

# Bites of the European pigeon tick (*Argas reflexus*): Risk of IgE-mediated sensitizations and anaphylactic reactions

Jörg Kleine-Tebbe, MD,<sup>a</sup> Anja Heinatz, MD,<sup>a</sup> Inken Gräser, MD,<sup>a</sup> Hans Dautel, PhD,<sup>b</sup> Gitte Nordskov Hansen, BSc,<sup>c</sup> Sabine Kespohl, PhD,<sup>d</sup> Hans-Peter Rihs, PhD,<sup>d</sup> Monika Raulf-Heimsoth, PhD,<sup>d</sup> Günther Vater, PhD,<sup>e</sup> Manfred Rytter, MD,<sup>a</sup> and Uwe-Fritjof Haustein, MD<sup>a</sup> Leipzig, Berlin, and Bochum, Germany, and Hørsholm, Denmark

**Background:** Local and systemic reactions can occur after bites of *Argas reflexus* (*Argas*), a soft tick parasitizing pigeons.

**Objective:** Risk assessment of IgE-mediated sensitizations and systemic reactions after *Argas* bites.

**Methods:** Case histories, skin prick tests (SPTs) with a whole-body extract of *Argas* containing major allergen Arg r 1, and common inhalants and specific IgE measurements were obtained from 148 subjects who had had *Argas* bites and 20 volunteers as a control group.

**Results:** Systemic reactions (urticaria, angioedema, dyspnea, cardiovascular dysregulation, unconsciousness) were reported in 12 of 148 (8%); 146 of 148 (99%) had local reactions. Atopy was found in 37 of 146 (25%) with local reactions and 3 of 12 (25%) with systemic reactions. SPT to *Argas* was positive in 24 of 148 (16%) with a high proportion of atopics 10 of 24 (42%); specific IgE to *Argas* was detectable in 12 of 135 (8% of 148) with moderate concordance to systemic reactions. No positive SPT or specific IgE results to *Argas* were obtained in the control group. Immunoblotting of 23 sera revealed an IgE-binding protein in 19 of 23 sera (82%) at 22 kD, indicating a major allergen of *Argas*. **Conclusion:** Severe anaphylactic reactions were infrequently (approximately 8%) found after bites of the soft tick *Argas reflexus*. Atopy is a risk factor for skin sensitizations to *Argas*, but not for systemic reactions after bites by *Argas*. Using a whole-body extract of *Argas*, diagnosis through SPT and specific IgE is hampered by false-negative and irrelevant positive results, particularly in atopy. (J Allergy Clin Immunol 2006;117:190-5.)

**Key words:** Arthropod allergy, pigeon tick, *Argas reflexus*, tick bite, IgE-mediated reaction, anaphylaxis, whole-body extract, skin prick test, allergen specific IgE

## Abbreviations used

LR: Local reaction  
NPV: Negative predictive value  
PPV: Positive predictive value  
r: Recombinant  
SPT: Skin prick test  
SR: Systemic reaction

Bites of the European pigeon tick (*Argas reflexus*; Fig 1) can cause local inflammatory reactions, but also anaphylactic systemic reactions (SRs). *Argas reflexus* (*Argas*) is a soft tick, having a life span of as long as 10 years, while feeding on blood only once or twice per year.<sup>1,2</sup> Without eating, it can survive for 3 to 5, maximally 9 years. Its survival capabilities are based on specific features: (1) low metabolism, (2) extremely low whole-body water loss rates,<sup>3</sup> (3) discontinuous ventilation,<sup>4</sup> and (4) formation of stable aggregations within microsites like wall cracks and wooden clefts. Finally, it is (5) resistant to low temperatures as well as heat.<sup>5,6</sup>

Because of the growing number of feral domestic pigeons in Middle and Southern Europe, infestations of pigeon breeding sites by *Argas* became an increasing problem. From microhabitats in the vicinity of pigeon breeding sites in buildings, *Argas* will seek and accept human beings as a substitute host after removal of pigeons or in case of overpopulation of *Argas*.

