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A Rapid Increase in Foot Tissue Temperature Predicts Cardiovascular Collapse during Anaphylactic and Anaphylactoid Reactions

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Background: **Cardiovascular collapse during anaphylactic and anaphylactoid reactions results from release of histamine and other vasoactive substances. Intense arteriolar vasodilation associated with severe allergic reactions is likely to increase convective transfer of heat and peripheral tissue temperature, and finally to provoke cardiovascular collapse. Therefore the authors tested the hypothesis that during anaphylactic and anaphylactoid reactions, an acute increase in peripheral tissue temperature precedes cardiovascular collapse and that the magnitude of the increase correlates with the severity of the reaction.**

Methods: **During a 13-yr period, approximately 120,000 patients were screened for clinical evidence of intraoperative anaphylactic and anaphylactoid reactions. Core temperature was measured in the distal esophagus, and "deep" foot tissue temperature was measured on the sole of one foot in all these patients. Otherwise unexplained cardiovascular collapse accompanied by bronchospasm and/or cutaneous signs such as urticaria, flushing, or angioedema occurred in 32 patients who were entered into a prospective diagnostic protocol. Among these, 15 met laboratory criteria for anaphylactic or anaphylactoid reactions. Anaphylaxis was confirmed in nine of them by a positive skin test to the suspected agent, the *in vitro* leukocyte histamine-release test, or the Praunitz-Küstner test. Reactions were considered anaphylactoid in six others when laboratory evidence did not support anaphylaxis, but plasma histamine or tryptase concentrations were much greater during episodes than 6 weeks later.**

Results: **Development of anaphylactic and anaphylactoid reactions followed a characteristic pattern: (1) Foot temperature, which was initially 3.3 ± 1.7°C less than core temperature, increased to within 0.3°C of core temperature 3.2 ± 1.4 min after drug administration; (2) onset of cardiovascular collapse ensued 1.8 ± 0.8 min later; and (3) core temperature increased from 34.7 ± 1.0°C to peak values 37.1 ± 0.6°C 13 ± 5 min after drug administration. The most severe reactions were associated with shorter times to comparable core and foot temperatures, faster onset of cardiovascular collapse, and higher maximum core temperatures.**

Conclusions: **The normal core-to-peripheral tissue temperature gradient was obliterated several minutes before hemodynamic consequences associated with anaphylactic and anaphylactoid reactions. Further, a rapid increase in deep foot temperature and maximum core temperature correlated with clinical severity. (Key words: Temperature: core; tissue. Anaphylactic. Anaphylactoid. Carbon dioxide: end-tidal. Hyperthermia. Fever. Anesthesia.)**

THE clinical features of anaphylactic and anaphylactoid reactions are similar. Anaphylaxis is defined as an immunoglobulin E-mediated allergic reaction.[1,2] Anaphylactoid reactions differ in that they are mediated by various

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independent pathways and agents, all of which result in mast cell degranulation.[3,4] Both, however, are characterized by systemic release of vasoactive substances that mediate profound vasodilation.[2]

Induction of anesthesia is associated with inhibition of thermoregulatory control,[5,6] nearly complete arteriovenous shunt dilation,[7] and consequent core-to-peripheral redistribution of body heat.[8,9] Nonetheless, a thermal gradient between core, peripheral tissues, and skin persists. This gradient is typically 3–4°C,[8,10] but is likely reduced by intense vasodilation associated with anaphylactic and anaphylactoid reactions. This "second redistribution" might be manifested clinically as an additional rapid decrease in core temperature accompanied by a comparable increase in peripheral tissue temperature.

The most important mediator of anaphylactic and anaphylactoid reactions is histamine.[2] Histamine is a central thermoregulatory neurotransmitter[11] that produces dose-dependent hypothermia in unanesthetized rats and mice.[12,13] In contrast, similar injections in anesthetized rats induce hyperthermia, which can be antagonized by cimetidine administration.[14] Other mediators of anaphylactic and anaphylactoid reactions, such as prostaglandins, leukotrienes, and platelet-activating factor are likely to be endogenous pyrogens.[2] Further, compounds released during these reactions activate leukocytes, which in turn are likely to liberate other pyrogens. Intraoperative anaphylactic and anaphylactoid reactions are thus likely to increase core temperature by augmenting the central temperature-control set point.

Onset of anaphylactic and anaphylactoid reactions are thus apparently associated with simultaneous but conflicting thermal processes: (1) peripheral vasodilation and consequent core-to-peripheral redistribution of body heat, and (2) an increase in the central set point, which normally produces fever. How these factors combine to alter core temperature and distribution of heat within the body remains unknown. Nonetheless, it seems likely that severe hemodynamic effects resulting from intense vasodilation will be preceded by redistribution of heat to peripheral tissues. Furthermore, the most intense vasodilation should be associated with the most redistribution and the worst cardiovascular consequences. Subsequently, an increased thermoregulatory set point may compensate for vasodilation-induced redistribution, resulting in clinical fever. Therefore we tested the hypothesis that during anaphylactic and anaphylactoid reactions, an acute increase in foot tissue temperature precedes cardiovascular collapse and that the magnitude of the increase correlates with hemodynamic severity.

