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The Hymenoptera venom study II: Skin test results and safety of venom skin testing

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Data are summarized in this Hymenoptera venom study (HVS) article on the safety of skin testing with venom extracts. Of the 3236 subjects studied, 89% had experienced an historical sting systemic reaction (SSR). Seventy-four percent of all subjects and 76% of subjects who had experienced an historical SSR had a positive skin test to at least one venom. More subjects tested positive to yellow jacket venom (51.8%) than to any other venom. There were no significant differences of the wheal and erythema sizes associated with different venoms or different historical sting reactions. Forty-five percent of subjects with positive venom skin tests (VST) were positive to wasp, and 89% of these subjects were also positive to at least one of the following venoms: yellow jacket, yellow hornet, or white-faced hornet. Sixty-four of the 3236 subjects studied (2%) had a systemic reaction (SR) during VST; 13 of the SRs (0.4%) were severe. Thirteen of 64 adverse reactions (20%) were possibly vasovagal, and six other subjects (9%) demonstrated no symptoms of immediate-type hypersensitivity. Thus, 45 (1.4%) of the 3236 subjects tested had an SR that was considered to be a reaction of hypersensitivity, of which eight reactions (0.25%) were severe. Allergic SRs are associated with VST but are unusual and are rarely severe. (J ALLERGY CLIN IMMUNOL 1989;84:967-74.)

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Supported by the American Academy of Allergy and Immunology, Milwaukee, Wis.; Hollister-Stier Laboratories, West Haven, Conn.; Pharmacia Laboratories, Piscataway, N.J., and Center for Drugs and Biologics, Food and Drug Administration, Bethesda, Md.

Received for publication June 14, 1988.

Revised Feb. 13, 1989.

Accepted for publication Feb. 15, 1989.

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1/1/15485

Abbreviations used

HVS: Hymenoptera venom study
LLR: Large local reaction
LR: Local reaction
SR: Systemic reaction
SRI: Systemic reaction index
SSR: Sting systemic reaction
VST: Venom skin test
WBE: Whole body extract

The HVS was initiated by the Committee on Insects of the American Academy of Allergy and Immunology in 1979 when venom extracts became commercially available. The study, conducted from 1979 through

TABLE I. SRI*

Severe	Unconsciousness	0.376
	Shock	0.376
	Drop in blood pressure	0.126
Moderate	Lower airway obstruction	0.050
	Upper airway obstruction	0.050
	Gastrointestinal symptoms	0.013
Mild	Angioedema/urticaria	0.003
	Pruritus	0.003
	Other	0.003
Possible total		1.000

*See text for explanation.

1982, was based on the case histories and VST results of 3236 subjects who had previously reacted adversely, either with an SR, LR, or both to stings by Hymenoptera insects. Information was submitted by 84 Fellows and members of the American Academy of Allergy and Immunology, and follow-up data were available for most of the subjects.¹ The diagnostic results are summarized in this HVS article, and the safety of skin testing with Hymenoptera venom extracts is discussed.

METHODS

Initially, a five-page questionnaire and instructions were sent to participating physicians to be filled out for each subject. Forms 1 and 2 were described previously.¹

Entry forms 3 and 4 outlined methods for VSTs and scoring and were used to record data. Physicians were requested to explicitly follow instructions in the package inserts accompanying the venom extracts and to record the date on which VSTs were performed. If the screening prick test (with 0.01 µg of venom protein per milliliter) was positive, intradermal VST was to be initiated with 0.0001 µg/ml in 0.05 ml volume. If the prick test was negative, the initial intradermal test was to be initiated with 0.001 µg/ml in 0.05 ml volume. Skin test reactions were to be measured in centimeters (later converted to millimeters) 15 minutes after injection and recorded separately for both erythemas and wheals. The longest diameter and the orthogonal diameter for each were measured and summed.

A VST was considered positive (a 1+ reaction) when the sum of the orthogonal diameters of a wheal was ≥10 mm and the sum of the orthogonal diameters of erythema was also ≥22 mm. The lowest concentration of venom producing the 1+ response and the sum of the orthogonal diameters of the wheal and erythema at this concentration were then recorded.

