

# Application of thermography for the assessment of allergen-induced skin reactions

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**Purpose:** The allergic response is commonly identified and assessed by skin testing. The usual method to quantify skin reactions is to mark wheal and erythema regions and assess the surfaces affected by the reactions; however, subjective interpretation of the outcome may cause errors. Skin thermography supplemented by a mathematical model based on the pathophysiology of heat generation was evaluated as a novel, objective, and sensitive indicator of the skin prick test result.

**Methods:** TH measurements were performed simultaneously with routine skin prick tests for 24 patients. Eight allergens and control (histamine) were examined. Thermographic images of both forearms were acquired every 70 s from 0 to 910 s after skin prick and analyzed with the use of dedicated software. The introduction of potential allergens and histamine at sites on the skin induces a complex sequence of events known as the local inflammatory response. The crucial steps of the process have been considered in the model. In the model, the authors assumed that the reaction takes place in the thin skin layer and that histamine is the principal mediator of the allergic reaction. Histamine penetrates the skin and binds to receptors of nearby capillaries and venules. The engorged vessels are, in turn, responsible for skin redness and an increase in skin temperature.

**Results:** The model parameters were determined by fitting the analytical solutions to the spatiotemporal distributions of the differences between measured and baseline temperatures. The model reproduces experimental data very well. The coefficient of determination ranged from 0.805 to 0.995. Seven model parameters were tested to find the optimal marker of the intensity and kinetics of the allergic reaction. The parameter which quantifies a release of histamine after allergen injection has appeared to be the best indicator of the allergen-induced response. The parameter correlates with the routine assessment based on wheal and erythema areas (correlation coefficient=0.98).

**Conclusions:** It was demonstrated that the thermographic measurements supplemented by the mathematical model offer a new approach to the quantification of allergen-induced skin reactions. Despite the applied simplifications, the proposed model reflected properly the mechanism of heat generation during skin prick test. Moreover, the continuous recording of the skin temperature represents an additional possibility to investigate the mechanism of the allergic reaction. © 2011 American Association of Physicists in Medicine. [DOI: [10.1118/1.3533940](https://doi.org/10.1118/1.3533940)]

Key words: thermography, allergy, skin prick test, mathematical model

## I. INTRODUCTION

Allergic response is commonly identified and assessed by skin tests.<sup>1-3</sup> Small amounts of potential allergens and histamine (control) are introduced at the specific skin sites by superficial scratching. The usual method to quantify immediate allergic skin reactions is to mark wheal and erythema regions and assess the surfaces affected by the reactions using planimetry. Frequently, the results of skin tests are related to the size of the histamine control and are reported in a 0–5 scale.

The advent of new imaging technologies offers possibilities to quantify allergic reactions using a variety of the imaging modalities, the thermographic (TH) camera being an example. It should be noted that the application of infrared (IR) imaging starts in the breast cancer diagnosis about 50

years ago.<sup>4</sup> Nowadays, TH imaging is a well established method for health monitoring and examinations, as well as for assisting diagnosis.<sup>5-13</sup> Among other things, it is now possible to evaluate allergic skin reactions using TH cameras. The current use of IR imaging in the allergic skin response is, however, a direct extension of the routine planimetry.<sup>14,15</sup> The TH camera is used to quantify the area of the elevated temperature region or the intensity of the reaction is expressed in so called thermographic units (area times average rise in temperature).

In the presented studies, the TH measurements of the skin allergic reactions are supplemented by a mathematical model based on the pathophysiology of heat generation. A set of new parameters are proposed to quantify the intensity and kinetics of the allergic skin responses. The main objective of

this work is to describe and analyze a possible usefulness of TH measurement supplemented by the model for the skin prick test assessment.

## II. MATERIALS AND METHODS

### II.A. Physical model of the allergic reaction

Here we are concerned in the development of a model to quantify the allergic skin reaction. The introduction of histamine and potential allergens (antigens) at sites on the skin induces a complex sequence of events known as the local inflammatory response.<sup>16,17</sup> If a person is allergic, local mast cells degranulate and release histamine. We assume that the reaction takes place in the thin skin layer and that histamine is the principal mediator of the allergic reaction. The involvement of other mediators in the process is neglected. Histamine penetrates the skin and binds to receptors of nearby capillaries and venules, causing vasodilation (increase in the diameter of the blood vessel). The engorged vessels are, in turn, responsible for skin redness and an increase in skin temperature. The novel feature of the model studied here is the quantitative description of the skin temperature distribution. It should also be noted that immediate reactions with allergens and histamine are taken into consideration. The late-phase reactions are omitted. The assumption is validated by the examination time, never longer than 1000 s.

