The Effects Of Pulsed Therapeutic Plasma Exchange On Gastrointestinal Symptoms In Limited Systemic Sclerosis: A Case Series[1]

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Abstract

Background: Up to 90% of patients with systemic sclerosis (SSc) experience significant gastrointestinal (GI) symptoms such as gastro esophageal reflux disease (GERD), small intestinal bacterial overgrowth (SIBO), and Gastric Antral Vascular Ectasia (GAVE) with associated anemia. Conventional systemic treatments including immunosuppression have no effect on the development of severe GI symptoms. Previous research on the use of therapeutic plasma exchange (TPE) as a treatment for SSc has typically described clear improvements in clinical symptoms and laboratory markers with very few adverse events. However, there has been almost no documentation on the effects of TPE on GI symptoms. This case series documents the effects on GI symptoms in four patients diagnosed with limited cutaneous systemic sclerosis (lcSSc) who have been on a specific pulsed plasma exchange (PPE) protocol for 15 months to 28 years.

Methods: All patients received a one blood volume TPE treatment per week for four weeks using albumin as the plasma replacement. This was followed by eight weeks with no treatment before the next cycle of four weekly treatments. Clinical assessment tools included the Scleroderma Health Assessment Questionnaire (SHAQ) and the UCLA Gastrointestinal Tract survey (GIT 2.0). No patients are on concurrent immunosuppressants.

Results: Data are summarized in Table 1. All four patients showed significant improvement in GI symptoms, including significant reduction or complete elimination of GERD in two patients, sustained normalization of hemoglobin in a patient with GAVE who had required six ablations and three iron infusions prior to starting PPE, and nearly complete elimination of severe esophageal spasms in a fourth patient. Two patients reported significant reduction of pain and fatigue, and in one patient, significant improvement was observed in diffusing capacity for carbon monoxide (DLCO). No significant adverse events related to TPE treatments were reported in any patient.

Conclusion: While all four of these patients exhibited significant improvements in a variety of clinical signs and symptoms, the observed improvements in a broad spectrum of GI symptoms is significant, since conventional treatments do not lead to GI symptom improvements. Given that GI involvement can severely affect quality of life in patients with SSc and that previous research has demonstrated that TPE has an excellent safety profile,

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[1] Harris E, Weiss J, Lacson S. The Effects of Pulsed Therapeutic Plasma Exchange on Gastrointestinal Symptoms in Limited Systemic Sclerosis: A Case Series. J Clin Apher. 2022;37(2):168.

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these preliminary results suggest that pulsed plasma exchange should be considered in lcSSc patients with significant GI symptoms. Additional research is needed to better understand the mechanisms of action for this treatment modality and whether they will replicate in SSc patients with different antibodies and clinical profiles.

Table 1: Patient Pre-PPE and Current Clinical Status

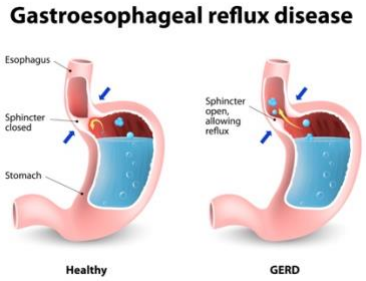
Age at start of PPE / Sex / ANA / Antibody	**Chief Complaints pre PPE**	**Pre-PPE SHAQ / GIT Scores**	**PPE Start Date / Nr. Treatments to date**	**Current SHAQ / GIT 2.0 Scores**	**Current clinical status**	**Notes**
43 / M / 1:1280 / centromere[1]	Severe GERD, frequent Raynaud's attacks, chronic chilling, swollen hands, reduced DLCO (68%)	SHAQ-DI: 0 SHAQ-VAS: 1.80 GIT: 0.59 (post hoc)	Nov 1993 / ~487	SHAQ-DI: 0 SHAQ-VAS: 0 GIT 2.0: 0	Very mild Raynaud's, last DLCO normal (2000) 82%	Two interruptions of protocol (1996: 6 months, 2020: 4 months) led to return of GERD. GERD resolved in one year (1997) and five months (2020) after resuming normal protocol.
64 / F / 1:2560 / centromere	GAVE; chronic anemia (low Hgb); Raynaud's; Sjoegren's ; mild GERD	SHAQ-DI: 0.1 SHAQ-VAS: 0.38 GIT: 0.28	Oct 2019 / 40	SHAQ-DI: 0 SHAQ-VAS: 0.17 GIT: 0.06	Hgb normal; Raynaud's, Sjoegren's, GERD unchanged	No ablations or iron infusions required since starting PPE; patient has hiatal hernia
55 / F / 1:640 / centromere	Gastroparesis; severe Raynaud's; SIBO; calcinosis;	SHAQ-DI: 0.3 SHAQ	Mar 2019 / 36	SHAQ-DI: 0 SHAQ	GERD and gastroparesis significantly improved; fatigue, pain,	No longer requires high calorie/protein supplements