Methods

With institutional review board approval, we screened approximately 120,000 patients for clinical evidence of intraoperative anaphylactic and anaphylactoid reactions. The study was conducted at the University of Hirosaki School of Medicine and associated hospitals during a 13-yr period (September 1983 to February 1996). There were no formal entry criteria for the study, and core and foot tissue temperatures were measured in 30–90% of the patients at the participating hospitals. Data from uncomplicated anesthesia was not preserved, and we do not know precisely how many patients were evaluated. (In this regard, our data are similar to the American Society of Anesthesiologists' closed claims database, which also lacks a precise numerator.) However, patients meeting our definition of otherwise unexplained cardiovascular collapse were uniformly treated according to prospective guidelines and were entered into a prospective diagnostic protocol.

Clinical features that we considered characteristic of the disorders were otherwise unexplained cardiovascular collapse (sustained systolic blood pressure < 80 mmHg or mean arterial pressure < 60 mmHg) accompanied by bronchospasm or cutaneous signs including urticaria, flushing, or angioedema. Rather than formally define the time required to be considered "sustained," we allowed participating clinicians to identify cardiovascular collapse based on the degree and duration of hypotension. Bronchospasm was defined by expiratory wheezing accompanied by an obvious reduction in tidal volume. It was considered mild when it responded quickly to bronchodilator therapy and saturation was reasonably maintained by administration of 100% oxygen. Bronchospasm was considered severe when patients were unresponsive to bronchodilating drugs and oxygen saturation on 100% oxygen was $< 90\%$.

Once a patient was identified as having otherwise unexplained hypotension, accompanied by cutaneous or pulmonary symptoms, the onset of cardiovascular collapse was considered the time when systolic blood pressure first decreased to < 80 mmHg or mean arterial pressure first decreased to < 60 mmHg.

The severity of the presumptive anaphylactic and anaphylactoid reactions were classified according to a slight modification of the Ring and Messmer scale[15]:

score 1 = rash and mild fever; score 2 = non-life-threatening cardiovascular response, mild bronchospasm, or both; score 3 = shock, severe bronchospasm, or both; and score 4 = electromechanical dissociation or cardiac arrest.

Presumptive anaphylactic and anaphylactoid reactions were managed by intravenous administration of epinephrine (titrated to blood pressure) and methylprednisolone (20–30 mg/kg), and intravascular volume expansion was managed with lactated Ringer's solution. Treatments were continued until patients' mean arterial blood pressures recovered to pre-episode levels. Aminophylline was also administered when bronchospasm persisted more than 15–30 min, patients showed a persistent Sao_2 of < 95% during administration of 100% oxygen, or both.

Laboratory Diagnoses

With written informed consent, we used three methods to diagnose anaphylaxis: a skin test, the *in vitro* leukocyte histamine-release test, and the Praunitz-Küstner test. We considered the diagnosis confirmed when at least one test was positive, based on the criteria of Laxenaire *et al.*[16] Skin tests were administered 6 weeks after operation based on the protocol of Fisher.[17] The drug panel included pentazocine, cefmetazole, mitomycin, dextran, aprotinin, menatetrenone, sulpyrine, hydroxyethylstarch, and cyclosporine. We also administered the suspected drug at a test dose suggested by the pharmaceutical company, published case reports, or 10^{-5}–10^{-6} of the normal dose. Positive responses were characterized by a wheal exceeding 10 mm in diameter, arising within 10 min of drug administration, and persisting for at least 30 min. The test was considered diagnostic when reactions were uniformly negative except to the suspected agent.

The leukocyte histamine-release test was performed as described by Hirshman *et al.*[18] Briefly, leukocytes were isolated from whole blood and suspended at a concentration of 10^7/ml. These aliquots were incubated at 37°C for 1 h with six concentrations of each test drug, ranging from 10^{-8}–10^{-3} g/ml. Histamine release was measured by an enzyme-linked immunosorbent assay (histamine enzyme immunoassay kit; Immunotech, Luminy, France).

The Praunitz-Küstner test was performed according to the protocol of Fisher.[19] Patients were first tested for HIV, syphilis, and hepatitis B and C. When all results were negative, serum isolated from patients was injected into multiple sites on the forearm of consenting human volunteers who, 24 h later, were challenged by intradermal injection of the suspect drugs. A wheal and flare reaction within 20 min identified a positive reaction. Because this test sometimes causes viral hepatitis, we performed it only when the skin test and leukocyte histamine-release test results were negative.

