Role and Rationale for Extended Periarterial Sympathectomy in the Management of Severe Raynaud Syndrome: Techniques and Results

Vascular Disorders – Hand Clinics
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Synopsis

There is no consensus regarding etiology or best surgical technique for severe Raynaud syndrome in connective tissue disease patients. Observations after 30 years' experience in over 100 cases led to the conclusion that an "extended periarterial sympathectomy" (with or without vein graft reconstruction) and adjunctive use of Botox® topically will offer benefits that exceed palliation and reduce recurrent ulcerations. The rationale for this approach is reviewed, techniques and results outlined, and hypothesis for the mechanism of Raynaud's attacks offered.

Key Points

1. Experimental studies of periarterial sympathectomy demonstrate profound adrenergic effect only at the site of adventitial stripping with some limited decrease of vasoconstriction distally and no decrease in the proximal vasculature vasoconstriction, likely due to the anatomical arrangement of segmental sympathetic branching from the adjacent nerves directly to the vessels.
2. Patients with connective tissue disease will likely later develop occlusions proximal to sites of palmar and finger periarterial sympathectomy, and can be protected by "extended periarterial sympathectomy," which includes adventitial stripping of the ulnar artery in the distal forearm and the dorsal radial artery in the snuffbox region.
3. In connective tissue disease patients with ulnar artery occlusion, vein graft reconstruction can usually be accomplished by end-to-side technique to the superficial vascular arch and proximal ulnar artery, leaving collaterals intact, and the donor veins are found in the forearm. In this group of patients vascular reconstruction should be accompanied by extended periarterial sympathectomy.
4. At surgery, topical Botox on the exposed arteries and vein grafts afford prolonged vasodilatation, and Botox injections of the unoperated hand at that time will allow bilateral relief from ischemic discomfort.
5. Extended periarterial sympathectomy may offer prolonged improvement by reducing the frequency and severity of ischemic Raynaud's attacks, and decreasing recurrence of ischemic ulcerations; the mechanism may be by reducing vascular change induced by reperfusion injury following frequent severe Raynaud's attacks.

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On comprendra sans peine, jel'espere, qu'en presence d'une maladie dont tant de points sont encore obscures, je ne sois pas en mesure de formuler un traitement complet a lui opposer. (I hope it will be readily understood that for a disease so many aspects of which are still obscure, I cannot formulate a complete treatment.) M. Raynaud, 1862[1]

Introduction

More than 150 years after Raynaud's description of this disorder, his disclaimer remains valid. Severe Raynaud syndrome remains a controversial unsolved problem because of our inability to "formulate a complete treatment" that is universally successful, and because "so many aspects...are still obscure." This is especially true of patients with connective tissue disease who all too often present to the hand surgeon weeks or months after digital necrosis or gangrenous changes, having suffered unremitting ischemic pain. In the past, simple amputations of gangrenous fingertips led to reoperation more proximally because of ischemic change in the amputation stump. Furthermore, adjacent digits developed similar change, requiring further amputations. **[fig. 1]** Many articles on Raynaud syndrome are pessimistic about any long-term benefit from surgery, other than debridement and digital amputation.[2-5] Much of this pessimism derives from poor results reported in cervicothoracic sympathectomy when done in connective tissue disease patients.[6] After Flatt's 1980 contribution describing successful distal digital artery periarterial sympathectomy for Raynaud syndrome in eight patients, mostly frostbite (including two with connective tissue disease[7]) the value of this operation for connective tissue disease patients became an important question. ***There is much debate and little consensus regarding surgical indications (palliative or beneficial), surgical technique (extent of dissection), or even if the procedure is worthwhile at all ; however, among the relatively small number of reports available, results of distal microvascular adventectomy seem encouraging, although quite variable.***

At present, most clinicians still regard surgery for Raynaud syndrome as a salvage procedure for gangrenous change after failed pharmacologic management. Over the past 33 years this author has dealt with more than 100 of these difficult patients, which has led to significant alteration in surgical indications, preoperative evaluation, surgical technique, and attitude about the procedure from one of palliation to a belief that there can be a sustained benefit. Because the connective tissue disease patient represents the most severe of the digital artery sympathectomy surgical candidates, this chapter emphasizes procedures for this group of patients, including experience with mixed connective tissue disease (55% of the series), scleroderma (38%) and lupus (4%), evolving into a surgical approach we describe as "extended periarterial sympathectomy" that is not appropriate for other causes of Raynaud syndrome, such as frostbite, trauma or hypothenar hammer syndrome. An effort is made to explain the rationale and results of our current surgical approach in this specific group of patients.

The Conundrum of Evidence-based Data in Raynaud Syndrome

Clinical syndromes often suffer from lack of objective standardized diagnostic criteria, and Raynaud's is no exception. Initial criteria by Maurice Raynaud included the characteristic triad of digital skin vasospastic color change in response to cold exposure or emotional stress. This triad is no longer considered essential for diagnosis, though it occurs in two-thirds of patients. Precise objective criteria for

diagnosis are not agreed upon, with many investigators who believe a carefully documented history is the best criteria, and a simple questionnaire the best tool for diagnosis. Furthermore, measurement parameters for study results are equally variable, with some reporting the incidence and severity of Raynaud's attacks, and others the healing of ulceration and amputation stumps, or changes in cold recovery testing. Under such circumstances, each investigator determines their own parameters for diagnosis and outcome measurements, and no meaningful comparisons can be made for evidence-based conclusions among the various reports.

Although all Raynaud syndrome reports suffer these limitations, surgical management is especially difficult to study because patients are typically referred with an ischemic crisis after medical management failure from variable precipitating causes, and, as such, they are not amenable to randomization given the different etiologies. Instead, they need individualized management for the particular circumstance, using the best clinical experience and common sense available.

