

Original article

Facial thermography is a sensitive and specific method for assessing food challenge outcome

Background: Oral challenge is widely used for diagnosing food allergy but variable interpretation of subjective symptoms may cause error. Facial thermography was evaluated as a novel, objective and sensitive indicator of challenge outcome.

Methods: A total of 24 children with a history of egg allergy underwent oral challenge, which were scored positive when objective symptoms occurred or negative after all doses were consumed without reaction. Facial temperatures were recorded at baseline and 10-min intervals. The difference between mean and baseline temperature (ΔT), maximum ΔT during challenge ($\Delta T_{\max}$) and area under curve of ΔT against time (ΔT_{AUC}) were calculated for predefined nasal, oral and forehead areas, and related to objective challenge outcome.

Results: There were 13 positive and 11 negative challenges. Median nasal ΔT_{AUC} and $\Delta T_{\max}$ were greater in positive compared with negative challenges (231- and 5-fold, respectively; $P < 0.05$). In positive challenges, nasal temperatures showed an early transient rise at 20 min, preceding objective symptoms at median 67 min. There was a sustained temperature increase from 60 min, which was reduced by antihistamines. A cut-off for nasal $\Delta T_{\max}$ of 0.8°C occurring within 20 min of the start of the challenge predicted outcome with 91% sensitivity (positive predictive value [PPV] 100%) and 100% specificity (negative predictive value [NPV] 93%). Subjective symptoms occurred in four of 13 positive and three of 11 negative challenges.

Conclusions: Facial thermography consistently detects a significant early rise in nasal temperature during positive compared with negative food challenges, which is evident before objective symptoms occur. Thermography may therefore provide a sensitive method to determine outcome of food challenges and investigate the pathophysiology of food allergic reactions.

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Food allergy is a common problem in the developed world, but diagnostic methods vary in efficacy. In clinical practice, food allergy is often diagnosed on the basis of a typical clinical history and the presence of specific IgE (1, 2). Recently, predictive values for skin prick test (SPT) wheal and serum specific IgE results have been suggested for peanut, egg and milk which are associated with high likelihood of clinical allergy (2–5). Whilst this approach is satisfactory in some clinical situations, in patients with specific IgE values below the 'predictive range' the risk of misdiagnosis remains (5). Further, tests for specific IgE are of no use in diagnosing non-IgE mediated food hypersensitivity.

The double blind placebo controlled food challenge (DBPCFC) is considered the gold standard for diagnosis of food allergy, especially when there is doubt about the diagnosis or to confirm resolution (1, 6). However, oral challenges can be time and resource

consuming, carry the risk of severe reactions and challenge reactivity may not match real-life experience (7–9). Further, any symptoms which occur during a challenge may still be interpreted erroneously by observers. We aim to further improve the objective definition of clinical reactivity by investigating a potentially sensitive and specific outcome measure.

Infrared thermography has been shown to detect small increases in temperature associated with positive SPTs, areas of atopic dermatitis, and histamine or allergen-induced rhinitis (10–13). This is the first application of thermography in oral food challenges and investigates the temperature changes observed in the facial area during positive and negative challenges. It is hoped that thermography may be developed as a noninvasive, sensitive and specific method to aid interpretation of food challenges outcomes and to investigate the pathophysiology of food allergy reactions.

Method

Food challenges

Children with an apparent history of egg allergy were openly recruited from our allergy clinic. Subjects were enrolled consecutively. Children were invited to participate if they had a clear history of a typical type-I hypersensitivity reaction to egg (i.e. angioedema $\pm$ urticaria $\pm$ vomiting $\pm$ wheeze). IgE sensitization to egg was detected by SPT with standard whole egg extract (weal $\geq$ 3 mm; Allergy Therapeutics, Worthing, UK), and serum specific IgE (ImmunoCAP FEIA, Phadia [Uppsala, Sweden], positive $\geq$ 0.35 kU/l). Antihistamines were stopped 72 h before the challenge and children received incremental doses of either cooked or uncooked egg (UE) (dose ranges 0.38, 0.75, 1.5, 3, 6 g and 0.5, 1, 2, 6, 12 g of egg, respectively) at 10-min intervals. Children with a history of tolerance to cooked egg (CE) received UE challenge, others received CE. Symptoms and signs were recorded and the challenge was stopped when either all the challenge doses had been consumed or an objective reaction had occurred. Objective reactions were defined as the development of two or more of erythema, urticaria (not including the peri-oral skin) or angioedema, rhinoconjunctivitis, wheeze, abdominal pain (occurring with a noticeable suppression of normal behaviour and activity) or vomiting. Assessments were made by two clinical observers experienced in allergy. Skin prick and serum specific IgE tests were performed on the challenge day. Children with a negative challenge were encouraged to continue eating the same form of egg at home.

