

Postprandial exercise-induced anaphylaxis

Harold S. Novey, M.D., Ronald D. Fairshier, M.D., Kym Salness, M.D.,
Ronald A. Simon, M.D., and John G. Curd, M.D. Irvine and La Jolla, Calif.

A variety of systemic reactions associated with exercise are increasingly being recognized. We studied an atopic individual whose job-related activities involved strenuous running that often terminated in an episode of syncope and hypotension preceded by cutaneous pruritus, warmth, urticaria, and angioedema. These attacks occurred only after meals, but no foods appeared to elicit symptoms without subsequent exercise. The subject underwent three exercise challenges in the laboratory under the following conditions: (1) fasting state, with heat-dissipating clothing, (2) fasting, with heat-retention clothes, and (3) after a meal. Blood pressure decreases and minimum skin reactivity were observed for (1) and (2), and reproduction of syncope, hypotension, and further cutaneous manifestation were observed only after (3). Venous and arterial plasma determinations for complement activation (C4, C4d, and CH₅₀) and histamine before, during, and after exercise were not abnormal. Although other vasodepressor mediators may have been liberated, at least part of the mechanism for postprandial exercise-related syncope may be attributed to a shift of blood flow to the splanchnic as well as skeletal muscle vasculature. (J ALLERGY CLIN IMMUNOL 71:498, 1983.)

Systemic reactions associated with strenuous exercise have been subjects of frequent reports since 1979.¹⁻⁹ The reactions vary from seemingly life-threatening ones manifested by diffuse pruritus and erythema, urticaria, angioedema, asthma, arrhythmias, and vascular collapse, to milder ones encompassing two or more of these findings. Predisposing events in the form of either a specific food or any meal have been evident in a few,^{1, 8} and a familial tendency is suggested in some reports.^{2, 5, 7} Although a likely heterogeneous group, they are to be distinguished from idiopathic anaphylaxis, in which exercise is not a factor, and exercise-induced asthma, in which asthma is the sole reaction. Asthma is either absent or not a prominent feature of exercise-induced anaphylaxis.⁶

The subject of this study experienced seven episodes of pruritus, erythema, angioedema, and syncope only after strenuous running had been preceded 1 to 2 hr by a meal. In an attempt to evaluate this

disorder, the patient was studied in an exercise laboratory where monitoring of physiologic and biochemical parameters could be performed.

CASE REPORT

The patient, a 41-yr-old deputy sheriff, was referred to one of the authors by the physicians who had treated him for shock at another hospital's emergency room 3 wk earlier. The patient had been well that day when he lunched at 2 P.M. on a cola drink, pastrami sandwich with lettuce, mustard, and salad dressing, and french fried potatoes, and he performed desk chores for an hour afterwards. He then led a group of police cadets in a running exercise. After about 1.5 miles of running he was sweating as usual but also experienced itching on his back, which progressed to unbearable itching over much of his trunk and extremities. He returned to his locker, broke open a 50 mg diphenhydramine hydrochloride capsule, swallowing the powder for quicker relief. There was no relief of the pruritus within 15 min or after a cold shower. While drying himself, he suddenly passed out, striking the right side of his face and scalp on the bench. He awoke with an urge to defecate but lost consciousness again near the toilet. A fellow officer summoned paramedics. The patient was next aware of their presence and of vomiting part of his lunch. His throat and chest felt constricted but no wheezing was heard.

The paramedics could not detect any BP. They placed the patient in a MAST suit (military or medical antishock trousers), started intravenous fluids, and transported him to the hospital. In transit, a BP of 60/0 mm Hg was measured. At the emergency room, physicians recorded puffy eyelids,

From the Department of Medicine, University of California, Irvine, and the Department of Clinical Research, Scripps Clinic and Research Foundation, La Jolla, Calif.

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Reprint requests to: Harold S. Novey, M.D., Division of Basic and Clinical Immunology, University of California, Irvine, Medical School, 101 City Drive South, Orange, CA 92668.

Abbreviations used

E _{max} :	Maximum exercise
$\dot{V}_E$:	Expired minute volume
$\dot{V}O_{2\max}$:	Maximal oxygen consumption
AT:	Anaerobic threshold
V _d /V _t :	Physiologic dead space to tidal volume ratio
A-a PO ₂ :	Alveolar-arterial oxygen gradient
BP:	Blood pressure
HR:	Heart rate
KPM:	Kilopondmeters
PEFR:	Peak expiratory flow rate
FEV ₁ :	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
CH ₅₀ :	Total hemolytic complement activity

swelling of the fingers, a pulse rate of 90 regular beats per minute, normal respiration, and a BP of 98/70 mm Hg. After treatment with 0.4 mg epinephrine (subcutaneous), 250 mg hydrocortisone, 2 units of Plasmate (250 ml each), and 30 mg KCl, all intravenously, his BP rose to 150/70 and the patient felt normal.

