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Re-thinking Strategies for a Pharmaceutical Approach to Pain-related to Connective Tissue Related Raynaud's Phenomenon in the United States

Running title: Rethinking Raynaud's in the United States

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Abstract:

Introduction: There are no Food and Drug Administration (FDA) approved therapies for Raynaud's phenomenon (RP) treatment in the United States (U.S.). Clinical trials have been challenged by study design. Important advances in RP patient reported outcome measures and mechanistic quantification allows RP-related pain characterization. The rationale for this narrative review is current RP treatment guidelines that focus on vasodilation.

Methods: The question of why there are limitations to RP treatment in the US is addressed through a comprehensive search strategy of published RP-treatment guidelines up until September 1, 2025. Search databases included Medline (PubMed), Embase, and Scopus for index terms, "Raynaud's phenomenon treatment guidelines". If a society guideline was updated, only the most recent was included. Eligibility, data extraction, risk of bias and quality assessment were subject to review by two independent reviewers with a third reviewer resolving discrepancies. US specific considerations of published guidelines are reviewed.

Results: There were 118 published articles that were identified by the search terms 'Raynaud's phenomenon treatment guidelines,' and 27 abstracts were reviewed. There were 4 articles that were published as RP treatment recommendations or guidelines, which were reviewed for full content. Pain management for RP is not included in guideline-based care.

Conclusion: There are advances in outcome measures for quantifying pain now available for RP clinical trials. Large U.S. based registries for systemic sclerosis (SSc) utilizing patient reported outcomes can allow serial data collection on RP and RP-related digital lesions to provide real-world data on medication efficacy for pain relief.

Significance and Innovation:

Recent significant advances in the development of patient reported outcomes which are grounded in the patient experience allow proper quantification of RP in systemic sclerosis (SSc) that can allow for understanding longitudinal patterns of pain and pain transitions related to RP. The use of vasodilators for pain management in the U.S. are significantly impacted by access for off-label use of non-Food and Drug Administration (FDA) approved therapies for this indication. There are innovative new assessment tools, such as automated interpretation of capillaroscopy reports and remote training, that may assist in improved diagnosis. In this review article, new mechanistic insights for pain management with vasodilator treatment for RP is discussed.

Introduction

Raynaud's phenomenon (RP) is a common painful neuro-sensory symptom related to digital (finger and toes) vasospasm in response to cold temperature and emotional stress, which has a prevalence of approximately 8% in the United States (US) [1]. RP is a symptom complex related to digital vascular compromise, which always includes blanching triggered by cold exposure but is associated with various conditions with different outcomes [2]. Primary RP, while symptomatically bothersome, is not associated with vascular damage or auto-antibodies [3]. Whereas, secondary RP related to a connective tissue disease (CTD), exhibits abnormal nailfold microscopy and in its severe form, most commonly systemic sclerosis (SSc)-related, results in vasculopathy-driven digital lesions. RP is often the earliest symptom of autoimmune disease, which is diagnosed by performing a physical exam of the hand, specifically assessing

digital pitting, ulceration, telangiectasias and performing nailfold capillaroscopy, in the context of evaluating a patient with this complaint. History and physical exams can be helpful in distinguishing painful mimics of RP. Ancillary studies, such as hand radiographs can identify severe autoimmune disease features such as digital tip resorption (acro-osteolysis) and calcinosis, which are thought to be tissue response to sustained or prolonged hypoxia and possibly prevented with vasodilator therapy [4]. If the physical exam or ancillary studies are consistent with RP and abnormal, laboratory testing can identify connective tissue disease (CTD) autoantibodies. In fact, a patient with RP, digital lesions (pits and/or ulcers), abnormal capillaroscopy, and a systemic sclerosis (SSc) autoantibody meets classification criteria for this CTD, which has among the highest morbidity and mortality of all rheumatic diseases [5]. Thus, it is critically important to standardize the screening and treatment of RP patients, specifically if treatments are preventative [6]. Ethnic, cultural, and clinical phenotypic factors appear to contribute to geographic variation in RP symptom burden in SSc, highlighting the value of regional studies [7]. This narrative review addresses the challenges of treatment and opportunities for understanding longitudinal patterns of pain and pain transitions related to RP in the United States (US). The rationale for this review is that the pain component of RP is not included in current treatment guidelines that focus on vasodilation and advances in outcome measures can inform a 'state-of-the-art' approach to studying this symptom.