Anaphylactoid reactions are characterized by mast cell degranulation, mediated by pathways independent of immunoglobulin E. Consequently, skin testing, the *in vitro* leukocyte histamine-release test, and the Praunitz-Küstner test usually fail to be diagnostic. Further, anaphylactic and anaphylactoid reactions cannot be distinguished on clinical grounds. We diagnosed anaphylactoid reactions when laboratory evidence did not support anaphylaxis, but plasma histamine or tryptase concentrations exceeded the 99th percentile in asymptomatic patients. Tryptase is a protease with a plasma half-life of 1.5–2 h.[20] In contrast, the plasma half-life of histamine is only a few minutes.[4] Concentrations of each are excellent markers of mast cell degranulation, from whatever mechanism.[3,4]

Arterial samples were obtained for histamine and tryptase analysis 10 min and 6 weeks after development of clinical symptoms. Blood was centrifuged at 4°C (1,000*g*) for 15 min in tubes containing 10 mg ethylenediamine tetraacetic acid. Plasma, without a white cell layer, was aspirated and frozen in aliquots at -80°C pending analysis. Histamine concentrations were assayed in triplicate by an enzyme-linked immunoassay (histamine enzyme immunoassay kit, Immunotech). The lower limit of detection was 0.2 nM. Tryptase concentrations were measured in triplicate by an immunoradiometric assay (Tryptase RIACT kit; Pharmacia, Uppsala, Sweden). The lower limit of detection was 0.5 U/l (1 U = 1 mg purified human lung tryptase). The tryptase assay was not generally available until 1990; consequently, it was applied to aliquots of frozen plasma from patients enrolled in previous years.

To establish control values in our population, we also measured plasma histamine and tryptase concentrations in 100 consenting patients who had no symptoms suggesting anaphylactic or anaphylactoid reactions. With informed consent, samples were obtained 20 min after induction of anesthesia. The mean concentrations of plasma histamine and tryptase levels were 1.3 ± 0.6 nM and 1.1 ± 1.0 U/l, respectively. The 99% confidence intervals for plasma histamine and tryptase levels were 4.3 nM and 4.1 U/l. These values are similar to those reported previously.[4]

Intraoperative Monitoring

Foot tissue temperature (T_{foot}) was measured on the sole of one foot with a 4.5-cm diameter Coretemp (model 204 or 205; Terumo Medical Corp., Tokyo, Japan) "deep-tissue" thermometer. This thermometer uses an active heating element to null cutaneous heat flux, a system originally described by Fox *et al.*[21,22] and subsequently improved by Togawa *et al.*[23] The method is based on thermodynamic theory specifying that when heat flow across the skin is zero, skin-surface temperature equals subcutaneous tissue temperature. In practice, the device records tissue temperature approximately 1 cm below the skin surface. This method has been used in many previous studies to estimate foot tissue temperature,[5,8-10] and has a time resolution of about 30 s. The deep-temperature thermometer displays values continuously and prints them on a paper record at 30-s intervals.

Core temperature (T_{core}) was measured in the distal esophagus.[24] Core and foot tissue temperatures were considered comparable when they differed $\leq$ 0.3°C. Blood pressure was recorded at 1- to 3-min intervals oscillometrically (Dinamap; Critikon, Tampa, FL) by a continuous indirect method (JENTOW 7700, Japan Colin, Tokyo, Japan) or from an intra-arterial catheter. End-tidal pressure of carbon dioxide (P_{CO_2}; 5250 RGM, Ohmeda, Madison, WI; or Respina IH26, NEC, Tokyo, Japan) was displayed continuously and routinely recorded at 5-min intervals. However, measurements were made and recorded at intervals not exceeding 1 min during periods of cardiovascular instability. During the last 5 yr of the study, vital parameters were recorded by an automated anesthesia record keeper. A sustained systolic arterial pressure $<$ 80 mmHg or mean arterial blood pressure of $\leq$ 60 mmHg identified the onset of cardiovascular collapse.

Statistical Analysis

Morphometric characteristics, onset time, severity, plasma histamine and tryptase concentrations, minimum mean arterial pressures, and requirements for epinephrine and vascular volume expansion in patients having anaphylactic and anaphylactoid reactions were compared with those having clinically suspicious episodes that were not confirmed immunologically using one-way analysis of variance and the Fisher PLSD tests. Plasma histamine concentrations during and after episodes were compared using paired, two-tailed *t* tests.

The relations between severity scores and times to comparable core and foot temperatures, onset of cardiovascular collapse, and maximum core temperature were evaluated with one-way analysis of variance and Scheffé's F tests. Because preliminary analysis indicated that these responses were similar during anaphylactic and anaphylactoid reactions, data from all 15 patients were combined. Data were expressed as means $\pm$ SD; $P < 0.05$ was considered statistically significant.