The chronologic tabulation of the BP, HR, complete blood counts, and the electrocardiogram readings is shown in Table I. There was no eosinophilia, thrombocytopenia, or reticulocytosis. Urinalysis, blood chemistries, cardiac enzymes, thyroid function panel, and serum protein electrophoresis were normal. A serum and urine panel for hypnotics, narcotics, analgesics, and stimulants detected only diphenhydramine and hydrocortisone. The chest radiograph was negative, but the initial electrocardiogram recorded T-wave inversions in leads 2, 3, avf, and V₆. However, a subsequent thallium cardiac scan and an exercise treadmill test were normal and the cardiologist found no pathologic cardiac conditions.

This episode occurred on October 27. Six prior attacks had been recorded on February 7 and 28, March 23 and 26, and October 13 and 16. Each episode came 1 to 2 hr after a meal. Exercise was free running with the single exception of a volleyball game. Treatment at a hospital emergency room was sought twice. No common food was detected.

Past history revealed eczema at 2 yr and asthma from 7 to 15 yr, with recurrent mild hay fever. He sustained a skull fracture at age 10 without loss of consciousness. Drug reactions, hives, and insect sensitivity were denied. There was a 22 pack-year smoking history, excess alcohol was denied, and there was no history of cardiovascular disease.

Allergy diagnostic tests

Scratch tests to a panel of 80 common allergens (all 1:20 w/U, obtained from Hollister-Stier, Spokane, Wash.) produced major reactions to multiple grass, tree, and weed pollens. Smaller and barely positive reactions occurred to the following foods: strawberry, halibut, rice, peach, coffee, and tea, but not to wheat, milk, cola, egg, beef, or pork.

MATERIALS AND METHODS

Experimental protocol

The patient was studied on 2 separate days, 1 wk apart. The first test (study 1) was performed with the patient fasting for the previous 8 hr and wearing light clothing. The second test (study 2) was performed 2 hr later with the patient still fasting but wearing a tight plastic suit under a sweat suit, thereby allowing minimal heat dissipation, as described by Soter et al.¹⁰ One week later, the third test (study 3) was performed with the patient wearing light clothing 60 min after a lunch similar to the one described in the Case Report.

Exercise was performed on a cycle ergometer (Elema-Schonander Type AM 368). The incremental work-rate protocol consisted of 4 min of unloaded cycling followed by 4 min of cycling at different work levels until the patient was maximally exercised; the work levels were 400, 800, 1200, 1600, and 2000 KPM/minute (the highest possible cycle ergometer level).

Arterial blood samples were obtained from an indwelling radial artery catheter and venous specimens from an indwelling antecubital venous catheter. Arterial and venous samples were taken just before exercise and then during the last minute of exercise at each work level, at E_{max} immediately after exercise and 10 min after exercise. Arterial BP was monitored by connecting the radial artery catheter to a pressure transducer (Bell & Howell, Type 4-327-I) and the VR-6 recorder. Electrocardiographic monitoring was performed throughout the study. Pulmonary function tests and arterial blood gas analyses were done prior to and 10 min after each exercise study.

Physiologic measurements

PEFR, FEV₁, FVC, and the ratio FEV₁/FVC% were determined with a pneumotachograph (Merriam Instrument Div., The Scott & Fetzer Co., Cleveland, Ohio; Model 50 MC2-2) connected to a differential pressure transducer and a carrier demodulator (Validyne Engineering Corp., Northridge, Calif.). The signal was amplified and displayed by a physiologic recorder (Electronics for Medicine, Inc., Pleasantville, N.Y.; Model VR-6) and stored on a computer (Digital Equipment Corp., Marlboro, Mass.; Model PDP 11-34); the pneumotachograph signal was also integrated by the computer to obtain FVC. Arterial blood gas analyses were done by means of standard electrode techniques.

