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EDITOR'S MESSAGE

This issue of CHARM focuses on some updates in the treatment and management of scleroderma. We start with a general overview on this uncommon but important connective tissue disease that poses a lot of challenges to rheumatologists. There are two articles on interstitial lung disease and pulmonary hypertension among the various morbidities that also contribute to higher mortality in these patients. Gastrointestinal involvement is not uncommon and we shall read about treatment consideration from the perspectives of our gastroenterologists. Moderate to severe Raynaud's phenomenon is the earliest and most frequent clinical manifestations of scleroderma. Exacerbations with associated abscesses in the fingertips during winters often bring these patients to primary medical care. Other than medical treatment of Raynaud's phenomenon, we have also invited an anaesthetist to share with us the challenges of stellate ganglion block in the relief of this vascular complication.

With this issue of CHARM, we're coming up on the end of 2015. May I wish you all happy New Year!

SYSTEMIC SCLEROSIS (SCLERODERMA)

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Systemic sclerosis or scleroderma (SSc) is a systemic autoimmune disease of unknown aetiology that is characterized by excessive deposition of connective tissue matrix in the skin and internal organs with prominent fibroproliferative alterations in the microvasculature, and abnormal cellular and humoral immune response. SSc affects individuals of all races[1]. However, incidence rates, severity and mortality vary among ethnic groups. Recent studies suggested higher general and age-specific incidence rate in blacks than in whites. It has also been shown that affected African Americans develop more severe disease and have poorer outcomes compared with other ethnicities. The risk of systemic sclerosis is 4-9 times higher in women than in men[2] but the underlying mechanisms have not been elucidated. The peak onset occurs in individuals aged 30-50 years.

SSc is a complex and heterogeneous disease with clinical forms ranging from limited skin involvement (limited cutaneous SSc) to diffuse skin sclerosis with severe and progressive internal organ involvement (diffuse cutaneous SSc). Occasionally SSc can take on fulminant clinical course. Limited cutaneous SSc involves cutaneous areas distal to the elbows and knees but may involve the face

Systemic sclerosis (Scleroderma)

and neck. CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) is a clinical variant of limited cutaneous SSc. Diffuse cutaneous SSc involves skin thickening affecting the trunk and areas proximal to the elbows and knees besides involvement of the face.

Skin manifestations of SSc involve progressive tightness and induration, often preceded by swelling and puffiness (edematous stage) that does not respond to diuretic therapy. Skin induration initially affects the fingers (sclerodactyly) and extends proximally. Raynaud's phenomenon is an initial presentation in 70% of SSc patients and affects 95% of patients during the course of their disease. Raynaud phenomenon may precede overt SSc features by months or even years. Other vascular manifestations of SSc include pitting ulcers or scars in fingertips, finger amputation related to previous fingertip gangrene or osteomyelitis, and cutaneous and mucosal telangiectasia. Digestive system is also commonly affected in SSc patients. In addition to acid reflux, gut dysmotility and malabsorption may occur. Rarely, SSc can affect function of the heart, lungs or kidneys which can be life-threatening.

Diagnosis of SSc can be made clinically based on sclerodermatous involvement in association with Raynaud's phenomenon and varying degrees of internal organ involvement. In early disease, Raynaud's phenomenon may be the only manifestation. Nailfold capillaroscopy may be helpful in determining whether Raynaud's phenomenon is primary (Raynaud's disease) or secondary to a systemic autoimmune disorder such as SSc. The 2013 American College of Rheumatology (ACR) / European League of Associations of Rheumatology (EULAR) revised classification criteria for SSc has increased sensitivity and specificity. Patients with total score > 9 are considered as having definite SSc[5].

Table 1: ACR/EULAR Revised Systemic Sclerosis Classification Criteria

Item	Sub-item(s)	Score*
Skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints *(presence of this criterion is sufficient criterion for SSc classification)*	None	9
Skin thickening of the fingers *(count the higher score only)*	Puffy fingers	2
	Sclerodactyly (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(count the higher score only)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	None	2
Abnormal nailfold capillaries	None	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	None	3
Systemic sclerosis-related autoantibodies *(maximum score is 3)*	Anticentromere	3
	Anti-topoisomerase I	3
	Anti-RNA polymerase III	3

Systemic sclerosis (Scleroderma)

SSc has the highest case-specific mortality among various systemic autoimmune diseases. Pulmonary hypertension, interstitial lung disease and SSc renal crisis are the most frequent causes of mortality[3,4]. Mortality associated with SSc renal crisis has declined significantly in the last decades related to the use of angiotensin-converting enzyme (ACE) inhibitors. In contrast, pulmonary involvement (interstitial lung disease and/or pulmonary arterial hypertension) has become the commonest cause of death in SSc patients. Survival has improved in recent decades and correlates with the clinical disease subtype and with the extent of organ involvement. Five-year survival among patients with diffuse cutaneous SSc improved significantly from 69% to 84% whereas that for patients with limited cutaneous SSc remained high (91-93%).

