RAYNAUD’S PHENOMENON

INTRODUCTION

In 1862, Maurice Raynaud recognized that some people who were exposed to cold temperatures had transient digital ischemia that he ascribed to an exaggerated response of the central nervous system. The term "Raynaud's phenomenon" is now used to describe these episodic events, which represent vasoconstriction of the digital arteries, precapillary arterioles, and cutaneous arteriovenous shunts.

We now understand that Raynaud’s phenomenon is the clinical manifestation of disease of the thermoregulatory vessels in the skin and disease of medium and small vessels in the peripheral arterial system of the limbs and acral parts of the body. Triphasic color changes (pallor, cyanosis, and hyperemia) occur as an exaggeration or perturbation of normal responses to the environmental temperature and activity (i.e., vasospasm). It occurs primarily in the fingers with relative sparing of the thumbs. It can also occur in the toes, tongue, ears, and nose. Typically Raynaud’s attacks are symmetrical, involving both hands with patients noting that there is a dominant more sensitive finger(s), usually the index and middle fingers. A typical attack will continue with signs and symptoms of ischemia until rewarming (removal of the cold or stress trigger). In a warm environment, the attack will usually resolve in about 15–20 min.

Sir Thomas Lewis in about 1925 predicted from clinical observations that Raynaud's phenomenon was caused by a ‘local defect’ in the digital and cutaneous arteries and was not secondary to central nervous system malfunction. We now appreciate that the biology of the blood vessels and regulation of local blood flow is complex. The vascular endothelium (inner layer of the blood vessel), smooth muscle cells, and nerve terminals form an integrated unit in which specific interactions and soluble mediators released in the microenvironment contribute together to determine the final balance between vasodilatation and vasoconstriction. These interactions are influenced by a variety of factors including the level of physical activity, the ambient temperature, the individual's emotional state, and direct traumatic or inflammatory insults to the vessels. An imbalance in the local control of the vascular response to these factors leads to the clinical picture of Raynaud’s phenomenon.

In over 80 percent of patients with Raynaud's phenomenon who are seen by an internist, the condition is simply an exaggeration of the physiologic response to cold temperatures or emotinal stress. However, it can also represent a clinical manifestation of a serious underlying disease or be the first sign of critical ischemia of a digit or limb. Depending on the severity of the vascular insult and the size of the vessel involved, superficial ulceration or deep-tissue necrosis with gangrene and amputation can result. Clinical criteria are used to distinguish patients with uncomplicated or primary Raynaud's phenomenon (also called Raynaud’s disease) from those with secondary Raynaud's phenomenon. The suggested
criteria for primary Raynaud's phenomenon are symmetric attacks; the absence of tissue
carcinosis, ulceration, or gangrene; the absence of a secondary cause on the basis of a
patient's history and general physical examination; normal nail-fold capillaries; a negative
test for antinuclear antibody; and a normal erythrocyte sedimentation rate. Clinicians can
examine a patient's cutaneous capillaries by placing a drop of grade B immersion oil on the
patient's skin at the base of the fingernail and viewing the area with a stereoscopic
microscope or a hand-held ophthalmoscope set at 10 to 40 diopters. Normal capillaries
appear as orderly, delicate vascular loops, whereas the capillaries of patients with an
underlying rheumatic disease are frequently distorted or are anatomically abnormal. The
median age at the onset of primary Raynaud's phenomenon is 14 years, and only 27 percent
of cases begin at the age of 40 years or later. The symptoms are generally mild among
patients with primary disease. In one study of 313 patients with primary Raynaud's
phenomenon, only 38 (12 percent) reported having severe attacks. About a quarter of
patients with primary Raynaud's phenomenon have a family history of Raynaud's
phenomenon in a first-degree relative.

