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Calorimetry in Allergy Diagnostic

Evgeni Stanev and Maria Dencheva

Abstract

Calorimetry is an indisputable diagnostic method. Over the years, there has been an improvement in the equipment and methods for measuring the calor that accompanies various processes. Using a thermal camera, we can measure the surface temperature of the skin at the beginning and the end of each skin allergy test. They are epicutaneous, cutaneous, and percutaneous. In case of a positive reaction, allergic inflammation is observed with the obligatory symptoms, one of which is warming (calor). Measuring and visualizing this warming is essential in the diagnosis of allergic reaction. The methodology of imaging the skin areas and processing the results is the key point in the objectivity of the study. Diagnostic skin allergy tests report mainly immunopathological reactions of the first and fourth types (Coombs and Gel classification). Their course is different and this necessitated the development of various thermovisiographic imaging methods. Through the results of our thermal imaging studies, we derived a scale, that determines the intensity of the allergic reaction, for each of the skin allergy tests. The use of thermovisiography in addition to the standard reporting of allergic skin reactions provides precision and more information about the subtle temperature changes that accompany allergic reactions.

Keywords: allergic inflammation, thermocamera, local anesthetics, allergens, haptens, prick test, patch test, intradermal test

1. Introduction

Diagnosis in allergology is based on anamnestic data, clinical and laboratory tests. Despite the development of *in vitro* tests, skin allergy tests are used as the gold standard in clinical practice. They aim to provoke a local allergic reaction in the study area. Allergic inflammation is characterized by the same five signs of inflammation—tumor, rubor, calor, dolor, and functio laesa. In standard clinical practice, the strength of the reaction is determined by the size of the erythema (rubor) and the size of the papule (tumor). With the help of modern thermal imaging cameras, it is possible to take into account another parameter of the inflammatory reaction—calor. The warming covers the area of skin that has been in contact with the allergen or the hapten.

Skin allergy tests are easy to perform, inexpensive, quick to read, and ideal for diagnosis even in patients with limited mobility, but standard reporting carries with it a degree of subjectivity.

Methodology and implementation of the test:

The test is usually performed on the volar side of the forearm skin according to the skin prick test—European standards. The skin is cleansed with an alcohol swab. The

places of application of the allergen—most often inhaled household, pollen allergens, insect and food allergens, some drugs, local and general anesthetics, iodine contrast agents, and vaccines—are marked with a skin marker. Against each marking is placed one drop of the substance. With a separate plastic lancet, the skin is pricked. Positive and negative controls are obligatory in this test. Conventional reading is after 20 minutes [1].

Method of performing an intradermal test:

In the intradermal test, a certain amount of the allergen is injected into the deeper skin layers. The reading is also 20 minutes [1].

The results of controlled skin sensitization in Prick and the intradermal test are reported by measuring in millimeters the diameters of the papule and erythema that form.

Methods of epicutaneous testing:

Testing with hypoallergenic patches, which are most often placed on the back. This is a test method for proving contact allergy/contact dermatitis, metal allergy, drug allergy, dental materials. The set of allergens for epicutaneous testing is applied separately in special chambers on the test patches, then glued to the back for a period of 48 hours.

It is reported to be a cell-mediated mechanism (Coombs and Gell type 4) of reaction on the 3rd and sometimes on the 7th day [2, 3].

The clinician needs to have accumulated practical knowledge and experience to be able to correctly report skin reactions. With the inclusion of thermal imaging analysis, this process is supported, and the image from the thermal imager can be objectively analyzed. The method is rapid, non-invasive, and may accompany standard reporting of allergic skin reactions [4].

The thermal imaging image provides information about the size of the inflamed area and its temperature. There are different types of thermal cameras, but FLIR T620 can be used for clinical practice. The analysis is performed using specialized software, as well as comparisons between the reaction to the allergen and reactions to the positive control, negative control, or intact skin area.

After performing the test and standard reading, a thermal camera is taken of the skin areas of interest. The thermal imaging methodology developed by us is different for each of the three skin allergy tests. The image is analyzed by extracting certain (basic) temperature parameters for each zone. Based on them, the additional parameters are calculated, which determine whether the reaction is positive and what is its intensity, which in turn supports the standard reading and minimizes the possibility of misinterpretation of the result.