During the exercise studies, the patient breathed through a Koegel Y-valve connected to the pneumotachograph, differential transducer, VR-6 recorder, and computer as described. The pneumotachograph signal was integrated to determine $\dot{V}_E$; inspired minute volume was obtained from $\dot{V}_E$ and from expired gas measurement by means of the Haldane transformation.¹¹ Expired air was sampled just distal to the Koegel valve and routed through a condensing dryer¹² into an oxygen analyzer (Beckman Instruments, Inc., Palo Alto, Calif.; Model OM11) followed by a medical gas analyzer (Beckman, Model LB 2). The data were amplified and displayed by the VR-6 recorder and digitized by the computer. Ventilatory measurements were made on a

TABLE I. Chronology of cardiovascular measurements after exercise-related syncope

Location	BP (mm Hg)	HR (beats/min)	Hb (gm/dl)	Hct	WBC ($\times 10^3$)	Polys (%)	Lymphocytes (%)	ECG
Field	0/0							
Field, after MAST suit, IV fluids	60/0							
Hospital ER								
During T (epinephrine, hydrocortisone, KCl, plasmate)	98/70	90	19.0	57	11.4	45	54	Nonspecific ST, T abnormality
Immediately after T	150/70	80						
4 hr after T	114/70		15.7	45	16.6	93	6	
14 hr after T	116/70	50	14.9	44	13.8	81	17	Sinus bradycardia, reversal of ST, T-wave changes
72 hr after T	114/70		14.6	43	8.6	67	23	

Hb = hemoglobin; Hct = hematocrit; WBC = white blood cells; Polys = polymorphonuclear cells; T = treatment; ER = emergency room; IV = intravenous; ECG = electrocardiogram.

TABLE II. Pulmonary function test results* before and 10 min after exercise

Parameter	Before exercise	After exercise
FEV ₁ (L)	3.7	3.9
FEV ₁ /FVC (%)	4.8	4.9
FEV ₁ /FVC (%)	81.4	81.5
PEFR (L/sec)	10.5	10.1
Pao ₂ (mm Hg)	93	108
Paco ₂ (mm Hg)	40	31
pH	7.40	7.22
A-a Po ₂ (mm Hg)	10	12
Vd/Vt (%)	27.1	25.9

Pao₂ = arterial oxygen tension; Paco₂ = arterial carbon dioxide tension.

*Pulmonary function tests were performed before and after each exercise challenge. Since the data were very similar on each occasion, mean results are presented in this table.

breath-by-breath basis, averaged, and reported for each 15 sec interval of the study.

In addition to the variables already noted, exercise measurements included $\dot{V}O_{2\max}$, oxygen consumption at the AT, carbon dioxide production, oxygen pulse, respiratory rate, tidal volume, Vd/Vt, and the A-a Po₂. Results from this patient were compared with results from 10 similarly aged, identically tested fasting normal subjects (eight men, two women) participating in an exercise research program in our laboratory.

Biochemical measurements

Nearly simultaneously obtained arterial and venous blood samples, 10 ml each, were kept frozen at -20°C until they were subjected to histamine and complement assays. Freez-

ing at -20°C is adequate for preservation of the histamine¹³ but might lead to artifact in complement assays compared with freezing at -70°C . This artifact, though, always appears as activation of the complement system. Ten paired specimens were assayed for each of the three challenges for a total of 60 determinations.

The histamine assay was a modification of the automated fluorometric assay of Siraganian,¹⁴ with a sensitivity limit of 1 ng histamine/ml plasma. The following modifications were made: isobutanol in place of *n*-butanol and heptane, sulfuric acid instead of hydrochloric acid, and elimination of the Brij reagent. The reagents were adjusted so that the solution just prior to the phosphoric acid has a pH from 11.5 to 13.5, which was then brought down to a pH from 2.0 to 4.0 by the phosphoric acid before entering the fluoronephelometer. Blood was collected in plastic syringes and then transferred to heparinized glass Vacutainers. This technique has not inhibited our finding significant elevations of histamine in the past.¹³ The following complement studies were performed: CH₅₀, complement components C1q, C2, C3, C5, properdin, and factor B by immunoprecipitation techniques,¹⁵ and tests for complement activation by a rocket electrophoresis method to detect C4 and C4d.¹⁶

RESULTS

Pulmonary function and gas exchange results before and 10 min after exercise

Baseline (resting) pulmonary function was normal, as was gas exchange on all three studies (Table II). Ten minutes after exercise there were no significant changes from baseline values of FEV₁, FVC, FEV₁/FVC, or PEFR. Arterial blood gas studies demonstrated metabolic acidosis and hypocapnia after exercise, reflecting anaerobiasis and increased alveolar ventilation. The Pao₂ was increased after exercise,