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Interstitial lung disease in Scleroderma

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Introduction

Interstitial lung disease (ILD) is a common complication of scleroderma (SSc). The prevalence of ILD varies from 35% of patients with limited cutaneous SSc (lcSSc) to about 53% of patients with diffuse cutaneous SSc (dcSSc). Early diagnosis of ILD is important as it is the leading cause of morbidity and mortality in patients with SSc[1].
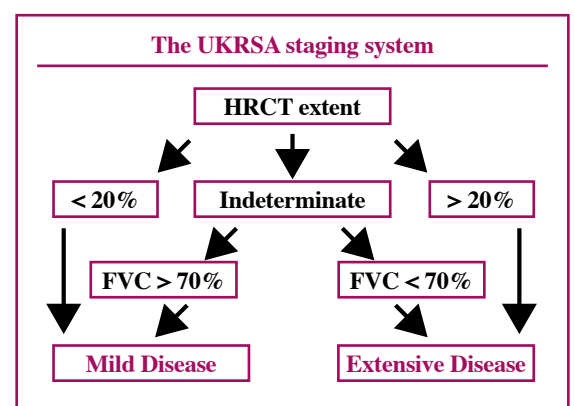
Clinical presentation and diagnosis

Respiratory symptoms in SSc-ILD are usually non-specific, they can vary from asymptomatic, persistent cough, shortness of breath to decreased exercise tolerance and impaired activities of daily living. Severity of symptoms does not always correlate with disease severity as assessed by high resolution computed tomography (HRCT) thorax and pulmonary function test.

Autoantibodies can predict the risk of ILD in patients with SSc. Anti-topoisomerase I antibody (ATA), also known as anti-Scl-70 antibody, is usually associated with dcSSc and is strongly predictive of ILD. Pulmonary fibrosis had been found to be present in more than 85% of ATA positive SSc patients[2]. The presence of the anti-centromere antibody (ACA) is more commonly found in patients with lcSSc and is associated with a much lower risk of ILD.

Chest radiography is a common initial screening test, but is not sensitive to detect early ILD. HRCT thorax is useful to diagnose and classify the type of ILD, assess the extent of pulmonary involvement and predict prognosis. Goh et al showed that interstitial changes involving more than 20% on HRCT thorax are associated with higher mortality[3]. The most common type of ILD is non-specific interstitial pneumonia (NSIP), the HRCT features of which reveal a mixture of ground-glass attenuation and reticulation without honeycomb change. Other types of ILD include usual interstitial pneumonia (UIP) with prominent honeycomb changes and active alveolitis. In an autopsy series, NSIP and UIP were present in 78% and 8% of patients with SSc-ILD respectively[4].

Pulmonary function test (PFT) is used to assess the dynamic function of lung. Typical findings in SSc-ILD include restrictive ventilatory defect, with reduced forced vital capacity (FVC), a forced expiratory volume at 1 second to FVC ratio (FEV1/FVC) of > 0.8, reduced carbon monoxide diffusing capacity (DLCO), and reduced lung compliance.

Using both HRCT thorax and pulmonary function test, severity of ILD can be classified as mild or extensive disease by the UKRSA staging system. If the interstitial lung changes on HRCT thorax is less than 20% and FVC is >70% of predicted, it is classified as mild disease. If the interstitial changes on HRCT thorax is more than 20% and FVC is < 70%, it is classified as extensive disease. It has significant prognostic value[1,3].

The UKRSA staging system

HRCT extent → < 20% | Indeterminate | > 20%

Indeterminate → FVC > 70% | FVC < 70%

< 20% → Mild Disease
FVC > 70% → Mild Disease
FVC < 70% → Extensive Disease
> 20% → Extensive Disease

Interstitial lung disease in Scleroderma

Prognostic factors

Most SSc patients with ILD has a slowly progressive course, however, some of them may develop rapid progressive deterioration of lung disease, which usually occurs in the first few years from disease onset. Poor prognostic factors include male sex, an extent of lung fibrosis more than 20% on HRCT thorax, FVC of < 70% of predicted in those with indeterminate extent on HRCT thorax, low DLCO < 55% of predicted, high serum interleukin-6 levels, anti-topoisomerase I antibody positivity and dcSSc. They are strongly predictive of mortality and subsequent rapid disease progression, in particular, the extent of lung involvement on HRCT thorax. Low DLCO also predicts the development of pulmonary hypertension. However, the histopathologic pattern of ILD, such as NSIP or UIP does not predict the disease course in SSc-ILD patients[5].

Treatment

Treatment of patients with SSc-ILD depends on the severity of ILD, risk of disease progression and presence of poor prognostic factors. Patients who have extensive disease on HRCT thorax, or an indeterminate extent of disease with FVC less than 70%, or a significant decrease of DLCO or FVC should be treated[6]. High dose corticosteroid should be avoided in SSc-ILD due to the risk of renal crisis. Cyclophosphamide (CYC) is the drug of choice for induction therapy of ILD-SSc based on two randomized placebo-controlled trials. Intravenous monthly pulse CYC has better safety profile compared to oral preparation. In the Scleroderma Lung Study (SLS I), treatment with oral CYC for 1 year was shown to have statistically significant beneficial effects on FVC, dyspnea and quality of life[7]. In the Fibrosing Alveolitis in Scleroderma Trial, monthly intravenous CYC followed by oral azathioprine was showed to have treatment benefits on FVC8. Azathioprine can be used in CYC responders as maintenance therapy. Mycophenolate mofetil (MMF) up to 1500 mg BD, has recently been reported to show comparable improvement in FVC and is associated with lower withdrawal rate and side effect at 24 months compared with CTC in the Scleroderma Lung Study II trial[9]. Rituximab has been reported to preserve pulmonary function and improve FVC in patients with early diffuse disease with or without ILD[10], and prevent FVC decline in those with established ILD with good safety profile[11]. Other treatment options include low dose imatinib for unresponsive patients and lung transplantation for those with end stage lung disease.