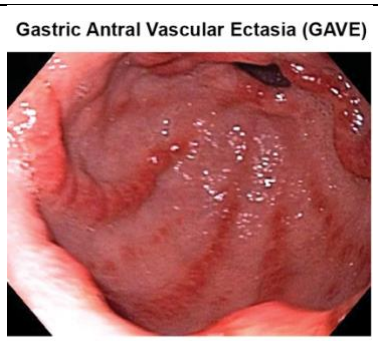
	swollen fingers; GERD; fatigue; pain, chronic chilling	-VAS: 2.11 GIT: 1.42		-VAS: 0.03 GIT: 0.13	and chronic chilling subsided; Raynaud's significantly improved	to maintain weight
63 / F / >1:1280 centromere pattern	Poor motility; dysphagia; severe esophageal spasms; SIBO; mild GERD; mild Raynaud's; chronic chilling; telangiectasias; muscle/joint pain; fatigue; finger curvature	SHAQ-DI: 0.3 SHAQ-VAS: 0.75 GIT: 0.85 (post hoc)	Nov 2020 / 24	SHAQ-DI: 0.3 SHAQ-VAS: 0.74 GIT: 0.67	Major reduction in esophageal spasms; significant improvement in muscle/joint pain; reduced telangiectasias; reduced finger curvature; reduced fatigue; GERD, Raynaud's unchanged	No longer has anxiety associated with eating (This was due to severe esophageal spasms/difficulty swallowing pre PPE.)

[1] Harris E, Meiselman H, Moriarty P, Weiss J. Successful long-term (22 Year) treatment of limited scleroderma using therapeutic plasma exchange: Is blood rheology the key? Clin Hemorheol Microcirc. 2017;65:131–6.

Background

- Systemic sclerosis (SSc) is an umbrella term for a family of rare autoimmune diseases with the common factor being abnormal skin fibrosis and thickening in association with Raynaud's phenomenon.
- All forms of SSc include dysregulation of the immune system and extensive microvascular injury leading to fibrotic damage to internal organ systems, including the lungs, gastrointestinal system, kidneys, and heart.
- Up to 90% of patients with systemic sclerosis (SSc) experience significant gastrointestinal (GI) symptoms such as gastro esophageal reflux disease (GERD), small intestinal bacterial overgrowth (SIBO), and Gastric Antral Vascular Ectasia (GAVE) with associated anemia, and fecal incontinence. [1,2].
- No conventional treatment has been reported to reverse overall GI symptoms, although GI symptoms can be mitigated to some extent by treatments such as proton pump inhibitors (PPIs) for GERD and antibiotic regimens for SIBO/malabsorption.
- Therapeutic plasma exchange (TPE), has been tried as a possible treatment for SSc since 1978, mostly outside of the US. Previous research on the use of TPE has typically described clear improvements in clinical symptoms and laboratory markers with very few adverse events. [3] However, there has been almost no documentation of the effects of TPE on GI symptoms.
- This case series documents the effects TPE on GI symptoms in four ANA positive patients diagnosed with anti-centromere positive lcSSc, all of whom have been on the identical pulsed plasma exchange (PPE) protocol for time periods ranging from 18 months to 28 years.





Chatterjee S. Watermelon stomach. CMAJ. 2008;179(2):162. doi:10.1503/cmaj.080461

Methods

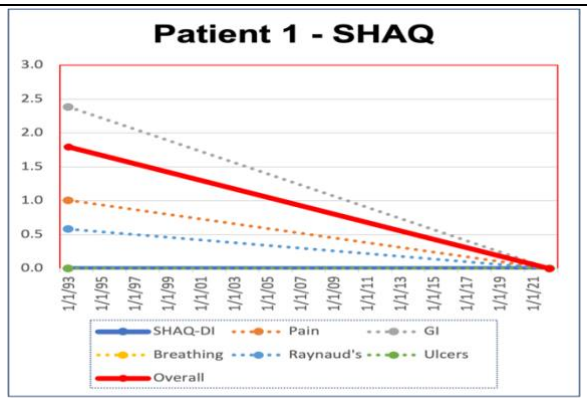
- Case series involving three or fewer patients are exempt from IRB approval at the University of Wisconsin, Madison. Patient one data is from a previously published case report. [4] All patients included in this case series signed consent forms.
- Protocol: all patients receive a one blood volume TPE treatment per week for four weeks using 4% to 5% albumin as the plasma replacement. This is followed by an eight-week no-treatment interval before the next cycle of four weekly treatments begins.
- Clinical assessment tools include the Scleroderma Health Assessment Questionnaire (SHAQ) and the UCLA Gastrointestinal Tract survey (GIT 2.0).