Thermography

Images were obtained by a single thermography operator who was independent of the main study team. The study was carried out in a temperature controlled room, only cold light sources were used and daylight was excluded. Challenges were performed at identical times during the day. The room temperature was preset to 23°C and monitored for the duration of the challenge. The camera (FLIR systems Thermocam 500; FLIR Systems; West Malling, UK) was equipped with 24° optics, resolution was 320 $\times$ 240, sensitivity 0.07°C and accuracy $\pm$ 2°C. The camera was allowed to acclimatize in the challenge room for 2 h. The camera was set a distance of 1.5 m from the subject and focused manually. Several baseline thermographic recordings were acquired at 10-min intervals and allowed to stabilize to within 0.5°C before the challenge was commenced and images were then acquired at 10-min intervals until the end of the challenge. Thermographic recordings were not used to determine whether a challenge should be stopped. The study was approved by the local Research Ethics Committee.

Statistics

Thermographic imaging software (FLIR Researcher 2001; FLIR Systems) was used to determine mean temperature within predefined areas of the face (forehead, nose and mouth) from timed thermographic recordings (Fig. S1). These areas were chosen because they are in a plane parallel to the recording device and are most likely to be affected by allergic inflammation. Intra-observer error was $<$ 0.21% for image analysis (calculated in five repeat assessments of three images). The baseline temperature was taken to be the mean temperature for each facial region prior to the first challenge dose. Temperature changes in relation to baseline (ΔT) were calculated for each time point. The largest temperature change in relation to baseline during challenge ($\Delta T_{\max}$) or within the first 20 min ($\Delta T_{\max 20}$) was also reported. Area under the curve (AUC) of

the plot of ΔT over 120 min was calculated for each subject. (120 min was chosen as this was the duration of the shortest negative challenge). Means of normally distributed variables were compared by unpaired *t*-tests. Medians are reported for non-normally distributed variables and were compared using the Mann–Whitney *U*-test, using two-tailed probability (GraphPad Prism V3.02, 2000, GraphPad Software, San Diego CA, USA).

Results

Subject characteristics and challenge results

A total of 24 children (median age 7.2 years range 2.6–14) were challenged to either UE or CE (Table 1). There were 13 positive challenges (10 to UE, three to CE) and 11 negative challenges (six to UE, five to CE). Nine children with positive challenges had gastrointestinal symptoms and eight had rhinoconjunctivitis, two children had wheeze which resolved after nebulized beta-2 agonist. Median time to onset of objective symptoms was 67 min. The frequency of positive SPT and the levels of specific IgE levels were significantly ($P < 0.05$) lower in the group with negative challenges, although five of 11 subjects retained positive SPT and specific IgE to egg. The age difference between the groups with positive and negative challenges was not significant. Minor symptoms such as oral itching were experienced by four of 13 subjects with a positive challenge and three of 11 with negative challenges.

Increase in mean nasal temperature correlates with challenge outcome

For quantitative comparisons between the two challenge groups, temperature changes were normalized to baseline temperature. The largest temperature increase recorded during the challenge ($\Delta T_{\max}$) and AUC of temperature changes from 0 to 120 min of challenge ($\Delta TAUC$) were calculated (Table 2). The $\Delta TAUC$ for the nasal and oral regions was significantly greater in positive challenges compared with negative challenges. The $\Delta TAUC$ for the forehead regions was also greater in positive challenges but this did not reach significance. The $\Delta T_{\max}$ of the nasal, oral and forehead regions were significantly greater during positive challenges. Representative curves of mean nasal temperature against time for individual subjects are shown in Fig. S2.

