Treat Raynaud's Crisis in Scleroderma as Emergent

The patient who is holding a cold, painful hand downward is 'having a heart attack of the hand.'

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Contributing Writer

BOSTON — Raynaud's phenomenon secondary to scleroderma can quickly progress to catastrophic ischemic events resulting in the loss of fingers, toes, and even limbs; at the same time, the efficacy of therapies varies widely.

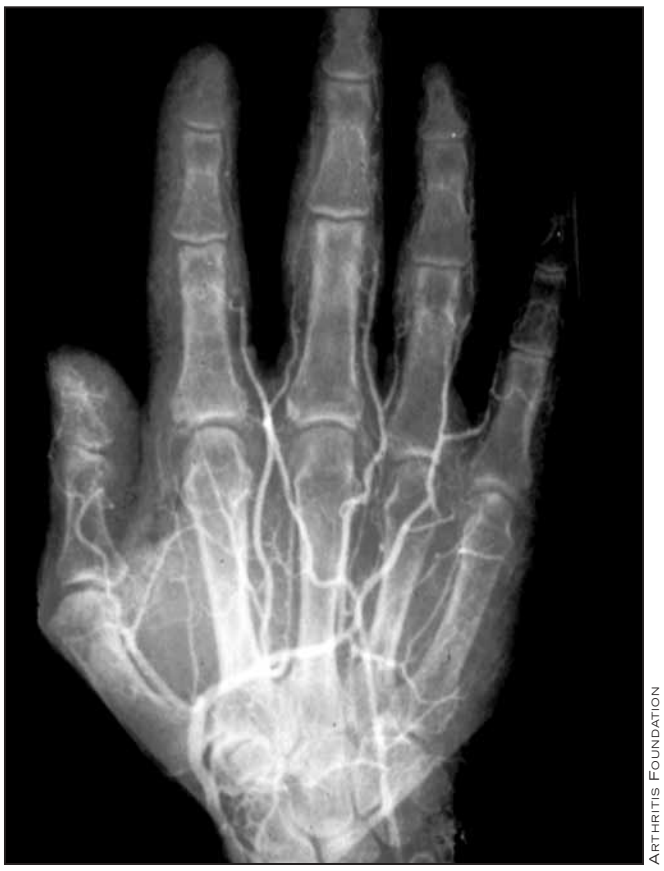
Determining the root causes of a Raynaud's crisis can be difficult during an emergency. Local vasospasm and/or more complicated and widespread vascular disease can trigger the event. Initial therapies should target vasospasm; if the patient does not respond, treatment should shift to addressing small vessel disease and occlusions, according to Fredrick Wigley, M.D.

Dr. Wigley, of Johns Hopkins University in Baltimore, reviewed the therapies for treating a Raynaud's crisis at a recent meeting on rheumatology sponsored by Harvard Medical School.

In patients with primary Raynaud's disease that is not complicated by scleroderma, the loss of blood flow to the extremities and the subsequent pain or discomfort is typically caused by vasoconstriction, not vasculopathy.

Warmer temperatures or stress reduction may relieve the symptoms in these patients, he said. If lifestyle changes are not sufficient, he recommends trying a calcium channel blocker (for example, amlodipine).

In patients with scleroderma, the clinical picture is considerably more complex. "We see major vascular disease," said Dr. Wigley. There's occlusion, structural disease, and thrombotic events. Treatment should address vascular disease as well as the vasospasm, he said.



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This arteriogram shows irregular narrowing and occlusion of the digital arteries. The proximal vessels, arcades, and metacarpal vessels are widely patent. These abnormalities may be reversible.

Not all scleroderma patients are equally susceptible to catastrophic Raynaud's episodes, said Dr. Wigley. In his experience, those most prone to a crisis are scleroderma patients who have coexisting macrovascular disease, typically accompanied by recurrent digital ulcers and amputation.

These patients tend to have limited skin disease, are anticentromere positive, and demonstrate granzyme B cleavable autoantigens.

The macrovascular disease is often observed as palmar arch and ulnar artery disease. Symptoms during a crisis are markedly more severe than during a typical episode of primary Raynaud's. "Persistent widespread ischemic pain heralds tissue infarction and gangrene," he said.

"If a patient comes to your office and says, 'I'm having a Raynaud's attack and my finger will not get warm. And not only that, the palm of my hand is hurting,' and the patient is holding the hand in a downward position, that patient is having a heart attack of the hand," said Dr. Wigley, adding that it needs to be treated as a medical emergency.

Angiograms of scleroderma patients' hands reveal that not just tiny vessels but also medium-sized arteries "just disappear. … Only collateral flow is keeping the finger alive."

Dr. Wigley offered the following observations about various treatment options:

► **Prostaglandin infusions.** For those patients already taking a calcium channel blocker, Dr. Wigley administers repeated infusions of a prostaglandin (epoprostenol in the United States and Canada; iloprost in Europe).

"It's effective and quite dramatic," he observed. And for short periods of continuous infusion, the drugs are relatively inexpensive.

In randomized trials, Dr. Wigley and his colleagues have shown prostaglandin infusions to be beneficial (Ann. Intern. Med. 1994;120:199-206). However, oral therapy is ineffective (Arthritis Rheum. 1998; 41:670-7).

