Physiologic Manifestations of Human Anaphylaxis

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ABSTRACT In the course of a controlled study to evaluate different forms of immunotherapy for subjects with insect-sting hypersensitivity, we observed 11 subjects who had systemic cutaneous urticarial reactions and 3 subjects who experienced systemic anaphylaxis. With the exception of tachycardia, there were no cardiopulmonary changes in the subjects with urticaria, whereas the major manifestation of anaphylactic shock in the other three subjects was severe hypotension that was probably secondary to peripheral vasodilation. Significant abnormalities in gas exchange developed in two subjects. In one, bronchospasm precipitated a respiratory arrest followed by endotracheal intubation with mechanical ventilation. Although plasma histamine levels were not related to the development of cutaneous reactions, the plasma histamine levels correlated with the severity and duration of the cardiopulmonary changes observed during anaphylactic shock. The two subjects with the most severe shock showed evidence of intravascular coagulation characterized by a diminution of Factor V, Factor VIII, fibrinogen, and high molecular weight kininogen, as well as changes in components of the complement system. Standard therapy with epinephrine and fluids, usually recommended for the treatment of systemic anaphylaxis, did not immediately reverse either the hemodynamic or the respiratory abnormalities in the two subjects with the most severe anaphylactic shock. Hemodynamic recovery was gradual and did not seem directly related to any specific therapeutic intervention.

INTRODUCTION

Anaphylactic reactions occur in sensitized individuals exposed to foreign antigens or low molecular weight substances which act as haptens. The consequent release of basophil and mast-cell mediators results in the varied manifestations of this syndrome that most often involve the cutaneous, respiratory, or vascular systems. Since these reactions are usually unexpected and occasionally fatal, opportunities to investigate systematically the detailed pathophysiology with controlled studies are exceedingly rare. Most of the available data concerning the pathophysiology and treatment of human anaphylaxis are derived from anecodotal clinical case reports and postmortem studies (1–5).

Anaphylaxis resulting from insect stings represents a distinct and constant threat to almost 1% of the general population (6). In the course of a controlled study to evaluate immunotherapy for insect hypersensitivity, we had reason to anticipate anaphylactic reactions. To detect and reverse the reactions as early as possible, patients at risk were monitored closely during incremental antigenic (insect venom) challenges and a subsequent insect sting. Of the 22 patients challenged, 14 had systemic reactions and they are the subject of this report.

METHODS

The rationale and details of the clinical trial have been reported elsewhere (6). Briefly, the purpose of the initial study was to determine whether immunotherapy with purified

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insect venom (Hymenoptera) was more effective than whole body extract, the commonly used treatment regimen for insect hypersensitivity. We undertook this clinical trial because preliminary evidence suggested that the standard form of immunotherapy was ineffective and that treatment with purified insect venom was more effective. There are numerous moral and ethical difficulties in testing the possible effectiveness of a new form of therapy that would replace a standard regimen that has been used to treat a life-threatening condition. Ultimately, we felt that a systematic trial and subsequent provocation was justified because of the continuing severe risk to a segment of the population that was being immunized with an unproven and perhaps ineffective form of immunotherapy. Furthermore, we felt we could lower the danger of provocation to an acceptable level. All subjects had both positive skin reactivity and a history of a systemic reaction to a Hymenoptera insect sting. After giving their informed consent, the subjects were separated at random into three therapeutic groups and treated with either placebo (histamine), whole body extract, or purified insect venom. When the venom-treated subjects had reached the 100-μg maintenance dose, subjects were randomly selected from each group to be challenged. They were placed in a critical-care setting designed to minimize any risks. Initially the subjects were challenged with incremental doses of subcutaneously administered venom (1, 10, 100 μg) in an attempt to produce a minimal but graded response that would not elicit a serious anaphylactic reaction. If no serious reaction occurred during the venom challenge, we felt justified in administering a live insect sting, having prepared ourselves to treat any serious consequences, e.g., systemic anaphylactic shock.

