

Diagnostic work-up for food-dependent, exercise-induced anaphylaxis

Romano A, Di Fonso M, Giuffreda F, Quarantino D, Papa G, Palmieri V, Zeppilli P, Venuti A. Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. *Allergy* 1995; 50: 817–824. © Munksgaard 1995.

Fourteen patients with suspected food-dependent, exercise-induced anaphylaxis (EIAN) were subjected to prick tests with commercial food extracts and common airborne allergens, prick + prick tests with fresh foods, determination of total IgE levels, and specific IgE for 31 foods (CAP System FEIA RAST). All were positive for two or more foods; 10 presented hypersensitivity to 11 or more foods. On the basis of these findings, history data, and responses to food-exercise challenges (treadmill stress tests 90 min after meals containing none of the suspected foods and none associated with skin-test and/or RAST positivity) and suspected food-exercise challenges (SFECs – administered after meals containing the suspected food), three patients were diagnosed as having specific food-dependent EIAN (for wheat in two cases, tomato in one). In nine others, the presence of specific IgE for numerous foods (including those suspected on the basis of histories and utilized in the SFECs) suggests involvement of specific food hypersensitivity, although SFEC confirmation could not be obtained. Avoidance of all foods associated with test positivity 4 h before exercise has prevented all further EIAN episodes in these 12 patients. In two others, the reactions did not appear to be related to IgE directed against specific food allergens, and these subjects have eliminated further reactions by avoiding all meals for the 4 h preceding exercise. These findings emphasize the importance of allergologic testing with a wide panel of food allergens (including foods used for seasoning, such as garlic or parsley) in all patients with suspected food-dependent EIAN. Prick + prick tests with fresh foods and the CAP System RAST disclosed numerous hypersensitivities.

A. Romano, M. Di Fonso, F. Giuffreda, D. Quarantino, G. Papa, V. Palmieri, P. Zeppilli, A. Venuti

Istituto di Medicina Interna e Geriatria and
Centro Studi di Medicina dello Sport, Università
Cattolica del S. Cuore, Rome, Italy

Key words: anaphylaxis; exercise; food hypersensitivity.

Dr Antonino Romano
Istituto di Medicina Interna e Geriatria UCSC
Complesso Integrato Columbus
Via Pineta Sacchetti, 506
00168 Rome
Italy

Accepted for publication 5 July 1995

Exercise-induced anaphylaxis (EIAN) is a severe reactive syndrome that can be provoked by any type of physical exertion (23). The initial symptoms include flushing and pruritus, followed by generalized urticaria and, in many cases, angioedema. If exercise continues, symptoms may extend to the upper and lower airways (cough, laryngeal stridor, bronchospasm), gastrointestinal tract (nausea, cramps, vomiting, diarrhea), and the cardiovascular system (hypotension and vascular collapse).

There have been a number of reports of patients who developed EIAN only when exercise occurred after eating (food-dependent EIAN – FDEIAN). In some cases, the episode was linked to the ingestion of certain foods (specific food-dependent EIAN – SFDEIAN) prior to physical exercise. These reactions appear to be IgE-mediated in light of the re-

ports of skin-test and/or RAST positivity for the foods reportedly consumed prior to the EIAN, such as shellfish (4, 9, 16, 17), wheat products (2, 4, 10, 13), vegetables (11, 21, 25), fruits (1, 3, 4, 15), and, in one case only, hen's egg (9). However, ingestion of the implicated food without subsequent physical exertion is not sufficient to provoke the systemic allergic reaction. In 1983, Kidd et al. (11) used the term "nonspecific food-dependent EIAN" (NSFDEIAN) to describe a patient who suffered anaphylactic reactions whenever he engaged in postprandial exercise (regardless of the composition of the meal). There was no evidence of food hypersensitivity in this case, and the authors hypothesized that the reactions might have been caused by nonreaginic mechanisms. Similar conclusions have been reached by other authors (4, 9, 18) regarding patients with

histories that are strongly suggestive of FDEIAN but negative in all allergologic tests for foods consumed prior to previous reactions.