Severe reactions after an *Argas* bite have repeatedly been reported<sup>7</sup> in European countries: France,<sup>8,9</sup> Germany,<sup>10,11</sup> Italy,<sup>12</sup> Poland, and Switzerland.<sup>13</sup> Bites usually occur at night because of the nocturnal activity of the tick. Severe allergic reactions with cutaneous, respiratory, gastrointestinal, and cardiovascular symptoms requiring immediate emergency treatment and subsequent hospitalization have been described in 12 cases in France.<sup>14</sup> Allergen specific IgE to *Argas* allergens was demonstrated by using a whole-body extract.<sup>15</sup> It had been speculated that children, elderly people, or atopic individuals have an increased risk to develop an IgE-mediated immune response to *Argas* allergens. However, no data exist about such a risk. A high number of infested buildings together with frequent reports of tick bites in citizens of Leipzig, Germany, prompted us to evaluate

From <sup>a</sup>the Division of Allergy, Occupational Dermatology and Environmental Medicine, Clinics and Outpatient Department of Dermatology, Venerology and Allergology, University of Leipzig; <sup>b</sup>the Institute of Biology/Animal Ecology, Freie Universität, Berlin; <sup>c</sup>ALK-Abelló A/S, Hørsholm; <sup>d</sup>the Research Institute for Occupational Medicine of the Berufsgenossenschaften, Institute of the Ruhr-University Bochum; and <sup>e</sup>Landesuntersuchungsanstalt für das Gesundheits- und Veterinärwesen Sachsen, Außenstelle Leipzig.

Supported by intramural funds of the Clinics and OPD of Dermatology, Venerology and Allergology, University of Leipzig, the Institute of Biology/Animal Ecology, Freie Universität, Berlin, and the Research Institute for Occupational Medicine of the Berufsgenossenschaften, Institute of the Ruhr-University Bochum.

Received for publication November 30, 2004; revised August 24, 2005; accepted for publication August 31, 2005.

Reprint requests: Jörg Kleine-Tebbe, MD, Allergy and Asthma Center Westend, Spandauer Damm 130, Haus 9, 14050 Berlin, Germany. E-mail: kleine-tebbe@allergie-experten.de.

0091-6749/\$32.00

© 2006 American Academy of Allergy, Asthma and Immunology  
doi:10.1016/j.jaci.2005.08.056

the risk of allergic sensitizations and anaphylactic SR after an *Argas* bite. In addition, the utility of skin prick test (SPT) and specific IgE measurements were investigated.

## METHODS

### Study population

Print, radio, and television media promoted the recruitment of volunteers interested in participating in the study, which was approved by the ethics committee of the university. After informed and written consent, individuals were included in the study depending on their clinical case history suggestive for pigeon tick bite reactions:

- Living close to current or former pigeon breeding sites (mainly in attics) and reporting overnight occurring bite reactions, presenting as itchy papular nodes with a small central cutaneous defect, resembling a tick bite
- Presence of the pigeon tick in the apartment or proven infestations by *Argas* close to the apartment

In total, 148 individuals, 90 female and 58 male subjects, were examined over a period of 2 years. Their age ranged from 7 to 80 years (average, 36 years). Twenty volunteers without any bite reaction served as a control group.

### Questionnaire

Specific questions were addressed by using a standardized questionnaire. Basic data like age, sex, and location of the apartment where the bite reactions took place were recorded. Special emphasis was put on information about former or current pigeon breeding sites close to the living space and pigeon tick infestations. The family history with regard to immediate-type allergies and the individual atopic predisposition was requested. Extensive case reports of each bite reaction were established through questions for each local and/or SR, subsequent symptoms, time, course and individual medical and emergency treatment, if necessary.

### Allergen source and preparation

Several hundred specimens of adult pigeon ticks were collected and frozen at  $-20^{\circ}\text{C}$ . After homogenization, the whole-body extract was prepared. After extraction (1:10 in 125 mmol/L  $\text{NH}_4\text{HCO}_3$ , overnight at  $+5^{\circ}\text{C}$ ), the extract was centrifuged, filtrated, and dialyzed  $3\times/\text{day}$  against 5 mmol/L  $\text{NH}_4\text{HCO}_3$  and 1 day against milliQ  $\text{H}_2\text{O}$  before lyophilizing. A final protein detection revealed 300 mg lyophilized allergenic material stored at  $-70^{\circ}\text{C}$ .

### SPT

For SPT, 2 mg was reconstituted in 0.5 mL sterile Coca solution (0.5% wt/vol NaCl, 0.25% wt/vol  $\text{NaHCO}_3$ ) without phenol. The solution was filtrated through a sterile 0.22- $\mu\text{m}$  filter, and an equal volume (0.5 mL) of sterile glycerol was added. SPTs were performed on the volar forearm by using common inhalant allergens (ALK-Abelló, Hørsholm, Denmark) to determine the atopic risk: birch, grass, and mugwort pollen; dust mites *Dermatophagoides pteronyssinus* and *farinae*; cat dander; and *Alternaria alternata*. Histamine-hydrochloride (10 mg/mL) and normal saline, both supplemented with 50% vol/vol glycerol, served as controls. Reactions were evaluated after 20 minutes, documenting wheal sizes with a marker pen and a strip of tape. Average wheal diameters were calculated by the mean of the largest and smallest diameter. An average of 3 mm or larger was considered a positive result. One or more positive skin reactions to common inhalants indicated an increased risk of atopic predisposition.