Clinical studies. Physiologic monitoring in these subjects was directed toward measuring respiratory and circulatory parameters, because changes in these systems should reflect the major serious systemic effects of anaphylaxis. The pulmonary parameters studied included measurement of dynamic compliance and resistance, measured by a modification of the Mead-Whittenberger technique (7). Airway resistance and thoracic gas volume were measured in a variable pressure, constant volume body plethysmograph by the method of Dubois and associates (9). Airway resistance was converted to its reciprocal airway conductance, which in turn was corrected for thoracic gas volume and expressed as specific airway conductance (8, 9). Spirometry was performed on a Stead-Wells spirometer (Warren E. Collins, Inc., Braintree, Mass.) and the best of three consecutive spirograms was selected. Arterial blood gases were sampled from a catheter inserted percutaneously in the brachial artery and were measured on a blood-gas analyzer (Instrumentation Laboratory, Inc., Lexington, Mass.). Pulmonary mechanics and blood gases were recorded after each injection of test venom and after the insect sting. In the three patients who developed anaphylactic shock, we did not attempt to follow changes in pulmonary mechanics because treatment of the patient took priority. However, we continued circulatory monitoring of direct blood pressure measurements and blood gases from a brachial artery catheter. In those patients who developed anaphylactic shock, an electrocardiogram was recorded continuously and measurements of central venous pressure were made intermittently.

Laboratory studies. To measure blood histamine levels, arterial and venous blood samples were collected both during the venom challenge and after the insect sting. Samples were collected either in citrate (0.4% final concentration) for coagulation-kinin studies or in 0.01 M EDTA for histamine analysis. The samples were cooled, centrifuged immediately, and the plasma was separated and frozen at −70°C. Histamine was determined by the automated fluorometric technique of Siraganian (10). Values were expressed as nanograms per milliliter histamine base using a standard curve generated from simultaneously run histamine standards diluted in human serum. The technique is sensitive to 1 ng/ml with a precision of ±10% at 1 ng and ±5% over 3 ng/ml.

Coagulation and kinin studies. Factors V, VIII, Hageman factor, prekalikrein and high molecular weight (HMW)[1] kininogen were assessed by the ability of samples to correct the partial thromboplastin time of plasmas that are selectively deficient in each of the above factors. The partial thromboplastin time was performed by the method of Proctor and Rappaport (11). Pooled citrated plasma collected from 10 normal controls was serially diluted and a standard curve was generated to represent the normal levels of each protein. Several dilutions of unknown samples were then quantified as a percent of normal based upon this standard curve. Fibrinogen was determined by the method of Clauss (12). Complement components C3 and C4, and an enzyme, C3 activator (Factor B), were quantified as are proteins by radioimmunodiffusion using antisera, plates, and controls supplied by Behring Diagnostics, Div. American Hoechst Corp., Somerville, N. J. Levels of α_2 macroglobulin, ceruloplasmin, and IgG were similarly determined in order to control for dilutional effects. Immunoelectrophoresis was performed by the method of Scheidegger (13).

RESULTS

None of the subjects had a systemic reaction to the incremental subcutaneous injections of venom. After the challenge sting, 7 of 11 whole body extract- and 7 of 12 placebo-treated subjects had systemic reactions. Only 1 of 19 subjects receiving venom immunotherapy had a mild cutaneous reaction. The 14 treatment failures from the placebo and whole body extract groups were given venom immunotherapy followed by a rechallenge which caused only one mild reaction (6). Of the initial responses to insect stings in these subjects, 11 of the 14 reactions were entirely cutaneous whereas the remaining 3 were characterized by hypotension. In the two patients with the most severe episodes of hypotension, we observed significant changes in respiratory function and gas exchange.

All hemodynamic reactions began 1–3 min after the insect sting and peak effects were reached within 1 min. In the 11 subjects with cutaneous manifestations, immediate administration of epinephrine reversed most of the cutaneous reactions. Except for tachycardia, there were no cardiopulmonary changes in the subjects with urticaria, even in those with involvement of 50–75% of the body surface area.

We will describe in detail the reactions of the three patients who developed anaphylactic shock. Patient 1 had a marked, though transient, episode of hypotension that began shortly after the insect sting (Fig. 1). At 1 min, he complained of dizziness and nausea and these symptoms persisted throughout shock. There was

[1] *Abbreviation used in this paper*: HMW, high molecular weight.