The mechanism by which physical exertion provokes these reactions is still poorly understood, but an important role seems to be played by mast cells, and, in particular, a decrease in their threshold for histamine release after exercise (4, 24). In patients with SFDEIAN, exercise-induced mast-cell release of histamine may be increased when patients are previously exposed to foods to which they are sensitive (4). In addition, several groups have found significant correlation between positive responses to exercise challenges after meals with suspected foods and postexercise plasma levels of histamine in patients with SFDEIAN (3, 4, 10). The ability of gastrin to influence histamine release by tissue mastocytes (26) and the autonomic nervous system abnormalities noted in patients with FDEIAN (9) are probably also relevant to the pathogenesis of this syndrome.

The increasing number of reports of EIAN during the last few years is not only a reflection of greater physician awareness of this syndrome, but also of the increasing emphasis placed on exercise and sports. The unpredictable and life-threatening nature of these reactive episodes may discourage amateur or even professional athletes from participation in sports. In the present study, a specific diagnostic protocol was used in 14 patients with suspected FDEIAN in an attempt to identify as many foods as possible that might be expected to provoke anaphylactic reactions when consumed prior to exercise.

Material and methods

Study population

The study population included all patients seen by our staff between 1990 and 1994 with histories of EIAN episodes occurring within 2 h after a meal. Informed consent for all procedures was obtained from each patient (or the parents of those under 18 years of age). The histories of all patients were consistent with the criteria for FDEIAN suggested by Kidd et al. (11). Each patient was carefully questioned to identify all foods consumed during the 24 h preceding each episode. Those that had been repeatedly eaten prior to exercise without provoking symptoms were also noted. Complete physical examinations, including electrocardiogram, echocardiogram, and pulmonary function tests, were also performed in each case.

Skin tests

Each patient was then subjected to prick tests with multiple commercial allergens (18 airborne and 26

food allergens) (Dome/Hollister-Stier – Bayropharm Italiana, Milan, Italy) prepared 1:20 wt/vol. Airborne antigens included grasses; mugwort; *Parietaria*, *Plantago*, olive, beech, and plane-tree pollens; *Dermatophagoides pteronyssinus* and *D. farinae*; dog and cat dander; *Alternaria tenuis*; *Cladosporium herbarum*; *Aspergillus* mixture; and *Penicillium* mixture. Food allergens included meat mixture (lamb, rabbit, beef/veal, pork, chicken), egg, cow's milk, cod, shrimp, wheat, rye, barley, oats, corn, rice, peas, peanuts, soybeans, beans, walnuts, almonds, tomato, carrot, garlic, onion, apple, celery, banana, peach, and potato. Fresh-food prick tests using the prick + prick technique described by Dreborg & Foucard (5) were also performed for the last nine foods cited above and for kiwi, lentils, fennel, lettuce, parsley, and basil. All pricks were administered with steel lancets (Allergy Pricker – DHS Prick Lancet), and responses were compared to positive controls produced by pricks with histamine 10 mg/ml, as recommended by the Subcommittee on Skin Tests of the European Academy of Allergy and Clinical Immunology (7).

IgE assays

Total serum IgE levels (PRIST – Pharmacia, Uppsala, Sweden) and serum levels of specific IgE (expressed as kU/l) for each of the food allergens mentioned above (with the exception of the meat mixture) were measured in all patients. The latter assays were performed with the CAP System FEIA RAST (Pharmacia), which has been described in detail elsewhere (8). RASTs for the same panel of 31 allergens were also performed on blood samples from a negative control population, and the normal cutoff was established by receiver-operating characteristic (ROC) curve analysis.

Food-exercise challenges

Treadmill ergonometric stress tests with progressively increasing speeds were administered to all patients 90 min after a meal containing none of the foods associated with skin-test or RAST positivity (food plus exercise challenge – FEC) and 90 min after the same meal with the addition of one of the foods suspected of causing the EIAN reaction (suspected food plus exercise challenge – SFEC). In the latter challenges, the suspected food was selected according to the following criteria:

- 1) positive allergologic findings
- 2) absence of history data that would exclude it as a cause of the reactions
- 3) frequency of consumption by the individual subject.

During both challenges, the electrocardiogram

was continuously monitored, and pulmonary ventilation (l/min), oxygen consumption (ml/min/kg body weight), and carbon dioxide production (ml/min) were measured with an open-circuit spirometer (Oxycon Beta, Mijhardt, Best, The Netherlands). Equipment and personnel for emergency resuscitation were present during all challenges, and tests were interrupted immediately if the patient began to experience specific symptoms (pruritus, erythema, lacrimation, conjunctival injection, or abdominal cramps); otherwise, tests were continued until muscle exhaustion occurred.