FIG 1. European pigeon tick (*Argas reflexus*). Dorsal (left) and ventral view (right). Scale: millimeter.

### Measurements of allergen specific IgE

Using pigeon tick specimen from Italy, allergens from *Argas* had been previously extracted and coupled to a solid phase (ImmunoCAP) according to an internal protocol (Pharmacia Diagnostics, Uppsala, Sweden). Serum measurement of allergen specific IgE was performed according to the manufacturer's instructions. Cutoff value was considered 0.35 kU/L of IgE. Levels above this threshold indicated circulating IgE to *Argas* allergens.

### Allergen characterization by electrophoresis, IgE immunoblot, and expression of recombinant Arg r 1

Ten milligrams of lyophilized *Argas* extract (ALK-Abelló) were dissolved in 1 mL PBS and incubated for 3 minutes in an ultrasonic bath. Insoluble particles were excluded by centrifugation 30,000g, 30 minutes,  $4^{\circ}\text{C}$ , before protein concentration was determined.<sup>16</sup> One-dimensional SDS-PAGE and IgE-specific immunoblot analysis of pigeon tick extract were performed by using 300  $\mu\text{g}$  protein on a 10% NuPAGE Bis-Tris gel (Novex, San Diego, Calif) under reducing conditions as described recently.<sup>17</sup> In addition, 2-dimensional electrophoresis of the *Argas* extract with IgE blotting, expression of recombinant (r) Arg r 1, a recently described major allergen,<sup>18</sup> as a fusion protein, subsequent IgE binding, and inhibition studies have been performed and described (see Methods and Results in the Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Statistical analysis

Qualitative results were depicted by  $2 \times 2$  tables; statistical significance was calculated by  $\chi^2$  test. The statistical significance of different values between different groups was analyzed by using the Mann-Whitney  $U$  test. Association between 2 parameters was determined by Spearman rank test. Values were considered significant at  $P < .05$ .

## RESULTS

### Local reactions are predominant after a bite of the soft tick *Argas reflexus*

During a period of approximately 2 years, 148 subjects with suspected bites by the soft tick *Argas* were included in a retrospective study to estimate the frequency of severe allergic reactions and determine the rate of IgE-mediated sensitizations to allergens of *Argas*. Specific questions revealed individual bite reactions ranging from 1 to approximately 30, with an average of  $5 \pm 0.5$  (mean  $\pm$  SEM) per person, related to neither sex ( $P_s = .9$ ) nor individual age ( $P_s = .7$ ). Former or current pigeon breeding sites close to

**TABLE I.** LR and SRs after a bite of the pigeon tick *Argas reflexus* in 148 subjects (37 atopics, 24%, and 111 nonatopics)

| Symptoms                  | Frequency |    |
|---------------------------|-----------|----|
|                           | n         | %  |
| Local                     | 146       | 99 |
| Redness                   | 142       | 96 |
| Local itching             | 124       | 84 |
| Inflammatory node         | 93        | 63 |
| Lymphatic secretion       | 36        | 24 |
| Wheal                     | 25        | 17 |
| Pruritic secretion        | 20        | 14 |
| Lymphangitis              | 12        | 8  |
| Lymph node swelling       | 10        | 7  |
| Vesicle                   | 10        | 7  |
| Systemic                  | 12        | 8  |
| Urticaria                 | 11        | 7  |
| Angioedema                | 6         | 4  |
| Vascular dysregulation    | 2         | 1  |
| Dyspnea                   | 7         | 5  |
| Unconsciousness           | 4         | 3  |
| Gastrointestinal symptoms | 3         | 2  |
| Rush with pruritus        | 3         | 2  |

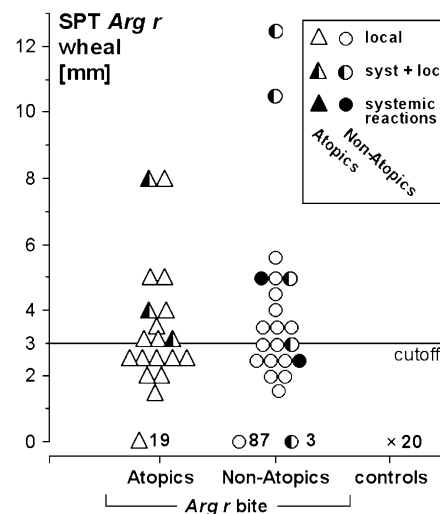
their apartment (eg, in the attic) were reported by 130 individuals; 99 knew of past or current pigeon tick infestations, and 133 people had found *Argas* in their apartment, 128 more than once. Nearly all subjects (146/148) had had local reactions (LRs; Table I), varying from small papular nodes with local itching to grotesque, painful swellings or superinfected lesions eventually becoming purulent abscesses or resulting in massive local lymphatic inflammation.