For example, an ischemic ulcerated digit in a Buerger disease patient may be cured by Botox injection if the patient stops smoking, whereas the scleroderma patient with gangrenous digits and an occluded ulnar artery may need vein graft reconstruction and extended periarterial sympathectomy with topical arterial Botox to heal amputation stumps and avoid further progressive digit loss. Meanwhile, the hypothenar hammer syndrome Raynaud's patient needs only resection and replacement of the occluded ulnar artery segment with a vein or arterial graft for cure.

Furthermore, there is no agreement among surgeons regarding which vessels and how much adventitia to strip, with variation from only 3-4 mm per vessel[7] to an extensive amount from forearm to fingers.[8] **[Table 1]** Attempts to pool these reports cannot provide meaningful data due to variable techniques, variable indications, variable etiologic factors, variable diagnostic criteria and variable result parameters. Our best hope at present is to extrapolate animal studies and resort to common sense and clinical experience until we can better agree on diagnostic criteria, treatment result measurements, and standardized procedures to meet the higher levels for evidence-based data.

Pathophysiology of Raynaud Syndrome

In 1862 Maurice Raynaud described vasospasm causing the triad of fingertip color change, classically described as Raynaud Syndrome:

- *white* (pallor)
- *blue* (cyanosis)
- *red* (hyperemia)

This triad is often followed by pain, numbness and sometimes digital gangrene. **[fig 2]** Now, 152 years later, we still cannot explain the biologic mechanisms for these dramatic changes, nor any consistently successful method of management.

There is a puzzling spectrum of over 40 precipitating or associated factors that are widely varied[8], including: *anatomic factors* such as thoracic outlet syndrome, dialysis shunting and obstructive arteriosclerotic disease; *injuries* such as vibratory (white finger syndrome) and frostbite; *toxic drugs*, such as nicotine, lead, vinyl chloride and beta-blocking antihypertensive medications; *diseases* such as scleroderma (95% incidence), lupus (91%), dermatomyositis (30%), rheumatoid arthritis (11%), cancer and hypothyroidism; and *rheologic causes* such as cryoglobulinemia and polycythemia vera. However, the largest group of patients described as *Raynaud disease* or *primary Raynaud syndrome* has no known associated factors at all, other than being 10 times more common in women.

That such different disorders are united by similar manifestations attracts search for a single systemic or local factor, but no such factor is yet held accountable. The two most widely debated theories are whether the syndrome represents (1) central changes causing hyperactivity of the sympathetic nervous system as believed by Raynaud in 1862[1] or (2) local vessel changes at the periphery as believed by Lewis in 1926.[9]

After 88 years of debate a unifying hypothesis is needed. Raynaud observed vasospastic attacks precipitated by emotional as well as cold stress, leading him to reason that increased central nervous system sympathetic activity must be the explanation. Indeed, emotional stress is currently reported in one-third of patients with characteristic attacks.[10,11] However, evidence that local factors might be more important than the central nervous system includes experiments using skin microelectrodes that do not measure any increased activity in sympathetic outflow, only altered response to cold stimuli,[12] and measurement of circulating catecholamines showing no increase over normal levels in Raynaud's patients.[13] Although there are findings suggesting altered responsiveness of alpha and beta-blocking receptors to catecholamines, isolation of any specific responsible endothelial factor has not been achieved, even though obvious pathologic change in distal vessels is well documented.

Central Neuropeptide Dysregulation

Kahaleh, et al (1995) proposed a provocative hypothesis suggesting that dysregulation of the central neuropeptide system could provide the mechanism for Raynaud's attacks.[14] This concept is attractive because it reconciles studies that show both central and peripheral mechanisms to be present. A powerful neurologic influence on both vasodilatation and vasoconstriction can be mediated by the release of neuropeptides present in the *sensory nervous system* (substance P [SP] and calcitonin gene-related peptide [CGRP]), *sympathetic nervous system* (neuropeptide Y [NPY] and norepinephrine) and *parasympathetic nervous system* (vasoactive intestinal peptide [VIP] and acetylcholine). Some are vasoconstrictors (NPY) and some are vasodilators (CGRP, SP and VIP), and their action may be endothelial-dependent (SP) or they may act directly on the smooth muscle cell (CGRP, NPY, VIP).

These neuropeptides are known to be synthesized in the mid-brain and spinal cord, where some mediate pain perception, but also may be secreted at peripheral nerve endings, such as afferent pain endings and sympathetic endings, where they cause a number of vasoactive and inflammatory responses.[15] Regulation of this neuropeptide system is poorly understood, but it is known that temperature alteration may induce their secretion and that sensory neuropeptides are found in abundance in human digital skin.[16] In support of this hypothesis, Bunker, et al demonstrated that direct infusion of the neuropeptide CGRP (a potent vasodilator) reverses vasospasm in Raynaud's attacks, and is reported to promote healing of ischemic ulceration.[17] The fact Raynaud's patients have frequent placebo response, TENS unit and temperature biofeedback response, and vasospastic episodes in response to emotional stress certainly implies the presence of centrally mediated mechanisms, whereas distal obvious anatomic vascular change and failure of sympathetic blocks and proximal sympathectomy along with favorable response to distal Botox injections implies a peripheral origin. Dysregulation of the neuropeptide system causing repeated Raynaud's attacks with subsequent vascular alteration due to reperfusion injury could explain the presence of both central and peripheral factors, as well as the peculiar tricolor sequence of vascular response known as the "French triad," with differing neuropeptides having profound opposing vasoactive responses in sequence: *white*, *blue* and *red*. Raynaud syndrome certainly occurs at anatomic sites where there are the highest numbers of arteriovenous anastomoses that control thermal regulation and capillary blood flow, and also dense concentration of afferent nociceptor sensory nerve endings, such as fingertips, toes, tongue tip, pinnae of the ears and tip of the nose, with symptoms having been reported in all of these sites.