Results

Patient characteristics

Table 1 shows history data for the 14 patients (10 men, four women; 16–27 years of age; mean age: 20.5 ± 3.61 years) we studied. Eleven (patients 3–9, 11–14) had experienced more than one episode suggestive of FDEIAN. In two cases, the patient could not recall any specific food that might have provoked the reactive episode. One of these, patient no. 10, had suffered only one true anaphylactic re-

action, after which he began to interrupt his activity at the first appearance of prodromal symptoms (urticaria, angioedema), which gradually disappeared without any treatment. No specific food could be associated with any of these episodes or the initial anaphylactic reaction. In 12 cases (patients 1–9, 12–14), a specific food could be suspected in at least one of the episodes (i.e., all of the other foods eaten during the meal had, on other occasions, been consumed prior to exercise without provoking symptoms). In some cases, each episode appeared to be related to a different food. Three of the patients had taken nonsteroidal anti-inflammatory drugs (NSAIDs) shortly before one or more of the attacks. The family history was positive for allergic disease in seven cases (patients 1, 2, 4, 5, 6, 12, 13). Four patients (patients 3–6) had histories of pollen allergies (seasonal rhinitis with or without bronchial asthma), and two of these (patients 3 and 6) reported a higher frequency of EIAN episodes during the spring. Three other patients (patients 1, 9, 13) suffered from urticaria/angioedema syndromes unrelated to food intake or exercise, and a fourth (patient 7) reported cholinergic urticaria. The physical ex-

Table 1. For each patient, number of EIAN episodes experienced (episodes), foods suspected of having caused reactions (food), type of exercise associated with reaction (exercise), amount of time between meal and initiation of exercise (interval), symptoms of reactions (symptoms), drugs used within 4 h of reaction (drugs), and other forms of allergy-like diseases reported (allergy) are shown

Patient no.	Age (years) Sex	Episodes	Food	Exercise	Interval	Symptoms	Drugs	Allergy
1	20/F	1	Fennel	Running	60 min	U, facial A, V, S		U, A, adverse reactions to NSAIDs
2	20/M	1	Lettuce	Soccer	120 min	OR, BA, U, A		past BA
3	17/M	20	Tomato	Soccer	≤ 120 min	Facial A, D, OR		SAR
4	17/M	2	Vegetable oil	Soccer	≤ 90 min	U, facial A, D, C		SAR and BA
5	17/M	2	Wheat	Track sports	≤ 120 min	U, A, $\downarrow$ BP		SAR
6	21/F	7	Wheat	Running	≤ 120 min	U, A, OR, BA, AP, $\downarrow$ BP		ACD, SAR and BA
7	23/F	3	Peach ?	Aerobics Tennis	≤ 60 min	U, A, D	ASA	Cholinergic urticaria
8	17/M	10	Tomato Garlic	Soccer Tennis	≤ 90 min	Facial A, D, E, $\downarrow$ BP		
9	26/M	2	Beans ?	Water polo Soccer	≤ 30 min	OR, A, U, $\downarrow$ BP	ASA	U, A
10	27/M	1	?	Running	20 min	U, A, $\downarrow$ BP, S		
11	25/M	2	?	Soccer	≤ 60 min	U, A, D, $\downarrow$ BP		
12	16/M	21	Wheat Tomato Garlic	Soccer	≤ 120 min	U, A, D, $\downarrow$ BP		
13	20/F	2	Vegetable oil Legumes	Running	≤ 60 min	A, D	Ibuprofen	U, A
14	21/M	6	Tomato Wheat	Soccer Gymnastics	≤ 120 min	A, D		

Abbreviations: food: ? = none identified; symptoms/allergy: A = angioedema; ACD = allergic contact dermatitis; AP = abdominal pain; BA = bronchial asthma; $\downarrow$ BP = hypotension; C = cyanosis; D = dyspnea; E = erythema; OR = oculorhinitis; S = syncope; SAR = seasonal allergic rhinitis; U = urticaria; V = vomiting.

amination and instrumental studies did not reveal any type of cardiovascular or respiratory pathology in any of the patients.