In this chapter, we will present each of the three allergy tests in turn. Approaches to temperature analysis will be proposed for each test, which will allow quantitative measurement of the calor due to allergic inflammation. The conclusion will summarize the limit values of the indicators and their clinical significance in the reporting of tests.

2. Thermal imaging analysis of allergic skin reactions in prick test

In the Prick test, two thermal imaging images are taken—one before it is performed and one after it. It is necessary to observe the conditions for thermovisionographic imaging [5]. In standard reading, clinicians touch the skin to sense the

presence and size of the papule. It is necessary to do this after the second scan, so as not to affect the temperature of the examined skin area. Temperature analysis requires measuring the change in each area of the skin. To achieve this, the hand needs to be positioned in the same way in both shots. The stand created by us (**Figure 1**) allows the patient's arm to be placed comfortably, and the curved shape of the two beds for the forearm to stabilize it in a certain position, regardless of its anatomical features. In addition to support elements, the stand includes a plastic template with five holes. The pattern fixation system above the volar surface of the forearm allows the arm to be removed and then repositioned, leaving the pattern position unchanged. The examined five skin areas can be marked with a skin marker after applying the template. The distance between the edges of each hole is 10 mm, enough to prevent the mixing of skin reactions between two adjacent tests (**Figure 2**).

The strongest skin reaction observed after the Prick test is to the positive control. Its size varies between 10 and 30 mm [6]. The diameter of the holes in the template is 20 mm, which may not, in some cases, cover the full size of the reaction to a histamine solution. However, this size is large enough for the temperature reactions of the negative control and the tested allergens.

Figure 1.
Stand for fixing the patient's forearm during the prick test.

Figure 2.
Placing the patient's hand and outlining three skin areas (depending on the number of tested allergens) in which the prick test will be performed.

2.1 Analysis of the temperature of the skin areas BEFORE performing a prick test

Before conducting the test, the places where it will be performed are determined. The initial temperature of the skin areas on which the reactions will be observed should be uniform, without large amplitudes. These are observed in cases of superficially located large blood vessels (v. Cephalica; v. Basilica; v. Mediana anterbrachii). For this reason, it is necessary to initially capture the skin areas and reposition the arm (Figure 3). Most studies do not analyze the initial skin temperature, although it is the starting point for the temperature change [6–8]. There were no statistically significant differences in skin temperatures prior to the test when subcutaneous main blood vessels were avoided [9]. If the blood vessel passes through the examined area, it will not allow significant changes in temperature to be reported, regardless of the severity of the allergic inflammation. On the other hand, there is a risk of injury to the blood vessel and compromise of the allergy test [10].

The Prick test is most commonly used to test for sensitization to local anesthetics, foods, and medications. Before the test, two or three anesthetics are selected to be checked for sensitization.

The initial survey gives us information about the following main temperature parameters (Figure 4). With the help of specialized software, the skin areas of interest are outlined, and then a table with the temperatures of each of them is displayed.

X_1 – the average temperature of the skin area in which the test allergen will be located before the test.

Neg_1 – the average temperature of the skin area in which the negative control before the test will be located

Pos_1 – the average temperature of the skin area in which the positive control will be located before the test

2.2 Analysis of the temperature of the skin areas AFTER performing a prick test

After shooting, the test is performed in the standard way [10]. Before proceeding to the standard reading, the hand is carefully placed on the stand and the template is positioned so that the openings coincide with the marked skin areas. The second thermal imaging is done.

Figure 3.
Location of subcutaneous main blood vessels.

Figure 4.
First temperature imaging and determination of the temperature in the skin areas where the prick test will be performed.

X_2 – the average temperature of the skin area where the test allergen will be located after the test.

Neg_2 – the average temperature of the skin area in which the negative control will be located after the test

Pos_2 – the average temperature of the skin area in which the positive control will be located after the test (**Figure 5**).

There are different methods for analyzing the data obtained. Some authors believe that the information obtained from the second image is sufficient to determine whether a reaction is positive or negative [11]. The parameter to be analyzed is only the value of X_2 . The disadvantage of this type of analysis is that they do not include

Figure 5.
Second temperature imaging and determination of the temperature in the skin areas in which the prick test was performed.

the initial skin temperature, which is individual for each patient and may affect the final assessment. The results also show large variations in different patients, so conclusions based on this indicator alone may be wrong.