VST results, the manufacturer that distributed the venom, venom type, concentration of venom, wheal size, and erythema size were recorded. Spaces were also provided for recording the subject's reaction to a histamine-induced positive control and a diluent-induced negative control.

Entry form 5 was for recording details concerning the presence or absence of an SR during VSTs. The presence

or absence of the following signs or symptoms were recorded by "yes," "no," or "unknown" responses: generalized pruritus, cutaneous angioedema and/or urticaria, upper airway obstruction, lower airway obstruction, drop in blood pressure, gastrointestinal symptoms (vomiting, diarrhea, and/or abdominal colic), unconsciousness, shock, or "other." (When "other" was checked, a specific description of symptom(s) was to be listed.) Physicians were also requested to indicate on this form by a "yes," "no," or "unknown" response whether they intended to treat their patient with venom immunotherapy.

The SRI is a numerical scale devised for the ranking of the severity of all SRs, regardless of the etiology of the reaction (Table I). Unconsciousness, shock, and a drop in blood pressure are considered to be the most severe; the drop in blood pressure is not considered as severe as the other two signs or symptoms. Moderately ranked signs or symptoms are lower and/or upper airway obstruction and/or gastrointestinal symptoms; gastrointestinal symptoms are not considered as severe as the other two SRs. Angioedema (not involving the respiratory tract) and/or urticaria, pruritus, and/or other signs or symptoms are considered to be mild. These differences are reflected in the values assigned to each.

The SRI was designed so that the combined values for mild reactions would not equal the lowest value of the moderate reactions, and the combined values of the moderate reactions, including the added mild reaction values, would not equal the value of the lowest value severe sign (drop in blood pressure).

An information system was designed to store and facilitate analysis of the HVS data.¹

RESULTS

Skin tests were performed on 3236 subjects with five Hymenoptera venoms: yellow jacket, yellow hornet, white-faced hornet, wasp, and honeybee (Table II). All subjects had previously experienced an adverse reaction to Hymenoptera sting(s); 2866 (89%) reported an SSR in history. Seventy-four percent (2399) of all subjects tested had a positive VST to at least one venom; 2181 subjects had both an SSR in history and at least one positive VST. These subjects were 67% (2181/3236) of subjects tested, 76% (2181/2866) of subjects who reported an historical SSR, and 91% (2181/2399) of all HVS subjects with a positive VST.

LR were divided into two categories, large and small. An LLR was defined as a visible reaction ≥2 inches (5 cm), and a small LR as any visible LR <2 inches (5 cm). Of the 370 subjects who had only an LR in history, 59% (218/370) had a positive VST. Fifty-nine percent (173/296) of subjects with a history of LLR had positive VST compared to 61% (45/74) of subjects with an historical small LR.

In Table IIIA, the positive VST results are sum-

TABLE II. Frequencies of positive VST to one or more venoms

No. of venoms for which subject was skin test positive	All subjects tested (N = 3236) (%)	All with SR in HX (N = 2866) (%)	Only small LRs* in HX (%)	Only LLRs† in HX (%)	Total only LRs in HX (N = 370) (%)
Venoms					
1	853 (26)	741 (26)	18	94	112 (30)
2	380 (12)	341 (12)	10	29	39 (11)
3	357 (11)	333 (12)	6	18	24 (6)
4	522 (16)	497 (17)	8	17	25 (6)
5	287 (9)	269 (9)	3	15	18 (5)
Total subjects positive	2399 (74) ‡	2181 (76)	45 (61)	173 (59)	218 (59)
Negative skin test§	837 (26)	685 (24)	29	123	152 (41)
Total subjects	3236	2866 (89)	74	296	370

HX, History.

*Any visible reaction <2 inches (5 cm) and no reported SR.

†A visible reaction ≥2 inches (5 cm) and no reported SR.

‡Boxed figures are referred to in text.