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Pulmonary Hypertension in Systemic Sclerosis

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Introduction

Pulmonary hypertension is a serious complication and one of the leading causes of death in patients with systemic sclerosis. It is primarily a disease of pulmonary vascular resistance caused by proliferation and contraction of vascular smooth muscle cells. Pulmonary hypertension is progressive and is associated with poor prognosis. This condition accounts for 30% of deaths among patients with systemic sclerosis. Pulmonary hypertension is defined as a resting mean pulmonary arterial pressure of 25 mmHg or higher, pulmonary capillary wedge pressure or left ventricular end diastolic pressure 15 mmHg or lower, and a pulmonary vascular resistance 240 dyn/cm^{-5} or higher on right heart catheterization. The prevalence of pulmonary hypertension in systemic sclerosis by right heart catheterization is between 7% and 12%[1]. The incidence was estimated to be 0.61 cases per 100 patient-years[2]. Predictive factors associated with pulmonary hypertension include presence of serum anticentromere and anti-topoisomerase antibodies, number of telangiectasias, reduced capillary nailfold density, pulmonary fibrosis, Raynaud's phenomenon for over three years and male gender[3].

PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

Clinical Features

Pulmonary hypertension typically presents 10 to 15 years after the onset of Raynaud's phenomenon. It may occur earlier, particularly in patients with diffuse cutaneous systemic sclerosis. In the early phase of the disease, patients can be asymptomatic. Patients typically present with exertional dyspnea as the condition progresses. It may be accompanied by lethargy and fatigue. In advanced phase, syncope, chest pain, edema, or symptoms at rest due to right heart failure may ensue. Some patients may have cough, hemoptysis and hoarseness of voice as a result of compression of the left recurrent laryngeal nerve by the dilated main pulmonary artery. On physical examination, jugular venous distension, pitting oedema, ascites and hepatomegaly may be found. On auscultation, a loud pulmonary second heart sound with pansystolic murmur of tricuspid regurgitation and diastolic murmur of pulmonary insufficiency can be heard.

Screening Tests

Screening for pulmonary hypertension is essential since patients are asymptomatic in early disease and the condition is associated with poor survival. Patients with systemic sclerosis are recommended to undergo baseline and annual lung function test with DLCO, transthoracic echocardiogram and NT-proBNP measurement[4]. Echocardiogram is a non-invasive and effective way for detection of pulmonary arterial hypertension. The European Society of Cardiology / European Respiratory Society (ESC/ERS) diagnostic algorithm in systemic sclerosis patients with suspected pulmonary hypertension is based on the maximal tricuspid regurgitant jet. However, right heart catheterization remains gold standard for diagnosis.
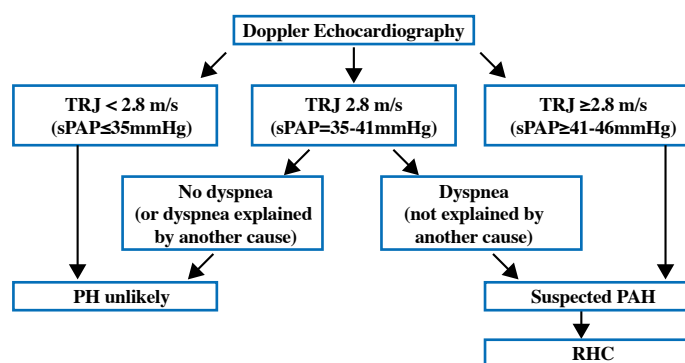
TRJ =	tricuspid regurgitant jet
sPAP =	systolic Pulmonary Arterial Pressure
PAH =	Pulmonary Arterial Hypertension
PH =	Pulmonary Hypertension
RHC =	Right Heart Catheterization

N-terminal pro–brain natriuretic peptide (NT-proBNP) has been shown to predict current and future development of pulmonary hypertension in systemic sclerosis, despite normal echocardiogram[5]. NT-proBNP level over 3 times the upper limit of normal is highly suggestive of pulmonary hypertension. Adding NT-proBNP to DLCO and FVC was shown to predict pulmonary hypertension with sensitivity and specificity as high as 100% and 77.8% respectively in a retrospective cohort study[6]. Although measurement of NT-proBNP is simple and non-invasive, this test is not specific as other causes of myocardial stress raise NT-proBNP level. It does not differentiate left from right heart disease as well as pre- from post-capillary pulmonary hypertension.

Exclusion of other diseases is essential to establish the diagnosis of pulmonary hypertension. Pulmonary function testing with measurement of DLCO, ventilation-perfusion lung scan, chest X-ray, CT pulmonary angiography, high-resolution computed tomography, ECG and blood tests for underlying diseases are useful tools for evaluation.

