

Exercise-induced anaphylaxis: a distinct form of physical allergy

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Seven individuals with exercise-induced anaphylaxis under natural circumstances, characterized by the appearance of pruritic cutaneous erythema and urticaria and associated vascular collapse and/or upper respiratory tract symptoms and signs of angioedema, were subjected to a controlled period of exercise in a laboratory. Experimental challenge consisted of running in an occlusive suit on a treadmill of moving grade with maintenance or acceleration of speed for 5 to 17 min. Cutaneous pruritus and erythema without urticaria developed in four of the subjects and progressed to angioedema in two of them; the other three subjects were unaffected. Repeat challenge of three of the abnormal responders elicited a clinical response similar to that of the previous exercise challenge. In those subjects with a clinical response to exercise challenge, mean change from baseline levels of histamine to peak levels was 7.0 ± 3.0 ng/ml (mean $\pm$ SEM), whereas in the group without clinical symptoms the mean change from baseline was an increase of 0.6 ± 1.6 ng/ml (mean $\pm$ SEM). The abnormal elevations in serum histamine during the seven exercise-induced symptomatic episodes returned to normal in about 20 min while clinical signs were also subsiding. There were no changes in pulmonary function. Exercise-induced anaphylaxis is clinically separable from cholinergic urticaria and represents a distinct form of physical allergy. (J ALLERGY CLIN IMMUNOL 71:311, 1983.)

Exercise-induced anaphylaxis is characterized by the sensation of cutaneous warmth and pruritus and the development of cutaneous erythema and urticaria with the common association of vascular collapse and upper respiratory tract obstructive symptoms.¹ About one half of those patients susceptible to these episodes have personal atopy, and a family history occurs in two thirds.² The conventional 10 to 15 mm diameter of the wheal, the failure of the episodes to develop with an increase in core body temperature from a fever or warm bath, and the prominence of vascular collapse in two thirds of the patients¹ rule against a diagnosis of classic cholinergic urticaria. In classic spontaneous cholinergic urticaria evoked by conventional exercise there is a sensation of generalized

warmth and pruritus, with the appearance of punctate wheals^{3, 4} and, rarely, pulmonary manifestations of wheezing or shortness of breath.⁵ Experimentally induced attacks by exercise in a plastic occlusive suit elicited the same punctate urticaria but with the uniform development of pulmonary symptoms in seven consecutive patients with cholinergic urticaria, along with documented alterations in pulmonary function and elevations in serum histamine concentrations.⁶ To distinguish further exercise-induced anaphylaxis from other physical allergies developing during exercise^{3, 7, 8} and from exercise-induced asthma,^{9, 10} seven patients with exercise-induced anaphylactic collapse¹ were subjected to exercise challenge in a plastic occlusive suit, and their clinical manifestations, pulmonary function, and serum histamine levels were assessed.

MATERIALS AND METHODS

Patient population

Seven individuals (Table I), two men and five women, ranging in age from 18 to 44 yr (mean 30 yr), experienced exercise-related episodes of pruritus and urticaria with progression to collapse if the exercise was continued in the presence of the initial symptoms. One of the group experienced cutaneous angioedema and hoarseness indicative of upper respiratory tract angioedema. The attacks occurred in a va-

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Abbreviations used

SGaw:	Specific airway conductance
FEV ₁ :	Forced expiratory volume in 1 second
MMF:	Maximum midexpiratory flow

riety of exercise-related settings, including running, playing paddle tennis, fast walking after a meal, and performing sitting-up exercises. Two subjects had allergic rhinitis and three had family histories of allergic rhinitis; three had no personal or family histories of atopy. Physical examination and laboratory assessments, during an asymptomatic state, of hematocrit, white blood count with differential analysis, erythrocyte sedimentation rate, and serum calcium, phosphorus, urea nitrogen, glucose, uric acid, total protein, albumin, bilirubin, alkaline phosphatase, lactic dehydrogenase, glutamic oxalacetic transaminase, and creatinine phosphokinase were normal for each patient. Immunochemical determinations of serum C1q and C4,¹¹ hemolytic assay of whole complement,¹² and measurements of IgG, IgM, IgA, and IgD¹³ were normal. IgE levels (Phadebas IgE PRIST Kit, Pharmacia Diagnostics, Piscataway, N. J.) were elevated in two patients.