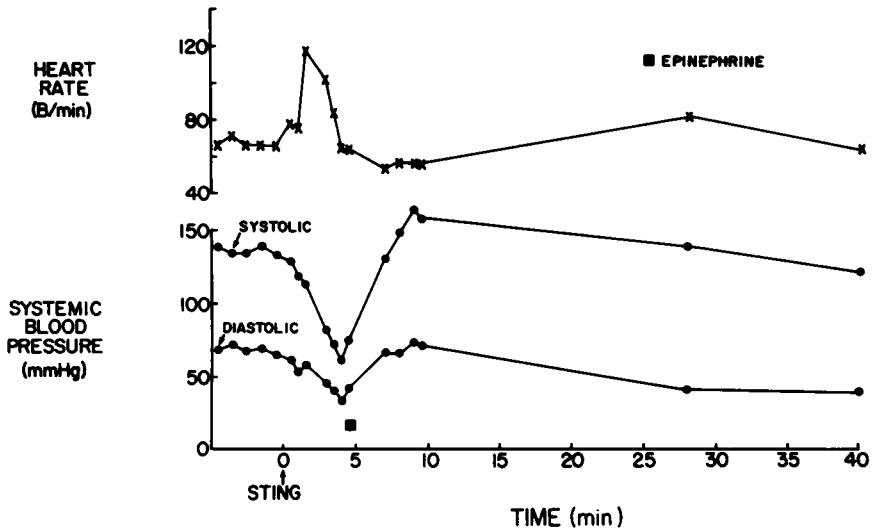

FIGURE 1 Blood pressure (●) and pulse rate (×) of the first patient with severe anaphylaxis. The solid black square represents 0.5 ml of 1:1,000 (0.5 mg) epinephrine s.c.

an initial mild tachycardia; but as blood pressure fell, the subject became bradycardic to a heart rate of 50–55 beats/min. Treatment was initiated by lowering the patient to a Trendelenburg position and rapidly infusing normal saline. Blood pressue did not increase and a subcutaneous dose of 0.5 ml 1/1,000 (0.5 mg) epinephrine was then given. This was associated with a return to base-line blood pressure during the next 2–3 min. Blood gas analysis 1 and 30 min after the insect sting showed a PaO_2 of 100 and 84 mm Hg, respectively. Measurements of pulmonary mechanics taken 45 min after the onset of anaphylaxis and the administration of epinephrine showed bronchodilation as evidenced by an increase in forced expiratory volume, specific airway conductance, and compliance (Table I).

In Patient 2 both the duration and severity of hypotension were worse and required more aggressive therapy (Fig. 2). There were no cutaneous manifestations. Therapy was begun with a rapid infusion of normal saline and plasmanate which was immediately followed by 0.5 mg of epinephrine i.v. Nevertheless, blood pressure continued to fall to 50/25 mm Hg. After ~1 U of plasmanate, 1 liter of saline, and a total of 2.0 mg of epinephrine i.v., neither the mean arterial pressure nor pulse pressure had improved during the initial 24 min of anaphylactic shock. Subsequently, there were transient 1–2-min rises in blood pressure associated with the bolus administration of intravenous epinephrine. At 38 min, when the mean arterial pressure was 37 mm Hg, a 2-min infusion of norepinephrine was followed by a rise in blood pressure to 100/45 mm Hg. After this the arterial pressure continued to rise but neither it nor the pulse rate had returned to baseline levels during the initial 90 min of anaphylaxis. Even though the patient denied chest pain, a 12-lead electrocardiogram at this time revealed ST segment depression in leads 2, 3, and aVF. There were frequent episodes of vomiting during shock, usually associated with the injections of epinephrine. Although there were no obvious respiratory symptoms such as tachypnea or wheezing, the PaO_2 fell to 52 mm Hg during anaphylaxis and eventually returned to 86 mm Hg. 2 h after the onset of anaphylaxis and its treatment, which included epinephrine, a repeat forced expiratory volume was slightly improved over base line; but specific airway conductance had not returned to base line (Table I). The total drug and fluid therapy administered to this patient was 875 ml of plasmanate (3.5 U), 1.5 liters of normal saline, and 3.5 mg of epinephrine. Laboratory data, including complete blood count, SMA 12, urinalysis, chest x ray, and blood gases, obtained 2 h after the insect sting, were normal. The ST segment abnormalities noted on electrocardiograph returned to normal within the next 12 h, and the patient made an uneventful recovery.

In Patient 3 there were again no cutaneous reactions. The onset of hypotension was rapid and systemic blood pressure fell to 50/25 mm Hg (Fig. 3). This degree of hypotension persisted for 10 min despite 3 U of plasmanate, 4 mg epinephrine i.v., and 1 liter of normal saline. Mean arterial pressure rose over the following 40 min. Approximately 4 or 5 min after the insect sting the patient began to wheeze, became cyanotic, and required respiratory assistance. Blood gas analysis at this point revealed a PaO_2 of 39 mm Hg, $PaCO_2$ of 45 mm Hg, and pH of 7.16. While he was being intubated no significant upper airway edema was noted. He was ventilated with an Ambu bag and received supplemental oxygen. Even after the endo-

TABLE I

Arterial Blood Gases, pH, and Pulmonary Mechanics of Three Patients during Anaphylactic Reactions to Insect Sting