Methods:

A comprehensive search strategy of published RP-treatment guidelines up until September 1, 2025, was performed. Search databases included Medline (PubMed), Embase, and Scopus for index terms, "Raynaud's phenomenon treatment guidelines" OR (Raynauds AND phenomenon AND treat/exp OR treatment) AND (guidelines/exp OR guidelines). Articles that were diagnostic guidelines, treatment systematic reviews or meta-analyses of randomized trials, poster presentations, and non-English guidelines were excluded. If a society guideline was updated, only the most recent was included. Eligibility, data extraction, and quality assessment were subject to review by two independent reviewers (TF, CF) with a third reviewer resolving discrepancies (JB).

Results:

As shown in Figure 1, there were 118 published articles that were identified by the search terms 'Raynaud's phenomenon treatment guidelines,' and 27 abstracts were reviewed. One potentially eligible abstract from the Chinese Rheumatology Association was excluded as non-English[8], others were diagnostic (not treatment) recommendations, or a poster. There were 4 articles that were published as RP treatment recommendations or guidelines. These articles included European Union League Against Rheumatism (EULAR) 2023 recommendations for the treatment of systemic sclerosis (SSc) [9], the European Society for Vascular medicine (ESVM) 2017 recommendations for the diagnosis and management of RP[2], 2018 Treatment Algorithms by Consensus of SSc Experts [10], and the British Society for Rheumatology /British Health Professionals in Rheumatology (BSR/BHPR) 2016 guideline for treatment of SSc [11] were included (Figure 2). Pain management for RP is not included in any of the guideline-based recommendations. Intravenous prostanoid therapy for RP is in all published guidelines but are cost-prohibitive in the US for routine use.

What is already known about this subject?

There are guidelines for the treatment of RP [2,9-11], which are designed to escalate therapies for severity. The guidelines focus on connective tissue disease -related RP and include use of prostanoid, which is not covered by insurance companies in the US, thus cost-prohibitive. While patient education and lifestyle adaptations are first-line guideline-based treatment for RP, access for the wide range of pharmacological options outlined in international guideline-based care for RP can be difficult in the US because there are no Food and Drug Administration (FDA) approved drugs for this indication. While treatment for RP aims to minimize the occurrence of painful episodes and prevent hand-related disability, the medication management in guidelines focuses on vasodilators. It is also noted that some medications are associated with exacerbation of RP, thus should be stopped if digital symptoms worsen [12,13]. These medications can include stimulants taken for attention deficit disorder, certain migraine medications, and beta-blockers. A medication review is a critical aspect of clinical trial exclusion criteria for RP.

The FDA requires pharmaceutical intervention to achieve significance in impacting feel, function, or survival for approval. The regulatory authorities in the United Kingdom (Medicines and Healthcare products Regulatory Agency), European Union (European Medicines Agency), and Japan (Pharmaceuticals and Medical Devices Agency) have approved the use of calcium channel blockers (CCB), phosphodiesterase inhibitors (PDE5-I), endothelial receptor antagonists (ERA), and prostacyclin analogs (PCA) for the treatment of RP- related to SSc. Since 1980, there have been several clinical trials tested for RP and its severe manifestation of digital ulceration (DU). Key aspects of this timeline include the importance of a clinical trial length that is specific to cold weather months to capture drug effect, global representation of study subjects but regional sub analysis to capture environmental effects, stratification of RP severity, including failed prior therapies and disease duration of SSc. A critical component of outcome measures that are used in clinical trials is the ability to quantify disease activity versus prevention or occurrence of irreversible damage.