Reperfusion Injury

It is of interest that patients with scleroderma typically give a history of Raynaud's attacks an average of 11.5 years prior to positive laboratory diagnosis.[18] Because these Raynaud's attacks may be a symptom of occult connective tissue disease for such a long interval, Blunt and Porter[19] suggest the term *Raynaud disease* and *Raynaud phenomenon* be abandoned, using only the term *Raynaud syndrome* for all patients. Pathologic study of postmortem scleroderma patients show digital artery intimal fibrosis and thickening, with the lumen narrowed to less than one-fourth of its diameter in 79%[20] and ulnar artery thickening to an extent that may completely occlude this vessel in almost 50%, which is the principal blood supply of the hand. It is conceivable that the dysregulated neuropeptide system may be the primary mechanism, suggesting the intimal fibrosis and thickening may actually be the result of frequent and severe Raynaud's

attacks due to reperfusion injury to the vessel walls from the ischemia and reperfusion cycles.[14] ***In other words, the vascular anatomic changes may be the result rather than the cause of Raynaud's attacks, but as the vessel wall thickens and narrows the attacks will become increasingly severe. If so, early control of vasospastic attacks by either pharmacologic or by extensive microvascular perivascular sympathectomy conceivably could prevent some of these changes.***

Nonsurgical Management

Hand Therapy

There is no cure for patients with Raynaud phenomenon associated with connective tissue disease[2,21] and the hand therapy, pharmacologic and surgical management should be coordinated, with surgery postponed until other measures fail. Not infrequently, patients present to the surgeon without comprehensive medical management, and rarely have they ever been seen by a hand therapist. They need to be taught preventive measures that can reduce attacks, such as avoiding cold exposure, cigarette smoking, caffeinated beverages, vibratory exposure, and vasoconstrictive drugs like most decongestants, beta-adrenergic antihypertensive medication, amphetamines and cocaine. Biofeedback therapy,[22] "induced vasodilatation,"[23] and specific exercise therapy[24] are successful hand therapy measures in some patients who have not developed ischemic ulcerations and the hand therapist is an invaluable partner in monitoring and encouraging these patients. Other measures, such as acupuncture,[25] TENS,[26] stellate ganglion block,[27] and spinal cord stimulation[28] are of less convincing value in the connective disease patients.

Pharmacologic Management

Pharmacologic management is the principal treatment for Raynaud syndrome, but is reported to benefit only 40-66% of patients, and rarely ever offers complete relief.[29-31] The US Food and Drug Administration has approved no single pharmacologic agent as safe and effective for Raynaud syndrome, although several are classified as "possibly effective."[32] Most of the Raynaud syndrome literature is devoted to controversy over which medicines are most effective, with choices varying from medications *designed to vasodilate*, such as intravenous calcitonin gene-related peptide, or *prevent vasoconstriction*, such as calcium channel blockers, alpha-adrenergic blockers, angiotensin-converting enzyme inhibitors, and serotonin receptor antagonists; drugs that *alter prostaglandin metabolism* such as prostaglandin E1 (Prostin) and drugs that have a *rheologic effect*, such as aspirin and pentoxifylline. The most effective and widely accepted medications are the calcium channel blockers (especially nifedipine, diltiazem, amlodipine besylate), and aspirin. Prostaglandin E1 (Prostin) parenteral infusion will reverse a crisis situation, but if used for more than three days will cause generalized edema.[8] Calcitonin gene-related peptide will also reverse vasospasm, but is available only experimentally at present.

Botulinum toxin (Botox®)

Botulinum toxin will paralyze smooth muscle, and injection along the vasculature has proven a recent rewarding addition for patients having vasospastic crisis. In surgical patients with bilateral difficulty we use injections in the unoperated hand at the time of surgery with pronounced relief, as well as for patients with an ischemic pain crisis. **[fig. 3A,B]** When effective, this produces relief from vasospastic pain soon after injection, and has resulted in healed ulcerations.[33,34] Neumeister[35] measured a 300% increased laser Doppler perfusion immediately after injection. Unfortunately, Medicare and many insurance health management organizations still do not approve this simple measure, regarding it as "experimental," although alternatives are far more expensive and morbid. In our experience, most patients redevelop symptoms approximately three to six months following Botox injection, and we have regarded it as an adjunctive measure in patients with severe disease. It is particularly useful to cure Buerger disease without surgery if the patient will stop smoking. Connective tissue disease patients with an occluded ulnar

artery are less likely to get adequate relief from Botox alone, although in the absence of frank gangrene it should be attempted whenever insurance authorization can be obtained.

Preoperative Patient Evaluation

Objective diagnostic criteria for Raynaud syndrome is not agreed upon, with history and questionnaires used by most investigators.[36] The characteristic "French tricolor" vascular change is no longer considered essential for diagnosis, although it occurs in two-thirds of the patients.

Cold Recovery Testing

If the diagnosis is in question our hand therapists use cold recovery time as the primary diagnostic tool, placing digits in a water bath at 20 degrees Celsius for one minute, with a positive diagnosis when there is no recovery of baseline temperature measurement after 20 minutes or longer. This method was introduced by Porter, et al,[37] who found control subjects recovered within 5-20 minutes (averaging 10 minutes). However, we do not use cold exposure in patients whose diagnosis is obvious, especially if they have ischemic change and are at risk of harm. This cold recovery test lacks specificity, in that heavy smokers with no characteristics of Raynaud syndrome frequently cannot pass the test.