	Post-insect sting	Pa_{O_2}	Pa_{CO_2}	pH	F_IO_2*	FEV_1‡	FVC§	SGAW‖	Compliance
	min	*mm Hg*				*liters/s*	*liters*	*liters/s/ cm H_2O*	*cm H_2*
Patient 1	Base line¶	74	37	7.44		3.45	4.48	0.1385	278
	1	100	31	7.47					
	30	84	35	7.43		3.70	4.86	0.2404	344
Patient 2	Base line	89	39	7.42		4.46	5.57	0.4743	
	55	52	38	7.39					
	90	64	39	7.40					
	120	86	36	7.41		4.71	5.85	0.3295	
Patient 3	Base line	71	33	7.43		3.86	5.06	0.1780	
	1	83	25	7.46					
	15	39	45	7.16					
	30	73	50	7.21	(40% O_2)				
	40	71	52	7.07	(40% O_2)				
	45	56	55	7.06	(40% O_2)				
	55	64	44	7.23	(40% O_2)				
	65	50	36	7.30	(40% O_2)				
	105	58	37	7.37					

* Arterial blood gases were performed on room air, unless otherwise indicated.
‡ FEV_1, forced expiratory volume.
§ FVC, forced vital capacity.
‖ SGAW, specific airway conductance.
¶ Base-line blood gases were taken just before insect sting.

tracheal tube was inserted, the patient continued to wheeze and this airflow limitation was reflected physiologically by 35–40 cm H_2O respiratory swings in central venous pressure recordings during spontaneous breathing. In addition, alveolar ventilation decreased as reflected by the $PaCO_2$ which rose to 55 mm Hg and then fell to normal as the bronchospasm resolved. Despite an inspired O_2 of 40%, hypoxemia persisted throughout the initial 2 h of anaphylaxis (Table I). Therapy during these 2 h included a total of 7 mg of

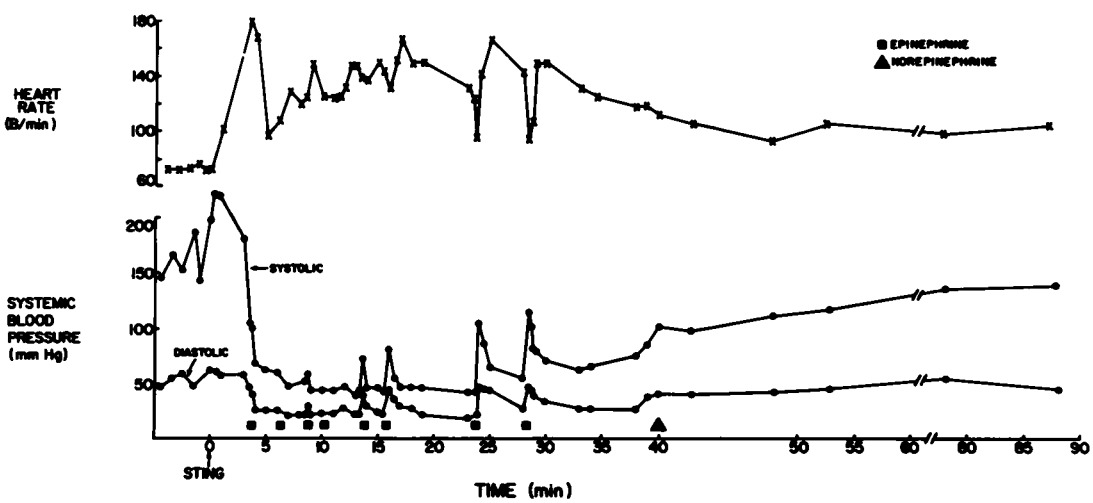

FIGURE 2 The course of blood pressure (●) and pulse rate (×) of the second patient who developed severe anaphylaxis. Each solid black square represents 4–5 ml of 1:10,000 epinephrine (0.5 mg) given as an intravenous bolus over 10–15 s. LEVO represents the start of a 2-min infusion of norepinephrine (see text).