Due to the pivot role in the process, the administration of histamine is considered separately in the model. Suppose histamine is introduced by superficial scratching at the origin. A given amount of histamine is released and it is transported across the skin. The histamine transport is treated as a complex process (hereby called migration), which is probably mostly influenced by the blood perfusion within skin. As histamine migrates, we assume it is additionally eliminated via first-order kinetics. The equation governing the histamine concentration  $c_H(r, t)$  is as follows:

$$\frac{\partial c_H}{\partial t} = -v \frac{\partial c_H}{\partial r} - \gamma c_H, \quad (1)$$

where  $v$  is the histamine migration rate and  $\gamma$  is the elimination rate constant. The solution with a boundary condition  $c_H(0, 0) = c_{OH}$ , representing a local introduction of histamine, is given by

$$c_H(r, t) = c_{OH} \delta\left(t - \frac{r}{v}\right) \exp\left(-\gamma \frac{r}{v}\right), \quad (2)$$

where  $\delta$  is a Dirac delta function.

As histamine is moving across the skin, the vessel system reacts in response to the local histamine level. It should be pointed out that the mechanism(s) underlying histamine-induced vascular reaction(s) is unclear and its relevance to the allergic reaction should be elucidated.<sup>16</sup> Several physiologically plausible mechanisms might be postulated. We assume that due to histamine-induced vasodilation, a supplementary heat source ( $Q_H$ ) is activated. The governing equation for the  $Q_H$ - $c_H$  relationship is

$$Q_H(r) = Q_0 c_H\left(r, \frac{r}{v}\right) = Q_0 c_{OH} \exp\left(-\gamma \frac{r}{v}\right), \quad (3)$$

where  $Q_0$  is the positive constant. Intuitively, we can see how mechanism (3) generates a skin temperature distribution. The histamine “wave” propagates with the velocity of  $v$  and exhibits a biochemical switch behavior. At point  $r$ , a supplementary heat source appears after time  $t = r/v$ . The increase of heating is constant in time and is linearly related to the maximal histamine concentration at point  $r$ . Initial delta function is, however, attenuated exponentially. Of course, there is a threshold histamine concentration ( $c_{TH}$ ) to produce the heating effect. If over the region of the skin  $c_H \geq c_{TH}$ , then a domain of permanently nonzero values of heating is generated. We can calculate the maximal radius of the histamine-activated region given the threshold concentration  $c_{TH}$ . We want the maximum value of  $r$  (denote by  $Z$ ), such that  $c_H = c_{TH}$ . From Eq. (2) with  $c_H = c_{TH}$  and  $t = r/v$ , we have

$$Z = \frac{v}{\gamma} \ln\left(\frac{c_{OH}}{c_{TH}}\right). \quad (4)$$

It should be noted that the radius of the region of the elevated temperature increases linearly with time until the value given by Eq. (4) is reached.

The temperature distribution of the skin is given by the solution of Pennes bioheat equation.<sup>18</sup> In the model, we made an additional approximation that the thermal diffusivity in the skin may be neglected. Further justification for this approximation comes from the calculation of the Biot's number<sup>19</sup> and from the numerical simulations of heat transport in the skin. Defining a new variable,

$$\Delta T_H(r, t) = T_H(r, t) - T_{s0}, \quad (5)$$

where  $T_{s0}$  is the skin temperature before examination and  $T_H(r, t)$  denotes the temperature after histamine injection; taking the metabolic heat generation rate as equal to 0, it is possible to rewrite the bioheat equation as

$$\frac{d(\Delta T_H)}{dt} + \tau \Delta T_H = S_H(r) \quad (6)$$

with initial condition  $\Delta T_H(r, 0) = 0$  and parameters

$$\tau = \frac{1}{\rho_s c_{shs}} (\omega \rho_b c_{shb} + \alpha), \quad (7)$$

$$\begin{aligned} S_H(r) &= \frac{1}{\rho_s c_{shs}} (\omega \rho_b c_{shb} (T_b - T_a) - \alpha (T_{s0} - T_a) + Q_H(r)) \\ &= S_0 + \frac{Q_H(r)}{\rho_s c_{shs}} \\ &= S_0 + \frac{Q_0 c_{OH}}{\rho_s c_{shs}} \exp\left(-\gamma \frac{r}{v}\right) = S_0 + Q_{0H} \exp\left(-\gamma \frac{r}{v}\right), \end{aligned} \quad (8)$$

where  $\rho_s$  is the density of the skin,  $c_{shs}$  is the specific heat of the skin,  $\omega$  is the blood perfusion,  $\rho_b$  is the density of blood,  $c_{shb}$  is the specific heat of blood,  $\alpha$  is the heat transfer coef-

ficient,  $T_b$  is the blood temperature (assumed to be constant),  $T_a$  is the ambient temperature (assumed to be constant) and  $Q_H$  is the heat generation rate due to histamine action [Eq. (3)]. The solution of Eq. (6) is

$$\Delta T_H(r, t) = \frac{S_H(r)}{\tau} (1 - e^{-\tau t}). \quad (9)$$

In the modeling of the allergen action immunoglobulin E (IgE), mediated hypersensitivity is assumed.<sup>16</sup> A sensitization to an allergen was done some time ago. As a result, IgE antibodies occupy IgE receptors on skin mast cells, where they are ready to react promptly to the next encounter with an allergen. A subsequent exposure to the allergen leads to cross-linking of the bound IgE molecules. The linking process activates the mast cell and the cell releases histamine directly generating allergic symptoms.