Management

Screening tests enable early recognition of pulmonary arterial hypertension allowing early treatment with the goal of improving survival. Prostanoids is the first class of medication approved for the treatment of pulmonary hypertension. They are potent pulmonary and systemic vasodilators that stimulate cyclic AMP. Iloprost, a prostacyclin analogue, is a potent vasodilator which is administered by intravenous infusion. Prostanoids have been shown to improve clinical symptoms, functional capacity and hemodynamic parameters[7].

Endothelin (ET) receptor antagonists, such as Bosentan, are oral agents that block the interaction of ET-1 with its receptors interfering with its vasoconstrictive effects. Bosentan has demonstrated beneficial effects on improvement of 6-minute walk distance, delay in clinical progression and improvement in survival[8].

Phosphodiesterase-5 inhibitors are oral agents that increase the concentration of nitric oxide, with resultant vasodilatory, antiproliferative and proapoptotic effects that may reverse pulmonary artery remodeling. Sildenafil was shown to improve 6-minute walk distance, functional class, pulmonary artery pressure and pulmonary vascular resistance[9].

Oral calcium channel blockers including Nifedipine and Diltiazem, are effective long-term therapy in patients with idiopathic pulmonary hypertension who demonstrate acute vasodilatatory response to adenosine or nitric oxide during hemodynamic testing in right heart catheterization. However, most patients with systemic sclerosis fail to response to acute vasodilators during hemodynamic testing. Low-dose calcium channel blockers in scleroderma patients are thus mainly used for management of Raynaud's symptoms.

Pulmonary Hypertension in Systemic Sclerosis

Patients who had moderate to severe pulmonary arterial hypertension should be supplemented by domiciliary oxygen supplement, in particular if they are hypoxemic at rest (arterial blood oxygen pressure <60 mm Hg or arterial oxygen saturation <90%). Lung transplantation is reserved for patients with severe condition despite optimised medical treatment. Post-transplant survival rate improved from 59% to 93%, 49% to 80%, and 46% to 79%, for 1-year, 2-year, and 3-year respectively[10].

Prognosis

The median survival of patients with symptomatic moderate to severe pulmonary hypertension before availability of pulmonary vasodilator therapy was low with 3-year survival rate of less than 35%. Patients die from right heart failure or refractory hypoxemia. With modern therapy, the 1-, 2-, and 3-year survival rates of improved to 86%, 67%, and 65%, respectively.

Conclusion

The spectrum of systemic sclerosis ranges from rapidly progressive skin and serious internal organ disease, like pulmonary hypertension, to indolent course with relatively mild organ involvement. Risk stratification and systematic evaluation is an important aspect at baseline evaluations and systematic follow-up. Modern treatment for systemic sclerosis related pulmonary hypertension improves clinical outcomes, although treatment response is not as good as idiopathic pulmonary hypertension. Early recognition and screening test for pulmonary hypertension in patients with systemic sclerosis is important.

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Gastroesophageal reflux and gastrointestinal motility problems in scleroderma patients: from diagnosis to management

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Scleroderma is a systemic connective tissue disease with a predilection for gastrointestinal tract. Although most patients are asymptomatic, significant gastroesophageal reflux and altered gastrointestinal (GI) motility can add to the burden of disease. This summary reviews the commonly encountered GI manifestations of scleroderma, as a brief management plan will help rheumatologists deal with this important disease condition.

The esophagus is the most commonly affected GI organ in scleroderma and up to 90% of scleroderma patients have esophageal involvement[1,2]. Patients with systemic sclerosis often are clinically silent with motility problems detected by barium swallows and manometry testing. In affected patients, the smooth muscle fibrosis and atrophy results in decreased or absent peristalsis in the distal two thirds of the esophagus (Figure 1)[3]. The upper esophageal sphincter and the proximal esophageal contractions are often unaffected. Often the lower esophageal sphincter (LES) is incompetent and predisposes to clinically significant gastroesophageal reflux and its associated complications. Typical symptoms of heartburn and acid reflux are often elicited in patients. The importance of recognizing and treating this condition lies in the predisposition to microaspiration and may worsen the associated interstitial lung disease commonly encountered in scleroderma patients. Other associated complications including erosive esophagitis, peptic stricture, Barrett's esophagus and esophageal adenocarcinoma. In patients who have long-standing gastroesophageal reflux, the development of dysphagia or vomiting suggest a possibility of peptic stricture formation. Likewise, patients with impaired esophageal clearance or structural pathology and obstruction are also at risk of developing drug-induced esophagitis and food bolus impaction.

The acid reflux and the associated esophagitis in scleroderma patients often respond well to proton-pump inhibitors, lifestyle and dietary changes. Proton-pump inhibitors (PPIs) should be given twice daily since nocturnal acid reflux is common due to LES incompetence particularly in the supine position during sleeping. Calcium channel blockers such as nifedipine or amlodipine may be used in Raynaud's phenomenon but may further lower the esophageal sphincter pressure and aggravate acid reflux[4]. Those who fail to response to PPIs and with alarm symptoms (e.g. weight loss, anorexia, dysphagia) should undergo further investigations such as upper endoscopy plus biopsies. Patients who have "normal" upper endoscopies may then be selected to undergo esophageal motility studies based on their presenting symptom and symptom severity. The most common manometric findings include weak peristalsis, aperistalsis and a low LES resting pressure. Interestingly, esophageal hypomotility is common in scleroderma patients who develop Raynaud's phenomenon.