Allergologic test results

Normal cutoff values for RAST (CAP System). The negative control population comprised 21 athletes from the Italian national soccer team (aged 22–34 years; mean: 27.19 ± 3.07 years) with no histories or symptoms of EIA or food allergies. Seventeen of these control subjects presented specific serum IgE levels < 0.35 kU/l (negative cutoff suggested by the manufacturer) for all of the allergens tested. The remaining four had levels ≥ 0.35 kU/l for one or more food allergens: 0.78 kU/l for apple in one; 0.65 kU/l for corn in the second; 0.43 kU/l for wheat, 0.52 kU/l for carrot, 0.50 kU/l for apple, and 0.44 kU/l for celery in the third; and 1.39 kU/l for wheat, 1.60 kU/l for rye, 0.72 kU/l for barley, and 0.40 kU/l for oats in the fourth. According to the ROC curve analysis, the cutoff value for CAP System findings was 1.5 kU/l.

Skin-test, PRIST, and RAST results

Skin-test positivity for pollens was observed in nine patients, five of whom (patients 2, 7, 8, 12, 14) had never experienced hay-fever-like symptoms. All of these latter five patients displayed hypersensitivity to mugwort, and patient 14 was also positive for grasses. All of the patients with histories of seasonal allergic rhinitis (patients 3–6) were positive for grasses, and three (patients 3–5) were positive for mugwort as well. Patient 3 also appeared to be sensitive to *Plantago*, and patient 4 to olive pollen. None of the patients showed positivity for any of the other airborne allergens tested.

On the basis of skin-test positivity (≥ 1 + in prick and/or prick + prick tests) and/or specific IgE levels > 1.5 kU/l, all 14 patients presented hypersensitivity to two or more food allergens. Four (patients 1, 9–11) were sensitive to only two or three foods; in two of these four cases (patients 10 and 11), none of the positive foods could be linked to any of the previous reactions on the basis of history data. The remaining 10 patients were positive for 11 or more foods and eight displayed sensitivity to more than 20.

The foods most frequently implicated by these tests were soybeans (11/14 patients); lentils, rye, peanuts, and onion (10 patients each); wheat, rice, peas, beans, walnuts, tomatoes, garlic, peach, lettuce, and parsley (nine patients each); and barley, oats, corn, apple, celery, basil, and fennel (eight patients each). Ten were positive for one or more of the foods commonly used as seasoning agents (onion,

garlic, basil, parsley). Only one patient presented hypersensitivity to shrimp (RAST positive, skin test negative). None of the patients were positive for cow's milk, eggs, fish, or carrots. The foods suspected on the basis of history data (patients 1–9, 12–14) were associated with positive findings in all 12 cases.

Table 2 shows the correlation between results obtained in the prick, prick + prick, and CAP System assays, which displayed different degrees of sensitivity in revealing specific IgE against certain allergens. For foods assessed with both prick and prick + prick tests, the latter confirmed positive results obtained with commercial extracts in almost all cases and generally revealed other sensitivities that were not diagnosed with prick tests.

Total serum IgE levels in the 14 patients ranged from 12 (patient 13) to 978 (patient 5) kU/l (mean: 258.57 ± 276.68 kU/l). Only six patients (patients 4, 5, 7, 8, 10, 14) presented levels > 200 kU/l.

Table 2. Correlation between results obtained with different diagnostic methods

		CAP	
		+	-
Prick + prick	+	53	28 $\Leftarrow$ Including: 8 Celery, 6 Fennel, 5 Kiwi
	-	26 $\Uparrow$ Including: 7 Peach, 6 Apple, 3 Tomato	103
		+	-
		CAP	
Prick	+	81	26 $\Leftarrow$ Including: 9 Bean, 6 Celery
	-	54 $\Uparrow$ Including: 9 Peach, 8 Apple, 5 Garlic	189
		+	-
		PRICK	
Prick + prick	+	26	14 $\Leftarrow$ Including: 5 Garlic, 3 Banana
	-	1 $\Uparrow$ Tomato	85

Food-exercise challenges (FECs)

FECs (with none of the suspected foods) were administered to each of the 14 patients. None experienced cardiac arrhythmias or hemodynamic problems during or after the FEC. The only adverse reaction to this challenge occurred in the patient with a history of cholinergic urticaria, who developed classical papules (< 10 mm) during the stress test.

Patients 2, 4, 7, and 8 were positive for wheat in the allergologic tests, but all four reported that they had, on numerous occasions, engaged in physical activity shortly after meals containing bread and/or pasta without suffering any symptoms. Because these foods represented important components of these patients' diets, FECs were repeated with meals that included bread and/or pasta, and the results were negative.