Early increase in nasal temperature predicts challenge outcome

The mean change in nasal temperature from baseline (ΔT) of each challenge group is shown in Fig. 1. Mean nasal temperatures of subjects from the positive challenge group ($n = 13$) were above baseline at each time point, except at 130 min. In contrast, mean nasal temperature of subjects in the negative challenge group did not rise above baseline at any time point except at 80 min and in general declined throughout the challenge. Mean nasal ΔT values

Table 1. Subject characteristics and oral challenge results. SPT and serum IgE results were obtained on day of challenge

	Challenge result	Age at challenge (decimal y)	Egg SPT (mm)	Egg serum IgE ku/l (grade)	Type of challenge	Subjective symptoms during challenge**	Objective symptoms during challenge
1	Positive	2.7	5	25.3 (4)	CE	None	Ery, Urt, Ang
2	Positive	7.5	4	70.0 (5)	CE	None	Ery, AP, RC, Ang
3	Positive	8.1	2	4.6 (3)	CE	Itchy mouth 11 min	AP, RC, Vom
4	Positive	12.7	0	52.0 (5)	UE	None	AP, RC, nausea
5	Positive	10.0	3	0.55 (1)	UE	None	Urt, Ery
6	Positive	14.0	4	nd	UE	None	AP, Vom
7	Positive	11.8	5	1.8 (2)	UE	None	RC, Ang, Urt, AP
8	Positive	6.5	5	8.1 (2)	UE	None	RC, Urt, Vom, Wh
9	Positive	4.0	3	1.3 (2)	UE	None	RC, Ery, AP
10	Positive	10.3	4	0.76 (2)	UE	Itchy throat 34 min	Ery, Urt
11	Positive	13.7	3	0.79 (2)	UE	Itchy mouth 10 min	Urt, RC
12	Positive	3.2	0	5.31 (3)	UE	None	AP, Wh, Vom
13	Positive	7.8	0	6.11 (3)	UE	Itchy mouth 90 min	RC, Vom, Urt, Ery
Median		8.1	3	4.95*			
1	Negative	4.3	nd	3.2 (2)	UE	Itchy mouth 1 min†	None
2	Negative	12.7	0	< 0.35 (0)	UE	Itchy mouth 83 min†	None
3	Negative	6.1	7	8.0 (3)	CE	Itchy mouth 34 min†	None
4	Negative	7.0	0	< 0.35 (0)	UE	None	None
5	Negative	3.8	0	< 0.35 (0)	UE	None	None
6	Negative	3.5	0	< 0.35 (0)	UE	None	None
7	Negative	11.2	6	17.3 (3)	CE	None	None
8	Negative	11.2	0	< 0.35 (0)	UE	None	None
9	Negative	2.6	4	nd	CE	None	None
10	Negative	4	5	3.26 (2)	CE	None	None
11	Negative	3.5	5	0.88 (2)	CE	None	None
Median		4.3	2	0.35*			

SPT, skin prick test; Ery, erythema; Urt, urticaria; Ang, angioedema; AP, abdominal pain (occurring with change in behaviour and activity); Vom, vomiting; RC, rhinoconjunctivitis; Wh, wheeze; UE, uncooked egg; CE, cooked egg; nd, not done.

Erythema and urticaria had to occur distant to sites of direct contact with egg protein to be considered indicative of an objective reaction. No subjects experienced lip angioedema or urticaria.

† These subjects have subsequently been exposed to the same form of egg (cooked or uncooked) at home in large amounts without objective reaction.

* $P = 0.02$ for difference between medians, Mann–Whitney U -test ($< 0.35 = 0.35$ for analysis); ** Time from first challenge dose; subjective reactions were recorded if they occurred at any time point during the challenge.

Table 2. Median (range) Δ TAUC and $\Delta T_{\max}$ for nasal, oral and forehead areas during positive ($n = 13$) and negative challenges ($n = 11$)

	Δ TAUC ($^{\circ}\text{C}\cdot\text{min}$)			$\Delta T_{\max}$ ($^{\circ}\text{C}$)		
	Nasal	Oral	Forehead	Nasal	Oral	Forehead
Positive challenge	139* (66–235)	46.1* (11–125)	21.3 (0–46)	2.5*(1.3–3.3)	1.1*(0.4–2)	0.4*(0–0.7)
Negative challenge	0.6 (0–73)	1.8 (0–70)	0 (0–27)	0.5 (0–1.8)	0.3 (0–2.3)	0 (0–0.8)
P value	< 0.0001	0.005	ns	< 0.0001	0.001	0.03

Δ TAUC, area under the curve of ΔT over 120 min from start of challenge (units = $^{\circ}\text{C}\cdot\text{min}$); $\Delta T_{\max}$, largest temperature change in relation to baseline during challenge; ns, not significant.