Semmes Weinstein Monofilament Testing

Sensory testing is of particular help in these patients. Raynaud's patients have significantly greater loss of sensation compared with controls following cold exposure,[38] and patients with severe difficulty will have decreased Semmes Weinstein monofilament measurements, often with the unusual finding of better sensation in the palm and base of their digits than distally. **[fig. 4]** This is a useful measurement to verify improvement following periarterial sympathectomy, in that we expect severely afflicted digits to regain improved sensibility after surgery.

Allen and Doppler Testing

The Allen test should be done because of frequent ulnar artery occlusion, especially in scleroderma patients. Doppler ultrasound mapping of vessels is of enormous value in assessing all Raynaud syndrome patients, especially those for surgical consideration.[8] Particular attention should be paid to the ulnar artery at the distal forearm and wrist, superficial vascular arch in the palm and dorsal radial artery, as well as the common volar and proper digital vessels. However, patent common volar and proper digital arteries are often not audible in the office setting, but may be easily heard in the operating room after the vasodilatation induced by general or block anesthesia. Laser Doppler study has been reassuring in the immediate postoperative setting, with improvement generally measured at 50-300%,[8] but has not been essential for management, and seems quite variable in our experience.

Radiologic Testing

Radiologic evaluation is valuable in surgical candidates, especially if there is any clinical evidence of proximal occlusion. Although arteriography is regarded as the "gold standard" for evaluation,[39] it has not been as accurate as MR angiography in our experience for patients with connective tissue disease.[40] Arteriography has caused vasospasm that made the ulnar artery and superficial vascular arch appear occluded, which we later found to be patent at surgery. This was also observed by O'Brien, et al,[41] and may be due to radiopaque contrast media, which has been shown experimentally to cause arteriolar spasm.[42] Furthermore, patients with mixed connective tissue disease, lupus or scleroderma are already at greater risk for renal problems, which can also be a complication of allergy to radiographic dye.

MR angiography imaging is a noninvasive reliable alternative to conventional angiography of the hand and wrist[40] with the advantages of oblique, cross sectional and longitudinal views of the fingers and hands, lower morbidity and less expense than conventional angiography. It requires a radiologist with appropriate equipment and degree of interest to obtain all of the planes of measurement needed. **[fig.5]**

Radiographic dye angiography or CT angiography is preferred for Raynaud syndrome patients who do not have connective tissue disease, such as ulnar artery hypothenar hammer syndrome, atherosclerotic disease, occlusion from emboli or thoracic outlet syndrome, because arteriographic dye assessment provides a better evaluation of the intravascular anatomy. Unfortunately, at the present time, Medicare and some commercial insurance organizations may refuse to approve vascular evaluation with MR angiography in the upper extremity, even though it appears safer, more accurate in connective tissue disease patients, and a cheaper evaluation technique.

Hand Functional Assessment

A careful preoperative hand functional assessment should be done on all Raynaud syndrome patients, including measurement of sensation, manual dexterity, range of motion, strength, baseline temperature and skin and digit appearance, because many of these patients will have or will develop sclerodactyly changes that need to be monitored.

Fat Grafting

Grafting approximately 30cc of fat to hands of Raynaud's patients is reported as providing significant subjective improvement in pain, recurrent ulceration and reduction of Raynaud's attacks in 80% of 13 patients.[citation 1 below] The presumed benefit was by stem cells within the fat grafts, producing angiogenesis as had been reported in murine radiated model.[citation2 below] Objective parameters were equivocal in the 18-month follow-up, but this remains a provocative arena for investigation.

citation 1: Bank J, Fuller S, Henry G, Zachary L. Fat grafting to the hand in patients with Raynaud phenomenon: a novel therapeutic modality. Plast Reconstr Surg., 2014 May; 133(5): 1109-18.)

citation 2: Sultan SM, Stern CS, Allen RJ Jr, et al. Human fat grafting alleviates radiation skin damage in a murine model. Plast Reconstr Surg. 2011;128:363–372.)

Rationale for Periarterial Sympathectomy

Arterial smooth muscle has only one function, *vasoconstriction.* The concept of direct sympathetic denervation of arterial muscle to reduce vasoconstriction is by no means new, having been first suggested by Leriche and later performed by Jabollet in 1899 on axillary vessels of Raynaud's patients.[43] Leriche reported its value on the femoral artery in 1913. However, it was not until 1980 that Flatt introduced the concept of distal vessel periarterial sympathectomy.[7] Based on Pick's classic text on the autonomic nervous system[44] Flatt reasoned that proximal cervicothoracic sympathectomy failure could be caused by alternative pathways to the brachial plexus from the sinovertebral nerve, the carotid plexus and the nerve of Koontz. Contributions to the sympathetic supply in the hand is directly from the peripheral nerves with multiple segmental branches to the adjacent vessels in the forearm, wrist, palm and fingers; for example, digital nerves have multiple segmental sympathetic branches to the corresponding digital arteries, **[fig. 6]** and the distal ulnar artery in the forearm is supplied by the ulnar nerve, usually with a specific branch, the nerve of Henle, as well as multiple smaller segmental branches.[45,46] Pick's descriptions and our clinical observations show the sympathetic contributions to be particularly intense at sites of bifurcation, such as where the superficial arch branches into the common volar vessels, and then their bifurcation into the proper digital vessels. **[fig. 7]** Mitchell[47] observed that sympathetic fibers arborized in the adventitia of these vessels, and Morgan, et al[48] confirmed that these fibers are confined to the adventitia without deeper penetration into the media so that adventitial stripping should remove the adrenergic nerve endings. Rabbit ear experiments demonstrated that there was no sympathetic reinnervation after a year following periarterial stripping of vessels.[49]