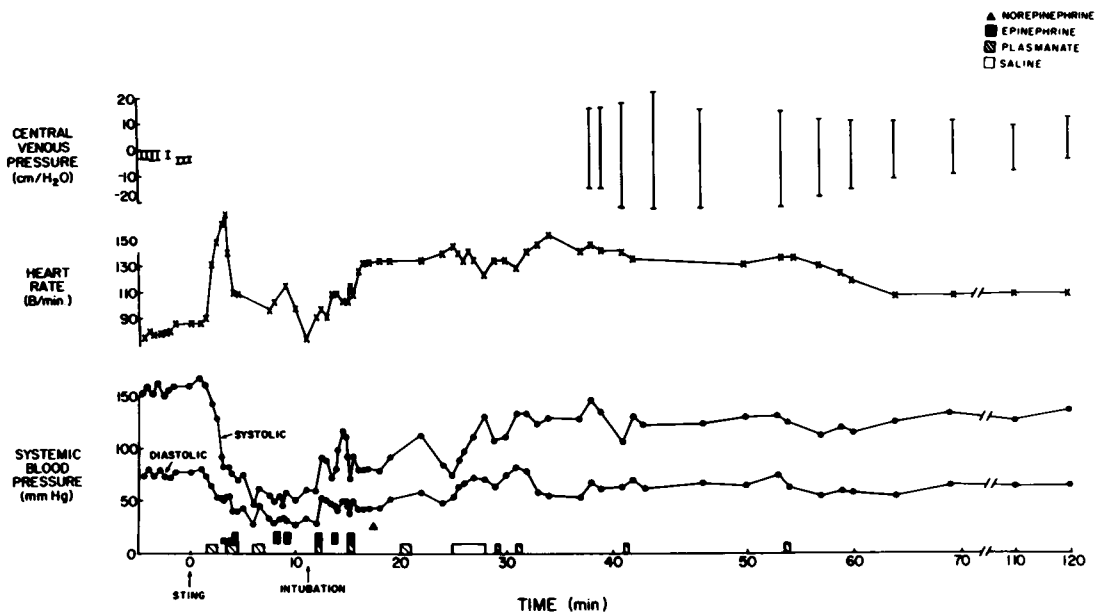

FIGURE 3 The course of blood pressure (●), pulse rate (×), and central venous pressure (I) in the third patient. The more positive central venous pressure recordings represent end-expiration pressure; the more negative recordings represent end-inspiratory pressures during tidal breathing. Small solid squares represent 5 ml of 1:10,000 epinephrine (0.5 mg) given as an intravenous bolus over 10–15 s. Large solid squares represent 10 ml of 1:10,000 epinephrine (1.0 mg) i.v., given over 15–20 s. An arrow indicates that the patient was intubated; a ▲ represents the start of a 2-min intravenous drip of epinephrine (see text). A rapid infusion of 300–400 ml of normal saline was given and is recorded by an open square. Large squares with hash marks indicate the end of an infusion of 250 ml of plasmanate; small squares represent the end of 100 ml infusions of plasmanate.

epinephrine i.v., 1,750 ml (7 U) of plasmanate, 2 U of sodium bicarbonate, 3 liters of normal saline, and 1 g of hydrocortisone acetate. A complete laboratory profile at this time, including chest x ray, EKG, SMA 6, and urinalysis was normal although the hematocrit was decreased to 31%. During the next 24-h period of observation, blood pressure and PaO_2 returned to base-line levels and the patient made an uneventful recovery.

Plasma histamine levels. Changes in plasma histamine levels did not parallel the cutaneous manifestations of the sting. Fig. 4 shows control and post-insect sting plasma histamine levels in symptomatic and asymptomatic subjects. Significant elevations occurred in only 60% of the patients and did not correlate with the occurrence of cutaneous reactions. The blood histamine levels of the challenged group do, however, differ significantly from their own base-line values which were equal to the control group and <1 ng/ml. The changes in plasma histamine and mean arterial pressure during the anaphylactic reaction characterized by hypotension are shown in Fig. 5. The two patients with the most severe anaphylactic episodes had the highest levels of plasma histamine. In addition, in these two subjects the plasma histamine returned to base line even though mean systemic blood pressure had not completely returned to normal.

Changes in the coagulation, kinin, and complement systems. Selected parameters of the coagulation, kinin, and complement pathways were studied in the two patients with the most severe episodes of anaphylaxis. Patient 2 (Table II) had values for Factor V and VIII in the control samples and the sample obtained at the time of the sting which varied from 40 to 83% of normal. Presumably our handling and transport of the samples resulted in base-line depression of the coagulation factors. Nevertheless, samples that were obtained during hypotension and processed identically revealed a marked depression of Factor V and VIII levels to 2 and 14% of normal, respectively, suggesting consumption of these factors. Base-line fibrinogen levels were within normal limits, but an eightfold depression of fibrinogen levels occurred during anaphylaxis. These observations suggest consumption of coagulation factors secondary to intravascular coagulation. Coagulation factors comprising the plasma kinin-forming systems were also evaluated and no changes in Factor XII or prekallikrein levels were seen. Levels of HMW kininogen, however, decreased.