§Did not meet criteria for positive skin test.

TABLE IIIA

Positive skin tests to specific venoms for 3236 HVS subjects tested; 2399 of these subjects (74%) had at least one positive skin test					
Venom	No. of subjects*	% (N) (N = 3236)	Mean wheal (mm)	Mean erythema (mm)	Mean concentration (µg/ml)
Yellow jacket	1675	51.8 †	17.3 ± 5.9	48.0 ± 17.6	0.45
White-faced hornet	1245	38.5	17.5 ± 5.8	46.3 ± 16.7	0.49
Yellow hornet	1130	34.9	17.6 ± 5.9	47.0 ± 17.1	0.54
Wasp	1082	33.4	17.4 ± 5.7	46.7 ± 17.2	0.58
Honeybee	1060	32.8	16.3 ± 5.2	44.7 ± 16.7	0.49
Positive skin tests to specific venoms for 2866 subjects with an SSR in HX. 2181 of these subjects (76%) had at least one positive skin test					
		% (N) (N = 2866)			
Yellow jacket	1561	54.5	17.3 ± 5.9	47.9 ± 17.7	0.45
White-faced hornet	1168	40.8	17.5 ± 5.8	46.3 ± 16.8	0.49
Yellow hornet	1056	36.9	17.6 ± 5.9	46.7 ± 17.1	0.54
Wasp	1016	35.5	17.4 ± 5.7	46.7 ± 17.3	0.58
Honeybee	954	33.3	16.2 ± 4.9	44.7 ± 16.9	0.50

HX, History.

*Many subjects reacted to more than one venom.

†Boxed figures are referred to in text.

marized by insect for all HVS subjects with at least one positive VST and for those subjects with a reported SSR and at least one positive VST. Also included in Table IIIA are the number of subjects with a positive VST to each venom type, the mean sum of the orthogonal diameters for both wheal and erythema and their standard deviations, and the mean venom concentration (micrograms per milliliter) inducing the

positive response (1+). More HVS subjects (51.8%) tested positive to yellow jacket than to any other venom.

The mean sum of the orthogonal diameter wheal size varied from 16.3 mm (honeybee) to 17.6 mm (yellow hornet), and the mean sum of the orthogonal diameter erythema size ranged from 44.7 mm (honeybee) to 48.0 mm (yellow jacket). The mean con-

TABLE IIIB

Positive skin tests to specific venoms for 2219 HVS subjects with SSR from MRSPES; 1693 of these subjects (76%) had at least one positive skin test					
Venom	No. of subjects*	% (N) (N = 2219)	Mean wheal (mm)	Mean erythema (mm)	Mean concentration (µg/ml)
Yellow jacket	1198	53.9	17.4 ± 6.2	48.0 ± 17.7	0.44
White-faced hornet	921	41.5	17.6 ± 5.8	46.6 ± 16.8	0.48
Yellow hornet	837	37.7	17.7 ± 6.1	47.2 ± 17.2	0.52
Wasp	797	35.9	17.4 ± 5.8	46.9 ± 17.2	0.57
Honeybee	729	32.9	16.3 ± 5.0	44.7 ± 16.8	0.48

Positive skin tests to specific venoms for 647 HVS subjects with no SSR in MRSPES and SSR in prior HX; 488 of these subjects (75%) had at least one positive skin test					
% (N) (N = 647)					
Yellow jacket	363	56.1	16.9 ± 4.8	47.6 ± 17.7	0.48
White-faced hornet	247	38.2	17.2 ± 5.7	45.3 ± 16.7	0.49
Yellow hornet	219	33.8	17.0 ± 5.0	45.1 ± 16.4	0.60
Wasp	219	33.8	17.2 ± 5.5	46.5 ± 17.6	0.59
Honeybee	225	34.8	16.0 ± 4.8	44.6 ± 16.9	0.55

MRSPES, Most recent sting prior to entry into study; HX, history.
*Many subjects reacted to more than one venom.

