova et al.