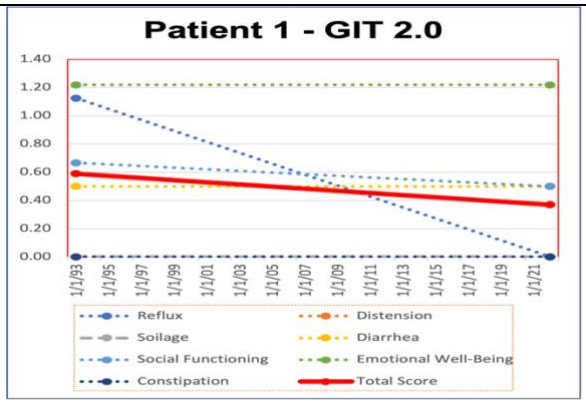
Results

Data for all four patients are summarized in Table 1. No significant adverse events related to TPE treatments were reported in any patient.

Patient One

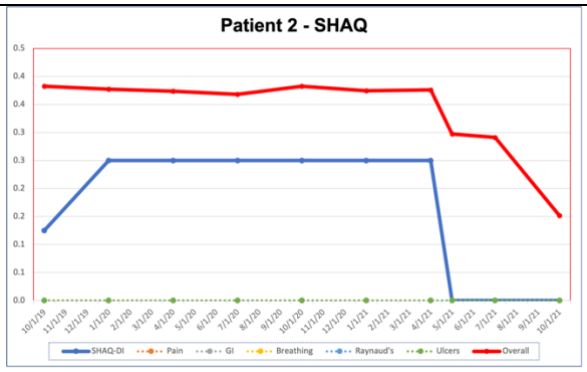
- Male, diagnosed with CREST syndrome in January 1990 at age 43.
- Patient complaints prior to starting pulsed plasma exchange (PPE) included severe GERD, chronic cold intolerance, severe Raynaud's phenomenon (no digital ulcers), and visible nailfold capillary enlargement. He also had significantly reduced DLCO/VA at 68%. He was on 40mg omeprazole BID for the severe GERD symptoms.
- Started PPE in November 1993 and has received approximately 490 treatments to date.
- After one year (16 TPE treatments), he reported significant reduction in GERD and was able to reduce omeprazole dosing to 20mg BID. He also reported significant reduction in Raynaud's attacks and reduced cold intolerance.
- At two years (32 TPE treatments), GERD was completely controlled with 20mg omeprazole QD, and he no longer reported cold intolerance. His DLCO/VA was stable at 68%. Over the next several years, his DLCO/VA score slowly increased and had returned to the normal range (82%) when last assessed in 2001.
- The patient is currently 74 and in excellent overall health for his age. He is very active physically (plays tennis almost every day). His only remaining SSc-related symptom is very mild Raynaud's. He was able to slowly taper completely off omeprazole in the late 90s and has no remaining GERD symptoms.

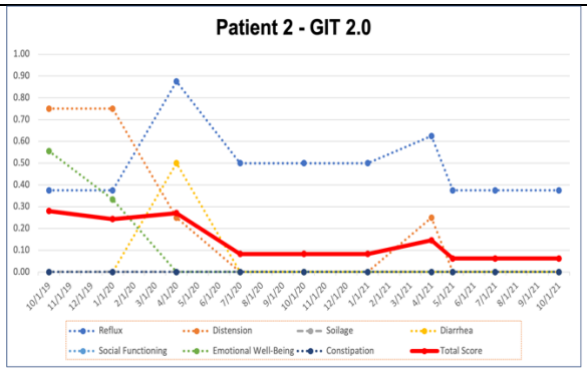




Patient Two

- Female, diagnosed with limited SSc in July 2019 at age 64.
- Pre-PPE complaints included GAVE, Raynaud's phenomenon, Sjogren's, GERD, telangiectasia, and visible nailfold capillary enlargement.
- She had six endoscopic laser ablations between 2013 and 2019 as well as periodic iron infusions to control the bleeding / iron loss from GAVE.
- She started PPE in October 2019 and has received 38 treatments to date.
- Since starting PPE, she has maintained normal hemoglobin levels and has not required any further laser ablations or iron infusions.
- She is currently 67, in very good health (participates in aerobics or weightlifting four days a week). She still suffers from Raynaud's, Sjogren's and GERD.
- She was diagnosed with a hiatal hernia about a year ago.