Assessment of complement components in patient 2 revealed a decrease in both C3 and C4 levels while Factor B was unchanged. There was no evidence of

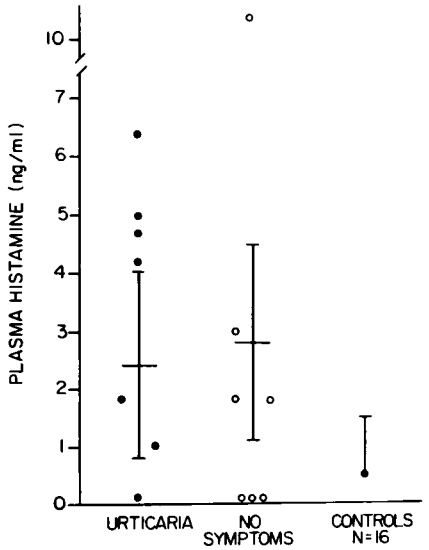

FIGURE 4 Post-insect sting plasma histamine (venous) in patients with no symptoms and in those with urticaria without circulatory anaphylaxis. Control values were from 16 normal laboratory controls.

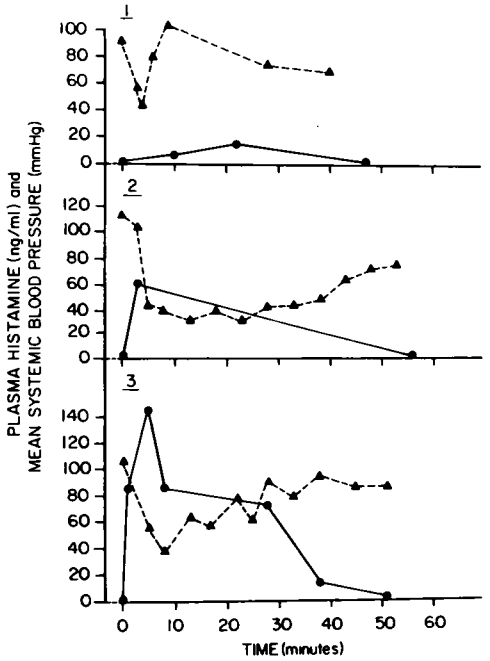

FIGURE 5 Mean systemic blood pressure and serum plasma histamine levels (venous) in the three patients with circulatory anaphylaxis. ●, Histamine (ng/ml); ▲, mean systemic blood pressure (mm Hg).

Factor B cleavage to the Ba and Bb fragments as assessed by immunoelectrophoresis. Although these data are compatible with activation of the classic complement pathway, it is more likely that the consumption of C3, C4, as well as HMW kininogen represents cleavage of these factors by other proteolytic enzymes.

Patient 3 had a significant diminution of Factor VIII and fibrinogen at the time of anaphylaxis whereas the Factor V levels were markedly diminished throughout and were uninterpretable. There was also evidence of depletion of HMW kininogen coincident with the hypotension but no changes in the components C4, C3, or Factor B were detected.

DISCUSSION

The sudden, usually unexpected onset of systemic anaphylaxis in man, with its rapid clinical course that leads to immediate recovery or death, has provided little opportunity for prospective immunologic, physiologic, and therapeutic investigation (14–18). Although urticarial eruptions are considered to be the most common manifestations of human anaphylaxis (16, 19)

TABLE II

Measurement of Coagulation Factors and Complement Components in Two Patients with Severe Anaphylaxis to an Insect Sting

	Patient 2			Patient 3		
	Control	Sting	Shock	Control	Sting	Shock
Factor V	66	83	2	6	14	0
Factor VIII	40	48	14	50	45	<5
Fibrinogen (mg/100 ml)	298	309	37	130	204	20
Factor XII	100	100	100	100	100	100
Prekallikrein	100	100	100	100	100	100
HMW kininogen	100	100	65	100	100	70
C4	100	100	60	100	100	100
C3	100	100	65	100	100	100
Factor B	100	100	100	100	100	100

Values for Factors V, VIII, XII, prekallikrein, HMW kininogen, C3, C4, and Factor B are expressed as a percentage of normal. Fibrinogen levels are expressed as milligrams per 100 milliliters.

and were found most frequently in this study, these cutaneous reactions are not life threatening. Interestingly, urticaria did not develop in the three subjects with hemodynamic shock. The shock organ most often involved in fatal human anaphylactic reactions is often thought to be the respiratory system. Bronchial obstruction and pulmonary hyperinflation result from acute upper-airway obstruction caused by angioedema of the larynx and epiglottis (1). Vascular reactions may accompany the respiratory failure or they may represent the primary manifestations of anaphylaxis (20). In the present study, the most common consistent physiologic response in the three patients with severe insect sting-induced anaphylaxis was peripheral vascular collapse manifested by extreme hypotension. In only one of the three was there documented evidence of airflow limitation and this was not caused by upper-airway edema or obstruction.