### Severe SRs are less common after an *Argas* bite

Systemic reactions turned out to be much less common than LR. Determined by critical evaluation of the case histories, only 12 of 148 (8%) developed systemic symptoms, most likely associated with an *Argas* bite (Table I). Cutaneous reactions with urticarial hives and itching were reported frequently (11/12), sometimes associated with swelling of the face—that is, eyelids and lips, representing angioedema. In addition, dyspnea, gastrointestinal symptoms like nausea or diarrhea, and severe vascular dysregulation occurred in some of the individuals, occasionally leading to unconsciousness (4/12). SRs were associated with the total number of bite reactions ( $P < .001$ ), but also with female sex ( $P < .001$ ).

### Infrequent SPT results with a whole-body extract of *Argas*

None of the control subjects showed a positive SPT response to the extract containing allergens of *Argas*. Using the same extract, variable results were obtained in 24 of 148 (16%) subjects with a history of *Argas* bite reactions, ranging from a wheal of 12.5 mm to no detectable skin response (0-mm wheal) in the majority of the individuals tested (Fig 2). A positive SPT result was obtained in

**FIG 2.** Skin test results obtained with a whole-body extract of the soft tick *Argas reflexus*. syst, Systemic reactions; loc, local reactions.**TABLE II.** Relationship among SRs after *Argas* bites, diagnostic results, and status of atopy

|                                                    | SPT |      |                                                    | IgE |      |
|----------------------------------------------------|-----|------|----------------------------------------------------|-----|------|
|                                                    | +   | -    |                                                    | +   | -    |
| SR                                                 |     |      | SR                                                 |     |      |
| +                                                  | 8   | 4    | +                                                  | 5   | 7    |
| -                                                  | 16  | 120  | -                                                  | 7   | 116* |
| Sensitivity 67% PPV 33%<br>Specificity 88% NPV 97% |     |      | Sensitivity 42% PPV 42%<br>Specificity 94% NPV 94% |     |      |
|                                                    | SPT |      |                                                    | SR  |      |
|                                                    | +   | -    |                                                    | +   | -    |
| IgE                                                |     |      | Atopy                                              |     |      |
| +                                                  | 10  | 2    | +                                                  | 3   | 34   |
| -                                                  | 14  | 109* | -                                                  | 9   | 102* |

\*Thirteen sera missing.

8 of 12 with a SR; however, 3 subjects with SR did not show any and 1 individual only a weak SPT response (wheal < 3 mm) to *Argas* allergens. A substantial number of subjects without reported SR (16/136) reacted with either small (<3 mm) or significant ( $\geq 3$  mm) SPT wheals as large as 8 mm (Fig 2). On the basis of a suggestive case history for SR, SPT to *Argas* was hampered by false-positive and false-negative results, providing a diagnostic sensitivity of 67% and a specificity of 88% (Table II, upper left portion). The positive predictive value (PPV; 33%), referred to the study population of patients with SR to *Argas* bite, turned out to be much lower than the negative predictive value (NPV; 97%), implying that skin test reactivity in subjects with an *Argas* bite reaction does not necessarily reflect an allergic reaction of clinical relevance, but that negative SPT responses do most likely exclude an anaphylactic SR, because of the rather low proportion of SR after an *Argas* bite.

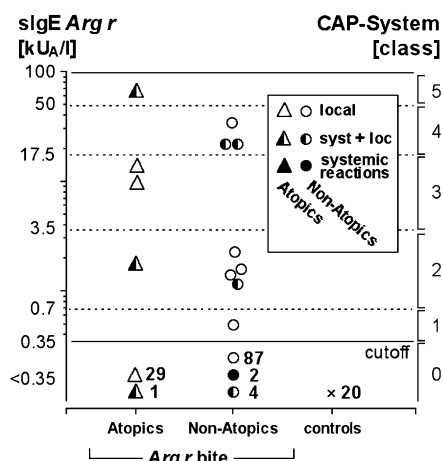


**FIG 3.** Allergen specific IgE to *Argas reflexus*. syst, Systemic reactions; loc, local reactions.

### Specific IgE to allergens of *Argas*

Specific IgE levels to *Argas* were detected in 135 sera; 13 were missing. No detectable IgE was found in 20 control subjects. In contrast, some individuals with a suggestive history (12/135; 9%) demonstrated allergen specific IgE levels above 0.35 kU/L. Only 5 of 12 with detectable IgE, ranging from levels as low as 0.44 to values of 68 kU/L (Fig 3), had reported SR. On the other hand, 7 individuals reporting SR to *Argas* were not picked up by allergen specific IgE (Table II, upper right portion). Again, on the basis of a suggestive case history for SR, test sensitivity (42%) and specificity (94%) of allergen specific IgE values as well as PPV (42%) and NPV (94%) do not result in high diagnostic efficacy. However, because of the low estimated prevalence of SR to *Argas*, allergen specific IgE measurements are more effective in excluding an allergic SR.