The problem arises how to treat the allergen transport in the skin. The description is based on the observation that most allergens are proteins or protein-bound substances having a molecular weight between 15 000 and 40 000.<sup>16</sup> This allows us to consider an assumption that the allergen migration can be ignored, while histamine migration is viewed as fast. In this approximation, allergen molecules are injected to the skin but they do not move comparing to histamine motion.

The overall mechanism of an allergen conversion, via a mast cell, into histamine consists of two steps. The first step relies on the activation of mast cells. The activation means that an allergen cross-links two receptors with bound IgE on the surface of a mast cell. Assuming that the activation of the mast cells is a very fast process, it follows that the total number of the activated mast cells  $M_0 \approx \text{constant}$ .

The second step of the histamine production relies on the degranulation of the activated mast cells. The rate of degranulation of a mast cell is also treated in the model as a fast process (degranulation rate  $\gg 1$ ). Finally, the concentration of histamine ( $c_{0A}$ ) at the origin after allergen injection is described by

$$c_{0A} = M_0 H_{0A}, \quad (10)$$

where  $H_{0A}$  is the amount of histamine accumulated in one mast cell.

Under the above described assumptions, the temperature distribution after allergen injection is given by Eq. (6) with the new value ( $S_A$ ) of the  $S_H$  constant (8)

$$S_A(r) = S_0 + \frac{Q_0 c_{0A}}{\rho_s c_{shs}} \exp\left(-\gamma \frac{r}{v}\right) = S_0 + Q_{0A} \exp\left(-\gamma \frac{r}{v}\right). \quad (11)$$

The solution of Eq. (6) with  $S_H = S_A$  and  $\Delta T_H = \Delta T_A = T_A - T_{s0}$  ( $T_A$  is the skin temperature after allergen injection) is

$$\Delta T_A(r, t) = \frac{S_A(r)}{\tau} (1 - e^{-\tau t}), \quad (12)$$

with the value of  $\tau$  given by Eq. (7). The histamine production after the allergen injection, i.e., the allergic response, may be quantified by the  $c_{0A}$  value or the  $Q_{0A}/Q_{0H}$

$= c_{0A}/c_{0H}$  ratio. In case of the  $S_A(r)$  value or the  $S_A(r)/S_H(r)$  ratio, the  $r$  value has to be specified.

## II.B. Measurements and data analysis

Twenty-four patients were subjected to the skin prick tests. The age of patients ranged from 20 to 58 yr. The study has been approved by the ethics committee of the Jagiellonian University Medical College. All subjects gave informed consent before participation in the studies. Commonly accepted procedure was applied before examinations (antihistamines or tricyclic antidepressants were not allowed for 7 days and long-term corticosteroids and astemizoles were prohibited for 3 months). The TH measurements were performed in a room controlled at 295 K. Patients were allowed to adapt to room temperature (testing area of forearms was disclosed) for 30 min. Next, the arms were placed on the special constructed table and fixed. A TH camera (VIGO, Warsaw, Poland) was placed  $\sim 30$  cm above the forearms. To perform the spatial calibration of thermal images, six light emitting diodes were mounted in the table. It should be noted that the pixel size depends on the distance between the TH camera and the skin surface. In the study, the pixel size ranged from 0.56 to 0.71 mm. The TH camera was calibrated to register temperatures in the range of 288–321 K.

The studies were performed using the commercial allergen panel (Allergopharma, Reinbek, Germany). Eight inhalant allergens were tested: Dermatophagoides pteronyssinus, Dermatophagoides farinae, mixed grasses, cat hair, mixed trees, mixed weeds, mildews, and feathers. A drop of the allergen was placed onto a marked area of the skin. Using a sterile lancet, a small prick through the drop was vertically made. Additionally, two controls were applied in the tests. The positive control was the solution (9 mg NaCl, 4 mg phenol, 563 mg glycerin, and injection water up to 3 ml volume) of 1.7 mg hydrochloride of histamine. A drop of the solution without histamine was used as the negative control to estimate the patient response to a prick.