Gastroesophageal reflux and gastrointestinal motility problems in scleroderma patients: from diagnosis to management

Along with the esophagus, the upper gastrointestinal tract and the small bowel may also be affected in scleroderma with a prevalence of 40%. The upper GI tract and small bowel show hypomotility problems such as gastroparesis, ileus, stasis, small bowel dilatation, bacterial overgrowth, and malabsorption (see Table 1). The most common symptoms related to hypomotility include abdominal pain, distension and bloating. In more advanced cases where malabsorption occurs, patients develop weight loss, steatorrhea and diarrhea. The pathological feature in common to stomach and small bowel involvement is vascular ischaemia, neural dysfunction, smooth muscle degeneration and collagen replacement, particularly of the circular muscle layer of the lamina propria. A small portion of patients may also have histopathological features of associated myenteric plexus damage. In specialized centres where small bowel physiology and motility studies are available, the characteristic features include abnormal motor patterns during fasting and after meal time. Myopathic conditions such as scleroderma with small bowel involvement lead to reduced contractile amplitude. If the colon is involved alone or in extensive disease, the phasic colonic contractions are absent and there may be a loss of the gastrocolic response. Patients with colonic involvement usually have pancolonic disease (the whole colon is affected) with constipation as the predominant symptom. Interestingly, these patients may also have diarrhea since patients with colonic involvement will often also have small bowel involvement and the presentation of constipation or diarrhea depends on which problem is dominant: small bowel dysmotility and bacterial overgrowth or colonic inertia[5]. Patients with predominantly diarrhea should have stool collection for cultures and hydrogen-breath test should there be a clinical suspicion of small intestinal bacterial overgrowth.

## Table 1. Gastrointestinal disorders in scleroderma patients.

Site					
Esophagus	Esophagitis	Peptic stricture	Barrett's change	Diverticuli	Adenocarcinoma
Stomach	Gastritis	Gastroparesis	⬇ Gastric emptying	GAVE*	–
Small bowel	Ileus	Pseudo-obstruction	Bacterial overgrowth	Malabsorption	–
Large bowel	Constipation	Pseudo-obstruction	Diarrhea	Fecal incontinence	–

*GAVE, gastric antral vascular ectasia

The management of intestinal dysmotility and hypomotility often include dietary counseling and a therapeutic trial of prokinetic drugs. Dietary advice include frequent small meals, particularly in patients with associated gastroesophageal reflux. Gastric and small bowel stasis may lead to nausea and vomiting and anti-emetics may also help symptoms who have exacerbations and acute symptoms. Persistence or worsening of symptoms suggest possible structural problems such as significant ileus or pseudo-obstruction which is sometimes seen in scleroderma patients. Patients with gastroparesis are often treated with metoclopramide (dopamine receptor antagonist) 10 mg 30 minutes before mealtime 3-4 times per day. Those with both gastroparesis and small bowel hypomotility generally respond less favorably and prolong therapy may lead to extrapyramidal side effects. Constipation generally responds to osmotic laxatives such as lactulose, polyethylene glycol compounds and milk of magnesia. Patients often respond within hours but bloating and abdominal cramps may also be experienced as a result of the increased colonic water content and stimulant effects. Dietitian referral is advisable with low residue, low fat diet often relieving some of the symptoms of hypomotility in conjunction with pharmacologic treatment. It is also important to correct any nutritional deficiencies or malabsorption that may be present.

In summary, scleroderma patients frequently have gastrointestinal tract involvement and the associated clinical problems include gastroesophageal reflux disease, esophageal motility disorders, gastroparesis and small bowel dysmotility. Management of these conditions with acid suppressant therapy, motility and prokinetic agents can improve quality of life and reduce morbidity and long-term gastrointestinal complications.

Figure 1.
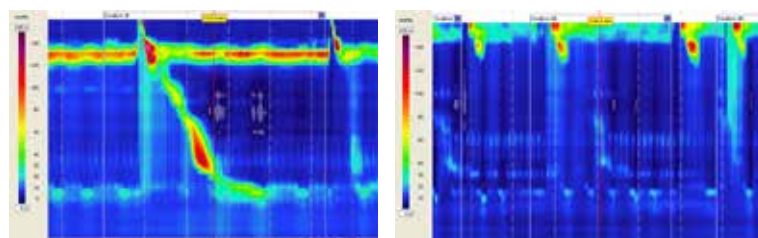
Left panel: High resolution manometry of a normal subject with wet swallow which was followed by upper then middle and lower esophageal peristaltic contractions and relaxation of the lower esophageal sphincter. Right panel: A patient with scleroderma presented with symptomatic acid reflux and high-resolution manometry shows some proximal esophageal contractions only with complete absence of peristalsis in the mid and distal portion of his esophagus. Low LES pressure and a structural hiatus hernia were also present.

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Medical Treatment of Raynaud's phenomenon in Systemic Sclerosis

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Introduction

Raynaud's phenomenon is an exaggerated vascular response to cold or emotional stress. Classically it is manifested by episodic tri-phasic color changes of the digits from white (ischemia), then blue (deoxygenation), to red (reperfusion). Raynaud's phenomenon can be classified as primary or secondary to a number of autoimmune diseases. More than 95% of patients with systemic sclerosis develop Raynaud's phenomenon.