TABLE III. Cycle ergometer exercise results*

Parameter	Result
$\dot{V}_E$ (L/min)	137
V_T (L)	3.33
f (breaths/min)	41
HR (beats/min)	177
AT (L/min)	2.38
$\dot{V}O_{2\max}$ (L/min)	4.12
$\dot{V}CO_2$ (L/min)	4.74
Oxygen pulse (ml/beat)	23.1
PaO ₂ (mm Hg)	100
Paco ₂ (mm Hg)	33
pH	7.25
A-a PO ₂ (mm Hg)	20
Vd/Vt (%)	9.9

V_T = tidal volume; f = respiratory rate.

*The results in this table were all obtained at maximum exercise excepting $\dot{V}O_2$ at the AT. Since the results presented in this table were very similar in all three exercise challenges, mean data are presented in this table.

with very little change in the alveolar-arterial PO₂ difference.

Exercise results

Exercise capacity was normal in all three tests (Table III); for the three tests, the mean $\dot{V}O_{2\max}$ was 4.12 L/min (46.7 ml/kg/min). Heart rate and O₂ pulse at Emax (1600 KPM/min) reached the predicted normal values. PaO₂ values remained equal to or higher than resting values throughout exercise; mild widening of the A-a PO₂ was observed at Emax. The ratio Vd/Vt was normal at rest, decreased with exercise, and returned to values close to baseline 10 min after exercise. Arterial BP was normal at rest. During exercise, BP initially increased appropriately on all three studies. However, after all three exercise studies, mean BP fell to levels well below the resting values (Fig. 1). The reduction in BP was most evident after the postprandial exercise study. The patient's mean BP fell to 57 mm Hg 10 min after exercise; at this time the patient became syncopal. He recovered to baseline after 30 min at rest in a supine position. The subject said that he had experienced a recurrence of the attack, except for pruritus, that culminated in his most recent emergency room visit (see Case Report).

Control subjects

These subjects had normal responses to exercise.^{17, 18} Representative average values for this group included a $\dot{V}O_{2\max}$ of 3.78 L/min (48.6 ml/kg/min), maximum HR of 182 beats per minute, oxygen pulse of 20.9 ml/beat, and an AT of 2.27 L/min. Increased

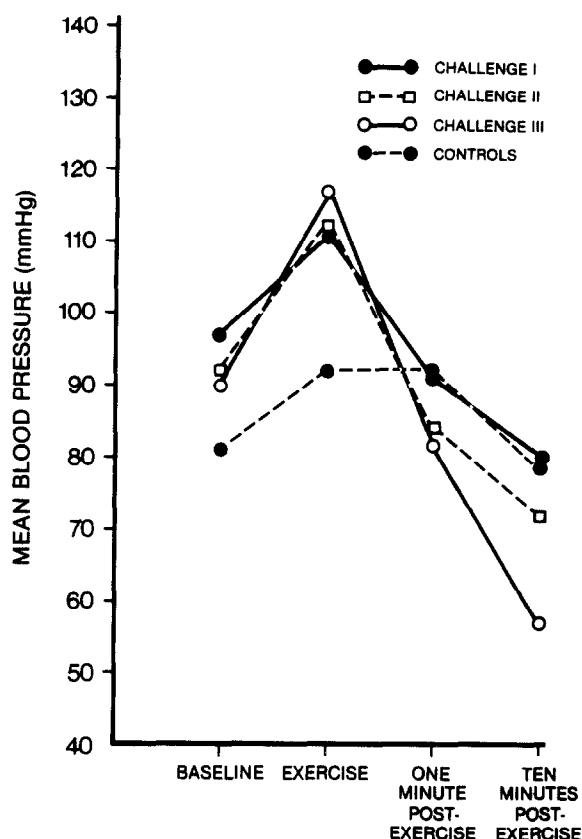


FIG. 1. Changes in mean intra-arterial BP (mm Hg) associated with exercise in our subject and in normal controls. The BP curve for the controls represents the lower 95% confidence limit (lower limit of normal). For situations where abnormality is unidirectional, this lower limit corresponds to the group average minus 1.645 SD.²⁵ For all three exercise challenges, our subject's postexercise BPs decreased to values well below his baseline and became most pronounced in the postprandial study (challenge III). In contrast, the BPs in the controls after exercise in the fasting state did not diminish. Postprandial exercise in normal subjects was not studied.

tidal volume and respiratory rate, decreased Vd/Vt, and mild widening of the A-a PO₂ were also observed at Emax. Mean BP was 94 ± 8 mm Hg at rest, 107 ± 9 mm Hg during exercise, 105 ± 8 mm Hg 1 min after exercise, and 95 ± 10 mm Hg 10 min after exercise.