The distributions of temperature of both forearms were acquired every 70 s from 0 to 910 s after skin pricks. The imaging frequency (one image every 70 s) was selected to collect minimal data points necessary for proper determination of the parameter values. It should be noted that an increase of the capture frequency, even one order of magnitude, does not change markedly the coefficient of determination ( $< 5\%$ ). Thermograms were evaluated using the software developed in our laboratory. The first step of calculations relies on the determination of the  $\Delta T_H$  or  $\Delta T_A$  distributions. For this purpose, subtraction of the images, according to Eq. (5), was performed. In some cases, a correction for the forearm movement had to be made. For the correction of the forearm movement, it was assumed that the positions of the maximum temperature points are fixed in space. Therefore, the correction is not influenced by the capture frequency. The error of  $\Delta T$  was determined experimentally using a homogeneously heated surface<sup>20</sup> and equaled to 0.3 K. Next, the heated region (HR) of the skin, correlated with particular allergen or histamine, was approximated by a

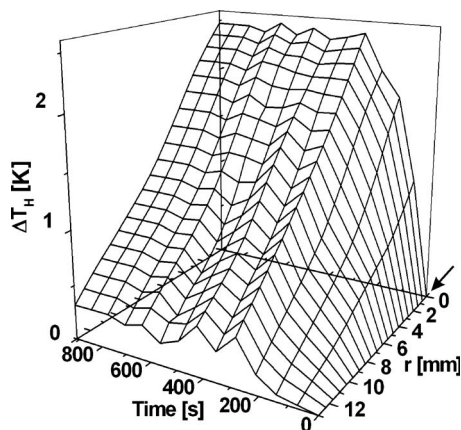


FIG. 1. The increase of skin temperature ( $\Delta T_H$ ) after histamine injection versus time and radius ( $r$ ) of the heated region. Histamine was injected at point marked by the arrow.

circle and the radius of the circle was determined. The error of the radius was estimated as the TH image pixel size.

The  $\Delta T_H(r, t)$  distribution was used to determine the model parameters describing the increase of the skin temperature after histamine injection. Assuming  $\Delta T_H = 0.90$  K (3 times  $\Delta T$  error), the radius of the HR as a function of time was extracted and  $Z$  as well as  $v$  values were calculated by fitting of the linear functions. Parameters  $\tau$ ,  $\gamma$ ,  $S_0$ , and  $Q_{0H}$  were obtained by fitting Eq. (9) to the experimental data. The parameters characterizing the temperature distribution after allergen injection were determined by fitting Eq. (12) to the  $\Delta T_A(r, t)$  data. It should be pointed out that for each patient, the values of  $v$ ,  $\tau$ ,  $\gamma$ , and  $S_0$  were extracted from analysis of the histamine data. Therefore, the evaluation of the allergen data relied on the determination of the  $Q_{0A}$  value Eq. (11).

For comparative purposes, the routine method was used to assess allergic reactions. The method relied on the evaluation of weal and erythema areas 10 min after the allergen injection. Next, the areas were related to the dimension of the histamine control and were expressed in a 0–5 scale.

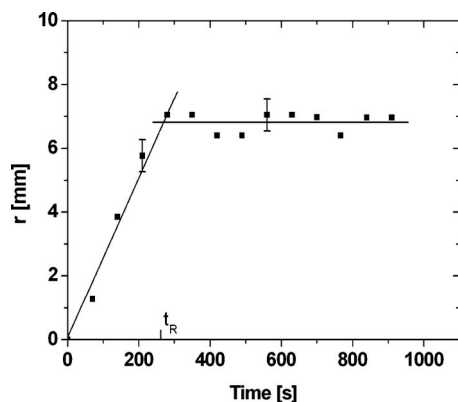


FIG. 2. The radius of the heated region ( $r$ ) versus time after histamine injection. An example of data collected for one patient is presented. The solid lines have been fitted to the experimental points using the linear functions. Error of the radius equals to the pixel size.

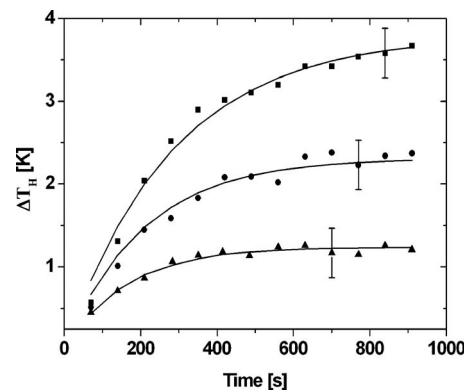


FIG. 3. The increase of skin temperature after histamine injection ( $\Delta T_H$ ) versus time for three patients. The distance from the histamine injection point equals to 5 pixels in all cases. The solid lines present the fits of the model curves [Eq. (9)]. Error bars mark the experimental errors.

### III. RESULTS

All patients showed positive skin reactions to histamine. An example of rough histamine results is presented in Fig. 1. The origin was selected at the injection point (arrow). It should be noted that the maximum increase of temperature was patient-dependent and ranged from 1.5 to 4.0 K despite of the identical dose of histamine in all cases.

The changes of the HR radius in time are presented in Fig. 2. The experimental points were extracted from Fig. 1 by cutting of the  $\Delta T_H(r, t)$  distribution parallel to  $r$ - $t$  plane at  $\Delta T_H = 0.9$  K (3 times  $\Delta T$  error). The fit of the function ( $r = vt$  for  $t < t_R$  and  $r = Z$  for  $t \geq t_R$ ) enables the determination of two model parameters ( $v$  and  $Z$ ). Additionally, the time necessary to reach the maximum radius of the HR ( $t_R$ ) was extracted from the fit.