### Poor agreement between SPT and allergen specific IgE to *Argas*

Comparing positive results from either SPT or IgE measurements revealed no close association between immediate-type wheal responses and allergen specific IgE levels to *Argas* (Fig 4). General qualitative agreement (concordance, 88%) was hampered by a significant number of positive reactions ( $n = 14$ ) with no detectable IgE (Table II, lower left portion). Ten subjects showed concordant positive results; 2 individuals with specific IgE failed to respond to the SPT with *Argas*.

### Atopic predisposition as a risk factor for IgE-mediated sensitizations to *Argas*

Relating the risk of SR to *Argas* allergens to the atopic predisposition did not reveal any close association (Table II, lower right portion). The proportion of atopic subjects with SR to *Argas* allergens (3/12; 25%) did not differ from the ratio of atopic subjects within the whole group (37/148; 25%). However, a positive SPT to *Argas* allergens occurred in 10 atopic versus 14 nonatopic

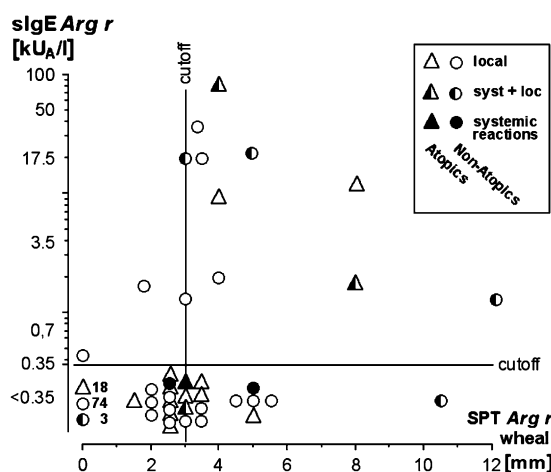


**FIG 4.** Association between individual SPT results ( $x$ -axis) and detection of IgE to *Argas* ( $y$ -axis). syst, Systemic reactions; loc, local reactions.

individuals, indicating a trend to more frequent skin reactions to *Argas* allergens in atopics.

### IgE immunoblot experiments, IgE binding, and further allergen characterization

Applying different SDS-PAGE conditions the SPT extract revealed a dominant protein component at about 22 kD plus thin protein bands at 50, 68, and 90 kD and additional bands at 10 and 12.5 kD under denaturing conditions (see Results and Fig E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)).

The dominant role of the 22-kD *Argas* allergen was supported by a high frequency of IgE binding in *Argas*-sensitized subjects. A 22-kD protein was recognized by 19 of 23 sera (Fig 5). Sera of patients without binding of the 22-kD protein recognized either a single allergen at 40 kD (Fig 5, lane 16) or a single allergen at 44 kD (Fig 5, lane 15) or no protein component (Fig 5, lane 21+22). No association occurred between individual IgE binding profiles and clinical symptoms or sensitivity of the patients.

The IgE-binding protein at 22 kD revealed several isoforms after 2-dimensional electrophoresis and blotting (see Results and Figs E3 and E4 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). In addition, selected sera recognized a rArg r fusion protein (see Fig E5 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)) expressed from mRNA/cDNA of salivary glands in Western blot experiments (see Results and Figs E6 and E7 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)) and in an IgE solid phase binding assay. Preincubation with the *Argas* extract inhibited the IgE binding to the rArg r 1 fusion protein, indicating that Arg r 1 is a component of the extract used for SPT (see Methods and Results in the Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### DISCUSSION

Because of an extraordinarily high number of pigeon and *Argas*-infested buildings with damaged attics, the city

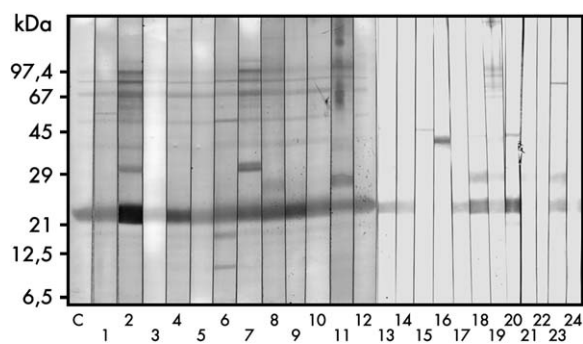


**FIG 5.** IgE blot of *Argas* proteins incubated with sera of subjects sensitized to *Argas* (lane 1-23), buffer control (lane 24).