* Where there is significant difference between medians for positive and negative challenge groups for each region, Mann–Whitney U -test.

were significantly higher in the positive challenge group compared with the negative challenge group (t -test; $P < 0.0001$). A distinct profile of mean nasal ΔT was seen in the positive challenge group. An early, transient increase occurring up to 20-min preceded a later, more sustained rise between 60 and 120 min. At 20 min the difference between the mean nasal ΔT of the positive and negative challenge groups was significant: 1.7°C (95% CI: 0.96 – 2.35°C). There were no differences nasal temperature changes in subjects who reacted to CE or UE,

although numbers were small. The later temperature rise that began at 60 min, coincides with the median time of onset of objective symptoms (67 min). Subsequently, the fall in mean nasal temperature in the positive group between 120 and 130-min coincided with median time of administration of oral antihistamines (124 min). In the positive challenge group the mean nasal ΔT remained elevated for 200 min after the first oral challenge dose.

The maximum increase in mean nasal temperature above baseline up to 20 min ($\Delta T_{\max 20}$) was dichotomized

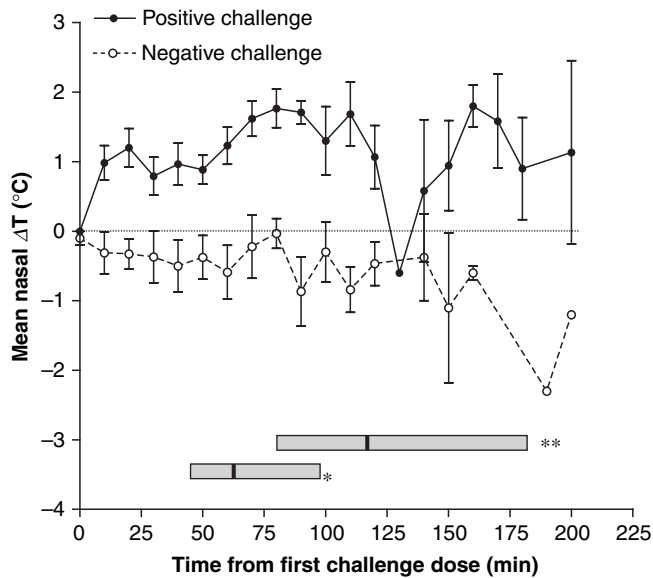


Figure 1. Change in mean nasal temperature from baseline over time of positive (filled circles; $n = 13$) and negative (open circles; $n = 11$) challenge groups. Points are mean values from positive subjects and negative subjects with standard error bars. Total AUC was 222.5°C.min and 0.14°C.min for positive and negative subjects, respectively. $P < 0.0001$ t -test for difference between positive and negative challenge mean nasal ΔT for all time points. Difference in mean change in nasal temperature between negative and positive challenge groups at 20 min was 1.7°C (95% CI: 0.96–2.35°C). *Median (line) and IQR (box) for time of onset of first objective symptoms: 67 min (45–95); **median (line) and IQR (box) for time of administration of oral antihistamines: 124 min (87–180).

into $\geq$ or $< 0.8^\circ\text{C}$ (chosen to give the highest values of sensitivity and specificity). None of the 11 subjects with a negative challenge outcome had $\Delta T_{\text{max}20} \geq 0.8^\circ\text{C}$, giving specificity of 100% (Table 3a). In contrast, all but one of 13 positive challenge subjects had $\Delta T_{\text{max}20} \geq 0.8^\circ\text{C}$, giving sensitivity of 91% (subject 3: $\Delta T_{\text{max}20} = 0.5^\circ\text{C}$; CE challenge). The positive and negative predictive values were 100% and 93%, respectively. $\Delta T_{\text{max}20}$ predicted challenge outcome in 23/24 (96%) subjects (Table 3).

Early onset of minor symptoms was observed in three of 24 subjects during the same period (< 20 min), of

those two had a positive challenge outcome. Hence, early symptoms predicted challenge outcome with sensitivity of only 23%.

Discussion

Medical thermography is a noninvasive technique that allows visualization and quantification of changes in skin surface temperature. In allergy research it has been shown to detect heat emitted by small areas of inflamed skin, e.g. SPT weals and atopic dermatitis (10). It can also detect dose-dependent increases in nasal temperature upon nasal challenge with ragweed or grass pollen; or after nasal histamine administration to normal subjects, the effects being abrogated by pretreatment with oral antihistamines (11–13). This is the first study to employ this technology to detect facial temperature changes during allergic reactions to oral food challenges.