Suspected food-exercise challenges

As shown in Table 3, eight of the 14 patients agreed to submit to the SFEC; all had experienced more than one anaphylactic episode. The suspected food added to the FEC meal was, of all those associated with positivity in the allergologic tests, the one most heavily implicated on the basis of the patient's history or the one most commonly included in the patient's normal diet. Two separate SFECs were administered to patient 8; the first with tomato, the second with garlic (both associated with test positivity and suspected on the basis of the patient's history). Neither of the challenges provoked symptoms.

Three of these eight patients responded positively to the SFEC. All reactions were promptly controlled with epinephrine, 6-methylprednisolone, and chlorphenamine maleate. The culprit foods identified in this manner were wheat (bread and pasta) in patients 5 and 6 and tomato in patient 3. The appearance of small papules in the patient with cholinergic urticaria (no. 7) was not considered a positive response.

Discussion

On the basis of the above findings, SFDEIA could be definitely diagnosed in only three patients (nos. 3, 5, 6). In these cases, the causative role of a specific food in the EIA reactions was confirmed by SFEC results. However, the histories, allergologic data, and responses to elimination diets (see below) in nine other cases (patients 1, 2, 4, 7–9, 12–14) also suggest a possible etiologic role for IgE directed against specific foods. The fact that the SFEC results in these nine patients failed to incriminate the food that was most heavily implicated by the patient's history must be weighed against other data. All nine of these subjects, as well as the three whose FDEIA diagnoses were SFEC-confirmed, had reported EIA reactions related to the ingestion of a particular food that was associated with positivity in one or more of the allergologic tests. They have been instructed to avoid all foods associated with allergologic test positivity during the 4 h preceding physical exercise, and none have experienced reactions during follow-ups ranging from 6 months to 5 years. This response provides indirect evidence that one or more of the foods associated with allergologic test positivity

Table 3. Results of suspected food-exercise challenges in eight patients with FDEIA

Patient no.	Food	Symptoms	Onset	Maximum speed	Response
3	Tomato	Conjunctival injection Facial edema Cough Hypotension	Recovery phase	16 km/h	Positive
4	Vegetable oil (soybeans, peanuts)	None	–	14 km/h	Negative
5	Wheat (bread, pasta)	Diffuse itching Dyspnea Conjunctival injection Hypotension	14 km/h	14 km/h	Positive
6	Wheat (bread, pasta)	Oculorhinitis Asthma (29% ↓FEV ₁) Diffuse erythema Abdominal pain	Recovery phase	13 km/h	Positive
7	Peach	Cholinergic urticaria	Recovery phase	11 km/h	Negative
8	Tomato	None	–	14 km/h	Negative
	Garlic	None	–	15 km/h	Negative
9	Beans	None	–	17 km/h	Negative
12	Wheat (bread, pasta)	None	–	13 km/h	Negative

might serve to trigger an EIAN reaction. However, since the causative role of a particular food can be confirmed only by positive SFEC reactions, all 12 of these patients should be subjected to additional SFECs to clarify the actual roles played by the numerous foods that elicited positive results in skin tests and/or RAST.

In the remaining two cases (patients 10 and 11), the presence of specific IgE antibodies did not appear to play an etiologic role in the reactive episodes. Unfortunately, neither of these patients agreed to submit to exercise challenges after ingestion of any of the foods associated with RAST positivity. Patient 11 (RAST positive for wheat and rye and skin-test negative for all food allergens tested) had experienced two anaphylactic reactions but did not recall eating wheat- or rye-based foods during either of the pre-exercise meals. Patient 10 (RAST positive for rye and shrimp and skin-test negative for all food allergens tested) had suffered only one episode of true anaphylaxis, but on numerous other occasions postprandial exercise had been interrupted because of prodromal symptoms. None of these episodes had been preceded by a meal containing either rye or shrimp, both of which were, in fact, quite rare in the subject's normal diet. The history and allergologic data in this case are somewhat more suggestive of a nonimmunologic reaction, as postulated by other investigators (9, 11, 18), although the patient did not experience any symptoms in the FEC. The lack of response to this latter challenge (also observed in patient 11) may be related to the interval between the meal and the exercise challenge (90 min) since all of the previous EIAN episodes reported by both of these subjects had occurred 1 h or less after meals. The cause of the reactions experienced by patients 10 and 11 thus remains unclear, and stress tests following ingestion of the foods associated with RAST positivity may have contributed to a better understanding of these cases. However, avoidance of exercise for at least 4 h after any type of meal has proved sufficient to prevent all exercise-related symptoms in both cases, suggesting that ingestion itself may contribute in some way to these patients' reactions.