Another variant found in the literature is to study the change in temperature that has occurred in the skin area of the respective allergen (Eq. (1)) [6, 11, 12].

$$\Delta X = X_2 - X_1 \quad (1)$$

When performing the test on the patient's back, an increase in the temperature of the positive reactions is reported, which reaches 2.9 degrees in the strongest reactions and is 1 degree in the other positive reactions. In our study on the volar surface of the hand, a slight rise in temperature was observed during the positive control, and in women, in some cases, even a slight cooling of the site was found. The reason for this difference is the place where the test was performed. The forearm during the test is located at a distance from the body and the temperature of her skin drops. The cooling in the negative reactions is significantly greater than the cooling that occurred in the positive control because they do not show inflammation to compensate for it. When the test is performed on the back, where the possibilities of temperature homeostasis of the body do not allow such a strong cooling within 15 minutes, a rise in temperature is observed even in negative controls [11].

The cooling of the negative reactions is more pronounced in women than in men. While in the field of positive reactions, the differences between the sexes are minimal [13].

The temperature change of the skin in the area of positive control increases in 94% of patients [14]. In such studies, this percentage reached 98% [13].

The temperature rise is significant from 1.5 to 4.00 degrees in some of the studies [6]. While in others the temperature rise in positive reactions is significantly lower: 0.9 ± 0.48 degrees [13]. The difference in results is due to the type of allergens used (local anesthetic—Mepivastesin and pollen allergens) and the intensity of the positive reactions.

Allergic inflammation in the negative reactions is absent, so the researchers did not report a change in temperature in them [8, 11, 12].

The change in temperature in most cases is indicative of the presence and strength of a positive reaction to the tested allergen. The analysis should be done according to the patient's gender, that is, variations between men and women are found.

To determine the change in temperature, which is due solely to allergic inflammation, it is necessary to take into account the drop in skin temperature during the test. It varies from patient to patient and depends on individual characteristics, such as subcutaneous tissue, blood supply, and thermal homeostasis. By changing the temperature in the area of the negative control, the cooling of the skin during the test can be monitored Eq. (2):

$$\Delta Neg = Neg_2 - Neg_1 \quad (2)$$

The difference between the value of ΔX and ΔNeg is the warming due to allergic inflammation, excluding all other factors influencing the skin temperature. Eq. (3)

$$\Delta Xa = \Delta X - \Delta Neg \quad (3)$$

The indicator ΔX has values below 0.5C for negative allergic reactions and over 0.5 for positive ones. The stronger the allergic inflammation, the higher its value. When the value is below 0.5 allergic inflammation has no clinical value. It can be considered null and void and explained by the difference in the location of the skin areas in

which the test was performed. This indicator does not depend on the sex of the patient and allows a comparison of the intensity of allergic reactions between men and women [13].

Of interest are patients with sensitive skin who have dermographism. This is a condition in which the skin reacts by inflammation to nonspecific irritants. Mechanical trauma during the test elicits a response that may be incorrectly reported as allergic [15]. This condition is the reason to include positive and negative controls in the Prick test. In patients with dermographism, measurements of papules and erythema are reported and compared with those of the negative control. **Figure 6** shows three reactions—to anesthetic, to negative control, and to positive control (closest to the patient’s tattoo).

All three reactions have papule sizes over 3 mm, which makes it difficult to read the standard. Thermovisiographic analysis also allows to check the temperature changes in the skin areas during the test. Four skin areas are examined (**Figures 7 and 8**):

Figure 6.
Reactions after prick test of a patient with dermographism.

Figure 7.
First shot before prick test of a patient with dermographism.

Figure 8.
Second imaging after prick test of a patient with dermatographism.

Ar1 – intact skin area in the area of which there is no legal test.

Ar2 – examination of a local anesthetic (mepivacaine).

Ar3 – negative control.

Ar4 – positive control.

After analyzing the main indicators, the additional ones can be calculated by Eqs. (1)–(3):

$$\Delta X = X_2 - X_1 = 33.7 - 34.5 = -0.8.$$

$$\Delta Neg = Neg_2 - Neg_1 = 34.2 - 35.1 = -0.9.$$

$$\Delta Xa = \Delta X - \Delta Neg = -0.8 - (-0.9) = 0.1.$$

The results show that there is no evidence of allergy to the studied local anesthetic. If we make similar calculations for the positive control, we will get a value of $\Delta Xa = 1.4$.

$$\Delta Xa = (Pos_2 - Pos_1) - \Delta Neg = (35.8 - 35.3) - (-0.9) = 1.4.$$

The calculations show that the reactions of dermatographism are subject to thermal imaging analysis. This is a major advantage over standard reporting in the presence of dermatographism. More studies of this type of patient are needed.