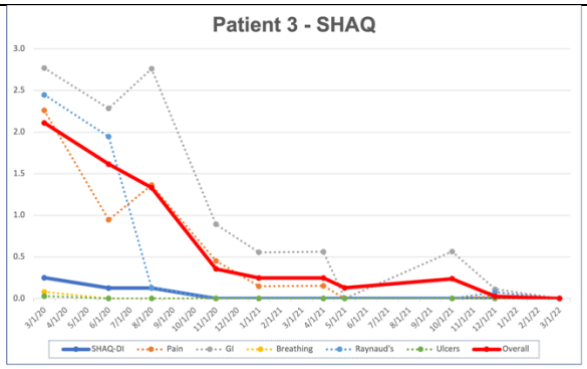


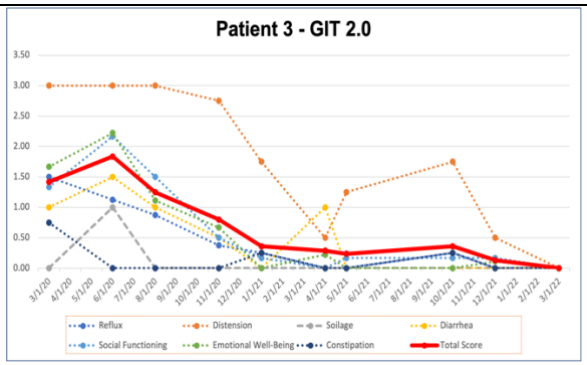


Patient Three

- Female, diagnosed with limited SSc in May 2017 at age 53.

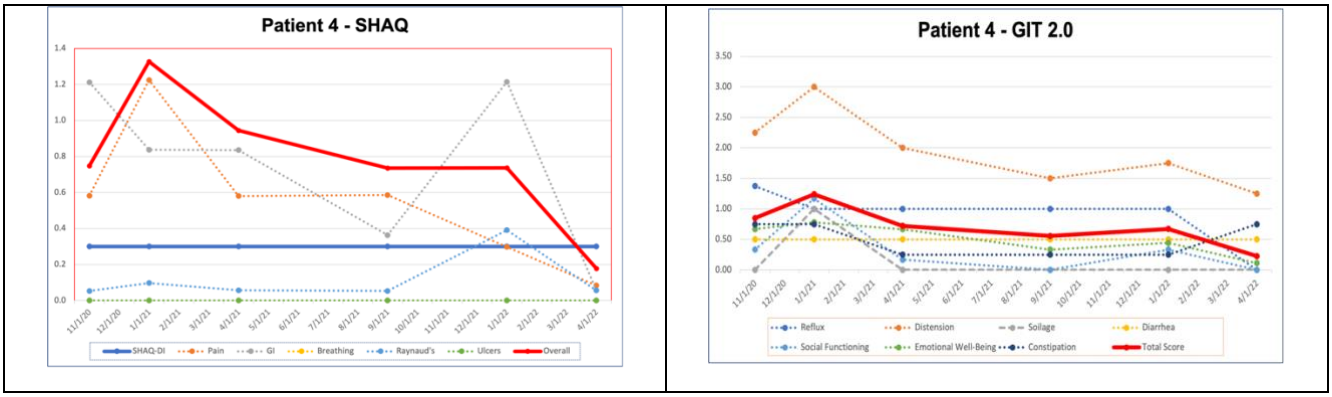
- Pre-PPE complaints included gastroparesis, Raynaud's of hands and feet, cold intolerance, swollen fingers in mornings and evenings, calcinosis, chronic SIBO, GERD, gastroparesis, esophageal spasms, constipation, fatigue, and myalgia. She was on 60mg dexlansoprazole QD for her GERD.
- She started PPE in March 2020 and has received 36 treatments to date.
- After 15 months of PPE, the esophageal spasms had significantly subsided and her GERD symptoms were significantly improved. She no longer had to sleep on a wedge. Her fatigue had also subsided.
- Her Raynaud's symptoms have greatly improved with continued PPE, and she has had no further calcinosis. She is slowly tapering off her reduced PPI dosing of 20mg esomeprazole QD.