Results

Thirty-two patients had clinical signs consistent with anaphylactic or anaphylactoid reactions. All agreed to laboratory testing, and none was lost to follow-up. Among these, nine were diagnosed as having had anaphylaxis: The skin test was positive in eight of them, and the leukocyte histamine-release test was positive in seven. Anaphylaxis was established in one additional patient by the Praunitz-Küstner test (table 1). Six patients were diagnosed as having had anaphylactoid reactions based on elevations in plasma histamine or tryptase concentrations without evidence of an immunoglobulin E-mediated process (table 2). In contrast, laboratory studies failed to demonstrate evidence of anaphylactic or anaphylactoid reactions in 17 patients (table 3).

All patients described here were given nitrous oxide and nondepolarizing muscle relaxants (pancuronium, vecuronium, or both) to maintain anesthesia. (Many were given succinylcholine during anesthetic induction, but tissue temperatures were not measured at that time.) Anesthesia was also maintained with droperidol and fentanyl or pentazocine in 15 patients, with enflurane in 9 patients, with halothane in 3 patients, and with isoflurane in 5 others. Operating room temperatures varied from 23-25°C, and relative humidity was maintained near 60%. Morphometric characteristics, onset time, severity scores, plasma histamine and tryptase concentrations, minimum mean arterial pressures, and requirements for epinephrine and vascular volume expansion were similar in the three groups.

Four of the 15 patients in whom anaphylactic and anaphylactoid reactions were confirmed had blood pressure measured oscillometrically at 1-min intervals, 5 had continuous indirect measurements, and 6 had arterial catheters. In the 17 patients in whom anaphylactic and anaphylactoid reactions were not confirmed, blood pressure was measured oscillometrically at 1-min intervals in 6 and at 3-min intervals in 4. Blood pressure in three of these others was measured using the continu-

Table 1. Anaphylactic Reactions

	Patient 1	Patient 2	Patient 3	Patient 6	Patient 8	Patient 10	Patient 12	Patient 14	Patient 15
Age (yr)	68	62	59	45	43	42	17	47	32
Gender (M/F)	M	F	M	F	F	M	F	F	M
Onset (min after induction)	135	214	179	239	95	34	325	210	241
Severity (grade)	3	2	2	4	2	2	4	4	3
Histamine control (nM/l)	2.1	1.3	1.5	2.2	0.5	1.4	2.4	1.2	0.8
Histamine during (nM/l)	24.8	13.9	34.8	35.6	19.4	9.7	125	221	32.1
Tryptase control (U/l)	0.8	1.3	<0.5	<0.5	<0.5	2.4	1.4	<0.5	1.4
Tryptase during (U/l)	6.4	8.8	7.5	21.9	5.7	18.7	23.7	23.3	14.7
Positive skin test	+	–	+	+	+	+	+	+	+
Positive Praunitz-Küstner		+							
Positive histamine release	+	–	+	+	–	+	+	+	+
Minimum MAP (mmHg)	47	55	51	*	54	57	*	*	48
Epinephrine (mg)	1.0	1.5	1.0	1.0	0.3	0.4	1.5	2.5	1.0
Fluid (l)	2.0	1.9	1.8	3.5	2.0	0.8	3.0	3.0	2.0
Core–foot temperature (min)	3.0	6.0	7.0	2.0	4.0	3.0	3.0	1.5	1.5
MAP ≤60 mmHg (min)	4.0	7.0	9.5	2.5	5.5	5.0	5.5	3.5	3.5
Time to maximum T_{care} (min)	9.5	16.5	25.0	13.5	15.0	16.5	8.5	7.0	9.0
Maximum T_{care} (°C)	36.4	36.1	36.9	37.2	36.3	37.1	37.6	38.2	37.4

The implicated drugs, in patient order, were: pentazocine, mitomycin, menatetrenone, vancomycin, pancuronium, cephalothin, vecuronium, and menatetrenone. Severity grade was determined according to the Ring and Messmer scale. "During" samples were obtained 10 min after the onset of reaction; "After" samples were obtained 6 weeks later.

* Unobtainable blood pressure. See table 3 for group averages and variance.