An example of the fits of the model curves [Eq. (9)] to  $\Delta T_H$  data is presented in Fig. 3. The results for three patients are shown. The distance from the histamine injection point equals to 5 pixels in all cases. It should be noted that the model described very well the histamine data. The coefficient of determination ( $R^2$ ) ranged from 0.898 to 0.995.

All model parameters, obtained on the basis of the histamine data are given in Table I. The ratio of maximum to minimum values is parameter-dependent and ranged from  $\sim 3$  to  $\sim 9$ . To check relations between model parameters, the

TABLE I. The values of model parameters obtained from fits of histamine and allergen data.

| Parameter      | Mean $\pm$ SD       | Range         |
|----------------|---------------------|---------------|
| $v$ (mm/s)     | $0.022 \pm 0.014$   | 0.007–0.055   |
| $Z$ (mm)       | $9.9 \pm 5.1$       | 3.2–19.9      |
| $t_R$ (s)      | $455 \pm 127$       | 270–790       |
| $\gamma$ (1/s) | $0.0030 \pm 0.0014$ | 0.0011–0.0059 |
| $\tau$ (1/s)   | $0.0058 \pm 0.0023$ | 0.003–0.012   |
| $S_0$ (K/s)    | $0.0024 \pm 0.0024$ | 0.001–0.009   |
| $Q_{0H}$ (K/s) | $0.013 \pm 0.006$   | 0.004–0.025   |
| $Q_{0A}$ (K/s) | $0.007 \pm 0.004$   | 0.001–0.020   |

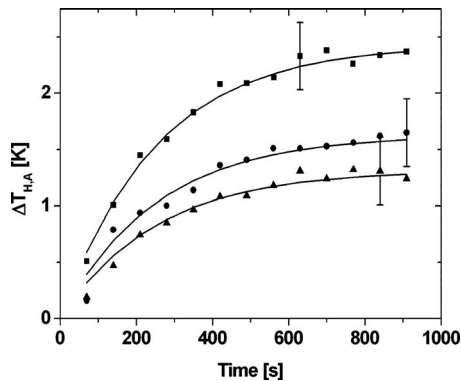


FIG. 4. The increase of skin temperature ( $\Delta T_{H,A}$ ) after injection of histamine (■) and two allergens [weeds (●) and *Dermatophagoides pteronyssinus* (▲)] versus time for one patient. The distance from the injection point equals to 5 pixels in all cases. The solid lines present the fits of the model curves [Eq. (9) or Eq. (12)]. Error bars mark the experimental errors.

correlation coefficients were calculated. The significant value (0.85) was found only between the maximum radius of the HR (Z) and the migration velocity ( $v$ ).

In the study, 192 allergic reactions were examined (24 patients times 8 allergens). In most cases (132), the allergic responses were not observed. A wheal-and-erythema did not develop and an increase of the skin temperature was not detected as well. The same pertained to the negative control, i.e., the patient did not respond to the prick. In the case of a positive reaction the allergen data have been fitted using Eq. (12). An example of the results is presented in Fig. 4, while the mean and minimum/maximum values of  $Q_{0A}$  parameter for all allergens under consideration are given in Table I. Additionally, the values of  $Q_{0A}$  parameter were calculated separately for each allergen applied in the study (Table II). Three allergens (cat hair, mildews, and feathers) exhibited positive reactions in two or three cases. Therefore, they were not mentioned in the discussion of allergen specificity. It was found that the mean values of  $Q_{0A}$  parameter are allergen-independent (Kruskal–Wallis test,  $p=0.64$ ) and ranged from 0.006 (mixed weeds) to 0.008 K/s (*Dermatophagoides pteronyssinus* and mixed grasses).

The model reproduces the allergen data very well in all cases. The coefficient of determination ranged from 0.805 to 0.982. Similarly to  $Q_{0A}$  parameter, the coefficient of determination does not exhibit allergen specificity (Kruskal–Wallis test,  $p=0.56$ ). It should be noted that the allergen data were fitted using one free parameter ( $Q_{0A}$ ). The remaining

TABLE II. The values of  $Q_{0A}$  parameter (K/s) obtained for five allergens under consideration.

| Allergen                              | Mean $\pm$ SD     | Range       |
|---------------------------------------|-------------------|-------------|
| <i>Dermatophagoides pteronyssinus</i> | $0.008 \pm 0.004$ | 0.002–0.015 |
| <i>Dermatophagoides farinae</i>       | $0.007 \pm 0.003$ | 0.001–0.012 |
| Mixed grasses                         | $0.008 \pm 0.005$ | 0.004–0.019 |
| Mixed trees                           | $0.007 \pm 0.002$ | 0.003–0.010 |
| Mixed weeds                           | $0.006 \pm 0.002$ | 0.003–0.010 |