Predisposing factors. As part of the clinical trial to evaluate the effectiveness of immunotherapy, we attempted to predict and limit the extent of any possible systemic reactions in two ways. First, incremental subcutaneous doses of Hymenoptera venom were administered. Venom in excess of the concentration in an insect sting caused no reaction in the three patients who developed severe anaphylaxis immediately after the actual insect sting. We had expected a response to injected venom in those who developed severe reactions to the actual sting because mild systemic reactions have occurred from injected venoms in other patients undergoing venom immunotherapy (21). Hymenoptera venoms contain several proteins that serve as allergens and a variety of less well-characterized vasoactive peptides and amines (6, 22). It is possible that in processing the venom these vasoactive substances were inactivated or lost. This would not have altered the usefulness of the venom for immunotherapy, although alterations in these vasoactive substances could decrease the rate at which these venom antigens become available to the systemic circulation, thereby aborting major systemic reactions. Perhaps we could have produced graded responses by intravenous administration of the venom. If so, we might have performed the trial with less risk, although ironically we avoided the intravenous route because of its presumed danger.

Our second approach to predicting and limiting any systemic reactions was careful physiologic monitoring throughout the venom challenges and the subsequent insect sting. Surprisingly, we found no detectable early physiologic changes that would predict development of a systemic reaction in the three subjects who developed severe anaphylaxis.

Retrospective examination of the allergic histories as well as the specific antigen skin reactivity to Hymenoptera venoms did not reveal any parameters that differentiated the subjects who developed a systemic anaphylactic reaction. Furthermore, the development of a systemic reaction could not be related to individual serum-IgE antivenom-antibody levels, or to in vitro studies of leukocyte histamine release (6). Subsequent investigation with a laboratory model of canine anaphylaxis has also failed to show any relationship between the severity of a systemic anaphylactic reaction and the degree of skin reactivity to specific antigen (23). Therefore, although it would have been scientifically and clinically useful, we were unable to find any predisposing physiologic or immunologic parameters that could be used to predict which members of this group of subjects would respond to an insect sting with a systemic reaction.

Physiologic manifestations of anaphylactic shock. Acute respiratory failure is characteristic of human anaphylaxis, and acute upper-airway edema may be a major cause of death (1, 3). In this study, two of the three patients with vascular shock demonstrated abnormalities of gas exchange but in only one was there evidence of airflow limitation. In this latter subject the respiratory abnormalities were similar to those observed in status asthmaticus. The acute respiratory failure secondary to airflow limitation with severe hypoxemia and hypercarbia was initially unresponsive to treatment with supplemental oxygen, bronchodilators, and mechanical ventilation. Airflow limitation in this man, who had no asthmatic history, was secondary to diffuse lower-airways obstruction. It was not because of acute laryngeal edema or upper-airways obstruction because the subject's airflow limitation continued after endotracheal intubation. The severity of the asthmatic attack could be assessed by wide respiratory swings in pressure measurement of central venous pressure (Fig. 3). These pressure swings are comparable to those observed during a severe asthmatic attack and reflect the large changes in pleural pressure necessary to maintain ventilation during acute hyperinflation with airflow limitation (24, 25).

The most severe clinical manifestation of systemic anaphylaxis was severe hypotensive shock. Although we did not directly measure cardiac output, it was probably decreased because arterial pulse pressure was markedly narrowed in two of the three patients. One patient with persistent hypotension developed transient electrocardiographic changes consistent with inferior myocardial wall ischemia. The electrocardiographic changes have been noted by previous investigators who have documented persistent electrocardiographic changes occurring in healthy individuals after anaphylaxis regardless of the cause (4, 5). There was no evidence of primary cardiac dysfunction. It seems likely that the circulatory collapse was from peripheral factors that prevented filling of the heart, since the administration of large amounts of plasmanate and saline did not worsen shock but rather led to the eventual restoration of blood pressure.

Laboratory-clinical correlations. There was no correlation between the plasma histamine level and the presence or absence of urticaria. There is evidence that some forms of urticaria, such as that caused by cold or cholinergic stimulation, are accompanied by elevated plasma and skin histamine levels (26), but patients with chronic "idiopathic" urticaria including those with elevated skin histamine levels may have normal plasma histamine.