Table 2. Anaphylactoid Reactions

	Patient 4	Patient 5	Patient 7	Patient 9	Patient 11	Patient 13
Age (yr)	24	54	47	28	52	60
Gender (M/F)	F	M	F	F	F	M
Onset (min after induction)	127	153	327	156	429	187
Severity (grade)	4	3	3	2	3	3
Histamine control (nM/l)	0.9	1.5	1.8	1.6	2.1	3.4
Histamine during (nM/l)	12.5	24.6	11.4	13.5	27.3	39.4
Tryptase control (U/l)	<0.5	1.9	1.5	1.3	<0.5	2.4
Tryptase during (U/l)	11.4	13.6	23.8	15.3	6.4	7.5
Positive skin test	–	–	–	–	–	–
Positive Praunitz-Küstner	–	–	–	–	–	–
Positive histamine release	–	–	–	–	–	–
Minimum MAP (mmHg)	*	49	51	59	47	49
Epinephrine (mg)	1.5	1.2	1.5	1.0	1.0	0.4
Fluid (l)	2.0	1.8	1.3	2.4	2.4	0.8
Core–foot temperature (min)	2.5	2.0	4.0	3.5	3.5	2.5
MAP ≤60 mmHg (min)	5.0	3.0	6.0	7.0	4.5	5.0
Time to maximum T_{care} (min)	10.0	11.5	12.0	22.0	9.5	6.5
Maximum T_{care} (°C)	37.5	37.8	37.7	36.6	36.8	37.0

Implicated drugs, in patient order, were: cefmetazole, dextran, aprotinin, sulpyrine, hydroxyethyl starch, cyclosporin, and neostigmine. Severity grade was determined according to the Ring and Messmer scale. "During" samples were obtained 10 min after the onset of reaction; "After" samples were obtained 6 weeks later. None of the morphometric, hemodynamic, or temperature responses differed from those in the patients having anaphylactic reactions. See table 3 for group averages and variance.

* Unobtainable blood pressure.

Table 3. Anaphylactic and Anaphylactoid Reactions, and Patients Who Showed Clinical Signs of Reactions Not Substantiated by Laboratory Testing

	Anaphylactic	Anaphylactoid	Unsubstantiated
Number of subjects	9	6	17
Age (yr)	46 ± 15	44 ± 15	49 ± 16
Gender (M/F)	4/5	2/4	8/9
Onset (min after induction)	187 ± 87	230 ± 121	273 ± 173
Severity (grade)	2.9 ± 0.9†	3.0 ± 0.6†	2.2 ± 0.4
Histamine control (nM/l)	1.5 ± 0.6	1.9 ± 0.8	1.3 ± 0.6
Histamine during (nM/l)	65 ± 69*	24 ± 10*	4 ± 6*
Tryptase control (U/l)	0.8 ± 0.9	1.2 ± 1.0	1.2 ± 0.8
Tryptase during (U/l)	13 ± 8*	13 ± 6*	4 ± 6
Positive skin test	8	0	0
Positive Praunitz-Küstner	1	0	0
Positive histamine release	7	0	0
Minimum MAP (mmHg)	35 ± 26†	43 ± 21†	54 ± 6
Epinephrine (mg)	1.1 ± 0.7†	1.1 ± 0.7†	0.4 ± 0.5
Fluid (l)	2.2 ± 0.8†	1.8 ± 0.6†	1.1 ± 0.6
Core–foot temperature (min)	3.3 ± 1.5†	3.0 ± 0.8†	9.4 ± 3.3
MAP ≤60 mmHg (min)	5.1 ± 2.1†	5.1 ± 1.4†	8.5 ± 3.2
Time to maximum T_{core} (min)	13.4 ± 5.7†	11.9 ± 5.3†	20.2 ± 7.2
Maximum T_{core} (°C)	37.0 ± 0.7†	37.2 ± 0.5†	36.3 ± 0.8

Severity grade was determined according to the Ring and Messmer scale. "During" samples were obtained 10 min after the onset of reaction; "After" samples were obtained 6 weeks later. Undetectable tryptase levels were considered zero. Unobtainable blood pressures were considered zero for purposes of computing lowest mean arterial blood pressure.

* Statistically significant differences between "Control" and "During" histamine and tryptase concentrations.

† Statistically significant differences from the patients who had clinically suspect episodes of anaphylactic or anaphylactoid reactions that were not confirmed immunologically. None of the morphometric, hemodynamic, or temperature responses differed from those in the patients having anaphylactic reactions.

ous indirect method, whereas four had arterial catheters.

Development of anaphylactic and anaphylactoid reactions followed a characteristic pattern. (1) Foot temperature, which was initially 3.3 ± 1.7°C less than core temperature, increased to within 0.3°C of core temperature 3.2 ± 1.4 min after drug administration. End-tidal P_{CO_2} increased significantly during this period, from 33 ± 1 to 38 ± 2 mmHg. (2) Onset of cardiovascular collapse ensued 1.8 ± 0.8 min later. Foot temperature increased to within 0.3°C of core temperature before cardiovascular collapse in every case. Angioedema was first noted slightly later, at 5.1 ± 1.8 elapsed minutes. This was accompanied by a significant additional increase in end-tidal P_{CO_2}, to 44 ± 5 mmHg. (3) Core temperature increased from 34.7 ± 1.0°C to peak values 37.1 ± 0.6°C 13 ± 5 min after drug administration. (4) By the time anesthesia ended 34 ± 29 min after drug administration, end-tidal P_{CO_2} had nearly returned to normal but core and tissue temperatures remained elevated (table 4).