of Leipzig presumably had the highest rate of bite reactions in human beings compared with other places in Europe.<sup>19</sup> Despite the fact that only 12 of 148 (8%) reported SR after *Argas* bites, this number could still be overestimated because of the design of the study. Because the subjects were not randomly collected but actively asked for their participation, a selection bias might have led to an overestimation of SR: severely affected individuals are more likely to respond to the invitation of such a study. This might lead to high proportions, like >50% SRs after a bite of the jack jumper ant reported by a retrospective questionnaire-based study from Tasmania, New Zealand.<sup>20</sup> False-positive case histories can potentially corrupt the numbers of prevalence and diagnostic efficacy of subsequent allergy tests. Various reasons might lead to false-positive case histories: (1) unintentional overestimation of large LRs, (2) reactions modulated by severe anxiousness of the subject, and (3) purposeful false-positive histories for secondary disease benefits.

Interestingly, related models after an insect sting provide similar ratios of SRs comparable with our data. In the general population, 1.5% to 3% report SRs to *Hymenoptera* venom.<sup>21,22</sup> The epidemiology of allergic reactions to the imported fire ant in endemic areas<sup>23</sup> is far from clear<sup>24</sup> and illustrates the difficulties in estimating the number of clinically relevant allergic reactions after arthropod stings or bites. Despite careful interviews, an uncertain degree of overestimation of SR cannot be ruled out, because severe reactions after a presumed bite of *Argas* could not be confirmed by challenge procedures.

Using a whole-body extract from *Argas* for SPT could create inherent problems of nonstandardized material. No one in the control group showed a reaction to *Argas*, because small molecules were removed by dialysis to exclude irritating components, but low-molecular-weight allergens could have been lost too. In addition, the allergenic proteins might represent only a minor proportion of the extract, leading to false-negative results in individuals with low-grade sensitivity. The high proportion of positive skin responses—even in subjects without SRs after an *Argas* bite—is indicative of the biological activity of the extract, an observation similar to whole-body extracts of the imported fire ant used for skin test purposes<sup>24</sup>;

however, false-negative reactions cannot be ruled out, because no former experience with the extract existed. In analogy to *Hymenoptera* hypersensitivity, where venom extracts dramatically increased the diagnostic efficacy of skin test reagents compared with whole-body extracts,<sup>25</sup> an *Argas* extract from the salivary glands (as much as 1/10 of the whole body weight) of the soft tick might also improve SPT results.

A whole-body extract of *Argas* species from Italy has also been used for the development of solid phase-coupled allergens for further *in vitro* testing. These tests provided quantitative IgE levels to *Argas* allergens, not showing elevated levels in the control group. However, because the quality of such a test largely depends on the allergenic material used, analytical sensitivity can be limited in the case of whole-body extracts.<sup>26</sup> This might explain the smaller proportion of positive IgE results compared with SPT, even in subjects with a convincing history of an anaphylactic reaction to *Argas*.

Positive IgE results may be clinically irrelevant, representing only allergic sensitivities without symptoms, which is known for atopic (ie, pollen, mites, animal dander) and *Hymenoptera* venom allergens. Qualitatively concordant results of SPT and serum IgE to *Argas* (Table II) indicate an IgE-mediated mechanism in these individuals with a reported bite of *Argas*. Discordant results between SPT and allergen specific IgE in several subjects (Table II, lower right portion) and poor quantitative agreement (Fig 4) can be attributed to various reasons:

- (1) Different sources of *Argas* populations (collected in Germany for SPT; collected in Italy for IgE) could have resulted in nonidentical allergen compositions.
- (2) Different preparation and extraction methods (SPT extract developed by ALK-Abelló A/S, Denmark; solid phase-allergens for *in vitro* IgE measurements prepared by Pharmacia Diagnostics, Sweden) might have further influenced the extract profile.
- (3) SPT and *in vitro* IgE will hardly demonstrate perfect concordance, even if identical allergen sources (ie, *Hymenoptera* venom) are used.<sup>27</sup> Explanations are the following:

- *In vitro* methods can pick up allergen specific IgE unable to cross-link IgE on cutaneous mast cells, leading to negative SPT results.
- Skin responses can result from non-IgE-mediated mechanisms, especially if crude extracts, such as from arthropods with no former characterization, are used.<sup>28</sup>

Interestingly, our preliminary study does not provide evidence for an increased risk for atopic individuals of developing an anaphylactic SR after an *Argas* bite. Similar observations have been reported in subjects being diagnosed for venom hypersensitivity.<sup>29</sup> The risk of IgE-mediated clinical reactions to this group of injected allergens is not restricted to atopic individuals, but will also occur in nonatopic subjects. Therefore, allergens from *Argas* might not be considered atopic allergens, because relevant SRs were more frequently found in subjects without atopic risk.