The aim of the diagnostic protocol described here was to identify as many foods as possible that might be expected to provoke symptoms during postprandial exercise, and to this end we employed both *in vivo* (skin tests) and *in vitro* (RAST) methods to assess reactivity to 31 different foods. The vast majority of our patients were positive for 11 or more foods, suggesting that multiple hypersensitivities are a common feature of this syndrome. It is interesting to note that none of the patients were positive in any of the tests for cow's milk, fish, or eggs, which are among the most common causes of classical food allergies.

Kivity et al. (12) found that hypersensitivity to these foods was also rare in a group of 112 patients who had developed food allergies after the age of 10 years. Thirty-three percent of these subjects claimed to suffer cutaneous and respiratory symptoms following strenuous exercise, and approximately half of these reported that these episodes had occurred shortly after eating.

Nine of the patients we studied were sensitive to foods like parsley or garlic. These seasoners are present in many dishes, but they are rarely recalled by patients and almost never included in allergen panels used to assess cases of suspected FDEIAN. Various investigators have diagnosed FDEIAN (on the basis of history) in patients with negative allergologic findings for all foods consumed before exercise (4, 9, 11, 18), which would tend to exclude immune mechanisms for these reactions. However, it is also possible, in light of our findings, that a different or more extensive allergen panel might have revealed hypersensitivity to one or more foods in some of these cases.

The skin-test results observed in these 14 patients indicate that the prick + prick technique is, in many cases, able to reveal sensitivities to fruits and vegetables that are not disclosed by tests using commercial food extracts. Other investigators (19) have already suggested that antigens prepared from fresh foods are more reactive than the commercial variety. For this reason, we feel that both prick and prick + prick methods should be used to investigate hypersensitivity to fruits and vegetables in these patients.

Determination of total IgE serum levels proved to be of little use in these patients. There were a number of cases in which patients with skin-test and/or RAST positivity for a number of foods presented low total IgE levels.

The CAP System we used for the RAST disclosed numerous hypersensitivities, and, in some cases, proved to be more sensitive than skin testing with vegetables, fruit, and wheat. In fact, the high number of positive findings that emerged with these assays led us to establish a negative cutoff with 100% specificity. True positive results in the RAST have already been described in patients with negative prick tests (14, 20). Several groups have reported that the RAST proved to be less sensitive than skin testing for diagnosis of wheat allergies (4, 10, 13), but this discrepancy with our findings may be due to differences in methods. The tridimensional solid phase of the ImmunoCAP allows more rapid and efficient binding of specific IgE antibodies against individual allergens, resulting in increased sensitivity (27).

The data obtained with these *in vivo* and *in vitro* approaches were evaluated in light of the information provided by patients themselves and the re-

sponses to food-exercise challenges. For example, several patients with positive wheat-specific IgE titers (patients 2, 4, 7, and 8) recalled with certainty having engaged in sports shortly after a meal that included wheat-based products without suffering any symptoms, and, in fact, none of these patients experienced reactions during the treadmill stress tests following meals containing bread or pasta. These data allowed us to exclude the role of these foods in the pathogenesis of the anaphylactic reactions. History data were less helpful in interpreting the numerous positive skin-test or RAST results for foods such as parsley, onion, garlic, and basil, since the patients were often unsure of whether these ingredients were present in the foods they had eaten.

The positive reactions of three patients to the SFEC allowed us to establish the causative role of a particular food in the FDEIAN episodes, but the negative responses observed in the other five patients subjected to this challenge are more difficult to interpret. Negative SFECs in patients with postprandial exercise-induced disturbances have been reported by others (4, 12). In particular, the percentage of negative SFEC responses in the present study is similar to that observed by Kivity et al. (12) in 37 patients with nonanaphylactic food allergies that appeared to be related to exercise. These findings suggest that factors other than food allergy and physical exertion may be involved in these reactions. The use of certain drugs (NSAIDs, caffeine) prior to exercise, stress, menstruation, and unfavorable climatic conditions have all been proposed as contributing factors (4, 22, 23).