Patient Four

- Female, diagnosed with limited SSc in 1992 at age 34.
- Pre-PPE complaints included dysphagia, GERD, SIBO, and esophageal spasm along with increasing Raynaud's symptoms. She was unable to stand for long periods of time due to venous reflux and had difficulty sleeping at high altitudes.
- She started PPE in November 2020 and has received 24 treatments to date.
- After two treatment cycles, the patient reported reduced neck and shoulder pain and major improvement in esophageal spasms along with reduction of dysphagia. She reports further overall improvements with continued PPE.
- Her reduced venous reflux allows her to stand for longer periods of time and sleep at high altitudes has greatly improved.



Discussion

Non-GI Symptom Improvements

While the focus of this paper is on improvements in GI symptoms in four patients diagnosed with centromere positive lcSSc, it is important to note that all four of these patients also reported significant improvements in non-GI symptoms:

- Patient One had significant reduction in Raynaud's attacks, complete elimination of swollen hands and cold intolerance, and significant improvement of lung functioning (DLCO%) over several years to normal levels.
- Patient two no longer needs supplemental oxygen when traveling in high altitudes. She has also experienced a decreased frequency of blood clots in her leg. This recently allowed her to cancel scheduled surgery to treat, as had been required twice previously.
- Patient Three also reported significant reductions in fatigue, pain, and chronic cold intolerance.
- Patient Four had significant improvement in muscle and joint pain, reduced finger curvature, and reduced fatigue in addition to almost complete elimination of esophageal spasms.

Current Systemic Treatment Approaches for GI Symptoms

- GI symptoms severely impact overall quality of life for many patients with SSc [1] and are also a significant cause of death in SSc patients due to malabsorption and other issues. [5]
- Currently, treatment for GI involvement in SSc is almost entirely focused on symptom relief as conventional immunosuppressive treatments do not reduce the likelihood of developing severe GI symptoms [6].

- While lifestyle modifications are often indicated and can be somewhat helpful, the vast majority of patients will need more aggressive treatment options, for example, the use of proton pump inhibitors (PPIs) for GERD, antibiotics for SIBO, prokinetic drugs for gastroparesis, and iron infusions / laser therapy or radiofrequency ablations for GAVE.

Intravenous Immunoglobulin

- A 2016 observational study of fifteen patients diagnosed with SSc myositis overlap syndromes receiving intravenous immunoglobulin (IVIG) showed significant reduction in GERD frequency and intensity as well as significant improvement in GIT 2.0 scores while patients remained on IVIG. [7]
- A 2015 case series also described GI improvements in two patients following introduction of IVIG treatments. [8]
- While IVIG is relatively safe, there is a risk of allergic reactions, and long-term administration of IVIG is often cost prohibitive, as each treatment can cost upwards of $10,000, depending on body weight.

Autologous Hematopoietic Stem Cell Transplantation (HSCT)

- A case series published in 2015 documented clear improvement in Hgb levels in three patients with GAVE following autologous hematopoietic stem cell transplantation (HSCT). [9] The improvements in Hgb levels were sustained at one-year follow-up.
- In a 2018 study of four patients undergoing HSCT, all patients had significant pre-HSCT upper GI symptoms including GERD and dyspepsia. All patients experienced major improvement in upper GI symptoms following HSCT that were retained at the four-year follow-up. [10]
- While HSCT can be an effective treatment for a subset of patients with major organ involvement, this treatment modality has a significant mortality risk and is primarily used to treat patients with rapidly progressing diffuse disease. [11]

Pulsed Plasma Exchange – How Does it Work?

- While TPE is sometimes used long-term for conditions such as myasthenia gravis, recurrent focal segmental glomerulosclerosis, and thrombotic thrombocytopenic purpura, it is more typically used to treat acute issues such as Guillain-Barré syndrome.
- The protocols used for these acute treatments are heavily focused on rapidly removing antibodies or other pathogenic molecules. In these cases, patients often receive several treatments per week or even daily treatments for a few days to weeks. With these acute interventions, the immune system is significantly suppressed, both during

the treatment regimen and for varying periods of time after TPE treatments have stopped.

- In contrast, the PPE protocol used by the four patients in this case series can be considered to be a "light weight" protocol that has minimal effects on overall antibody levels and is not immunosuppressive beyond a very short period of time following each TPE treatment.
- Most SSc-related antibodies are IgG and live in both plasma and the lymphatic system. A single blood volume TPE treatment eliminates approximately 66% of any plasma circulating molecules, including antibodies. But, since only about 45% of all IgG antibodies reside in the intravascular space, two days after a TPE treatment, IgG antibody levels are already back to 70% of pre-TPE levels. [12]
- These results suggest that the primary mechanism of action for PPE is unlikely to be related to temporary auto-antibody reduction.