Soon after World War I, Leriche and Jabollet's periarterial sympathectomy concept became quite controversial because of the anatomic fact that there is little evidence of long centripetal sympathetic nerves running along the arteries, but rather it is recognized there are multiple segmental sympathetic

branches innervating arteries proximal and distal to the sites of perivascular sympathectomy. It was recommended that proximal cervicothoracic sympathectomy seemed more rational than segmental arterial stripping.[50] In 1991 an important series of studies on monkeys by Kaarela, et al did not show complete loss of adrenergic innervation in the vasculature distal to the operative site after a 1cm perivascular sympathectomy in the common volar vessels. Only the operative site itself and a few millimeters distally had complete loss of catecholamine fluorescence. [51] Quantitative measurement of catecholamines in rabbit ear vessels after perivascular sympathectomy by the same investigators showed response to be lower in the distal segment compared to the control side, but still about nine times higher than at the sympathectomy site itself.[52]

Furthermore, comparison of the ulnar artery in scleroderma patients using color duplex sonography shows significantly decreased blood flow velocity and significantly higher resistive indices than in controls.[53] It may therefore be concluded that ***periarterial sympathectomy (adventectomy) removes the sympathetic innervation at the site of surgery itself, and to a lesser extent reduces sympathetic activity distally, but would not be expected to alter any sympathetic response proximal to the site of surgery*.**

We therefore reason that a more extensive ("extended") perivascular sympathectomy of arteries likely to occlude may offer preventive measures at these sites, such as the ulnar artery in the distal forearm (including the nerve of Henle), the wrist, the proximal palm, and all of common volar and proper digital vessels, as well as the dorsal radial artery. Flatt performed distal sympathectomy at the level of bifurcation of the common into the proper digital arteries, stripping only a 3-4mm segment of adventitia under 2x magnification. We now reason that a much more extensive dissection is needed in patients with connective tissue disease to prevent later proximal occlusion. This seems especially relevant if the mechanism for endovascular thickening is reperfusion injury associated with chronic Raynaud's attacks.

Surgical Indications

In our early experience, most Raynaud syndrome patients were referred for amputations, with gangrenous changes often present for months. We knew that simple amputation would result in necrosis and failed healing of the amputation stump, leading to a more proximal amputation. **[fig. 1]** This sequence has been reversed by adjunctive periarterial sympathectomies, and sometimes revascularization (when the ulnar or radial artery is occluded) at the time of initial debridement and amputation, permitting removal of only devitalized tissue usually with predictable healing of the amputation stump. **[fig. 8A,B]**

Because of doubts regarding any long-term value of periarterial sympathectomy for connective tissue disease patients, our earlier indications for surgery required impending ischemic necrosis or gangrenous change. Over the years, observation of the profound and seemingly sustained surgical benefit has led us to change our criteria to include ***any patient who has unremitting ischemic pain that is not manageable by pharmacologic or hand therapy measures. It is preferable to operate before any ischemic necrosis occurs.***

Wilgis[54] and others suggested combining digital plethysmography with cold stress testing using bupivacaine blocks at the palmar area as a criterion to determine the potential benefit of surgery. We have seen patients with ischemic necrosis who did not respond to blocks, but did benefit from digital sympathectomy, as have Zachary, et al,[55] Koman, et al[56] and Yee, et al,[57] so we feel patients should not be excluded from surgery by this test. However, Botox injection may prove an excellent criterion for the response of sympathectomy. We have seen dramatic relief from ischemic discomfort, and have used Botox as a practical measure for amputations or elective digital surgery when an extended periarterial sympathectomy was not desired, permitting healing of the amputation stump, without precipitating an ischemic attack. Botox injection may obviate the need for sympathectomy in many patients, as suggested by Van Beek[58] and Neumeister[59] but it will not correct proximally occluded vessels, and these patients are less likely to respond.

Periarterial Sympathectomy Surgical Techniques

Although there are relatively few reports on long-term benefits of digital artery sympathectomy, these describe longer-lasting benefits and less morbidity than reports on cervicothoracic sympathectomy in connective tissue disease patients;[2,7,8,57,60-66] however, there is little consensus on how the operation should be done regarding which digits and the extent of dissection. **[Table 1]** Some surgeons confine the surgical approach to only the painfully ischemic or gangrenous digits,[54,61,62,65,67] stripping the distal common volar vessels and proper digital vessels to the PIP joint level. This is a good approach for patients with injury to specific digits, such as frostbite or trauma, but affords no prophylactic benefit to avoid reoperation in patients with progressive connective tissue disease, such as scleroderma or lupus. Levine, et al,[68] Jones,[69] Zachary[70] and others have used a more extensive procedure, including the other digits, but still confining their efforts to the common volar and proper vessels. Blair[71] included adventectomy of a segment of the radial and ulnar vessels as well as common volar and proper digital arteries using multiple vertical incisions but omitting the superficial arch. Koman[56] included 2cm segments of the radial and ulnar vessels of the wrist and the dorsal radial artery in the snuffbox, as well as the superficial arch at the takeoff of the common volar vessels. O'Brien et al described a more aggressive approach, stripping the ulnar artery at the wrist, superficial arch, common volar and proper digital vessels well into the fingers of all of the digits. Some of his cases were done as a staged procedure.[64]

Evolution of Extended Periarterial Sympathectomy and Technical Considerations

In our early digital artery sympathectomy experience in connective tissue disease patients reoperations led to the more aggressive approach we call "extended periarterial sympathectomy." At the time of amputations in our early cases we stripped vessels to all four fingers using a transverse palmar incision, with a 2-3cm segment involving the common volar vessels to their bifurcation into proper digital arteries, which in those days we thought was an aggressive amount of adventectomy. Our surgical criteria required either painful ischemic ulceration or frank gangrene. We were initially pleased, and presented our first 15 patients in 1985[72] with no recurring ulcerations in operated hands, and primary healing of amputation stumps. However, some of these patients later developed painful ischemic change in operated hands due to ulnar artery occlusion at or proximal to the wrist. **[fig. 9A,B]**

We then performed end-to-side vein graft bypass reconstruction of the occluded ulnar artery to the superficial vascular arch distally before they developed new ulcerations or gangrene. Dissection of the superficial arch was tedious due to the previous surgery, so now we include the patent ulnar artery at initial operation, stripping its adventitia in the distal one-third of the forearm including the area supplied by the nerve of Henle,[45,46] as well as the wrist, palm and digital vessels. This prophylactic periarterial stripping of the ulnar artery appears to have protected our patients with only one late occlusion following the procedure in a scleroderma patient who continued to smoke and use vibratory tools in a landscaping business, occluding his ulnar artery four years following sympathectomy. He had vein graft reconstruction and abandoned the landscaping business.