The magnitude of the hemodynamic changes in the three patients with shock did correlate with the level of plasma histamine. The maximal fall in mean arterial pressure was similar in all three patients but the duration was longer in the two patients with the highest levels of plasma histamine. Patient 3, who had the most severe reaction, had a more rapid return-to-normal of his blood pressure than did Patient 2. This may have been because of prompter and more vigorous therapy. Furthermore, in the two patients with severe anaphylaxis, the hypoxia and decreased mean blood pressure persisted after plasma histamine returned to base-line. This suggests that the persistent changes were either because of the effects of other mediators released during anaphylaxis or the individual variability in recovery time of different organs. Recently, a kallikreinlike enzyme has been described that is liberated after antigen-IgE-antibody interaction on human basophils; this mediator might have contributed to the hypotension since it can digest kininogen to generate kinin (27).

The changes in the clotting, kinin, and complement systems have not been reported in human anaphylaxis, although a failure of coagulation has been noted in both mean and animals after fatal episodes of anaphylaxis. Halonen and Pinckard have reported clotting abnormalities in rabbits undergoing IgE-mediated anaphylactic reactions, although the mechanism that causes these changes has not been clarified (28). The prominent depletion of Factor V, Factor VIII, and fibrinogen in this study is consistent with the rapid onset of intravascular coagulation. Such dramatic depletion of critical coagulation factors could account for the defective coagulation seen after clinical and experimental anaphylaxis. Although plasmanate and saline were given to these patients, values for α_2 macroglobulin, IgG, and ceruloplasmin, as determined by radial immunodiffusion, did not reveal significant concentration differences during anaphylaxis as compared with the control samples. Values for these proteins were diminished by $<10\%$ of control and a correction factor was, therefore, not applied to our data. Thus, fluid shifts or volume changes, although undoubtedly occurring, cannot account for the profound changes that were observed in some coagulation factors.

We can only speculate about the pathway that initiates coagulation. Recently, it has been shown that stimulated neutrophils release tissue thromboplastin (29) and a similar release from basophils or mast cells might trigger the extrinsic coagulation pathway. On the other hand, activation of Hageman factor which initiates the intrinsic coagulation pathway and the generation of bradykinin (30) could also contribute to these abnormalities. Basophils have a mediator that can cleave Hageman factor. However, without any demonstrable depletion of Hageman factor or prekallikrein after the anaphylactic episode, it is unlikely that a massive activation of this pathway accounted for the prominent coagulopathy seen.

Significant activation of the complement system by antigen-antibody complexes in the sub-nanogram per milliliter range is unlikely. Thus, it is possible that either direct enzymatic digestion by cellularly derived proteases or activation of the coagulation-fibrinolysis cascade lead to depletion of complement and HMW kininogen. This is consistent with the observation that the coagulant activity of HMW is not diminished by digestion with kallikrein (31), although digestion by proteases such as plasmin can destroy its coagulant activity in proportion to the release of bradykinin (32). Also, it is possible that the activation of fibrinolysis that accompanied intravascular coagulation and depleted Factors V, Factor VIII, and fibrinogen could also contribute to the decrease in HMW kininogen as well as the complement abnormalities.

Treatment of Anaphylaxis. With a well-planned therapeutic approach and careful physiologic monitoring we felt that any significant anaphylactic reaction could be aborted by initiating appropriate therapy early in the course of the reaction. This assumption proved incorrect in two patients. Therapeutic maneuvers included treatment with large amounts of colloid and crystalloid fluids as well as intravenous epinephrine administered in excess of the usual recommended doses (20). In fact, even in these high concentrations, epinephrine did not initially reverse the hypotension in two of the patients. Only as the reaction continued and the level of histamine declined did the subjects become more responsive to epinephrine and volume replacement. The unresponsiveness to epinephrine in these two patients may be because of functional β-adrenergic blockade which, it has been suggested, occurs in some asthmatics (33). This lack of response of the airflow limitation and vascular tone to β-adrenergic stimulation could be because of primary alteration of β-receptors during anaphylactic shock or the release of a mediator with β-adrenergic-blocking activity. After this initial refractory period, both fluid and epinephrine caused initially transient and finally more prolonged improvement in arterial pressure (Figs. 2 and 3).

It is difficult to evaluate the effectiveness of our interventions in the patients with shock. Indeed, we must admit that we do not know whether the medical therapy effected either the recovery time or ultimate

outcome. We were able to respond rapidly to the profound life-threatening symptoms of circulatory collapse and respiratory failure. Yet the length of time between our therapeutic interventions and a significant clinical response suggests to us the disturbing possibility that there might be no ideal therapy for severe anaphylaxis even under optimal conditions.

ACKNOWLEDGMENTS

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