Among the anaphylactic and anaphylactoid reactions, greater severity scores were associated with shorter times to comparable core and foot temperatures, faster onset of cardiovascular collapse, and higher maximum core temperatures (figs. 1–3). In the patients demonstrating circulatory collapse without laboratory evidence of anaphylactic and anaphylactoid reactions, foot and core temperatures also increased. However, the increases were significantly less than in the patients who had laboratory evidence of anaphylactic or anaphylactoid reactions. Consequently, the minimum difference between foot and core temperature in these patients averaged 0.8 ± 0.6°C. Similarly, end-tidal P_{CO_2} increased, but the magnitude was significantly less than in the patients with anaphylactic and anaphylactoid reactions.

Two patients with anaphylaxis and three having anaphylactoid reactions were given aminophylline to treat bronchospasm. Three of them experienced prolonged bronchospasm and required postoperative intubation for approximately 6 h. All other patients recovered pulmonary and hemodynamic stability soon after intravenous administration of epinephrine, methylprednisolone, and fluid.

Among the 17 patients who had critical clinical episodes without laboratory evidence of anaphylactic or

Table 4. Temperatures and End-Tidal P_{CO_2}

	Drug Administration*	$T_{core}-T_{foot}$	Maximum T_{core}	End of Anesthesia
T_{core} (°C)	34.7 ± 1.0	34.8 ± 0.9	37.1 ± 0†	36.0 ± 0.5†
T_{foot} (°C)	31.5 ± 2.4	34.5 ± 0.9†	36.4 ± 0.5†	34.8 ± 1.3†
End-tidal P_{CO_2} (mmHg)	33.4 ± 1.4	38.3 ± 2.1†	44.2 ± 5.4†	34.1 ± 2.5

* The time at which the precipitating drug was injected.

† Statistically significant differences from "Drug Administration."

anaphylactoid reactions, morphometric characteristics and onset times were similar to those in the other two groups. However, minimum mean arterial pressure was significantly higher, and the severity scores, requirements for epinephrine, and vascular volume expansion were significantly less than those in the other two groups. In addition, plasma histamine and tryptase concentrations during the reaction were lower than those in other two groups. Core and foot temperature increased, although the increase was less than in the other two groups. Similarly, end-tidal P_{CO_2} increased, but only slightly, to a maximum of only 38 ± 3 mmHg.

Our study did not include a formal evaluation of false-positive responses. However, sudden increases in foot tissue temperature generally were observed only in two situations: administration of the ganglionic blocker trimetaphan camsylate and immediately after successful aortofemoral or femoropopliteal revascularization. Core temperatures in each case decreased or remained constant, rather than increased.

Discussion

The anaphylactic and anaphylactoid reactions we evaluated were serious, with minimum mean arterial blood pressures near 40 mmHg. These patients typically

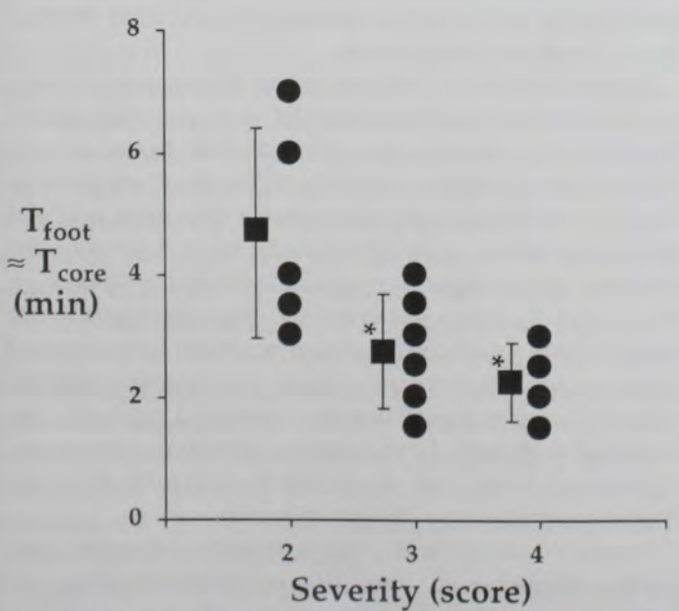

Fig. 1. The time required for foot and core temperatures to equilibrate (within 0.3°C) was reduced when the Ring and Messmer[15] anaphylaxis and anaphylactoid reaction severity scores were greater. *Circles* identify individual responses, with the adjacent squares showing the means and SDs. Asterisks (*) identify statistically significant differences from score 2. There was no significant difference between scores 3 and 4.

