
MYOCARDIAL DYSFUNCTION AFTER EPINEPHRINE TREATMENT OF PRESUMED INSECT VENOM ALLERGY IN A MARATHON RUNNER

Epinephrine is the treatment of choice for anaphylaxis. Although its therapeutic index is narrow, adverse effects are transient, and serious adverse events are rare.¹ We describe an individual who developed myocardial stunning and severe global myocardial hypokinesis after receiving multiple doses of epinephrine for presumed insect sting anaphylaxis.

On 3 separate occasions during army training, a nonatopic man received single stings from “wasps.” On each occasion, 30 to 45 minutes later he developed clonic spasms and generalized weakness without mucocutaneous or respiratory symptoms. Nevertheless, he was treated with epinephrine on each occasion and was considered to be sting allergic despite negative Hymenoptera venom skin test results. Medical records from these episodes were unavailable.

After a fourth unidentified insect sting at the age of 33 years (not associated with marathon running), he experienced chills, chest tightness, and syncope, followed by convulsions. He received a total of 5 intramuscular 0.3-mL doses of epinephrine (1:1,000). In the emergency department, he was alert, pale, and shivering, with blood pressure of 179/98 mm Hg. An initial electrocardiogram (ECG) showed possible ectopic atrial rhythm, nonspecific intraventricular conduction delay, and secondary ST-T wave changes but subsequently reverted to normal sinus rhythm with normal ST segments.

At the age of 35 years, 1 day after completing a marathon in just over 3 hours, he was stung again by an unidentified insect. Within 2 minutes he developed chest tightness and wheezing; he self-administered his EpiPen and then passed out. At a local clinic, 2 additional 0.5-mL doses of intramuscular epinephrine (1:1,000) were given, along with nebulized albuterol. Because of substernal pain and pressure, he was transferred to the emergency department, receiving 2 additional 1.0-mL doses of intravenous epinephrine (1:10,000) en route. On arrival in the emergency department, he was pain free, with blood pressure of 109/67 mm Hg. An ECG showed normal sinus rhythm with mild ST-segment depression in the inferolateral leads. Blood chemistry studies showed a potassium level of 2.5 mEq/L (reference range, 3.6–4.8 mEq/L) and a creatine phosphokinase level of 426 U/L (reference range, 52–336 U/L), with a creatine kinase MB fraction of 18.6 ng/mL (reference range, <9.6 ng/mL). A chest radiograph showed no abnormalities; serum tryptase level was not measured. Echocardiography showed a moderately to severely dilated left ventricle with a calculated ejection fraction of 15%. An emergency coronary angiogram had normal findings. He was hospitalized for 3 days, during which cardiac enzyme values were unchanged. On follow-up 1 month later,

his echocardiographic findings were normal, with a calculated ejection fraction of 52%, and Hymenoptera venom skin test results were again negative. One month later, under controlled conditions, a deliberate sting challenge with a live *Polistes* wasp was tolerated without symptoms. The patient declined a subsequent challenge test with 0.5 mL of intramuscular epinephrine (1:1,000).

This case illustrates several important points. First, the signs and symptoms after the first 3 sting reactions were more consistent with a grand mal seizure or hyperventilation than with an IgE-mediated reaction because no urticaria, angioedema, or wheezing was present. These episodes did not meet recently published consensus criteria for the diagnosis of anaphylaxis.² Although the chest tightness or wheezing and dyspnea described after the fourth and fifth stings raise the possibility of venom-induced anaphylaxis, this seems unlikely given the negative Hymenoptera venom skin test results and the lack of reaction to the wasp sting challenge.

The clinical and laboratory findings after the fifth sting may have been caused by the combined effects of marathon running and exogenously administered epinephrine. Endurance exercise training may produce resting bradycardia and an increased risk of vasovagal syncope, which are attributed to enhanced parasympathetic and reduced sympathetic tone.³ Serum creatine kinase MB fraction can remain elevated in asymptomatic marathon runners 24 hours after competition and has limited value for detecting acute myocardial injury in athletes.⁴ In addition, epinephrine administration alone may have induced the hypokalemia observed.⁵

The patient's ECG and echocardiographic findings are similar to those described in Takotsubo cardiomyopathy.⁶ This syndrome is most common in older women and is characterized by ischemic chest symptoms, ECG ST-segment changes, and elevated cardiac disease markers. Echocardiography shows a peculiar regional systolic dysfunction with akinesis of the midventricle and apex. In contrast, the left ventricular hypokinesis observed in the present patient was generalized. Plasma catecholamine levels are significantly elevated at presentation in Takotsubo cardiomyopathy,⁷ with mean plasma epinephrine levels similar to those produced by a single 0.3-mg dose of epinephrine administered intramuscularly in the thigh of adults.⁸ Although the patient's plasma epinephrine level was not measured, we postulate that it was considerably greater than the levels measured in Takotsubo cardiomyopathy cases.

In summary, the myocardial dysfunction exhibited by this patient was most likely epinephrine induced, but the effects of marathon running and transient hypokalemia were possible confounding variables. The risk-benefit ratio of epinephrine administration should be evaluated for individual patients.