Exercise challenge

The protocol for exercise challenge in the Pulmonary Physiology Laboratory of the Brigham and Women's Hospital was approved by the Human Subjects Committee, and each subject gave informed consent before entering the study and again before each exercise challenge.

Exercise challenge consisted of having the subject, non-fasting, run on the treadmill while wearing a plastic occlusive suit to reduce elimination of body heat.⁶ Initial running was at 5 mph with no grade, and the grade was increased to a 10 degree maximum with maintenance or acceleration of speed if possible. Duration of exercise ranged from 5 to 17 min and was interrupted when the subjects experienced fatigue.

Lung volumes and airway resistance were measured in a constant-volume, variable-pressure plethysmograph serially connected to an analogue recorder and a minicomputer.¹⁴⁻¹⁶ Airway resistance was expressed as a conductance-volume ratio termed SGaw.¹⁷ Five measurements of each variable were obtained at each time point and the mean was computed; the coefficients of variation were 5% or less. Spirometric measurements were performed in triplicate with a waterless spirometer. FEV₁ and MMF were computed by standard techniques. Pulmonary mechanics were measured before exercise and 5 to 10 min after its cessation. The paired *t* test was used to analyze alterations from baseline values; mean differences between previously studied control subjects⁶ and patients were analyzed with the unpaired *t* test.

Venous blood specimens were obtained at three intervals before exercise challenge, at interruption of exercise, and at subsequent intervals up to 20 min. Serum was aliquoted and stored at -70°C. Serum histamine levels were measured by a radioenzyme assay.^{18, 19} The relationship between the

serum histamine levels and clinical status of the patients was analyzed with the Mann-Whitney *U* test.²⁰

RESULTS

Exercise challenge in an occlusive suit in a laboratory setting failed to elicit symptoms and signs as marked as those experienced by the patients while exercising naturally. Abnormal responses to exercise appeared in only four of the seven subjects and were characterized by cutaneous pruritus and erythema without urticaria (Table II). Angioedema developed in four instances in two subjects, and on one occasion, symptoms of upper respiratory obstruction with coughing required epinephrine administration for relief. On rechallenge, this person developed a severe headache in addition to the aforementioned symptoms in milder form. No subject collapsed and blood pressure did not fall in any of the subjects. Wheezing was not auscultated at anytime. The pruritic sensation and erythema generally resolved within 30 min after the cessation of exercise.

There were no significant changes in pulmonary function in any subject as measured 5 to 10 min after cessation of exercise and at a time when other abnormal responses were manifest. Mean FEV₁ levels decreased 1.6% (from 3.68 ± 0.24 to 3.62 ± 0.22 L, mean ± 1 SEM) and MMF rose 2.6% (from 3.80 ± 0.32 to 3.90 ± 0.36 L/sec). SGaw did not change (baseline = 0.20 ± 0.01 L/sec/cm H₂O/L; response = 0.20 ± 0.02 L/sec/cm H₂O/L), and residual volume increased an average of 0.22 L (from 1.50 ± 0.11 to 1.72 ± 0.12 L). These values were not significantly different from the subjects' prechallenge values, and the pattern observed did not differ from that reported in a group of eight control subjects who exercised in a similar fashion.⁶