Subsequently, we then had connective tissue patients who developed late postoperative problems in their index and thumb digits that responded to periarterial dorsal radial artery sympathectomy from the level of the snuffbox distally to where the vessels bifurcate and go beneath the first dorsal interosseous muscle to form the deep palmar arch. One early patient developed radial artery occlusion after sympathectomy that had not included the radial artery, and two presented initially with occlusions that required vein graft reconstructions. **[fig. 10A,B]**

Therefore we now also include the dorsal radial artery in the initial stripping. These experiences led to our current philosophy in connective tissue patients, which is in keeping with the studies of Kaarela, et al[47] in monkeys, showing protection from vasoconstriction only at the level of surgery and to a limited extent distally, but no protection from proximal vasoconstriction. ***Given that postmortem studies in scleroderma patients suggest almost half may develop occlusion of the ulnar artery [20,64,73,67], primary periarterial sympathectomy of this vessel in the forearm and wrist may avoid a more difficult and tedious procedure in the future. Although radial artery occlusion is less frequent, adventectomy is easier than***

reconstruction, so our primary operation now includes both ulnar and dorsal radial arteries in connective tissue disease patients.

Current Recommended Technique

In connective tissue disease patients our primary operation now includes adventectomy of the dorsal branch of the radial artery from the snuffbox to its passage into branches beneath the first dorsal interosseous, the ulnar artery from a point approximately 8-10cm proximal to the wrist crease, to and including the entire superficial vascular arch, the common volar vessels preserving the communicating branches from the deep vascular arch (sometimes at their bifurcation), and the proper digital arteries to all fingers about 3-5mm distal from the common volar bifurcation into the base of the digit. **[fig. 11]** When ischemic necrosis or gangrene is present, we now usually include the proper digital arteries in the afflicted digit to the level of the PIP joint if they are patent. **[fig. 12A,B]** We believe high-risk vessels may be protected from occlusion by early adventectomy, and the results of this extended, more aggressive approach have been rewarding.

Anesthesia and Incisions

General or axillary block anesthesia is used, and the potential value of the periarterial sympathectomy becomes evident as soon as the patient is induced or blocked, because digits that previously were cyanotic become pink in the operating room. Doppler reassessment is convenient at that time for a more accurate appraisal than prior to anesthesia. We now prefer two incisions because of some early problems with an L-shaped flap that developed necrosis at its tip (none of which required secondary surgery). One is a distal transverse incision 1-1.5cm proximal to the finger flexion creases, and a second vertical incision made in the central palm placed with approximately a 1cm bridge of skin between the two incisions and exposing the entire vasculature. **[fig. 13]** The vertical incision originates in the central palm, then borders the hypothenar eminence in line with the level used for carpal tunnel release. At the wrist crease it is angled ulnarly and thereafter vertically along the ulnar artery in the forearm for approximately 8-10cm in a routine case. Intraoperative Doppler mapping of the ulnar artery is of assistance in placing this incision.

The initial incisions, flap elevation and isolation of the neurovascular bundles using small vascular loops are made under tourniquet control and 4x loupe magnification; the remaining dissection and vascular reconstruction is done without tourniquet using the microscope because it is easier to determine the amount of adventitia that can be safely stripped from diseased vessels during blood flow. Ophthalmic Vannas scissors are useful to strip, push and pull the adventitia circumferentially away from the vessel **[fig. 14] [Video1]** and an ophthalmic muscle hook helps retract vessels as they are stripped circumferentially. The greatest concentration of sympathetic neurofilaments will be found are at the bifurcations in the superficial vascular arch **[Video 2]** and at the termination of the common volar vessels, **[Video 3]** and at the wrist and distal forearm levels. Additional time spent at these sites is worthwhile.

The dorsal radial artery is exposed with incision on the dorsum of the thumb web, extending to the snuffbox, and adventitia is stripped from the level of the snuffbox, beneath the extensor pollicis longus, and as far distally as possible until the vessels branch and become inaccessible beneath the first dorsal interosseous muscle. We had three patients with occluded radial arteries who had vein graft reconstruction, and it was found that they reconstituted from collaterals at the distal level, where careful dissection allows distal arterial elevation at the site of branching to perform a difficult end-to-side anastomosis, and the vein grafts were placed over the extensor pollicis longus tendon to avoid any possibility of future compression beneath it. **[fig. 10B]**

Vein Graft Reconstructions Associated with Periarterial Sympathectomy

Because of the high incidence of ulnar artery occlusion (50%) in scleroderma patients, reconstruction of this vessel is a frequent technical consideration. Approximately 20% of our patients are referred with their

ulnar artery already occluded, and reverse vein graft reconstruction is indicated, along with extended periarterial sympathectomy. Jones[73] and Koman[56] described replacing the entire superficial vascular arch by end-to-end vein graft to the proximal ulnar artery with common volar vessels microvascularly reinserted into the vein graft (often the saphenous). In Jones' series of 14 patients with occlusion from various causes, recurrent ulceration occurred in 20%, with occlusion of the graft in 35%.[74]