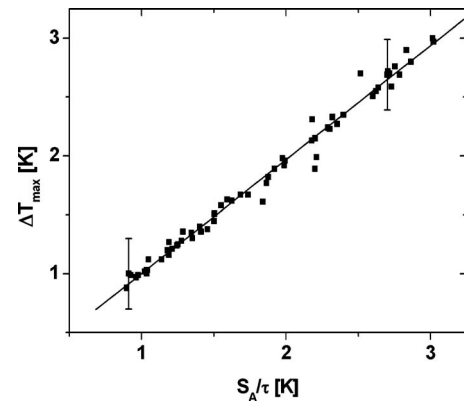


FIG. 5. The maximum increase of temperature ( $\Delta T_{max}$ ) versus  $S_A/\tau$  ratio [Eq. (12)]. The results for all allergens showing the positive reactions are presented. The distance from the injection point is 5 pixels for all cases. Error bars mark the experimental errors.

parameters ( $v$ ,  $\gamma$ ,  $\tau$ , and  $S_0$ ) were obtained on the basis of the histamine data. It was also found that  $Q_{0A}$  values do not correlate with parameters extracted from the histamine data.

#### IV. DISCUSSION

The collected results confirm that TH imaging is a noninvasive technique that allows visualization and quantification of changes in skin surface temperature caused by allergic reactions. This work has confirmed previous findings<sup>4,6,9,11,14,21</sup> that TH technique permits measurement of the size, intensity, and kinetics of inflammation reactions. The results reported so far were, however, limited to the temperature increase determination and/or the HR area. Sometimes, the largest temperature increase or the average increase of temperature multiplied by the area of the HR has been used for diagnostic purposes. This is the first study to employ a more sophisticated approach to quantify the skin prick test on the basis of the TH measurements. The rough TH data are interpreted using a mathematical model based on the pathophysiology of heat generation. Although, the proposed model is very simple, it reproduces very well the experiment. In Fig. 5, the maximum increase of temperature after allergen injection is compared to the  $S_A/\tau$  values [Eq. (12)] for all positive allergic reactions under investigations. The distance from the injection point equals to 5 pixels. The value of the correlation coefficient (0.99) confirms unequivocally the correctness of the model.

Two main simplifications concerning the heat generation after allergen/histamine injection have been used in the model. The first one deals with heat transport in the skin and the second simplification is the treatment of histamine release by the mast cells after the allergen injection. The heat transfer in the skin has been traditionally addressed using Pennes bioheat equation,<sup>18,22</sup> which accounts for the ability of tissue to transfer heat by both passive conduction and blood perfusion. In most cases, spatially distributed external heating occurs in skin exposed to radiation such as microwave, ultrasound, or laser light. In the model, the core of the body constitutes the homogenous heat source with constant

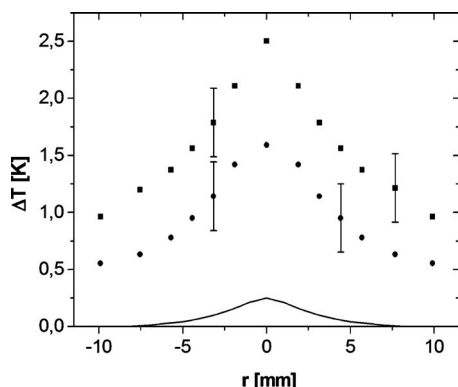


FIG. 6. The average increase of skin temperature 910 s after histamine (■) and allergen [mixed trees (◆)] injections versus radius ( $r$ ) of the heated region, as well as the result of the finite element method calculations (solid line) of the heat conduction in the skin. The histamine/allergen injections and the heat source used in calculations were localized at the origin. Error bars mark experimental errors.

temperature. The histamine injection changes the thermal insulation property of the skin. The process is approximated as formation of a supplementary heat source. Hence, the simplification that the skin temperature distribution is governed by the spatially distributed heat generation rate [Eq. (3)] and the surface heat loss while the heat conduction in the skin may be neglected seems to be reasonable.

Additional justification of the assumption arises from the numerical simulation. ANSYS (ANSYS Inc. Southpointe, PA) software was applied for the finite element method calculations of the heat conduction in the skin. The calculations were performed assuming axial symmetry and the two layer skin model (epidermis and dermis). The temperature of a point heat source, localized at the subcutaneous side of the dermis, equaled to blood temperature (310 K). The ambient and skin (average of all investigated cases) temperatures before examination equaled to 295 and 307 K, respectively. The rest of parameters (density, specific heat, thermal conductivity, and thickness equaled to  $1.2 \text{ g cm}^{-3}$ ,  $3.3 \text{ J g}^{-1} \text{ K}^{-1}$ ,  $0.45 \text{ W m}^{-1} \text{ K}^{-1}$ , and 1 mm and  $1.2 \text{ g cm}^{-3}$ ,  $3.59 \text{ J g}^{-1} \text{ K}^{-1}$ ,  $0.23 \text{ W m}^{-1} \text{ K}^{-1}$ , and 0.01 mm for dermis and epidermis, respectively, while heat transfer coefficient =  $6 \text{ W m}^{-2} \text{ K}^{-1}$ ) were adopted of the basis of previously published data.<sup>22</sup> The simulated time period was 910 s. The result of calculations of the skin surface temperature (epidermis outer surface) is presented in Fig. 6. For comparison, Fig. 6 also shows the average increase of the skin temperature 910 s after histamine and one allergen (mixed trees) injections. It is clearly visible that a contribution of heat conduction in the skin to temperature changes is negligible. The increase of skin temperature and the diameter of the heated region are mostly influenced by an unknown mechanism(s), approximated in the model by histamine migration, while thermal conductivity of the skin plays a marginal role.