TABLE IIIC

Positive skin tests to specific venoms for 370 HVS subjects with only large or small LR in HX and no SSRs in HX; 218 of these subjects (59%) had at least one positive skin test					
Venom	No. of subjects*	% (N) (N = 370)	Mean wheal (mm)	Mean erythema (mm)	Mean concentration (µg/ml)
Yellow jacket	114	30.8	16.7 ± 5.7	48.8 ± 16.7	0.42
White-faced hornet	77	20.8	17.1 ± 5.5	45.0 ± 15.6	0.51
Yellow hornet	74	20	17.4 ± 6.0	50.1 ± 15.6	0.56
Wasp	70	18.9	17.2 ± 5.4	44.6 ± 15.8	0.52
Honeybee	117	31.6	16.5 ± 7.1	44.9 ± 14.9	0.43

Positive skin tests to specific venoms for 296 HVS subjects with LLR in HX and no SSR from any HX sting; 173 of these subjects (58%) had at least one positive skin test; 80% (296/370) of the reported LR without SSRs were LLRs					
% (N) (N = 296)					
Yellow jacket	90	30.4	16.9 ± 5.1	48.4 ± 16.8	0.39
White-faced hornet	57	19.3	17.8 ± 5.7	43.7 ± 16.0	0.50
Yellow hornet	55	18.6	18.3 ± 6.4	51.6 ± 19.5	0.51
Wasp	54	18.2	18.0 ± 5.4	44.0 ± 17.1	0.54
Honeybee	93	31.4	16.5 ± 7.8	45.9 ± 14.4	0.44

HX, History.
*Many subjects reacted to more than one venom.

centration of venom extract producing a positive (1 +) reaction varied from 0.45 µg/ml for yellow jacket venom to 0.58 µg/ml for wasp venom.
The size of the mean sum of the orthogonal diameter

wheal and erythema response and frequency of positive VSTs were similar, regardless of whether subjects had an SSR after their most recent sting or had an SSR previously (Table IIIB).

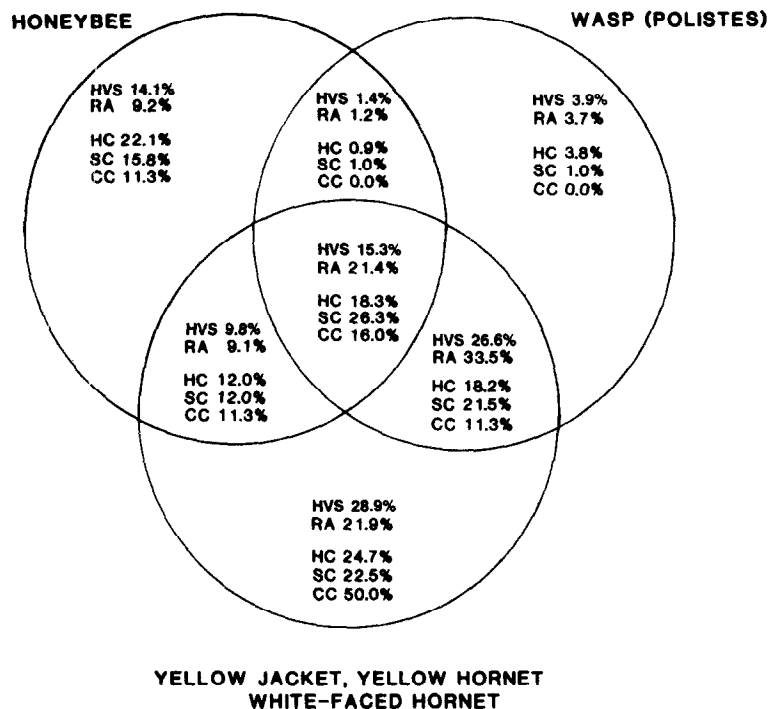


FIG. 1. Diagram of percentile incidence of positive VST and cross-reactivity to individual insects for the three studies and two groups referred to in text. *HVS*: adult, *N* = 1634; *RA*, Ramirez et al.⁸: adult, *N* = 164; *HC*, Hymenoptera venom study: children, *N* = 765; *SC*, Schuberth et al.⁴: children, *N* = 208; *CC*, Chipps et al.⁹: children, *N* = 44.