In our population, patients 3 and 6 reported a higher frequency of reactive episodes during the spring months, and patient 3 noted that he had suffered fewer attacks since his hay-fever symptoms had been treated with specific immunotherapy. In view of the fact that certain epitopes are shared by foods and pollens (6), allergies to the latter might be expected to contribute to the provocation of FDEIAN. The three patients that had taken NSAIDs before previous anaphylactic reactions were also among those that failed to react to the SFEC.

In subjects with multiple food allergies, it is possible to speculate that ingestion of two or more culprit foods is necessary to provoke the anaphylactic reaction. Although there are no experimental data that support this hypothesis, it might theoretically explain some of the negative responses to the SFEC, since only one suspected food was included in the pre-exercise meal.

The interval between the meal and the physical activity also emerged as an important factor. In some cases, the history indicated that ingestion of a specific food 1–2 h prior to exercise had been followed by a reactive episode, but when the same food was

consumed more than 3 h before activity, no reaction occurred. The fact that all treadmill tests were administered 90 min after the meal containing the suspected food may have contributed to the negative SFEC results observed in patients 7 and 9, both of whom reported that their reactions had occurred when they engaged in physical activity less than 60 min after eating. As mentioned before, the negative FEC results observed in patients 10 and 11 may also have been related to the timing of the challenge. This hypothesis suggests that the timing of FECs and SFECs should be individualized to reproduce as closely as possible the events of the subjects' previous attacks.

These considerations are an indication of the extremely complex nature of the FDEIAN syndrome. In most of the cases described here, there were a number of other foods that were not evaluated in SFECs in spite of the fact that they appeared to be possible triggers of EIAN based on history, allergologic data, and response to elimination diets. Further studies should be performed with SFECs to identify which of these foods are actually capable of provoking a reaction. In fact, the SFEC remains an integral component of the diagnostic work-up of a patient with suspected FDEIAN and, in spite of its apparent limitations, it is currently the only tool we have for confirming the potential of a given food to trigger an EIAN reaction. This information is essential to clarify the role of IgE-mediated reactions to foods with respect to nonimmunologic mechanisms associated with postprandial exercise. Also important is a knowledge of the food-hypersensitivity patterns displayed by patients who experience these reactions, and extensive allergologic testing can be quite helpful in this sense. Although false negative results are possible in both skin tests and RASTs, our experience suggests that sensitivity may be increased by the use of prick + prick tests with fresh foods and the CAP System for specific IgE assays. The results of these tests can reinforce suspicions raised by the patient history (which remains a fundamental reference point in the work-up of suspected FDEIAN) and identify other foods that require further investigation.

The patients included in this study have been followed by our staff for periods ranging from 6 months to 5 years. The precautions we have suggested (avoidance of meals or specific foods for 4 h before exercise) have allowed all of these subjects to engage in sports without suffering any disturbance, and these results can also be considered relevant from a diagnostic point of view. In patients with suspected NSFDEIAN reactions (such as patient 10), every attempt should be made to confirm the diagnosis by performing FECs and stress tests with any positive foods. When this is not possible, the safest course is

to eliminate all meals prior to exercise. For those patients with SFEC-confirmed or highly suspected SFDEIAn, all foods associated with positivity must be avoided during this period. If the patient responds to this measure, the role of each positive food should be further investigated if possible. Oral challenges are of no use since, without subsequent exercise, the result will always be negative. As for the SFEC, a negative response cannot always reliably exclude the risk that the food will provoke an EIAAn reaction. However, foods that have been repeatedly consumed prior to exercise without causing reactions might be allowed during the pre-exercise period (particularly those that represent important components of the patient's diet).