An exercise-related elevation in serum histamine, as compared with prechallenge individual values, appeared in five patients, of whom four experienced abnormal clinical responses (Fig. 1). In two of three subjects failing to experience a clinical episode, the histamine levels remained less than 1.0 ng/ml and did not change from prechallenge levels. The histamine levels at the height of the attack are shown in Table II. In those subjects with a clinical response to exercise challenge, the changes from baseline in histamine rose to mean peak levels of 7.0 ± 3.0 ng/ml (mean $\pm$ SEM), whereas in the group without clinical symptoms the mean increase was 0.6 ± 1.6 ng/ml (mean $\pm$ SEM). This difference between the responders and nonresponders was statistically significant at the 0.05 level (*U* = 1, *n*₁ = 3, *n*₂ = 4). Rechallenge by exercise after a 10 min rest in one subject and after 1 and 7 week intervals in two elicited a positive response that was similar to the initial experimentally

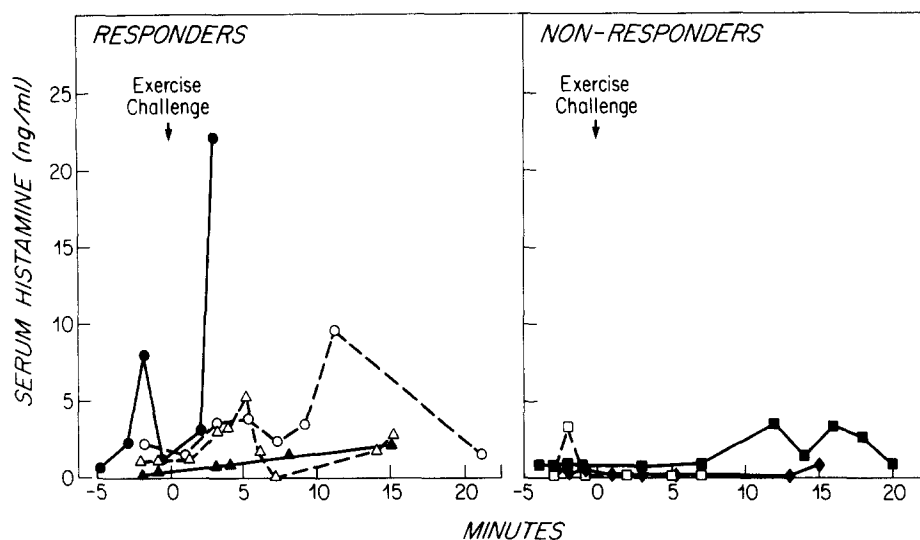


FIG. 1. Time-dependent serum histamine levels after experimental exercise challenge by running in a plastic occlusive suit, in seven patients with exercise-induced anaphylaxis by history. **Left**, Values for four patients experiencing clinical symptoms and signs. **Right**, Values for three patients failing to experience clinical manifestations.

TABLE I. Clinical features of exercise-induced anaphylaxis

Subject No.	Age (yr)	Sex	Age at onset (yr)	Clinical manifestations	Type of exercise	Atopy		IgE (IU/ml)
						Personal	Family	
1	33	M	23	Pruritus, urticaria, collapse	Running	Allergic rhinitis	None	2200
2	42	F	31	Pruritus, urticaria, collapse	Paddle tennis	Allergic rhinitis	Allergic rhinitis	225
3	18	F	16	Pruritus, urticaria, collapse	Running	None	Hymenoptera anaphylaxis	225
4	23	M	22	Pruritus, urticaria, collapse, choking, angioedema	Running	None	Allergic rhinitis	90
5	28	F	25	Pruritus, urticaria, collapse, choking	Running	None	None	20
6	44	F	27	Pruritus, urticaria, collapse	Fast walk after meal	None	Allergic rhinitis	350
7	24	F	20	Pruritus, urticaria	Sitting-up exercises	None	None	45

induced attacks in terms of distribution of symptoms and signs and relative elevation in serum histamine over baseline levels (Fig. 2). The abnormal elevations in serum histamine subsided within 20 min after cessation of exercise, whereas the clinical signs lasted somewhat longer.