In most of our patients with ulnar occlusion, collateral circulation to the superficial vascular arch was audible due to communicating branches from the deep to the superficial arch, although not always visualized on radiographic study.[75] We have been able to use an end-to-side method for vein graft reconstruction of occluded ulnar vessels in most patients, thereby preserving the collateral circulation with what appears to be less incidence of recurrent ulceration and occlusion than that reported. **[fig. 15A,B]** We are not aware of any patient losing a digit in approximately 30 cases of vascular reconstruction, but a few occluded the vein graft without any apparent adverse effect. One patient with associated cryoglobulinemia had reoperative surgery for symptomatic vein graft occlusion. We now maintain vein grafted patients on Plavix and have documented long-term patentcy. In fact, one lupus patient with four vein grafts has remained patent for 16 years. **[fig. 16A,B]** Savvidou, et al (2013)[76] agreed with the value of periarterial sympathectomy at the time of vascular reconstruction, even in patients who do not have connective tissue disease.

At the time of vein grafting it is useful to distend the venous segment to be grafted with heparinized saline and dot the surface with methylene blue before harvesting to avoid twisting the graft. Most frequently, the cephalic vein is utilized, and less frequently the median antecubital vein, or the basilic vein. Vein graft branches are suture ligated on the side of the vessel using interrupted 9-0 nylon sutures, and vascular clips are used on the distal portion of these branches. A curved vascular clamp is placed on the distal end and a straight clamp on the proximal to remind us to reverse the graft in its new position. All our vein grafts have been harvested from the volar forearm, commonly the cephalic vessel, and varied from 6-15cm in length. We never use the saphenous vein, but one scleroderma patient with severe skin induration had her ulnar artery vena comitans utilized for grafting.

We now also include a regimen of dripping Botox solution on the vein graft as well as the exposed arterial vasculature because of our impression that the vein graft has less traumatic vasospasm due to this maneuver, and our lab studies show long-term arterial response.[77] The arterial incision for vein graft reconstruction is done with a small pointed Alcon Beaver blade, **[fig. 17]** and the end-to-side anastomosis performed with 10-0 nylon at the distal end of the reverse vein graft. This is the more difficult anastomosis so it is done first. Many times the superficial arch lumen is narrowed from the thickened wall, and a 1.00mm Flo-Rester® vessel occluder is often useful when placing the initial distal end-to-side sutures to protect patency. **[fig. 17]** Doppler assessment will assist in determining the best site for anastomosis along the superficial arterial arch.

We developed a Rummel-type impecunious (cheap) vascular occlusion system that has proven safe and easy to utilize, which we affectionately call the "Hunnius clamp" after the nurse who scavenged the simple, inexpensive components. This is done using microvascular right-angle forceps to loop Sterion silicone microvessel tubing around the vessels to be controlled, and placing a segment of #8 Red Robinson pediatric catheter over the ends of the microvessel loops by means of a #7 tonsil snare wire. **[fig. 18]** Once the loops are through the tubing, a Hartman mosquito clamp can be used to cinch this down to occlude the vessel. **[fig. 19A,B]** Sufficient catheter length can be utilized to place the clamp outside the microsurgical field, facilitating the anastomosis. This is particularly valuable when there is an anastomotic leak that obscures vessels needing to be reclamped. Small collateral branches beneath the vessel to be sutured are more easily occluded with small microvascular clamps positioned so they do not interfere with the anastomosis.

The proximal anastomosis is usually sutured with interrupted 9-0 microvascular sutures after resecting a small ellipse of arterial wall using angled Vannas scissors. The vein graft is beveled, and both distal and proximal anastomoses are completed before release of the Rummel-type "Hunnius" clamps. It is preferable to place the vein graft on slight tension at the proximal anastomosis, because even though it

may seem under tension, it will lengthen as soon as blood flow is restored. Patency is confirmed with a Hayhurst test, though pulsatile blood flow through the vein graft is usually apparent.

Even though a large segment of occluded ulnar artery may be bypassed by the vein graft, we believe it is important to strip adventitia from the occluded portion of the vessel along with the other vessels sympathectomized. We reason that early surgery for hypothenar hammer syndrome was simply by excising the occluded segment of ulnar artery, which gave relief from ischemia and Raynaud phenomenon. While this prevented further emboli, it is also possible that sympathetic stimulation from the occluded vessel played a role, and we suspect resection of the occluded segment may give relief by means of sympathectomy.[56] Although the value of this additional adventectomy is uncertain, it seems prudent and is easier than resection of the occluded segment. ***This extended technique for periarterial sympathectomy is reserved for patients thought to have scleroderma or other connective tissue disease, and its greatest advantage may prove to be its early use to reduce or prevent further predictable occlusion.***

Closure is done using 3-0 chromic sutures for the dermal layer in the forearm and dorsum of the hand, and interrupted 4-0 Prolene for skin incisions. Marcaine is injected along the median and ulnar nerves at the wrist level, then the superficial radial nerve on the hand to reduce postoperative discomfort. Drains are not usually necessary, but are utilized if there is undue oozing in the palm. The hand is immobilized in a soft dressing with tongue blade splint, maintaining the wrist in approximately 15-20 degrees of extension, the MP joints flexed and the IP joints extended.

Patients are given ketorolac prior to the end of the procedure to reduce postoperative discomfort and to discourage platelet aggregation. Patients with vein grafts are maintained on Plavix postoperatively, and those who have not had vein grafts are on aspirin. The patients are usually outpatients, unless a vascular reconstruction is done (approximately one-fifth) and then they are observed overnight.