References

1. AÑIBARRO B, DOMINGUEZ C, DIAZ JM, et al. Apple-dependent exercise-induced anaphylaxis. *Allergy* 1994; 49: 481-2.
2. ARMENTIA A, MARTIN-SANTOS JM, BLANCO M, CARRETERO L, PUYO M, BARBER D. Exercise-induced anaphylactic reaction to grain flours. *Ann Allergy* 1990; 65: 149-51.
3. BUCHBINDER EM, BLOCK KJ, MOSS J, GUINEY TE. Food-dependent, exercise-induced anaphylaxis. *JAMA* 1983; 250: 2973-4.
4. DOHI M, SUKO M, SUGIYAMA H, et al. Food-dependent, exercise-induced anaphylaxis: a study on 11 Japanese cases. *J Allergy Clin Immunol* 1991; 87: 34-40.
5. DREBORG S, FOUCARD T. Allergy to apple, carrot, and potato in children with birch pollen allergy. *Allergy* 1983; 38: 167-72.
6. DREBORG S. Food allergy in pollen-sensitive patients. *Ann Allergy* 1988; 61: (Part II): 41-6.
7. DREBORG S. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989; 44 (Suppl 10): 22-30.
8. EWAN PW, COOTE D. Evaluation of a capsulated hydrophilic carrier polymer (the ImmunoCAP) for measurement of specific IgE antibodies. *Allergy* 1990; 45: 22-9.
9. FUKUTOMI O, KONDO N, AGATA H, SHINODA S, SHINBARA M, ORII T. Abnormal responses of the autonomic nervous system in food-dependent exercise-induced anaphylaxis. *Ann Allergy* 1992; 68: 438-45.
10. KATSUNUMA T, IKURA Y, AKASAWA A, IWASAKI A, HASHIMOTO K, AKIMOTO K. Wheat-dependent exercise-induced anaphylaxis: inhibition by sodium bicarbonate. *Ann Allergy* 1992; 68: 184-8.
11. KIDD JM III, COHEN SH, SOSMAN AJ, FINK JN. Food-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983; 71: 407-11.
12. KIVITY S, DUNNER K, MARIAN Y. The pattern of food hypersensitivity in patients with onset after 10 years of age. *Clin Exp Allergy* 1994; 24: 19-22.
13. KUSHIMOTO H, AOKI T. Masked type I wheat allergy. Relation to exercise-induced anaphylaxis. *Arch Dermatol* 1985; 121: 355-60.
14. LEIMGRUBER A, MOSIMANN B, CLAEYS M, et al. Clinical evaluation of a new *in vitro* assay for specific IgE, the ImmunoCAP system. *Clin Exp Allergy* 1991; 21: 127-31.
15. MARTIN MUÑOZ F, LOPEZ CAZANA JM, VILLAS F, CONTRERAS JF, DIAZ JM, OJEDA JA. Exercise-induced anaphylactic reaction to hazelnut. *Allergy* 1994; 49: 314-16.
16. MAULITZ RM, PRATT DS, SCHOCKET AL. Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979; 63: 433-4.
17. MCNEIL D, STRAUSS HR. Exercise-induced anaphylaxis related to food intake. *Ann Allergy* 1988; 61: 440-2.
18. NOVEY HS, FAIRSHTER RD, SALNESS K, SIMON RA, CURD JG. Postprandial exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983; 71: 498-504.
19. ORTOLANI C, ISPANO M, PASTORELLO EA, ANSALONI R, MAGRI GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989; 83: 683-90.
20. PASTORELLO EA, INCORVAIA C, PRAVETTONI V, et al. A multicentric study on sensitivity and specificity of a new *in vitro* test for measurement of IgE antibodies. *Ann Allergy* 1991; 67: 365-70.
21. ROMANO A, DI FONSO M, VENUTI A, PALMIERI V, ZEPILLI P. Food-dependent exercise-induced anaphylaxis: report of two cases. *Int J Sports Med* 1992; 13: 585-7.
22. SHADICK NA, LIANG MH, PARTRIDGE AJ, et al. The natural history of exercise-induced anaphylaxis [Abstract]. *J Allergy Clin Immunol* 1992; 89: 247.
23. SHEFFER AL, AUSTEN KF. Exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1980; 66: 106-11.
24. SHEFFER AL, TONG AKF, MURPHY GF, LEWIS RA, McFADDEN ER Jr, AUSTEN KF. Exercise-induced anaphylaxis: a serious form of physical allergy associated with mast cell degranulation. *J Allergy Clin Immunol* 1985; 75: 479-84.
25. SILVERSTEIN SR, FROMMER DA, DOBOZIN B, ROSEN P. Celery-dependent exercise-induced anaphylaxis. *J Emerg Med* 1986; 4: 195-9.
26. THARP MD, THIRLBY R, SULLIVAN TJ. Gastrin induces histamine release from human cutaneous mast cells. *J Allergy Clin Immunol* 1984; 74: 159-65.
27. YMAN L. Standardization of IgE antibody assays. *J Int Fed Clin Chem* 1991; 3: 198-203.