DISCUSSION

Exercise-induced anaphylaxis was originally postulated to be a form of physical allergy distinct from cholinergic urticaria.¹ Although the reaction began with the sensation of cutaneous warmth and pruritus

and with the development of cutaneous erythema and urticaria, it was the dramatic occurrence of collapse in 12 and upper respiratory distress in 10 of the original 16 patients that prompted the designation exercise-induced anaphylaxis. When one of the original series (subject 2) and six additional patients were challenged by exercise in an occlusive suit, only four developed clinical manifestations, which in all but one case were mild (Table II) compared with the severity of the natural attacks (Table I). The elevations in serum histamine that accompanied the experimentally induced clinical attacks in the four reactive patients are consis-

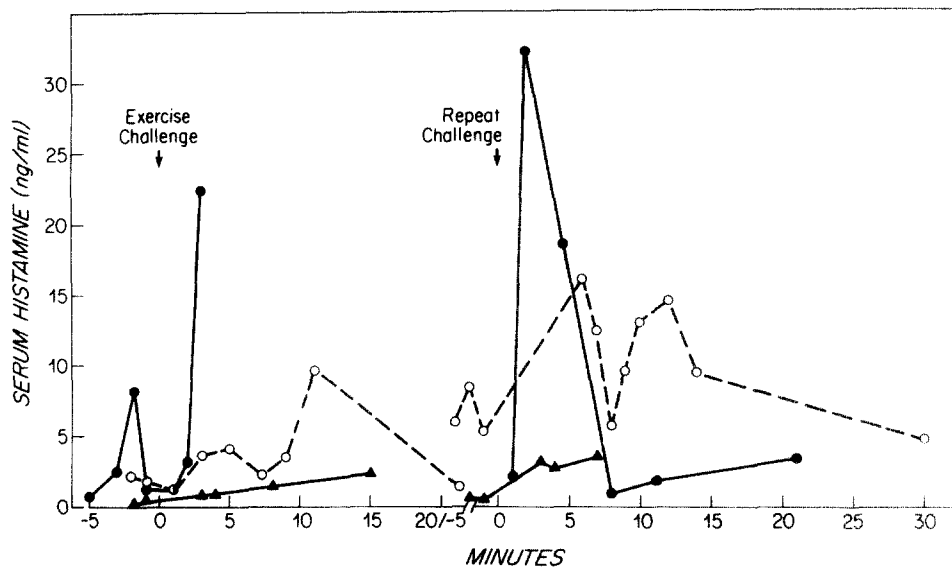


FIG. 2. Serum histamine levels in three patients with exercise-induced anaphylaxis who responded to the initial experimental challenge and were challenged again on the same day (●) or after an interval of 1 (○) and 7 (▲) wk.

TABLE II. Experimental exercise challenge of patients with exercise-induced anaphylaxis

Subject No.	Maximum exercise challenge			Challenge-induced symptoms	Peak histamine concentration (ng/ml)		Duration of symptoms (min)
	Duration (min)	Grade (deg)	Speed (mph)		Baseline	Exercise	
1	16	7	7	Pruritus, flushing, erythema	1.1	5.4	10
2	17	5	5	None	0.1	1.0	
3	15	5	5	Flushing, erythema	8.2	22.5	20
4	10*	5	5	Blotching, erythema, vertigo	2.0	32.3	20
	10	10	5	Pruritus, diaphoresis, choking indicative of angioedema, coughing (epinephrine required)	2.3	10.0	20
5	6†	10	5	Headache, pruritus, diaphoresis, coughing	8.8	16.2	30
	13‡	5	4.5	Flushing, erythema, pruritus, periorbital edema	0.8	2.1	15
6	10§	0	3	Mild periorbital edema	0.4	3.8	7
	5§	5-7	5	None	2.4	0.6	
7	5	5	5	None	1.8	0.1	
					0.9	3.5	

*After a 10 min rest.

†Repeat challenge 7 wk later.

‡Repeat challenge 1 wk later.