Postoperative Management

Following surgery, the patient is at rest with the hand elevated until the fourth or fifth day when hand therapy is instituted. Stiffness is common, but therapy sometimes recovers better motion than preoperatively. In general, however, the goal is to recover the preoperative range of motion. When sensation was diminished preoperatively, we generally measure improvement following surgery. The therapist uses a resting splint and encourages active motion recovery with use of the hand to the extent that it is comfortable. Most recover motion quickly, but those with sclerodactyly will have greater stiffness and a longer therapy regimen. Patients with a vein graft are not allowed out of their protective wrist splint until after the 10^{th} postoperative day.

Not infrequently, temporary neurapraxia occurs and the patient is reassured and monitored until they have recovered full sensation. It is surprising how little these patients complain of postoperatively. Therapy is continued until after the patient has recovered full amplitude of motion and full sensation, which varies from three weeks to as much as 12 weeks, especially in the sclerodactyly patients with postoperative stiffness.

Outcomes

All patients seem to experience relief from severe ischemic pain, usually immediately after surgery. There were no intraoperative or perioperative deaths; however, more than 20% of these patients have died during the late follow-up interval (up to 33 years), which likely represents the seriousness of the disease process. Although patients report subjective relief and have improved sensory measurements and enhanced nail growth, most continue to remain cold sensitive and still vulnerable to Raynaud's attacks, reportedly less frequently and less severe. A few report complete relief. Some formed hypertrophic scars but still had a favorable long-term result. **[Fig.20]** Several have had transient episodes of paronychia, sometimes stubborn, which respond to conservative management using topical gentian violet dye. Our dialysis patients with ischemia have not done as well as these connective tissue disease patients.

Long-Term Results

Several years ago Jonathan Isaacs, M.D., currently Chair of the Division of Hand Surgery at Virginia Commonwealth University, surveyed a group of our patients during his orthopedic surgery training over a decade ago, studying 21 patients after 31 sympathectomies.[78] The long-term results were better than expected. Average follow-up was seven years, with follow-up up to 14 years, and the average age at surgery was 27 years (18-87 years), with twice as many women as men. A favorable follow-up was present in 28 of the 31 operated hands, with two of the unfavorable results in the same scleroderma patient, a persistent heavy cigarette smoker. Both patients with failures had sufficient severity that amputations were necessary at initial surgery.

When he studied recurrent ulceration 77% of the patients remained improved or asymptomatic, and 83% of those who were surveyed more than five years after surgery had remained improved or asymptomatic. In answer to questions about ischemic pain, 90% of the patients stated they were improved or asymptomatic compared to the preoperative status, and this was true in 86% who were surveyed more than five years after surgery.

It is possible that patients with more serious disease involvement may have died, so that the long-term results represent patients with a more favorable course, but these surprising long-term beneficial results have encouraged the concept of earlier extensive periarterial sympathectomy to reduce the pattern of vasospasm and reperfusion injury, creating less frequent and less severe Raynaud's attacks. The findings suggest a surprising degree of benefit longer than five years after surgery in patients with previous medical failure.

Without controls, it is difficult to prove that the extended periarterial sympathectomy altered the outcome in these patients, but if one reviews the history of Raynaud syndrome in patients with connective tissue disease under medical management, the incidence of ischemic ulceration is reported as high as 20-30% per year[79] and ulnar artery occlusion is common, as high as 50% in scleroderma patients. [20,64,73] ***Given that this surgical series selected unfavorable patients with advanced disease who had already become medical failures, their 86% postoperative relief of ischemic pain and 83% decreased incidence of recurrent ulceration or gangrene more than five years after surgery enhanced our support and belief in this procedure as more than palliation.***

Summary

Disclaimer: It should be pointed out that extended periarterial sympathectomy is for patients with either known or suspected connective tissue disease, and not for patients with hypothenar hammer syndrome, emboli, aneurysm, frostbite or other causes of Raynaud syndrome. Although the pattern of vasospastic attacks may be similar, patients with hypothenar hammer syndrome need only the offending segment of vessel resected and replaced. Many of the symptoms from hypothenar hammer syndrome, radial artery occlusion or aneurysm may derive from emboli, so it is important to resect the damaged segment of vasculature. **[fig. 21A,B,C,D,E]** Patients with the gradual occlusion associated with Raynaud syndrome in connective tissue disease have vessel wall thickening and narrowed lumen, but do not seem to experience emboli.

Patients with Raynaud's from cryoglobulinemia associated with malignancy may have multiple areas of microvascular occlusion, but even these patients seem to improve from perivascular sympathectomy and topical Botox application. In one patient with occult myeloma causing unrecognized cryoglobulinemia, two ulnar artery vein grafts and one radial artery vein graft were done after initial periarterial sympathectomy for recurrent symptoms over a 12-year interval until the diagnosis was finally made by bone marrow biopsy (there were no manifestations other than cryoglobulinemia) and the patient remained pain-free without further difficulty on anticoagulation. Patients with Raynaud syndrome subsequent to digital trauma need only the involved digits treated by periarterial sympathectomy; a Botox injection trial may afford some prognostication about possible surgical benefit, and may actually be all that is needed

for some patients. Our few patients with Buerger disease seem to benefit from extended periarterial sympathectomy, at least initially, but long-term results will likely vary according to nicotine use. Those without significant gangrene have rewarding nonsurgical treatment with only Botox injection and nicotine abstinence.

While most clinicians still regard surgery for Raynaud syndrome as a salvage procedure[56] in patients who do not respond to pharmacologic or physical medicine management, experience with newer microvascular surgical techniques on distal vessels appears to offer improved benefit and less morbidity than previous proximal sympathectomy procedures, and our long-term follow-up suggests that later vasospastic occlusion may be reduced or prevented in connective tissue disease patients. However, the appropriate role, timing, indications and techniques for perivascular distal sympathectomy are still evolving, and, unfortunately, we must still agree with Maurice Raynaud's original 1862 observation: *"I hope that it will be readily understood that for a disease, so many aspects of which are still obscure, I cannot formulate a complete treatment."*