Pathophysiology of Raynaud's phenomenon

Although the exact pathophysiology of Raynaud's phenomenon has not been elucidated, it is believed to be associated with vascular and neural abnormalities. Studies have shown that endothelial damage is common in systemic sclerosis. It exacerbates vasoconstriction by mediating proliferation and contraction of vascular smooth muscle cells, reduction in vasodilator release, enhancement of platelet activation and formation of micro-thrombi.

Besides, exaggerated vasoconstriction in Raynaud's phenomenon can be related to several neural abnormalities. Calcitonin gene related peptide is a potent vasodilator secreted by neurons innervating the blood vessels. In patients with systemic sclerosis, a reduction in calcitonin gene related peptide-releasing neurons has been demonstrated in skin biopsies. Other studies have also reported an increased activity of $\alpha 2$ adrenergic receptors and expression of neuropeptide P, which is a potent vasoconstrictor, in patients with systemic sclerosis.

Table 1. Difference between primary and secondary Raynaud's phenomenon

Characteristics	Primary	Secondary
Age of onset	<30	>30
Digital ulcers or gangrene	Rare	Common
Associated disease	No	Yes
Capillaroscopy	Normal	Abnormal nailfold capillary
Autoantibodies	Absent	Present
Endothelial cell activation	Yes	Yes
Endothelial damage	No	Yes
Vascular structural abnormality	No	Yes
$\alpha 2$ adrenergic activity	High	High

Treatment options for Raynaud's phenomenon

Calcium channel blocker

Calcium channel blocker is the class of drug most widely used for the treatment of Raynaud's phenomenon. Long acting preparations of dihydropyridines are the treatment of choice i.e. Nifedipine or Amlodipine because of their selectivity for vascular smooth muscle. The efficacy and safety of calcium channel blockers in the treatment of Raynaud's phenomenon have been demonstrated in several meta-analyses. In general, the use of calcium channel blocker is associated with reduced frequency and severity of attacks[1]. However, a significant variation in the response to calcium channel blocker has been observed. Patients with systemic sclerosis are less likely to benefit from this therapy alone. The most common adverse reactions associated with the use of calcium channel blockers include headache, dizziness, flushing, tachycardia and dependent edema.

Other vasodilators

Prazocin, an $\alpha 1$-adrenergic receptor antagonist, has been reported to improve Raynaud's phenomenon. However, subgroup analyses showed that its beneficial effect in patients with systemic sclerosis was limited[2].

Losartan, an angiotensin II receptor blocker, has also been shown to improved Raynaud's phenomenon. In a randomized controlled trial comparing the effect of losartan 50mg per day versus nifedipine 40mg per day, a greater reduction in the severity and frequency of Raynaud's phenomenon were observed after 12 weeks of treatment with losartan[3]. However, the beneficial effects were greater in patients with primary Raynaud's phenomenon.

Phosphodiesterase 5 inhibitors

A meta-analysis including 6 randomized controlled trials has demonstrated a significant but modest efficacy of phosphodiesterase 5 inhibitors in secondary Raynaud's phenomenon. The use of sildenafil, tadalafil or vardenafil was associated with a decrease in daily frequency of ischemic attack by 0.5 and daily duration of attack by 15 minutes[4].

MEDICAL TREATMENT OF RAYNAUD'S PHENOMENON IN SYSTEMIC SCLEROSIS

Prostacyclin analogues

The use of prostacyclin analogues for patients with severe Raynaud's phenomenon is supported by many randomized controlled trials. The mechanisms of action may include potent vasodilatory effect, inhibition of platelet aggregation, and improvement of abnormal vascular reactivity.

The beneficial effect of iloprost has been evaluated in patients with Raynaud's phenomenon secondary to systemic sclerosis. On one hand, it could significant decrease the severity and frequency of acute attack. On the other hand, it could prevent the development and promote the healing of digital ulcers[5]. The effect of iloprost could be maintained even after infusions.

However, adverse reactions are more common with the use of iloprost. Most of them are relatively mild, including headache, flushing, nausea, vomiting and myalgia. If the patient cannot tolerate the adverse reactions or develops hypotension, the dose of iloprost and the rate of infusion can be decreased.

Endothelin 1 antagonists

Bosentan, a competitive antagonist of endothelin 1 receptor, has been tested in patients with systemic sclerosis. The use of bosentan was associated with a significant reduction in the number of new digital ulcers[6]. However, its effects on Raynaud's phenomenon have not been adequately assessed in the randomized controlled trials.

Sympathectomy

Sympathectomy should be considered in patients with severe Raynaud's phenomenon and critical ischemia not responding to medical treatment. It can be performed by injection lidocaine or bupivacaine at the wrists or by surgical techniques. Localized surgical digital sympathectomy has been reported successful with few complications for the treatment of digital ischemia in case series.

Approach considerations

Since complete reversal of Raynaud's phenomenon in patients with systemic sclerosis is not feasible, the goals of treatment are to improve the quality of life and to prevent ischemic injury.