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REFERENCES

1. Simons FER. Anaphylaxis, killer allergy: long-term management in the community. *J Allergy Clin Immunol.* 2006;117:367–377.
2. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117:391–397.
3. Thompson PD. Cardiovascular adaptations to marathon running: the marathoner's heart. *Sports Med.* 2007;37:444–447.
4. Siegel AJ, Sholar M, Yang J, Dhanak E, Lewandowski KB. Elevated serum cardiac markers in asymptomatic marathon runners after competition: is the myocardium stunned? *Cardiology.* 1997;88:487–491.
5. Spector SL. Adverse reactions associated with parenteral beta agonists: serum potassium changes. *N Engl J Allergy Proc.* 1987;8:317–321.
6. Bybee KA, Kara T, Prasad A, et al. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med.* 2004;141:858–865.
7. Wittstein IS, Thiemann DR, Lima JAC, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med.* 2005;352:539–548.
8. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol.* 2001;108:871–873.

DOWN-REGULATION OF ATOPIC DERMATITIS-ASSOCIATED SERUM CHEMOKINES BY WET-WRAP TREATMENT: A PILOT STUDY

The treatment for severe atopic dermatitis (AD) can be challenging because many patients do not respond to the conventional therapy of topical anti-inflammatory medications and moisturizers. Wet-wrap treatment (WWT) has been shown to be relatively safe for the treatment of severe AD, but its efficacy remains controversial because of a lack of large prospective studies and objective efficacy parameters.¹ To evaluate the efficacy of WWT in AD more objectively, we performed a pilot study to investigate the serum levels of 38 chemokines in 6 children with severe AD before and after WWT. Patients' ages ranged from 3 to 13 years. No patient had received any systemic corticosteroid, immunosuppressant, UV light treatment, or topical or systemic antibiotics at least 4 weeks before the study. Their mean $\pm$ SD total serum IgE level was $14,213 \pm 15,229$ IU/mL, and their mean $\pm$ SD

AD severity, as measured by objective SCORing AD (SCORAD), was 48.2 ± 3.9 . These patients underwent WWT based on a double-layer wet-wrap technique.² Briefly, the patients were bathed for 15 minutes and patted dry; 0.05% fluticasone propionate cream was applied on the active lesions and petrolatum ointment on the unaffected areas. A set of cotton long-sleeved sweatshirt, pants, and socks were soaked in warm water, squeezed dry, and worn by the patients. This set of damp clothing was overlaid with a second, dry set of cotton clothing and socks. The patients underwent WWT for 2 hours, twice a day, for 7 days. The study was approved by the hospital's institutional review board. Serum chemokine levels were measured at a core laboratory using a 38-chemokine array (http://www.raybiotech.com/map/human_chemokine_map.pdf). The relative levels of proteins obtained with this method have correlated well with enzyme-linked immunosorbent assay.³ The data were analyzed using RayBio analysis software. The ratio of relative expression (densitometric ratio) was established after subtraction of the background intensity and comparison with the positive spots available in the membrane. The objective SCORAD and chemokine levels before and after the treatment were analyzed by the Wilcoxon matched-pairs signed-ranks test and the 2-tailed paired *t* test, respectively. $P \leq .05$ was considered statistically significant.

After WWT, all patients showed significant clinical improvement as measured by objective SCORAD scores, which decreased from 48.2 ± 3.9 to 9.5 ± 6.1 ($P = .03$). Of the 38 serum chemokines analyzed, 7 showed significant decrease after WWT (Figure 1). These chemokines were macrophage

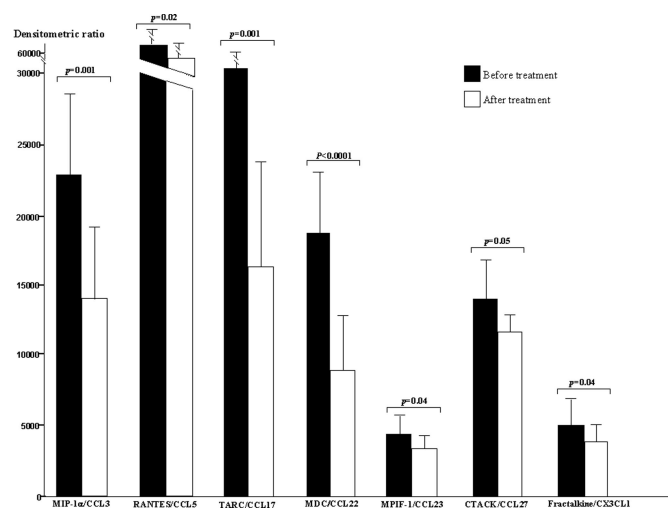


Figure 1. Serum chemokine levels after wet-wrap treatment in patients with severe atopic dermatitis. Chemokines were macrophage inflammatory protein 1α (MIP-1α/CCL3); regulated on activation, normal T cells expressed and secreted (RANTES/CCL5); thymus- and activation-regulated chemokine (TARC/CCL17); monocyte-derived chemokine (MDC/CCL22); myeloid progenitor inhibitory factor 1 (MPIF-1/CCL23); cutaneous T-cell-activating chemokine (CTACK/CCL27); and fractalkine (fractalkine/CX3CL1).

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