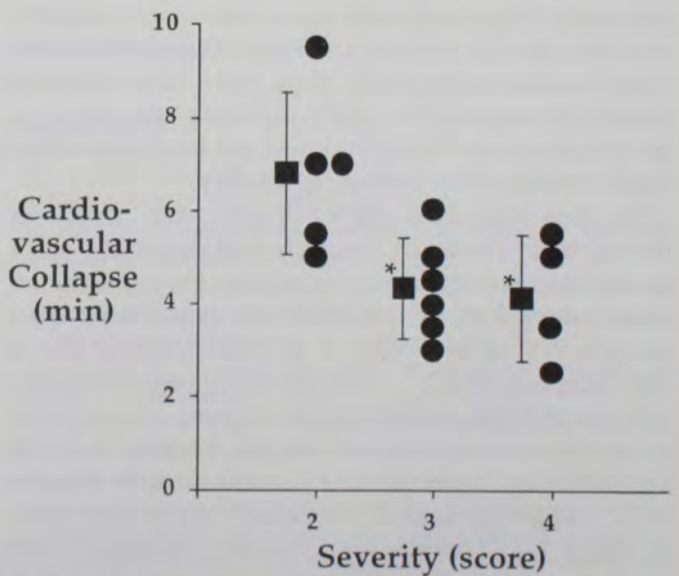

Fig. 2. The time to cardiovascular collapse was reduced when the Ring and Messmer[15] anaphylaxis and anaphylactoid reaction severity scores were greater. *Circles* identify individual responses, with the adjacent squares showing the means and SDs. Asterisks (*) identify statistically significant differences from score 2. There was no significant difference between scores 3 and 4.

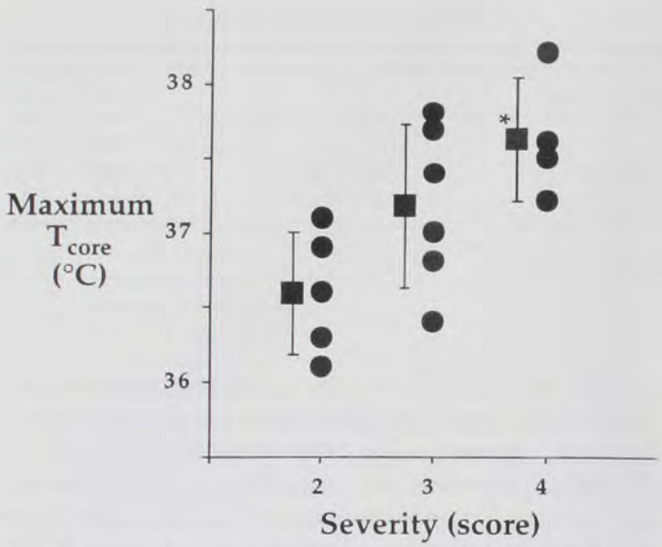

Fig. 3. Maximum core temperatures were higher when the Ring and Messmer[15] anaphylaxis/anaphylactoid reaction severity scores were greater. *Circles* identify individual responses, with the adjacent squares showing the means and SDs. Asterisks (*) identify a statistically significant difference between scores 2 and 4; patients having scores 3 and 4 did not differ significantly.

required intravenous administration of more than 1 mg epinephrine and approximately 2 l fluid to restore hemodynamic stability. Clinical symptoms were supported by laboratory evidence of immunoglobulin E-mediated allergic reaction or plasma tryptase and histamine concentrations more than three times baseline values. As suggested by previous work,[1] anaphylactic and anaphylactoid reactions could not be distinguished based on clinical symptoms or severity.

The data supported our hypothesis that in patients having anaphylactic or anaphylactoid reactions, onset of cardiovascular collapse would be preceded by an acute increase in peripheral tissue temperature: foot temperature increased 3.1 ± 1.8°C to within 0.3°C of core temperature 1.8 ± 0.8 min before onset of cardiovascular collapse. Peripheral tissue temperature monitoring thus provided several minutes warning of severe hemodynamic consequences associated with anaphylactic and anaphylactoid reactions. Further, the speed at which foot temperature increased correlated with reaction severity. Tissue temperature monitoring thus might not only provide warning of immunologically meditated cardiovascular collapse but may also guide therapy. A limitation of our protocol, however, is that we did not record data from hemodynamically stable patients. Thus we do not know how often acute increases in peripheral tissue temperature failed to predict cardiovascular collapse.

Core temperature in Japan is typically measured from the forehead, using the "deep-temperature" monitor. Once this method is chosen, there is no additional cost of using a second probe to monitor foot temperature simultaneously. But given that anaphylactic and anaphylactoid reactions are rare, it is unlikely that tissue temperature monitoring would otherwise be routinely indicated. Patient outcome after anaphylactic and anaphylactoid reactions appears to be improved by timely treatment. Tissue temperature monitoring thus may prove helpful in susceptible patients or in those given drugs associated with frequent reactions.