Skin reactions

Exercise studies 1 and 2 produced three to four small urticarial lesions (2 to 4 mm in diameter) on the back at areas of profuse sweating. Dermatographism was minimally increased over baseline levels when performed by gentle stroking of several areas with a rounded object. Changes were most pronounced after study 3. Bilateral supraorbital edema and left suborbital edema appeared. Dermatographism was elicited,

and pressure areas under the electrode tapes were edematous and erythematous. Generalized urticaria, angioedema, or erythema, however, did not occur.

Biochemical studies

Histamine and complement activation assays. None of the venous plasma determinations of histamine were over the detectable limit of 1 ng/ml except one value of 4 ng in the fourth sample in exercise study 1. The arterial plasma levels were not elevated except for slight increases in sample 2, study 1, of 2 ng, and samples 5 to 8, study 2, with respective values of 1.5, 4, 2, and 2 ng/ml. Study 3, in which the patient experienced the most profound reactions, did not produce any histamine elevations among the 20 specimens assayed.

Neither the venous nor arterial plasma specimens assayed showed evidence of complement component or CH₅₀ abnormalities or of complement activation by C4 and C4d analysis.

Progress note

During a 6 mo follow-up period in which the patient continued his work-related exercises but refrained from eating for 6 hr before, no further anaphylactic episodes have occurred.

DISCUSSION

The patient and his primary physician suspected that the anaphylactic reactions were a consequence of sensitivity to an unspecified food and were enhanced in some manner by exercise. Indeed, similar reactions between food and exercise-related anaphylaxis have been reported. Shellfish was incriminated in one patient¹ and celery in two others.⁸ In these cases, skin tests for the ingestants were strongly positive. While our patient may be sensitive to a specific food allergen, none was detected either by history or by skin tests to major ingredients in the meals associated with two of his syncopal attacks. Another difference between our subject and the shellfish reactor was the latent period between the meals and the exercise-induced reactions. In contrast to the 1 to 2 hr postingestion response in our patient, the other had his exercise reactions from 5 to 24 hr after eating shellfish.

The mechanism for the hypotension in some cases of exercise anaphylaxis has been attributed to a plasma volume shift resulting from generalized urticaria and angioedema.² Several patients who developed exercise-induced urticaria, usually without hypotension, were discovered to have elevated plasma histamine levels (>10 ng/ml) either during exercise or 10 to 20

min after exercise.^{3, 6, 10, 19, 20} Subjects who did not develop urticaria from exercise had no such histamine changes.^{19, 20} Exercise is known to increase whole blood histamine presumably as a result of associated leukocytosis but increased plasma histamine after exercise had not been reported until one patient was shown by Mathews and Pan¹⁹ to have such findings. Their subject's hyperhistaminemia developed, however, only with cold-induced urticaria or after exercise that produced asthma and dermatographism. Increased plasma histamine levels were not induced after exercise in six normal nonatopic persons, nine asthma patients, two with cold urticaria, and another with dermatographism. Harries et al.²⁰ measured whole blood and plasma histamine after exercise in six normal and 17 asthmatic subjects. There was no significant difference in levels between the two groups. While the plasma histamine level rose only 1.1 ± 1.56 ng/ml, whole blood histamine reached a peak 10 min after exercise of 31.25 ± 10.4 ng/ml. This peak coincided with the peak basophilia and a near doubling of the total white cell count. Only one patient had a large rise in plasma histamine as well as whole blood histamine, and he had developed acute urticaria with exercise. Our patient developed syncope and hypotension in the exercise laboratory as he did naturally, but he did not have pronounced urticaria or angioedema on any occasion. The challenge with the occlusive suit also failed to elicit cholinergic urticaria contrary to the subjects of Soter et al.¹⁰ Although they used the treadmill for exercise activity and we used the cycle ergometer, both of us exercised the subjects to exhaustion. Moreover, we failed to detect significant plasma histamine elevations in a total of 60 specimens obtained from both venous and arterial sources. Although there was also no evidence of significant complement activation or changes in complement levels, it is possible that anaphylatoxins may have been released locally or into small vessels. The measurement of C4 activation used here has been shown to be more sensitive than CH₅₀ for detecting activation of complement in plasma.¹⁶