Atopy, defined by cutaneous sensitivities to common inhalant allergens, seems to influence the test outcome using extracts of *Argas*, resulting in a higher proportion of positive SPT in this group, similar to diagnostic results in *Hymenoptera* hypersensitivity.<sup>30</sup> Despite displaying an increased risk of allergic sensitization to allergens of *Argas*, determined by SPT, atopics do not report anaphylactic reactions more frequently than nonatopics. Therefore, diagnostic tests with *Argas* extracts in atopics should be interpreted with caution, taking into account a higher rate of irrelevant positive SPT results in this group.

Because >80% of the sera from subjects with positive skin reactions to Arg showed IgE-binding to a protein of approximately 22 kd, it might represent a major allergen of *Argas*. The partial identity of or relationship to a recently described major allergen Arg r 1<sup>18</sup> and to another 22-kd binding protein<sup>31</sup> remains to be determined. Immunoblot, IgE binding, and inhibition experiments with a rArg r 1–fusion protein indicate that rArg r 1 is recognized by selected sera and that Arg r 1 is also a component of our extract. Considering the salivary origin of mRNA encoding Arg r 1 (see **Methods and Results** in the Online Repository at [www.jacionline.org](http://www.jacionline.org)) and the reactions exclusively occurring after an *Argas* bite, the most important allergens are likely to be of salivary origin.<sup>14,15</sup>

In conclusion, we could demonstrate positive SPT and IgE results in subjects with a case history of LR and/or severe SRs after a bite of the pigeon tick *A reflexus*. Atopy is a risk factor for positive SPT, but not for SRs, which might occur in some individuals (approximately 8%) after a bite of the soft tick *Argas reflexus*.

We thank Dr Dietmar A. Herold and Prof Dr Gert Kunkel (Allergy and Asthma Center Westend, Berlin, Germany) and Martin McCall for editorial assistance and Dr Franziska Rueff (Clinics and OPD of Dermatology, Venerology and Allergology, University of Munich, Germany) for helpful comments on insect related hypersensitivity reactions. Irmgard Löffler, Beate Göhler, Margot Röder, and Vera Passman (Allergy Division of the Clinics and OPD of Dermatology, Venerology and Allergology, University of Leipzig, Germany) provided excellent technical assistance. We acknowledge Dr Ingrid Möller, Dr Sigrun Hillert, and Dr Bodo Gronemann from the local health authorities for administrative support (Gesundheitsamt Stadt Leipzig, Saxony, Germany) and Dr Heide Boysen-Tilly for juristical advice (City of Leipzig, Saxony, Germany). Finally, we thank all participants for their interest in and commitment to the study on pigeon tick allergens. Allergen extract preparation was performed and provided by ALK-Abelló A/S.