Core temperature, which was initially 34.8 ± 0.9°C, subsequently increased 2.4 ± 1.2°C to peak values 13 ± 5 min after administration of the offending drug. This result is consistent with an increase in the central thermoregulatory set point that would be expected to accompany increased production and secretion of endogenous pyrogens during anaphylactic and anaphylactoid reactions. Of note, maximum core temperatures rarely exceeded normal (unanesthetized) values. This observation emphasizes how poorly development of fever during anesthesia is understood; for example, it remains unknown whether pyrogens increase body temperature in hypothermic patients by a certain amount or to a certain temperature.

Acute peripheral tissue warming during anaphylactic and anaphylactoid reactions did not have the classic features of redistribution hypothermia because core temperature failed to decrease. A localized increase in tissue temperature can result from a change in regional heat distribution or increased total body heat content. Because core temperature (and therefore core heat content) initially remained constant, increased peripheral tissue temperature and heat content must have resulted from an overall increase in body heat content. Subsequently, core temperature also increased markedly, indicating that body heat content increased even more. Consistent with this supposition, end-tidal P_{CO_2} increased significantly during episodes.

Increased tissue heat content appears to result from increased metabolic rate because end-tidal P_{CO_2} remained elevated and peripheral vasodilation persisted. However, the mechanism by which metabolic heat production increased is less obvious. All of our patients were paralyzed, and there was never clinical evidence of increased skeletal muscle activity. Nonshivering thermogenesis may increase metabolic rate by approxi-

mately 20–40% in unanesthetized adults[25–27] but apparently does not alter oxygen consumption in anesthetized adults[28] or infants[29] because volatile anesthetics inhibit the process peripherally.[30,31] Whether increased heat production in these cases results from classical nonshivering thermogenesis in brown adipose tissue (perhaps mediated by a stronger stimulus than in previous studies) or is mediated by a different mechanism remains unknown.

We made no effort to localize the vasodilation induced by anaphylactic and anaphylactoid reactions. However, much of the vasodilation may have been in skin arterioles, resulting in increased cutaneous capillary flow. Foot skin-surface temperature thus might have increased even faster than deep tissue temperature, thereby providing even greater warning of hemodynamic collapse during anaphylactic and anaphylactoid reactions. Nonetheless we chose to monitor tissue temperature because it is altered less by surface insulation (*i.e.*, positioning or removing surgical drapes) than skin temperature and thus less subject to artifact.

Induction of anesthesia inhibits thermoregulatory control,[5,6] allowing arteriovenous shunt dilation[7] and rapid core-to-peripheral redistribution of body heat.[8,9] The initial 30 min of anesthesia are thus routinely associated with a substantial increase in foot tissue temperature.[8,10] This normal increase might prove difficult to distinguish from that caused by an anaphylactic or anaphylactoid reaction. Further, the deep tissue thermometer requires as long as 15 min to equilibrate with subcutaneous tissues.[32] Tissue temperatures obtained immediately after positioning the monitor thus are unreliable. Consequently, the method we propose to detect anaphylactic and anaphylactoid reactions will be less useful during induction of anesthesia than subsequently. Among the approximately 120,000 patients evaluated in this study, only two had apparent anaphylactic and anaphylactoid reactions during induction (neither being included among the 32 patients reported above). Both reactions appear to result from succinylcholine administration, and diagnosis was relatively easy in each case because the characteristic cutaneous lesions were not obscured by surgical draping.

End-tidal P_{CO_2} increased slightly but significantly in the patients having anaphylactic and anaphylactoid reactions. Changes in end-tidal P_{CO_2} are common and result from various factors. They are thus unlikely to provide sufficient sensitivity or specificity to confirm the diagnosis of episodes as rare as serious anaphylactic and anaphylactoid reactions.

Tissue or core temperatures increased in the 17 patients whose suspicious episodes were not confirmed as immunologic in origin by laboratory testing. However, the increase in the temperature was significantly smaller than in the patients with anaphylactic or anaphylactoid reactions. Similarly, end-tidal P_{CO_2} also increased in these 17 patients, although much less than in those having documented anaphylactic and anaphylactoid reactions. It is likely that many of these patients actually did experience mild anaphylactoid reactions, a syndrome that is notoriously difficult to diagnosis. Consequently, these 17 patients should not be considered as controls for the others.

In summary, we identified 15 patients having clinical and immunologic evidence of intraoperative anaphylactic and anaphylactoid reactions. During development of these reactions, foot temperature increased 3.1 ± 1.8°C to essentially equal core temperature within 3.2 ± 1.4 min. Onset of cardiovascular collapse ensued 1.8 ± 0.8 min later. Greater severity scores were associated with shorter times to comparable core and foot temperatures, faster onset of cardiovascular collapse, and higher maximum core temperatures. Peripheral tissue temperature monitoring thus provided several minutes warning of the severe hemodynamic consequences associated with anaphylactic and anaphylactoid reactions.

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