That profound vasodilation was mainly responsible for the patient's lack of BP during the field examination is suggested by the vascular response to the MAST suit. This device, designed to increase external pressure on the lower extremities and abdomen, is believed to reverse hypovolemic shock by a combination of redistribution of venous blood flow above the diaphragm and elevation locally of peripheral vascular resistance.²¹ On the other hand, the initial hemoconcentration (Table I) is more compatible with third spacing of fluid from factors other than vasodilation

such as release of capillary permeability mediators. However, the mechanism for the hemoconcentration is obscured by the various medical interventions.

Cardiovascular reactions may also be induced by hypoxia from respiratory insufficiency, cardiac arrhythmias, and coronary or myocardial pathology.² Our subject's pulmonary response to exercise was normal. The reduced Vd/Vt during exercise is a normal finding and suggests an intact pulmonary vascular bed.^{16, 17} The observed mild widening of A-a PO₂ is the expected finding at Emax.^{16, 17} His normal before and after exercise spirometric values also serve to rule out airflow pathology, including exercise-induced asthma.

There were no cardiac arrhythmias or ST, T-wave abnormalities during the continuous electrocardiographic monitoring on our three exercise challenges. Normal cardiac function is also indicated by his normal maximum heart rate, O₂ pulse, and the normal VO₂ at the anaerobic threshold and at Emax. In addition, the previously normal treadmill test and thallium study tend to exclude ischemic heart disease.

Considerations other than histamine effects and cardiopulmonary disease might be responsible for the exercise-induced hypotension. Blood flow through vascular beds during exercise (and rest) is influenced by mechanisms that change the diameter of the resistance vessels and the contractibility of the precapillary sphincter. These involve (1) sympathetic tone, (2) circulating hormones, and (3) local metabolites.²² Histamine, the most potent vasodilator among the local metabolites, was apparently not a factor here. Other local metabolites, i.e., lactic acid, CO₂, and H⁺, based on values obtained from the arterial blood pH, PCO₂, and base excess measurements, were within the range of our control subjects.

Circulating hormones were not studied in our patient. Exercise usually elevates the serum catecholamines, norepinephrine, and epinephrine.²² Of the two, epinephrine may have a vasodepressor effect, especially in high doses. As the alpha-adrenergic effect of the hormone wanes, the beta effect may predominate in the large arteries believed to have more beta than alpha receptors.²³ Suggestion that a beta receptor-mediated metabolic or neurogenic mechanism could be operative arises from a report of exercise-induced syncope in a cardiac patient, which was prevented by pretreatment with pindolol, a beta blocker.²⁴ Cortisol levels have been found to be low in a rare group of patients who experience hyperpyrexia during general anesthesia but only when food was taken in combination with exercise.²⁵ However, the hypocorticism was not associated with syncopal

reactions as occurred in our subject. Although hypoglycemia may appear during exercise and even cause exaggerated rises in plasma epinephrine,²⁶ this effect predominates after longer periods of exercise than involved in our patient. Moreover, syncope was not reported to be associated with the exercise-induced hypoglycemia. In addition, our patient recovered without intake of glucose.

While the mechanisms for our patient's unusual response to exercise are unclear, it is evident that an abnormal tendency toward postexercise hypotension exists (Fig. 1), even without food intake. Perhaps he has an aberrant sympathetic tone or beta-receptor sensitivity to exercise. Studies with a tilt table or pretreatment with a beta-adrenergic blocker to assess these respective factors might have provided additional information. Whatever the etiology of this vasolabile tendency, it is amplified when a meal precedes exercise by 1 to 2 hr. It has been shown that a well-conditioned male shifts over 85% of his local cardiac output to the skeletal muscles during heavy exercise.²² Part of this shift is compensated for by a 23% decrease of the splanchnic blood flow from the resting state. This compensatory mechanism would be interfered with by digestion of a meal and could well enhance an already existing tendency for orthostatic hypotension after exercise.

Thus, although mechanisms for exercise-induced anaphylaxis may involve allergic reactions to foods as well as plasma histamine elevations in some subjects, the syndrome appears to encompass a heterogeneous group of individuals and reactions. While postprandial exercise-induced anaphylaxis is an entity, its pathogenesis in this case may stem from mechanical rather than immunologic factors.

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