In subjects only with LRs (Table IIIC), the size of the LR did not influence the VST size, VST mean concentration, or frequency of positive VST for each venom. However, patients with LRs (Table IIIC) compared to patients with SSRs (Table IIIB) had lower frequencies of positive VST to all venoms except honeybee, although the mean VST size and venom concentrations for positive VST remained similar.

Of the 3236 subjects tested, 2399 (74%) had a positive VST to at least one venom. Four hundred subjects of 3236 were VST positive to honeybee alone, 331 of these subjects also had a reported SSR; 93 were positive to wasp alone and 82 had a previous SSR. Twenty-nine subjects were positive to both honeybee and wasp, with 24 of these subjects having had a previous SSR. Eighty-four subjects were positive to both yellow jacket and honeybee; eighty of these subjects had a history of SSR; 10 to yellow hornet and wasp, all with a history of SSR; 287 to all five venoms, 269 with an SSR; 304 to yellow jacket alone, with 276 with an SSR; and 132 to yellow jacket, yellow hornet, and white-faced hornet, with 123 of these subjects reporting a previous SSR. There were 6192 different positive VSTs for the 2399 subjects with a positive reaction to one or more venoms (average, 2.6 positive reactions per subject). The 2181 subjects with a history of an SSR represent 5755 positive VSTs,

which is also an average 2.6 positives per subject. When the frequencies of VST positivity observed in HVS are changed to percentages, comparisons of the VST pattern of reactivity in the HVS are easily made to other published studies (Fig. 1).

Sixty-four subjects (2.0% of the 3236) were reported to have experienced an SR during VST. The mean SRI for these SRs was 0.0825, considered to have been of moderate severity. A mild reaction with SRIs in the range of 0.003 to 0.009 was experienced by 53% (34) of the reactors (mean, 0.004). Twenty-six percent (17) of the SRIs of reactive subjects ranged from 0.013 to 0.122 (mean, 0.033) or of moderate severity. A severe reaction, ranging from 0.126 to 0.947 (mean, 0.3268) was experienced by 21% (13), including one subject who had and SRI of 0.947. This male subject with a VST SR developed pruritus, angioedema/urticaria, gastrointestinal symptoms, upper airway obstruction, a drop in blood pressure, shock, and unconsciousness.

Forty-two percent (1360/3236) of all the subjects participating in the study had been treated with WBE before entry into the HVS. Of the 64 subjects who developed an SR during VST, 29 (45%) had been previously treated with WBE, whereas 35 of these subjects (55%) had never been treated with WBE. The 29 WBE-treated subjects had a slightly lower mean

SRI (0.0621) associated with their VST SR than did the 35 subjects not previously treated with WBE (0.0996).

Thirteen of the 64 subjects had a severe reaction, 10 of whom experienced a drop in blood pressure and seven of whom had other, more severe reactions; that is, three subjects were reported as having shock and four subjects experienced unconsciousness. Thirty-nine percent (5/13) of these severe reactions were considered to have been vasovagal by the submitting physicians or the authors. The submitting physicians and authors* also identified possible vasovagal reactions in eight additional subjects from the 51 subjects classified as having experienced mild to moderate SRIs. Thus, 13 of the total 64 SRs (20%) reported during VST were designated as possibly vasovagal.

Three of the 64 SRs associated with VST occurred in subjects who had a history of having only experienced an LR in the past and no SSR. Their SRIs associated with VSTs were mild, that is, 0.003 (reported as a vasovagal attack), 0.003, and 0.013.

Six of the 64 subjects with VST SRs were reported to have had "other responses" and were assigned an SRI score of 0.003 and manifested no symptoms of anaphylaxis. The comments by the reporting physicians included pain in neck and arm, ran temperature and malaise, chest tightness, dyspnea, no wheezing, numerous extrasystoles, generalized weakness, and generalized ill feeling and thirst.