The assumption concerning the rapid release of histamine after allergen provocation agrees well with the previously reported data. The investigations of changes in local blood flow after prick tests with histamine and allergen injections

using laser Doppler flowmetry<sup>23</sup> revealed that the initial rapid increase in blood flow has been observed after both provocations. The same conclusion may be drawn from the measurements of the exudation and vasodilation responses after skin prick test using the radioactive tracer.<sup>24</sup> The largest responses to histamine and allergens occurred immediately after provocation. Probably, there are two time scales in the model. The histamine release depends instantaneously on the allergen concentration, while the temperature distribution is controlled by the histamine concentration on a slower time scale.

Despite the applied simplifications, the proposed model reflects properly the mechanism of the allergic reaction. It should be pointed out that we have tried to describe histamine transport using a diffusion model. The analytical solution of the diffusion equation leads to the parabolic relation<sup>25</sup> between the radius of the heated region and time. Since the parabolic function does not correlate with the experiment (Fig. 2), it was excluded from the considerations. Probably, histamine transport in the skin is a complicated multistep process. The proposed model offers the simplest description of a total effect without recognition of the intermediate stages.

The unknown model parameters (Table I) are determined by fitting to the experimental data. On the other hand,  $\tau$  [Eq. (7)] and  $S_0$  [Eq. (8)] values may be estimated using the data reported previously.<sup>22,26</sup> Assuming  $\rho_s = 1.2 \text{ g cm}^{-3}$ ,  $c_{shs} = 3.3 \text{ J g}^{-1} \text{ K}^{-1}$ ,  $\rho_b = 1.06 \text{ g cm}^{-3}$ ,  $c_{shb} = 3.77 \text{ J g}^{-1} \text{ K}^{-1}$ ,  $\omega = 1.25 \cdot 10^{-3} \text{ m}^3 \text{ s}^{-1} \text{ m}^{-3} \text{ tissue}$ ,  $\alpha = 6 \text{ W m}^{-2} \text{ K}^{-1}$ ,  $T_b = 310 \text{ K}$ ,  $T_a = 295 \text{ K}$ , and  $T_{s0} = 306 \text{ K}$  for 1 mm thick skin layer, the values can be determined as  $\tau \approx 0.003 \text{ s}^{-1}$  and  $S_0 \approx 0.002 \text{ K s}^{-1}$ . Both values are within the ranges of the model parameters (Table I). The comparison may be treated as an additional proof of the model correctness.

The proposed approach of the skin prick test quantification was validated by the comparison to a routine diagnostic method. The examination of model parameters revealed that quantities connected with histamine production should be used for diagnostic purposes. In the routine quantification, wheal and flare areas are related to the histamine control. Therefore, for the description of the allergic response, the  $c_{0A}/c_{0H}$  ratio was used. The comparison of routine (0–5 scale) and TH evaluations of the skin prick test results is presented in Fig. 7. For each grade of the scale, the average  $c_{0A}/c_{0H}$  ratio was calculated. Both quantification methods correlate very well (correlation coefficient = 0.98).

It should be also noted that the negative allergic responses (grade 0) were observed for 132 cases both in routine as well as TH quantifications. In Fig. 7, grade 0 corresponds to the  $\langle c_{0A}/c_{0H} \rangle$  value of 0.25. It is due to the threshold histamine concentration necessary to produce a heating effect. Using the average values of parameters (Table I), the  $c_{TH}/c_{0H}$  ratio may be calculated [Eq. (4)]. The obtained value (0.26) is in the excellent agreement with the fit.

The collected results did not confirm differences between the mean allergic responses of different allergens. The mean values of  $\Delta Q_{0A}$  parameter (Table II) are allergen-

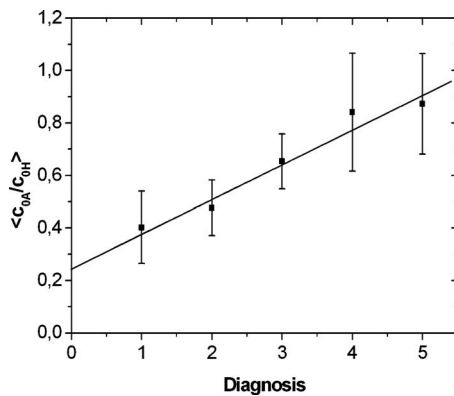


FIG. 7. Average  $c_{0A}/c_{0H}$  ratio (mean  $\pm$  SD) versus routine assessment of the allergic response. The routine quantification of skin tests is given in a 0–5 scale.