In one recent case series, five women who had suffered seven catastrophic Raynaud's crises received epoprostenol infusions over 5 days at a dose of 8 ng/kg per minute. The crises were completely resolved in two of the five patients, and improved in the remaining three, according to a paper presented at the 2004 annual meeting of the American College of Rheumatology (Arthritis Rheum. 2004; 50[suppl. 9]:S638).

Dr. Wigley recommends starting epoprostenol at a dose of 2 ng/kg per minute. "It's a very low dose and is well tolerated," he said. He warns against infusing patients who have pulmonary artery hypertension, as these patients require very close attention.

Perform a rapid chemical sympathectomy at the bedside or in the office using lidocaine for a digital block. 'It's short acting, but it decreases pain immediately.'

► **Chemical sympathectomy.** In a crisis, Dr. Wigley said he performs a rapid chemical sympathectomy at the bedside or in the office, using lidocaine for a digital block. "It's short acting, but it decreases pain immediately. You can get a dramatic flush to skin and reverse the event if it's vasospastic."

If the crisis is thrombotic, however, sympathectomy will be ineffective, he said.

► **Antiplatelet therapy.** "Aspirin works," said Dr. Wigley.

Calcium channel blockers and prostaglandins are also potent vasodilators. "When you give these agents, you affect platelet function."

Less is known about other agents, such as ticlopidine, clopidogrel, cilostazol, and pentoxifylline, he said.

► **Anticoagulation.** In patients who do not respond rapidly to prostaglandin infusion, sympathectomy, and/or antiplatelet therapy, the crisis is almost surely caused by thrombosis, said Dr. Wigley. In his experience, anticoagulation can help in the acute phase, and he advises treatment for 24 hours, although he acknowledged that there are no controlled trials to support this practice.

Anticoagulation is unproven as chronic therapy for Raynaud's phenomenon unless patients have a secondary hypercoagulation disorder, such as antiphospholipid antibody syndrome.

► **Thrombolytic therapy.** There is little evidence to support the use of thrombolytic therapy in patients with scleroderma who have catastrophic Raynaud's events, and he does not recommend it.

► **Surgical sympathectomy.** Surgical sympathectomy denervates the finger. '"We use a digital sympathectomy when medical therapy is not working," he said. However, there is conflicting evidence on the efficacy of this procedure.

In a retrospective review of 129 fingers in 38 patients with scleroderma and chronic digital ischemia, 86% reported improved symptoms with periarterial sympathectomy after a follow-up period of up to 41 months.

The study was presented at the 2003 annual meeting of the American College of Rheumatology (Arthritis Rheum. 2003; 48[suppl. 9]:S560).

However, a separate systematic review of 251 digits came to less optimistic conclusions. It found that 14% of all patients required amputation and 18% of patients had ulcer recurrence, after up to nearly 5 years of follow-up.

"Some type of postoperative complication was reported in 37% of patients with systemic sclerosis," according to the study's authors, who noted that the literature is marred by a number of shortcomings (J. Rheumatol. 2003;30:1788-92).

"Sympathectomy can reverse an ischemic crisis, but may not cure the problem," said Dr. Wigley. It sometimes leads to finger contractures and fibrosis, "so I don't use it lightly," he added.

"Usually it gets the patient out of a crisis. A year later the Raynaud's is back, but it tends not to be as severe."

► **Vascular surgery.** A retrospective case series reported on the outcomes of revascularization of occluded ulnar arteries in eight patients with scleroderma and severe Raynaud's phenomenon with digital ulcers.

The patients had a positive Allen's tests, had angiograms showing occlusive disease, and had failed to improve with nonoperative treatment.

All eight patients "experienced dramatic improvement in Raynaud's phenomenon and refractory digital ulcers," according to the authors (J. Rheumatol. 2002;29:102-6).

In isolated cases, "you need to consider it," said Dr. Wigley. However, he advises caution. "You have to be dealing with an experienced vascular surgeon and be very conservative about attacking these blood vessels. … Patients have lost not just their finger but parts of their hands."

Dr. Wigley said it's rare to find a lesion that is an appropriate target for microsurgical repair. "Most of the time you have the combination of a large vessel, such as an ulnar occlusion, and a microvascular disease, so there's nothing you can connect to, to make a repair."

Preventing Recurrences

For prevention of recurrent crises, "there's no drug more effective than warm temperatures," said Dr. Wigley

When cold is unavoidable, Dr. Wigley recommends using continued vasodilator therapy, aspirin, and antioxidants. Statins "will play a bigger role as we learn more about these agents."

Other options for preventing recurrences include:

► **Iloprost infusions.** Recent trials from Europe suggest that prophylactic infusions of iloprost may reduce the frequency and severity of Raynaud's events among scleroderma patients (Med. Clin. [Barc.] 2004;122:501-4; Clin. Rheumatol. 2002;21:244-50).

► **Bosentan.** Findings from a recent trial demonstrated a reduction in digital ulcers among scleroderma patients after treatment with the endothelin receptor antagonist bosentan (Arthritis Rheum. 2004; 50:3985-93). ■

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