If the 19 subjects with presumed nonallergic reactions (13 vasovagal and six "other" reactions) are subtracted from the 64 reactors, the remaining 45 subjects (1.4% of all HVS participants) are presumed to have experienced allergic adverse reactions (SR) associated with VST.

DISCUSSION

A prevalence of 76% positive VST observed in the HVS in subjects with insect sting and with an SSR is consistent with prevalence rates reported by other investigators, for example, 71%² and 63% in adults³ and 89% in children.⁴ The 59% prevalence of positive VSTs in subjects with LR observed in HVS is similar

to the 57% observed by Green et al.⁵ in adults with LR but lower than the 84% reported in children with LLR.⁶ The discrepancies among these studies may be due to differences in technique in skin testing, for example, the volume of venom injected and the criteria for positivity used in the different studies. The remarkable similarity of prevalence, however, suggests that the HVS population's skin reactivity to VST is typical of venom reactivity of insect sting-allergic subjects.

The pattern of yellow jacket > white-faced hornet > yellow hornet found in HVS subjects with SSR (Table IIIA) has been previously observed.⁷ The overall pattern of VST reactivity observed in HVS subjects is similar to VST reactivity previously reported (Fig. 1) for insect sting-allergic populations of adults⁸ and children⁹ in whom the reported pattern of reactivity is yellow jacket, yellow hornet, and white-faced hornet > honeybee > wasp. The overall rates of reactivity to the venoms in the different age groups studied are remarkably consistent among studies despite differences in volume of venom injected and criteria for venom positivity.

In Tables IIIA through IIIC a large reference data base are provided for comparing future studies of insect sting-allergic subjects skin tested with licensed venoms and for responses quantitated as described in the HVS. These data demonstrate the remarkable consistency in size of skin test responses and mean concentration of venoms producing these responses when standardized venoms are used as specified, illustrating the value of standardization. Skin tests were not completely titrated in each subject with each venom; therefore, it is not possible to estimate the proportion of the population reacting with a specified skin response (e.g., a 1+ positive skin test) at the minimal concentration of each venom protein dose tested. The percent of sting-allergic subjects reacting at ≤ 0.01 $\mu\text{g/ml}$ has previously been estimated at 25% with 50% reacting at 0.1 $\mu\text{g/ml}$, and 25% reacting at 1.0 $\mu\text{g/ml}$ of venom protein.¹⁰

Prior studies of skin tests with Hymenoptera venoms were not performed and evaluated by the methods used in the HVS; therefore, absolute rates of reactivity are not likely to be similar among such studies, but relative rates of venom cross-reactivity, based on internal comparisons within studies, might be similar. Thirty-seven percent of honeybee-allergic subjects in the HVS reacted to honeybee venom alone, and 18% of yellow jacket-allergic subjects reacted to yellow jacket venom alone. Other studies of subjects allergic to honeybee have found these subjects more likely to

*The authors designated seven subjects (in addition to the six by the submitting physicians) as having reactions compatible with vasovagal reactions in the absence of additional hemodynamic data (see DISCUSSION) indicative of anaphylaxis because generalized pruritus, urticaria, angioedema, flushing, gastrointestinal symptoms, upper airway obstruction, and lower airway obstruction, all symptoms compatible with immediate hypersensitivity, were not reported.

be exclusively sensitive to honeybee venom, which contains fewer cross-reacting allergens than yellow jacket venom.¹¹ Similarly, >50% of subjects positive to wasp venom react to yellow jacket and white-faced hornet, but only 20% react to honeybee.³ Only 89 subjects of the HVS reacted to venoms of both honeybee and yellow jacket, yellow hornet, and white-faced hornet, whereas 357 subjects reacted to wasp and to yellow jacket, yellow hornet, and white-faced hornet. Eighty-nine percent (960/1082) of the HVS subjects reactive to wasp venom were also reactive to either yellow jacket, yellow hornet, or white-faced hornet venoms. This resembles the 92% rate previously reported⁸ confirming the high degree of common reactivity to wasp and yellow jacket, yellow hornet, and white-faced hornet venoms and the lower degree of shared reactivity between honeybee and these venoms.^{10, 11}