In the present study, thermographic recordings revealed significant and sustained increases in nasal temperature (ΔTAUC) during all positive challenges. In contrast, significant nasal temperature increases were not detected in any negative oral challenges. In fact, mean nasal temperatures consistently decreased during negative challenges, although the reasons for this are unclear. Thus, the thermographic readout was concordant with challenge outcome defined by clinical observation of objective symptoms. However, it is desirable to identify an early predictor of challenge outcome. Minor subjective symptoms are occasionally observed early on in a challenge, but these have very low sensitivity for predicting challenge outcome (23%). The determination of the ΔTAUC requires the challenge to be completed before the data can be analysed. On the other hand, thermography detected nasal ΔT_{max} occurring within 20 min of the first dose, before the onset of any objective symptoms. This distinguished between positive and negative challenges with 91% sensitivity and 100% specificity and predicted challenge outcome in 96%.

A proportion of subjects do not present nasal symptoms and signs during food allergic reactions but present gastrointestinal reactions instead. In this study a significant rise in nasal temperature was detected in all eight children with nasal symptoms. However, we also observed a significant increase in nasal temperature in five of 13 children who had a positive challenge outcome, even though they did not have nasal symptoms. This suggests that thermography may be more sensitive and reliable than clinical observation for detection of nasal inflammation. If the technique were to be developed in a larger population, a threshold nasal $\Delta T_{\text{max}20}$ may be defined by likelihood ratios, to predict challenge outcome. A short, low dose challenge using thermography to define outcome could be an attractive alternative to a full oral challenge, especially for subjects with severe allergy, where there is anxiety about large doses of allergen and risk of severe

Table 3. Percentage (number) of subjects with positive ($n = 13$) or negative challenge ($n = 11$) and their maximum increase in mean nasal temperature above baseline up to 20 min ($\Delta T_{\text{max}20}$) dichotomized into $\geq$ or $< 0.8^\circ\text{C}$

$\Delta T_{\text{max}20}$	Objective challenge result	
	Positive	Negative
$\geq 0.8^\circ\text{C}$	91 (12)	0
$< 0.8^\circ\text{C}$	9 (1)	100 (11)

Sensitivity 0.91 (95% CI: 0.62–0.98); Specificity 1.0 (95% CI: 0.77–1.0); PPV 1.0 (95% CI: 0.72–1.0); NPV 0.93 (95% CI: 0.69–0.99).

symptoms. Our challenge protocol started with relatively large doses of egg (0.38–0.5 g), commonly used in clinical challenges and the technique could also be validated for lower starting doses that could be relevant in quantitative challenges.

The late onset of objective symptoms at median 67 min is consistent with the time course of allergen absorption through the intestines. However, gut absorption cannot entirely explain the early onset of nasal inflammation detected by thermography. The nose is highly vascular with a large mucosal area, bears large numbers of sensitized mast cells in allergic children (14, 15) and is a shock organ in food allergy (16). It is also possible that mast cells in the nasal cavity are sensitized with food specific IgE in these children. Therefore, one mechanism which might explain the early rise in temperature is passage of aerosolized challenge food into the nasal cavity via the oro-pharynx and rapid presentation to food-sensitized mast cells, although the amount of protein delivered to the nose is presumably small. Another possibility is rapid transport of allergen to the nasal mucosa via the circulation, following oral absorption. This is supported by evidence that peanut allergen is detectable in the serum 10 min after oral exposure, without swallowing (17). A third possibility is secondary vasomotor dilatation of the nose induced by oral allergic inflammation, although this is unlikely because of the lower temperature rise detected in the mouths of positive subjects.

In subjects with a positive challenge outcome a fall in nasal temperature occurred soon after administration of antihistamines. Whether this fall in temperature is caused by natural resolution of the allergic reaction or the action of antihistamines is uncertain. Previous studies demonstrated the efficacy of this drug class in reducing inflammation detected by thermography in rhinitis and SPTs (11, 12).

We used open rather than blinded challenges; the concern is that we may have misinterpreted symptoms. The minor symptoms observed in our subjects were short lived and likely to have been induced by anxiety (no subject who had oral itching during a negative challenge reacted to subsequent open egg exposure). We continued to administer doses after subjective symptoms appeared until either an unequivocal objective reaction was provoked, or all challenge doses were consumed without objective reaction, therefore blinding was unnecessary. During image analysis only objective measurements were made (by a single operator), using a predefined area of the face. Careful attention was applied to acclimatization, ambient temperature control, avoidance of external heat sources, timing of images and positioning of the subject.