independent. It should be pointed out that effective diagnosis using skin test reagents requires the optimal amount of allergens for testing. Skin reactions should be large enough to suggest clinical sensitivity but not so large as to produce excessive discomfort or the risk for a serious systematic reaction. The commercial allergen panels currently used in clinical practice are standardized to assure the identical biological potency for all allergens. Therefore, an allergen specificity is not included in the model. For each allergen, the ability of the immune system to respond to allergen challenge is quantified by the histamine production according to Eq. (10). The intermediate stages of the allergic response,<sup>16</sup> responsible for the reaction specificity, are not considered.

Although correlation of the average values is very good, the discrepancies were observed in the selected cases. Probably, an additional experiment should be performed to judge the observed differences. For example, both methods should be compared to the results of the specific IgE level in blood.<sup>27</sup> This highly sensitive technique is commonly considered as a “gold standard” in the diagnosis of allergic responses.

In addition to the quantification of the allergic reaction for diagnostic purposes, the continuous recording of the skin temperature might yield additional information on the mechanism of the allergic response. Since the biomedical aspect of the allergic response is out of the scope of this paper, only two examples will be described. First, the value of the Z-v correlation coefficient (0.85) reveals that the histamine transport in the skin is responsible for the maximal dimension of the HR. The HR radius is not influenced by the histamine concentration ( $c_{0H}$ ). It may be further concluded that planimetric data have a limited value in the quantification of allergic response.

Second, to determine whether migration velocity and age contribute to histamine sensitivity,  $v$  was plotted as a function of age (Fig. 8). We observed a trend toward reduced skin reactions to histamine in the higher age group in agreement with previously reported data.<sup>28,29</sup> It should be also noted that two groups of different  $v$  values might be distinguished. The explanation of the observed relation awaits further study.

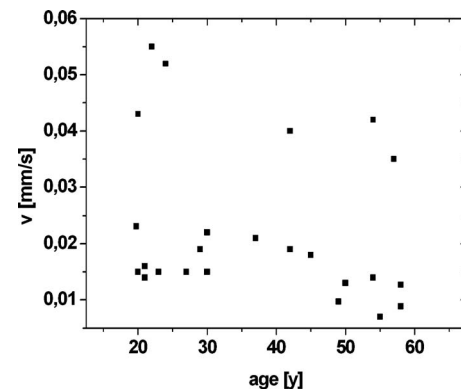


FIG. 8. Histamine migration velocity in the skin ( $v$ ) versus age.

The present study also allows three methodological conclusions to be drawn. First, the proposed method of the skin prick test quantification is based on the relative measurements. Differences of the skin temperatures are used in the model. Therefore, there is a problem to control and standardize experimental conditions only during the examination period ( $\sim 1000$  s). Second, the final score is based on allergen-histamine comparison and the identical time course was applied for histamine and allergen measurements. The applied approach eliminates or at least minimizes the influence of many factors (e.g., ambient temperature) on the temperature determination. Theoretically, differences of the selected parameters (e.g., skin emissivity) at different places of the forearm are possible. They were not confirmed, however, in test measurements. Third, the skin prick test is used in clinical practice for many years. In the proposed procedure, the commonly accepted stages of the test are not modified with one exception. The standard quantification step (planimetry) is replaced by thermography. The presented approach is, in fact, a new quantification method of the routine clinical procedure.

## V. CONCLUSIONS

It was demonstrated that forearm thermography is a non-invasive and sensitive method to study allergic response. Our findings reveal, for the first time, that the thermographic measurements supplemented by the model calculations offer a new approach to the quantification of allergen-induced skin reactions. Despite the applied simplifications, the proposed model reflected properly the mechanism of heat generation during skin prick test. Moreover, the continuous recording of the skin temperature represents an additional possibility to investigate the mechanism of the allergic reaction. Further studies are required to validate these findings in larger populations for different allergens, doses, routes, and timing intervals to develop its use as an objective clinical tool.

## NOMENCLATURE

Latin symbols

$c$  = Concentration

$c_{sh}$  = Specific heat

HR = Heated region  
 IgE = Immunoglobulin E  
 IR = Infrared  
 Q = Heat source  
 S = Amplitude of temperature increase rate  
 T = Temperature  
 TH = Thermography  
 v = Histamine migration rate in the skin  
 Z = Maximum radius of the heated region

#### Greek symbols

$\alpha$  = Heat transfer coefficient  
 $\gamma$  = Histamine elimination rate  
 $\Delta$  = Difference  
 $\rho$  = Density  
 $1/\tau$  = Time constant of temperature increase  
 $\omega$  = Blood perfusion

#### Subscripts

0 = Initial or at origin value  
 a = ambient  
 A = Allergen  
 b = blood  
 H = Histamine  
 s = skin  
 TH = Threshold

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