Adverse reactions after VST in a population as large as the HVS have not been previously reported. In two prior studies of 236⁸ and 33 sting-allergic subjects,¹² no adverse effects after VST were reported. In the HVS, SRs were observed in 64 of the 3236 sting-allergic subjects tested for an overall rate of 2.0%. The rates of adverse reactions were not affected by prior WBE immunization.

The major safety concern in VST is the remote possibility of inducing a serious SR. Separating the SR rate into allergic and nonallergic SRs reduces the rate of allergic SRs to 1.4%, of which 0.25% (8/3236) were serious. No cardiac or respiratory arrests were noted. In spite of the emotionally charged clinical situation of testing with venoms that are perceived as dangerous by physicians and their sting-allergic subjects, the rate of moderate/severe adverse reactions observed after VST in the HVS is low. It is less than that reported for blood donation (4%)¹³ but higher than that reported for venipuncture (0.5%)¹⁴ and prick-puncture allergy skin testing (0.04%)¹⁴ in a cross-sectional sample of the U.S. population. The low rate of adverse reactions to VST in the HVS resembles the adverse reaction rate of 1.0% observed after penicillin skin testing in subjects suspected of allergic adverse reactions to penicillin.¹⁵

The evaluation of adverse reactions to venoms requires discrimination between allergic SRs versus nonallergic (vasovagal) reactions. Physiologic studies of human anaphylaxis with profound shock after insect stings have recorded significant tachycardia (≥ 120 beats/min) with increase in heart rate of 70 beats/min over baseline in all subjects before pharmacologic intervention with epinephrine.^{16, 17} Sinus tachycardia was also observed in subjects with generalized cuta-

neous reactions (urticaria) after sting.^{16, 17} Despite tachycardia, when systolic blood pressure fell, it did so either after an initial and transient increase of 50 to 70 mm Hg before precipitously falling between 100 to 150 mm Hg or fell 70 to 80 mm Hg within several minutes of the sting.¹⁶

Tachycardia is not commonly associated with the vasomotor reactions resulting in hypotension during blood donation. The heart rate either remains normal or slows in these circumstances in association with the hypotension.¹⁸ Hypotension, in a phobic subject, however, is associated with an initial mild increase in heart rate and blood pressure of 10 beats/min and 10 mm Hg, respectively.¹⁹ This is followed, in subjects who faint or nearly faint, by significant bradycardia (average rate of 54 beats/min), an average drop in heart rate of 23 beats/min from baseline, and by a 10 to 20 mm Hg drop in blood pressure.¹⁹ The remarkable difference in hemodynamic response may help to discriminate between these two different mechanisms of hypotension. In either case, elicitation of other symptoms or signs of vasoactive mediator release, for example, pruritus, cutaneous warmth, flushing, and/or broncho- or laryngospasm, will assist in the proper diagnosis of allergic reactions. Similarly, measurement of peak flow or detection of wheezing will help to identify those dyspneic subjects with bronchospasm from subjects whose symptoms result from hyperventilation. Inspection of the upper airway will identify subjects with isolated laryngeal edema from subjects with globus hystericus. The correct identification of the serious allergic SR permits prompt institution of appropriate treatment.

The rate of moderate/severe adverse SRs observed in HVS after VST is similar to rates of other low-risk medical procedures.^{13, 14} Because catastrophic anaphylactic reactions have been reported to occur after allergen skin tests,²⁰ VST should be carried out with appropriate precautions for dealing with those rare instances when a serious allergic or nonallergic adverse reaction occurs.

We are grateful to the patients who participated in this study, to the physicians and their staff who contributed to the HVS, and to Patricia Walsh and Peggy Heles for their secretarial assistance. A list of participating physicians is included in reference 1.

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