§Repeat challenge 20 wk later.

tent with a physical allergy, as observed in previous studies for experimentally induced attacks of cholinergic urticaria^{6, 8} and cold urticaria/angioedema.^{8, 21} When three of the reactive patients were subjected to repeat challenge in the laboratory setting, the clinical manifestations (Table II) and the associated elevations

in serum histamine (Fig. 2) were similar to those observed on the first occasion. In contrast, during four challenges of three patients who failed to experience symptoms, the serum histamine level increased in only one (Fig. 1).

The exercise-related systemic reactions with cuta-

TABLE III. Classification of exercise-induced physical allergy

Type	Precipitating event	Urticaria: morphology	Associated collapse	Bronchospasm		Elevated serum histamine
				Clinical	Functional	
Cholinergic	Heat, stress, exercise	Punctate (2-5 mm)	—	±	+	+
Variant	Exercise	Punctate	+	—	—	+
Anaphylactic	Exercise	Conventional (10-15 mm)	+	—	—	+

— = absent; + = present.

neous manifestations can be divided into three recognizable clinical patterns (Table III), each of which is considered to represent a distinct physical allergy because of the associated rise in serum histamine. Classic cholinergic urticaria elicited by exercise^{6, 8, 22} characteristically occurs without clinical vascular collapse and/or by an elevation in core body temperature. A variant of cholinergic urticaria was recognized in two of the 16 patients reported to have exercise-induced anaphylaxis¹; the attacks began with punctate urticaria and progressed to collapse in subjects who failed to develop punctate urticaria with elevations of core body temperature.¹ Two patients with this variant form of exercise-induced anaphylaxis were subsequently shown by others²³ to demonstrate a rise in histamine during experimental exercise challenge on a bicycle ergometric exerciser. Fourteen of the original 16 patients and each of the additional patients (Table I) developed exercise-related pruritic urticarial lesions of conventional size with progression to the associated manifestations of angioedema and/or vascular collapse. Because these attacks appear with exercise and in response to no other recognized physical stimulus, this group is distinguished from patients with classic cholinergic urticaria by the history and from those with the variant form by the nature of the cutaneous lesion. It could also be argued that the patients experiencing the punctate lesions are within the spectrum of exercise-induced anaphylaxis rather than representing a variant of cholinergic urticaria.

Of the six patients reported by Lewis et al.²⁴ as having exercise-induced urticaria, angioedema, and anaphylactoid episodes, three experienced punctate urticaria, which in two were elicited in the absence of exercise by external heat, fever, and/or emotional distress. Of the three experiencing exercise-related conventional urticaria, an experimental attack was elicited by free running in two, and one of these demonstrated a rise in the serum histamine level. The occasional reports of exercise-induced asthma in association with cutaneous lesions^{7, 24, 25} represent the occurrence of bronchial asthma in patients with an exercise-related physical allergy.

A striking feature of exercise-induced anaphylaxis

is the failure of an apparently identical exercise program to reproducibly elicit a natural attack.¹ The lack of predictability suggests an additional variable, which need not be uniform except for the likelihood of augmenting mast cell responsiveness to the physical event of exercise. Not only is a personal or family history of atopy common,^{1, 2} but three subjects have been reported in whom the ingestion of specific foods before exercise was defined as the additional critical variable.^{26, 27} Neither exercise alone nor ingestion of the specific food alone had an adverse effect. The simultaneous presence of two physical allergies, such as cold and cholinergic, has been recognized in four patients,^{6, 22, 24} and the presence of cold urticaria in a patient with exercise-induced anaphylaxis has been recognized in one instance.²⁴ A single patient in whom the experimentally exercise-induced attacks of urticaria and angioedema occurred in a reliable fashion exhibited an increase in both serum histamine and lactate.²⁸ A familial element has been noted in two families with multiple cases of exercise-related cutaneous symptoms progressing to collapse in one member of each family.^{29, 30}

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