The analysis of the results obtained from the thermal imaging provides information about the temperature changes in the skin at the places where the test was performed. By considering various parameters, a better understanding of the inflammation at the sites of allergens and controls is achieved. The calculation of additional parameters based on the results of both controls helps to unify the process and to create limit values that do not depend on the sex of the patient and the individual characteristics of his/her skin.

3. Thermal imaging analysis of skin-allergic reactions in intradermal tests

The test has many similarities with the Prick test—it is performed on the patient's forearm, areas with superficial blood vessels are avoided. The hand is placed on a

stable base. The allergen is administered intradermally using a syringe and needle. The amount is about 0.02 ml. A papule of about 2–3 mm forms on the skin above the tip of the needle. In addition to the tested allergens, the test is performed with negative and positive control. In this test, it is necessary to avoid areas with superficial main blood vessels. Unlike the Prick test, here the number of allergens is usually significantly higher. Thermal imaging is done after the test. Due to the large number of tests located close to each other, the use of the Prick test stand is not appropriate. On this trichina, fine metal indicators are placed on the hand, which are clearly visible on the thermal image and indicate the place where the test was performed (Figure 9).

The thermal imaging image is similar to that of the Prick test, but due to the lack of an armrest with outlined areas, their size and location are determined subjectively depending on the course of the isotherms (Figure 10).

Analysis of the temperature of the skin areas AFTER performing an intradermal test.
The survey provides information on the main temperature parameters:
Z – the average temperature of the skin area in which the test allergen is located.
Neg – the average temperature of the skin area in which the negative control is located
Pos – the average temperature of the skin area in which the positive control is located (Figure 11)

As in the Prick test, the analysis here can be based on the absolute temperature value of the reactions [16]. Another approach is to find the difference between the

Figure 9.
Intradermal allergy test.

Figure 10.
Thermal imaging image after the intradermal test. Green arrows indicate positive reactions and blue arrows indicate negative reactions.

Figure 11.
Outline the zones of reactions on the thermal image.

reaction temperature and that of the negative control. The value of allergic inflammation is measured as in the Prick test, but the control area is replaced with the area of negative control (Eq. (4)).

$$\Delta Z = Z - Neg \tag{4}$$

At values of ΔZ above 0.6 degrees, the reactions can be considered positive and below 0.6 degrees - negative [13]. A similar comparison can be made with respect to the positive control (Eq. (5))

$$\Delta Z = Z - Pos \tag{5}$$

With the values of ΔZ above -1.0 degrees, the reactions can be considered positive and below -1 degree - negative [13].

In intradermal tests, needle pricking results in severe mechanical trauma that causes nonallergic inflammation at the puncture site. For this reason, comparing the changes in temperature in each of the skin areas is not as informative as in the Prick test. Also, the comparison of the temperature of the reactions with those of the negative and positive control gives sufficient information not only about whether the reaction is positive but also what is its intensity. With the help of both controls, the reactivity of the skin can be determined in the absence of allergic inflammation and in case of a strong skin-allergic reaction. The stronger positive reactions show closer temperature values to those of the positive control, while the weaker ones approach more to the negative control.

4. Thermal imaging analysis of skin-allergic reactions after patch test

In this type of test, the allergens are placed on a hypoallergenic sticker with chambers, which is glued to the patient’s back and remains there for 48 hours. The

long period of time presupposes a different approach in the thermal imaging analysis—a photograph is taken of the patient’s skin after the patch has been removed and the irritating reaction has passed since its removal. The problem is that the test is done on a large area of skin with underlying muscle groups, tendons, and vertebrae. Like the volar surface of the forearm, the temperature is different in different areas. This makes the use of negative control (empty chamber without hapten in it) unsuitable for temperature analysis, due to the large distance at which it is located relative to allergens. For example, if the empty chamber is located near the spine, the skin temperature in that area will always be lower than the temperature in an area above a muscle, regardless of the presence of an allergic reaction. On the other hand, unlike the Prick test, here the reactions are limited only to the size of the area with which the allergen has been in contact and do not affect **the surrounding skin areas** [17, 18]. Therefore, the correct approach is to compare the temperature of each reaction with the temperature of a nearby skin area that has not been in contact with the allergen.