Conclusion

In conclusion, we have described a novel use for facial thermography as a noninvasive, sensitive and specific method to aid interpretation of food challenge outcomes. Our findings reveal, for the first time, signs of early onset allergic nasal inflammation, not detected by clinical observation, and provide further insight into the pathophysiology of clinical food reactions.

Further studies are required to validate these findings in larger populations, for different food allergens, doses, routes and timing intervals to develop its use as an objective tool to define challenge outcome.

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Supplementary material

The following supplementary material is available for this article:

Figure S1. Representative thermography image showing forehead, nose and mouth gating areas (green circles) used to calculate mean temperature for each area. Scale shows image colour in relation to facial temperature (°C).

Figure S2. Individual plots of mean temperatures of the forehead, oral and nasal regions against time during oral egg challenge. The temperature at $t = 0$ min represents the baseline temperature for each study. The baseline temperature for the nasal region is represented by a dotted line. Results from three negative (A) and three positive (B) studies are presented.

This material is available as part of the online article from: <http://www.blackwell-synergy.com/doi/abs/10.1111/j.1398-9995.2007.01363.x> (This link will take you to the article abstract).

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Website figure 1

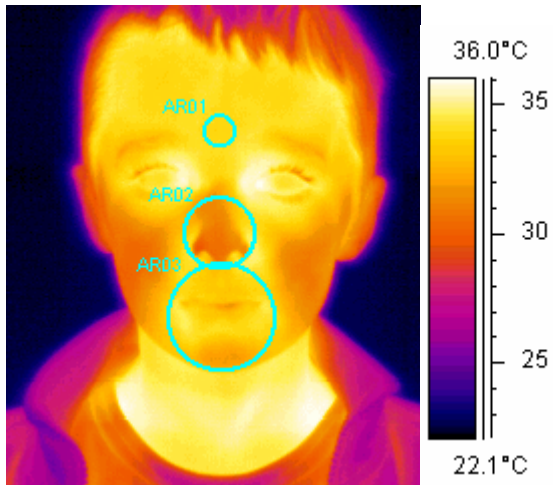


Figure 2a Negative challenges

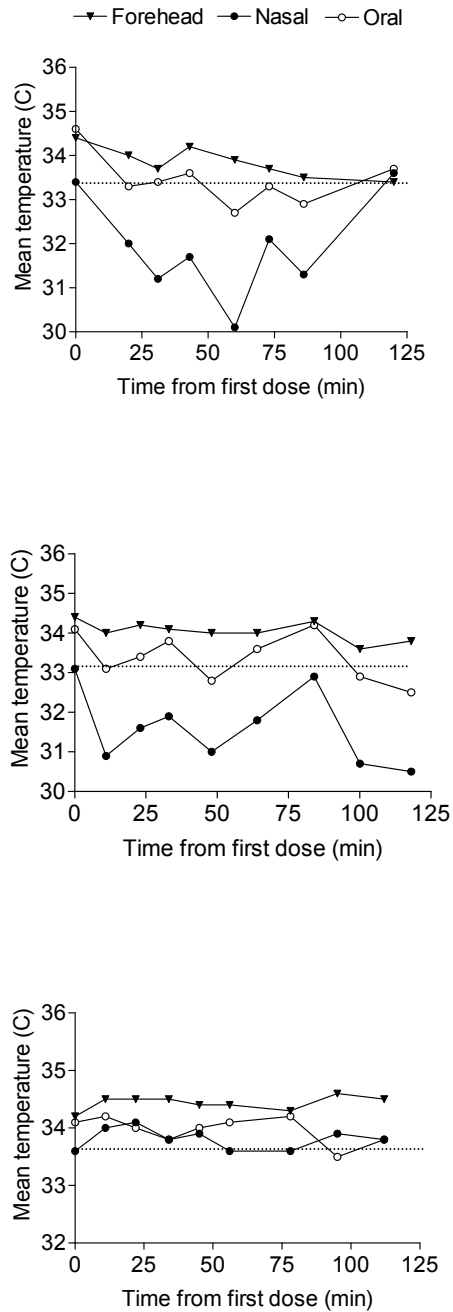


Figure 2b Positive challenges