Abnormal Blood Rheology in SSc

- Over the past 42 years, many published papers have documented that blood rheology in patients with SSc is highly abnormal, including elevated whole blood viscosity (WBV), decreased RBC deformability, and abnormal RBC aggregation/clumping. [13–20]
- It is important to note that abnormal blood rheology is not uncommon in other autoimmune diseases, including rheumatoid arthritis (RA) [21] and systemic lupus erythematosus (SLE) [22]. However, TPE does not improve clinical symptoms in RA [23] or SLE [24], suggesting a likely different mechanism of action in SSc pathogenesis versus RA and SLE pathogenesis.

The Potential Role of RBC Aggregation in SSc Pathogenesis

- In 1979, Kahaleh et al. [25] noted that, “Many, if not all, of the manifestations of scleroderma can be explained on the basis of functional and structural vascular compromise after repeated vascular insults, subsequent healing of vascular walls with proliferative vascular response, and luminal narrowing.”
- Two papers have documented that the RBC aggregates/clumps seen in patients with SSc are highly shear resistant and include non-linear clumps in addition to the Rouleaux formations (Figure 1). [15,17]

Figure 1: RBC Aggregation/Clumping

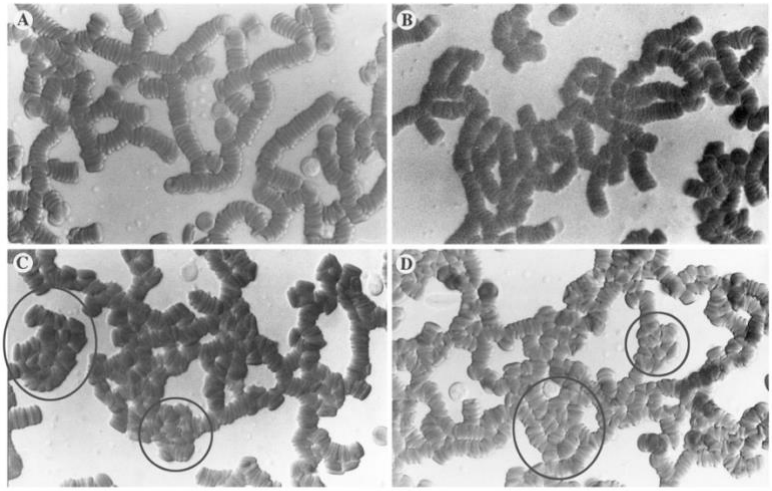
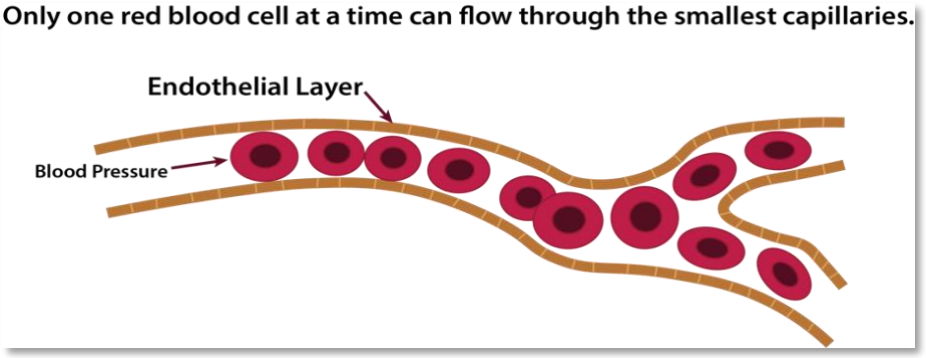
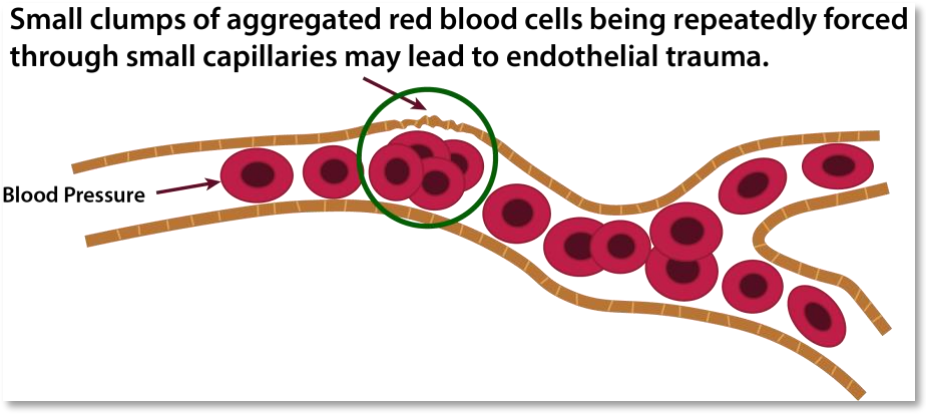