Although scleroderma is generally considered a fibrosing disease of the tissues, it is now
recognized that the underlying vascular disease is playing a fundamental role in its
pathogenesis and associated tissue injury. Raynaud’s phenomenon is present in over 95%
of scleroderma patients and often is the initial clinical manifestation of the disease process.
Raynaud's phenomenon is thought to be secondary to a vasculopathy of small and medium
peripheral blood vessels that are involved in both tissue nutrition and body
thermoregulation. Indeed, the unique
vascular disease is not limited to the vessels of the skin or limbs but is found in the multiple
organs involved. The clinical consequences of the scleroderma vascular disease are
therefore widespread and associated with organ dysfunction, significant morbidity, and
mortality.

Unlike patients with primary Raynaud’s phenomenon who have mild episodes that rarely
interfere with daily activities and generally improve with aging, scleroderma patients
experience intense and frequent ischemic events associated with recurrent digital ulcers in
25–39% of cases. A survey of patients at one center reported that younger patients with
more skin disease were at higher risk for developing ulcers, and they usually occurred
within 5 years of non-Raynaud’s symptoms. Digital amputation secondary to occlusion of
digital arteries occur in a subset of (11%) patients, usually with limited skin disease with
the presence of anticientromere antibody. Interestingly, evidence suggests a predilection for
significant occlusive disease in the ulnar artery (an artery in the arm going to the wrist on
the side of the little finger) in patients with limited scleroderma that is associated with
critical ischemic events. Although larger vascular disease can occur, it is in the peripheral
circulation; generalized premature atherosclerosis in typical locations is not uniformly
detected in scleroderma, as is thought to occur in other rheumatic diseases.
THE APPROACH TO THERAPY OF RAYNAUD'S PHENOMENON

The patients with scleroderma exhibit several components of vascular abnormalities, including (1) recurrent episodes of vasospasm (Raynaud's phenomenon); (2) a structural disease component that includes intimal fibrosis and narrowing of the vessel lumen; and (3) the potential for formation of intravascular thrombi. Therefore, therapy should be tailored to prevent and reverse each of these individual components. The goal is to decrease the frequency of attacks, prevent digital ulceration, and to limit progressive vascular damage because complete abrogation of Raynaud's phenomenon is observed rarely with current available therapy. Although nondrug therapy is the most effective mode of treatment, one can argue that all patients also should be treated with medications, even in the absence of digital ulcers. This is especially true because it is believed that recurrent ischemia-reperfusion injury contributes to the structural vasculopathy over time. Certainly, patients who have digital ulcers should be treated aggressively.

NONDRAUG THERAPY

All patients should be instructed to keep their whole body warm and to avoid aggravating factors, such as stress, digital trauma, and medications that lead to vasoconstriction. The frequency and severity of Raynaud's attacks are temperature-dependent as shown by the difference in digital complications in the winter compared with the summer. There is no more effective therapy for Raynaud's phenomenon than avoiding cold or rapidly shifting temperatures. Methods of biofeedback do not seem to work in patients with scleroderma.

DRUG THERAPY

VASODILATORS

The standard of care of patients with scleroderma and Raynaud’s phenomenon is to use drugs that open and relax arteries in the fingers and skin. These vasodilators have the potential of reducing the attack rate and the severity of the Raynaud’s events. A major goal of drug therapy is to prevent new digital ulcers and tissue injury that leads to skin fibrosis.

Calcium channel blockers

Calcium channel blockers (CCBs) remain the most widely used class of drugs to treat Raynaud's phenomenon and its complications (i.e. digital ischemia or ulcerations). A meta-analysis of 18 randomized, placebo-controlled, and double-blinded trials evaluated the efficacy of CCBs compared with placebo in patients with primary Raynaud's phenomenon. An average decrease of 2.8-5.0 attacks over a 1-week period and a 33% reduction in the severity was observed. These findings are similar to those of a meta-analysis on CCBs treatment for Raynaud's phenomenon secondary to scleroderma (decrease of four attacks over 1 week and 35% severity reduction). It is important to emphasize that in clinical practice, the effective dose of CCB may be higher than used in the research trials, and the