Long acting preparation of the dihydropyridine calcium channel blockers are the treatment of choice for Raynaud's phenomenon with no apparent ischemic injury. The doses of calcium channel blockers should be gradually increased, if necessary, depending on the response and the tolerance to the adverse reactions.

If initial therapy with calcium channel blockers fails, combination with other vasodilators can be considered. Although the efficacy of combination therapy has not been evaluated in randomized controlled trials, it has been increasingly used in clinical practice for Raynaud's phenomenon resistant to calcium channel blockers.

In patients with established digital ischemia not responding to oral vasodilators, treatment with prostacyclin infusion is recommended. The duration of treatment should be determined by the severity and the clinical outcomes. Although iloprost infusion is usually used as an acute treatment for established ischemia, maintenance infusion may be considered in patients with severe Raynaud's phenomenon complicated by ischemic injury.

Sympathectomy should be reserved for patients with critical ischemia despite the use of oral vasodilators and iloprost infusion.

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Stellate Ganglion Block for the management of severe Raynaud's Phenomenon

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Introduction

Pain is a key symptom in various vascular diseases associated with peripheral ischaemia. One of the commonest rheumatological conditions associated with ischaemia or impaired perfusion is Raynaud's phenomenon. Raynaud's phenomenon can be primary or secondary to an autoimmune disease. It is essential to look for the underlying causes and start symptomatic and disease modifying treatment. If pain persists despite treatment and is associated with dystrophic changes and ulcers over the digits, sympathectomy or sympathetic block may be considered. Stellate ganglion block is commonly performed for this purpose.

Indications

Stellate ganglion block is useful in the treatment of a variety of painful conditions of the head, neck, upper extremities and upper thoracic dermatomes such as

1. Pain due to acute herpes zoster and postherpetic neuralgia
2. Complex Regional Pain Syndrome type I and II
3. Cancer pain of the head, neck and upper extremities
4. Atypical facial pain
5. Painful syndromes related to the vascular system such as vascular insufficiency, vasospasm, arterial embolism

Contraindications

Absolute contraindications of stellate ganglion block include:

1. Anticoagulant therapy: bleeding risk from accidental vascular injury during needle insertion
2. Pneumothorax and pneumonectomy on the contralateral side: danger of pneumothorax on the ipsilateral side
3. Recent myocardial infarction: stellate ganglion blockade cuts off sympathetic supply to the heart
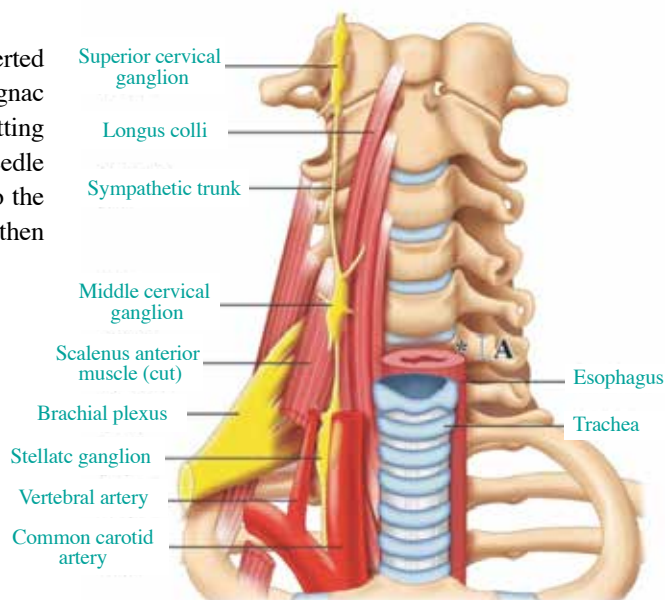
Anatomy

The sympathetic outflow arises from the preganglionic neurons located at the lateral gray horn of the spinal cord at the thoracic and upper two lumbar spinal segments. The sympathetic fibers for the head, neck, upper limbs and the heart arise from the first few thoracic segments, ascend through the sympathetic chains and synapse in the superior, middle and inferior cervical ganglion. The stellate ganglion is named because of its star-shaped appearance resulting from the union of the inferior cervical ganglion with the first thoracic ganglion. It extends from the level of the head of the first rib to the inferior border of the transverse process of C7 and lies medial to the vertebral artery immediately adjacent to the dome of pleura. The postganglionic fibers from the stellate ganglion to the cervical nerves and the first thoracic nerve provide sympathetic innervation to the upper limbs[1-4]. Injection of local anesthetic around the stellate ganglion interrupts sympathetic outflow to the head, neck and upper limbs.

## Technique of Stellate Ganglion Block

1. Classical approach

Paratracheal approach is most widely practiced. The needle is inserted toward the anterior tubercle of cervical sixth vertebra (Chassaignac tubercle) identified by fluoroscopy. Needle is withdrawn after hitting the bone. Contrast medium is injected to confirm position of the needle tip. This approach assumes that medication will spread caudally to the stellate ganglion. 5 ml of local anaesthetic with corticosteroid are then injected.