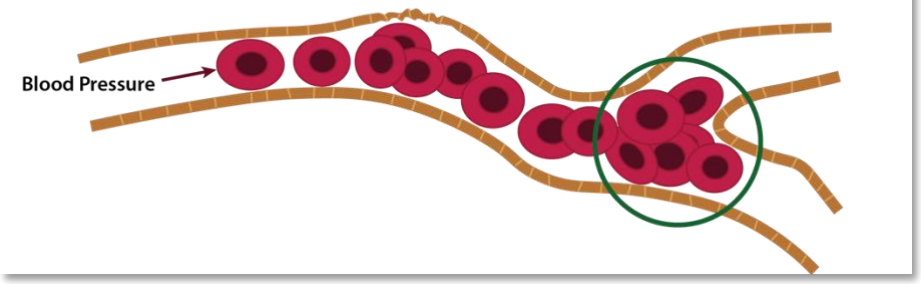
Fig. 6. Photomicrograph of blood at ×640 magnification. *A*: HC *no. 5* at 37%. Linear rouleaux are visible. *B*: SSc *patient 7* at 38%. Same appearance as for *A*. *C*: SSc *patient 6* at 40%. Clusters of compacted red blood cells were observed (*point 1*). *D*: SSc *patient 9* at 45%. Clusterlike aggregates are visible.

Picart, C, P H Carpentier, H Galliard, and J M Piau. 1999. "Blood Yield Stress in Systemic Sclerosis." The American Journal of Physiology 276 (2 Pt 2): H771-7.

- One possible explanation for some of the early endothelial damage seen in SSc is from mechanical effects that remodel vessel walls through local ischemia of abnormally clumped RBCs in the microcirculation (Figure 2). [4]

Figure 2: Hypothesis: Endothelial Damage from Clumped RBCs

Normal Blood Flow	
Endothelial Damage from Clumped RBCs?	

Microcapillary Blockage from Clumped RBCs?	Large clumps of red blood cells may lead to complete capillary blockage, resulting in symptoms such as pain and fatigue, often initial symptoms in diffuse systemic scleroderma. 

TPE and RBC Aggregation

- A series of four weekly TPE treatments essentially normalizes both WBV and RBC aggregation. [26]
- If TPE is then stopped to observe how long it takes for pre-TPE abnormal WBC and RBC aggregation levels to return, it takes between three and nine months for this to occur.
- The eight-week gap between treatment cycles in the current PPE protocol was chosen to keep average RBC aggregation levels significantly reduced from pre-PPE levels, potentially leading to a reduction in average endothelial trauma over time with the goal of reducing downstream fibrosis.

PPE: Safety and Vascular Access

Risks and Side Effects

- Cid *et al*. [27] reviewed the efficacy and safety of TPE in 317 patients and 2730 procedures over an 11-year period. Observed adverse events occurred in only 3% of procedures, and all events were mild and transient.
- Similarly, in a study of more than 20,000 therapeutic apheresis procedures performed in Sweden [28], mild adverse events requiring no intervention occurred 1.5% of the time, moderate events not requiring cessation of treatment occurred 2.8% of the time, and severe events requiring cessation of treatment occurred 0.8% of the time.
- The most severe complications in TPE occur with fresh frozen plasma as the replacement fluid. Albumin (5%) is used in our PPE protocol for this reason unless contraindicated.
- The most common short-term problem with TPE is hypocalcemia, usually presenting as mild paresthesias or perioral tingling from the use of citrate as an anticoagulant. Prophylactic use of oral calcium supplements is usually adequate to prevent or minimize TPE-associated hypocalcemia.