## REFERENCES

- Dautel H, Kahl O, Scheurer S, Knülle W. Seasonal activities of the pigeon tick *Argas reflexus* (Acari: Argasidae) in Berlin, Germany. *Folia Parasitol (Praha)* 1994;41:155-60.
- Dautel H, Knülle W. Life cycle and seasonal development of postembryonic *Argas reflexus* (Acari: Argasidae) at two thermally different locations in Central Europe. *Exp Appl Acarol* 1997;21:697-712.
- Dautel H. Water loss and metabolic water in starving *Argas reflexus* nymphs (Acari: Argasidae). *J Insect Physiol* 1999;45:55-63.
- Lighton JRB, Fielden LJ, Rechav Y. Discontinuous ventilation in a non-insect, the tick *Amblyomma marmoreum* (Acari, Ixodidae): characterization and metabolic modulation. *J Exp Biol* 1993;180:229-45.
- Dautel H, Knülle W. Cold hardiness, supercooling ability and causes of low-temperature mortality in the soft tick, *Argas reflexus*, and the hard tick, *Ixodes ricinus* (Acari: Ixodoidea) from Central Europe. *J Insect Physiol* 1997;43:843-54.
- Dautel H, Knülle W. Seasonal oviposition and temperature requirements of eggs may limit northern distribution of European *Argas reflexus* (Acari: Argasidae). *J Med Entomol* 1998;35:26-37.
- Alt K. Die Taubenzecke als Parasit des Menschen. *Münchener Medizinische Wochenschrift* 1892;30:531-3.
- Chappard C, Sainte-Laudy J, Emonet A. Anaphylactic reactions caused by a pigeon's parasite (*Argas reflexus*). *Biomed Res* 1996;7:11-4.
- Veraldi S, Scarabelli G, Grimalt R. Acute urticaria caused by pigeon ticks (*Argas reflexus*). *Int J Dermatol* 1996;35:34.
- Dautel H, Kahl O, Knülle W. The soft tick *Argas reflexus* (F.) (Acari, Argasidae) in urban environments and its medical significance in Berlin (West). *Journal of Applied Entomology* 1991;111:380-90.
- Trautmann A, Amschler A, Schultz KD, Bröcker EB, Klein CE. Anaphylaktische Reaktionen durch Taubenzecken. *Dermatosen* 1995;42:215-8.
- Miadonna A, Tedeschi A, Leggieri E, Flagiani P, Nazzari M, Manzoni M, et al. Anaphylactic shock caused by allergy to the venom of *Argas reflexus*. *Ann Allergy* 1982;49:293-4.
- Storck H. *Allergie*. Bern: Huber Verlag; 1973.
- Bessot JC, Kopferschmitt MC, de Blay F, Dietemann A, Nirrengarten A, Hutt N, et al., Chocs anaphylactiques après morsure de tiques de pigeon (*Argas reflexus*). À propos de douze cas. *Rev Fr Allergol* 1997;37:431-7.
- Sirianni MC, Mattiacci G, Barbone B, Mari A, Aiuti F, Kleine-Tebbe J. Anaphylaxis after *Argas reflexus* bite. *Allergy* 2000;55:303.
- Bradford MM. A rapid and sensitive method for the quantification of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem* 1976;72:248-54.
- Chen Z, Posch A, Cremer R, Raulf-Heimsoth M, Baur X. Identification of hevein (Hev b 6.02) in Hevea latex as a major cross-reacting allergen with avocado fruit in patients with latex allergy. *J Allergy Clin Immunol* 1998;102:476-81.
- Hilger C, Bessot JC, Hutt N, Grigioni F, De Blay F, Pauli G, et al. IgE-mediated anaphylaxis caused by bites of the pigeon tick *Argas reflexus*: cloning and expression of the major allergen Arg r 1. *J Allergy Clin Immunol* 2005;115:617-22.
- Vater G, Vater A, Sorge O. Schädlingsbekämpfung in Ostdeutschland, Teil 3. *Prakt Schädlingsbekämpfer* 1992;44:152-61.
- Clarke PS. The natural history of sensitivity to jack jumper ants (Hymenoptera formicidae Myrmecia pilosula) in Tasmania. *Med J Aust* 1986;145:564-6.
- Björnsson E, Janson C, Plaschke P, Norrman E, Sjöberg O. Venom allergy in adult Swedes: a population study. *Allergy* 1995;50:800-5.
- Golden DB, Marsh DG, Kagey-Sobotka A, Freidhoff L, Szklo M, Valentine MD, et al. Epidemiology of insect venom sensitivity. *JAMA* 1989;262:240-4.
- Caplan EL, Ford JL, Young PF, Ownby DR. Fire ants represent an important risk for anaphylaxis among residents of an endemic region. *J Allergy Clin Immunol* 2003;111:1274-7.
- DeShazo RD, Butcher BT, Banks WA. Reactions to the stings of the imported fire ant. *N Engl J Med* 1990;323:462-6.
- Schwartz HJ, Lockett RF, Sheffer AL, Parrino J, Busse WW, Yunginger JW. A multicenter study on skin-test reactivity of human volunteers to venom as compared with whole body Hymenoptera antigens. *J Allergy Clin Immunol* 1981;67:81-5.
- Santrach PJ, Peterson LG, Yunginger JW. Comparison of diagnostic tests for hymenoptera sting allergy. *Ann Allergy* 1980;45:130-6.
- Patrizzi R, Müller U, Yman L, Hoigne R. Comparison of skin tests and RAST for the diagnosis of bee sting allergy. *Allergy* 1979;34:249-56.
- Kleine-Tebbe J, Jeep S, Josties C, Meysel U, O'Connor A, Kunkel G. IgE-mediated inhalant allergy in inhabitants of a building infested by the rice weevil (*Sitophilus oryzae*). *Ann Allergy* 1992;69:497-504.
- Schäfer T, Przybilla B. IgE antibodies to Hymenoptera venoms in the serum are common in the general population and are related to indications of atopy. *Allergy* 1996;51:372-7.
- Przybilla B, Ring J, Grieshammer B. Association of features of atopy and diagnostic parameters in hymenoptera venom allergy. *Allergy* 1991;46:570-6.
- Rolla G, Nebiolo F, Marsico P, Guida G, Bigo P, Riva G, et al. Allergy to pigeon tick (*Argas reflexus*): demonstration of specific IgE-binding components. *Int Arch Allergy Immunol* 2004;135:293-5.