Superior cervical ganglion
Longus colli
Sympathetic trunk
Middle cervical ganglion
Scalenus anterior muscle (cut)
Brachial plexus
Stellate ganglion
Vertebral artery
Common carotid artery
* A
Esophagus
Trachea

* The target site for needle insertion in classical approach
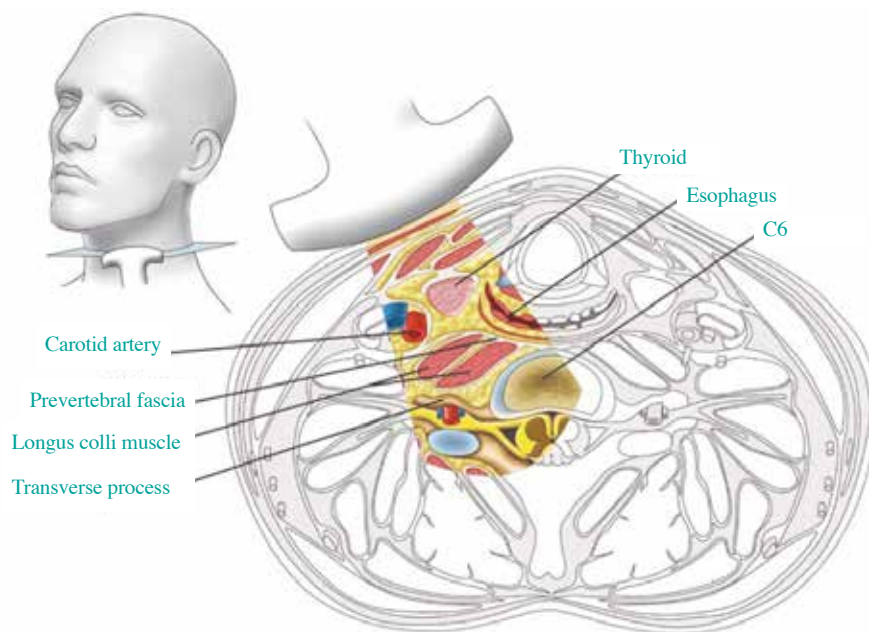(Adapted from Atlas of Ultrasound-Guided Procedures in Interventional Pain Management)
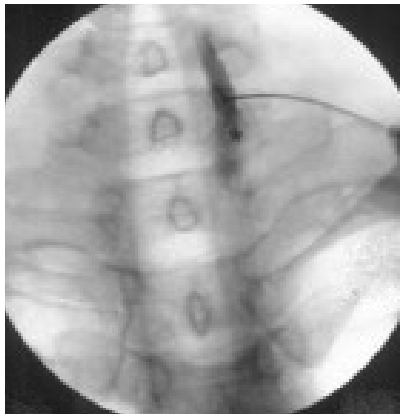
Anteroposterior and lateral X rays showing contrast spreading in the retropharyngeal space along the longus colli. (Adapted from P Raj and S Erdine. Pain-Relieving Procedures)

2. Ultrasound-guided approach

Ultrasound-guided approach is safer and is becoming more popular. The patient is placed in the supine position with the neck in slight extension. A high frequency linear transducer is placed at the level of C6 to allow cross-sectional visualization of anatomic structures including the transverse process and anterior tubercle of C6, longus colli muscle, prevertebral fascia, carotid artery and thyroid gland.

Cross section of the neck at the sixth cervical vertebral level correlating with the ultrasonographic image (Adapted from: Atlas of Ultrasound-Guided Procedures in Interventional Pain Management)

Under USG guidance, the needle tip is directed to the prevertebral fascia between the carotid artery and the tip of C6 anterior tubercle, avoid hitting the cervical nerve root. The internal jugular vein can be visualized by reducing the probe pressure and avoided by "pushing" way with the needle. Visualization of the spread of injectate under real-time scanning excludes inappropriate intravascular injection. It has been suggested that subfascial injection results in more caudal spread and higher rate of sympathetic block of the upper limb.

Signs of successful stellate ganglion block

Sympathetic interruption to the head can be revealed by evidence of development of Horner's syndrome and other features including conjunctival injection, nasal congestion and facial anhidrosis. Evidence of sympathetic blockade to the upper extremity includes visible engorgement of the veins on the back of hand and forearm. There is increase in skin temperature associated with redness.

Complications

In general, stellate ganglion block is safe under experienced hands and under ultrasound guidance. More commonly reported complications include:

Stellate Ganglion Block for the management of severe Raynaud's Phenomenon

1. Transient Horner's syndrome : miosis (pinpoint pupil), ptosis (drooping of the upper eyelid), and enophthalmos (sinking of the eyeball)
2. Recurrent laryngeal nerve block: hoarseness of voice, feeling of a lump in the throat, and sometimes subjective shortness of breath. Bilateral stellate blocks are rarely advised to avoid loss of bilateral laryngeal reflexes and respiratory compromise.
3. Phrenic nerve block: temporary paralysis of the ipsilateral diaphragm leading to respiratory embarrassment in those whose respiratory reserve is already severely compromised
4. Block of the branches of the brachial plexus

Serious complications include pneumothorax, inadvertent puncture of the carotid artery, vertebral artery and vein and epidural or subarachnoid puncture and injection. Accidental systemic administration of local anesthetic may cause hypotension which can be severe, unconsciousness, respiratory paralysis, seizures, and cardiac arrhythmia. Rarely, stellate ganglion block may lead to paratracheal haematoma, inadvertent puncture of the esophagus and osteitis of the transverse process.

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