- Some patients may experience mild hypotension, muscle cramps, or mild headaches from hypovolemia especially with lower concentrations of albumin than the recommended 5% solution. This issue is easily dealt with preventively or with saline if needed.
- The one known side effect of long-term TPE is mild iron-deficiency anemia, usually treatable by over the counter iron supplements. [29–31] This occurs because the centrifugal separation process used in TPE can cause hemolysis of older red blood cells, leading to premature cellular death and younger red blood cells on average than before TPE. [29]

Vascular Access

- All four patients were able to handle long-term TPE using peripheral IV access, which is the safest way to perform TPE.
- While the exact percentage of patients who would require alternatives to peripheral IV access for long-term TPE is not clear, the data indicate that most patients can undergo long-term TPE using normal peripheral IV access. [32]
- Central catheters are not a good option for most patients for long-term TPE because of significant infection risk.
- Alternatives such as surgically created fistulas or implantable vascular-access devices (ports), such as PowerFlow™, PowerPorts™ or Vortex™, may be better options for long term use of TPE if peripheral IV access is not an option.

Conclusion

- GI involvement frequently impacts quality of life in patients with SSc. Given that conventional immunosuppressive treatments do not lead to systemic improvements in GI symptoms, it is important to look at safe, potential treatment approaches to address this major complaint in the majority of SSc patients.
- Given that previous research has demonstrated that TPE has an excellent safety profile, these preliminary results suggest that pulsed plasma exchange (PPE) should be considered for lcSSc patients with significant GI symptoms.
- Additional research is needed to better understand the mechanisms of action for this treatment modality and whether they will replicate in SSc patients with different antibodies and clinical profiles.

Table 1: Patient Pre-PPE and Current Clinical Status

Age at start of PPE / Sex / ANA / Antibody	**Chief Complaints pre PPE**	**Pre-PPE SHAQ / GIT Scores**	**PPE Start Date / Nr. Treatments to date**	**Current SHAQ / GIT 2.0 Scores**	**Current clinical status**	**Notes**
43 / M / 1:1280 / centromere[1]	Severe GERD, frequent Raynaud's attacks, major cold intolerance, swollen hands, reduced DLCO (68%)	SHAQ-DI: 0 SHAQ-VAS: 1.80 GIT: 0.59 (post hoc)	Nov 1993 / ~490	SHAQ-DI: 0 SHAQ-VAS: 0 GIT 2.0: 0	Very mild Raynaud's, last DLCO normal (2000) 82%	Two interruptions of protocol (1996: 6 months, 2020: 4 months) led to return of GERD. GERD resolved in one year (1997) and five months (2020) after resuming normal protocol.
64 / F / 1:2560 / centromere	GAVE; chronic anemia (low Hgb); Raynaud's; Sjoegren's ; mild GERD	SHAQ-DI: 0.1 SHAQ-VAS: 0.38 GIT: 0.28	Oct 2019 / 38	SHAQ-DI: 0 SHAQ-VAS: 0.17 GIT: 0.06	Hgb normal; Raynaud's, Sjoegren's, GERD unchanged	No ablations or iron infusions required since starting PPE; patient has hiatal hernia
55 / F / 1:640 / centromere	Gastroparesis; severe Raynaud's; SIBO; calcinosis; swollen fingers; GERD; fatigue; pain, chronic cold intolerance	SHAQ-DI: 0.3 SHAQ-VAS: 2.11 GIT: 1.42	Mar 2020 / 36	SHAQ-DI: 0 SHAQ-VAS: 0 GIT: 0	GERD and gastroparesis significantly improved; fatigue, pain, and chronic cold intolerance subsided; Raynaud's significantly improved	No longer requires high calorie/protein supplements to maintain weight
63 / F / >1:1280 centromere pattern	Poor motility; dysphagia; severe esophageal spasms; SIBO; mild GERD; mild Raynaud's; chronic chilling; telangiectasias; muscle/joint pain; fatigue; finger curvature; unable to sleep at high altitudes without oxygen	SHAQ-DI: 0.3 SHAQ-VAS: 0.75 GIT: 0.85 (post hoc)	Nov 2020 / 24	SHAQ-DI: 0.3 SHAQ-VAS: 0.18 GIT: 0.23	Major reduction in esophageal spasms; significant improvement in muscle/joint pain; reduced telangiectasias; reduced finger curvature; reduced fatigue; GERD in remission; improved sleep in high altitudes; Raynaud's unchanged	No longer has anxiety associated with eating (This was due to severe esophageal spasms/difficulty swallowing pre PPE.)

[1] Harris E, Meiselman H, Moriarty P, Weiss J. Successful long-term (22 Year) treatment of limited scleroderma using therapeutic plasma exchange: Is blood rheology the key? Clin Hemorheol Microcirc. 2017;65:131–6.

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