A template is placed to identify the skin areas that have been in contact with the bittens. With its help, the location of each reaction can be clearly determined, both in standard and thermal imaging (Figure 12).

The size of the templates may vary depending on the number of haptens tested (Figure 13).

Figure 12.
Thermal imaging of a patient’s back after a patch test with a template for thermovisiographic reading. The skin areas of the four allergens and the lateral area used for the control area are marked with arrows.

Figure 13.
Investigated reactions and their respective control areas.

Figure 14.
Different positive reactions (standard and thermal imaging). 1 - slightly (weak) positive; 2 - strongly positive; 3 - extremely positive.

The standard reading divides the established reactions into several groups—negative, doubtful, weakly positive, strongly positive, and extremely positive (**Figure 14**).

In both the Prick test and the Patch test, different approaches can be used to analyze reactions. Some studies have involved measuring the absolute skin temperature of reactions without comparing control sites. When comparing the average values of the reactions, the negative ones have an average temperature of 34.7°C; weakly positive - 35.1°C, and strongly positive - 35.7°C. At the maximum temperatures, the values are—for the negative reactions - 35.0°C; in the weakly positive - 35.5°C, in the **strongly positive** - 36.0°C [18]. Despite the seemingly large differences in the values of the different reactions in practice, it is established that the same allergic inflammations can be manifested with different skin temperatures [19]. The main reason for this is the temperature differences on the surface of the skin on the patient's back. Often there are many nonallergic inflammations on the skin, which can be mistaken for positive and even very positive reactions (**Figure 15**).

Figure 15.
Thermal imaging of the back without skin inflammations and thermovision imaging of the back with nonallergic skin inflammations on which a patch test was performed.

Figure 16.
Extremely strong positive reaction with vesicles in three of the studied haptens.

Another approach is to analyze the difference between the skin temperature at the reaction and that of the corresponding control area. To determine the temperature, which is due solely to allergic inflammation ΔY , we subtract the temperature of the control area $Y_{control}$ from the temperature in the skin area that was in contact with the hapten $Y_{reaction}$ (Eq. (6)).

$$\Delta Y = Y_{reaction} - Y_{control} \quad (6)$$

The indicator ΔY with values above 1.6 is considered extremely positive. Values between 0.9 and 1.6 are characteristic of strongly positive reactions. It is difficult to distinguish the weakly positive reactions from the suspicious and negative reactions because in all three ΔY , it is below 0.9 degrees. The role of calorimetry in the Patch test is to strongly distinguish between highly positive and extremely positive reactions and to confirm the results of the standard reading.

Of particular interest are the extremely positive reactions in which vesicles form in the center of the skin reaction. They can be easily recognized by the thermal image—there is an area with a temperature higher than the surrounding above 1.6 degrees and in its center a few points with a significantly lower temperature corresponding to the vesicles. The bubbles that form are filled with serous fluid, which cools much more easily than the skin and therefore its temperature is much lower (**Figure 16**).

There is no difference in the thermal imaging test in the Patch test for early and late reading. The analysis may include both mean and maximal skin temperature. Of great importance is the choice of control site for each of the reactions. This should be an area close to the reaction area, but not exposed to a hapten. In patients with irritated skin on the back, an area where there is less inflammation should be chosen. This supports both standard and thermal imaging of the results.

5. Conclusion

The measurement of the temperature of the skin areas in allergic tests gives objective data on the inflammation and its intensity. Each test examines different

Figure 17.
Temperature indicators used in the various allergy tests and their limit values.

indicators, the value of which complements the results of standard reporting and assists clinicians in their practice (**Figure 17**).

In the Prick test, reactions with a value of $\Delta X\alpha$ below 0.5 are negative, while in higher values, they should be considered positive.

In intradermal tests, reactions with ΔZ (negative control) below 0.6 were negative, while at higher values, they were positive.

In intradermal tests, reactions with ΔZ (positive control) below -1.0 were negative, while at higher values, they were positive.

In Patch test, reactions with ΔY below 0.9 are negative or weakly positive; over 0.9 - strongly positive; over 1.6 - extremely positive.

The studies presented in this article have a high clinical value and provide a more complete understanding of the results of allergy tests. The high correlation between the clinical results and the thermal imaging examination (over 95% correlation) are the grounds for applying the method in parallel with the other diagnostic methods in allergology.

Conflict of interest

The authors declare no conflict of interest.

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