Nailfold capillaroscopy is used diagnostically to determine if RP is related to CTD. The importance of this diagnostic test highlights that RP secondary to CTD can result in tissue damage, such as DU. Abnormal capillaroscopy in the setting of SSc-specific antibodies has a high probability of the patient meeting classification criteria in the upcoming five years. Thus, this screening procedure is critical for rheumatologists to perform. However, there are no formal US-based training programs. Historically, this is because capillaroscopy is not a billable procedure to insurance companies and the gold standard equipment to perform capillaroscopy was expensive and time consuming to use in clinical practice. Advances in low-cost image acquisition with automated interpretation as well as online training programs have made this critical diagnostic tool feasible. Nailfold capillaroscopy also may be helpful for RP clinical trial enrichment, as capillary density dropout is strongly associated with DU, which is a painful end-stage manifestation. The correlation of other nailfold abnormalities, such as the presence of microhemorrhage and abnormal size and shape of the vessels, with pain is less clear. Nonetheless, with the reduction of costs of devices that capture nailfold images, the goal of online training offered by the European League Against Rheumatism (EULAR) Microcirculation group, and decentralized capillaroscopy interpretation offered by cloud-based systems[14,15], US based rheumatologists will be able to use nailfold capillaroscopy reliably. The lack of NVC as a diagnostic and prognostic tool in clinical practice has potentially impeded US-based RP studies.

What does this study add?

There are advances in outcome measures that capture pain, which can be used in RP clinical trials. The concept of how a therapeutic intervention impacts how a patient feels is a critical aspect of FDA regulatory approval and underscores the importance of understanding RP-related pain. Attack rates, severity scores, participant-preference scores and physiological measurements have underperformed in randomized control trials (RCT) [16,17]. Furthermore, the presence of pain related to RP may impact a patient's willingness to take therapeutics or enroll in a clinical trial with this symptom or a resultant DU as the primary outcome adding selection bias to possible RCT design. As such, easy to use instruments to measure RP must be sensitive to change, reliable, valid, and grounded in the patient experience [18]. The lack of patient involvement in the conceptual framework, domain generation, item generation, cognitive interviewing, and respondent burden has been the main criticism of the Raynaud's Condition Score (RCS), which is the most widely used instrument in clinical trials studying moderate to severe RP [19]. The Raynaud's condition score (RCS) uses a 0–10 Likert scale for patients document in a daily diary their assessment of the combination of severity, frequency, duration, and impact of their RP for that day [20]. The reporting value is the mean of two weeks of daily ratings, thus as a composite assessment the RCS does not adequately capture the potential shorter-term impact of drug effect on symptoms, which has critical importance of assessment of "feel" for FDA drug approval [21,22]. When the RCS diary threshold was applied to SSc patients in a real-world population, it failed to meet all three criteria of how a patient feels, functions, and affects their quality of life, highlighting the inability to use this outcome measure to enrich RP clinical trials for regulatory approval [23,24]. An additional concern is that RP outcome measures that incorporate a patient-perceived functional status can be impacted by coping strategies independent of prescribed therapeutics, which highlights that a focus on measures that capture impact on pain is a critical aspect of RP severity assessments [25,26]. Furthermore, RP clinical management and RP intervention trial designs should consider temperature patterns [27].

RP outcome measures that capture how patients feel, and function might prove superior to diary-based approaches for assessing condition severity. An international multicenter study validation study of the 27-item Assessment of Systemic Sclerosis-Associated Raynaud's Phenomenon (ASRAP) and 10-item short-form (ASRAP-SF) questionnaires are valid and reliable novel patient-reported outcome measure for assessing the severity and impact of SSc-RP [28,29]. ASRAP questionnaires had good correlation with instruments for assessing disability, hand function, global health assessment, but perhaps most importantly, if used for general RP assessments, intensity of pain. The benefit of this instrument is that it was developed with SSc patient partners. Its use in other CTD-related RP or primary RP is not proven. As such, pain numerical rating scales (NRS) or diaries may provide better measurement if used in all RP subsets regardless of etiology.

While patient reports can capture RP symptom characteristics, objective assessment of digital microvascular function and morphology are helpful for understanding potential mechanisms of disease. Measurement of the temperature of the digits and thermal gradient (temperature of digits minus temperature of dorsum of the hand) may help discern treatment effect in RP [30]. In conjunction with nailfold capillaroscopy, point-of-care thermographic imaging is a non-invasive, quantitative tool for assessing peripheral vasculopathy [31]. Functional microcirculatory changes are evident in both primary RP as well as RP-related to CTD, thus an important aspect of assessment, however, it is noted that pain and paresthesia is more common in RP related to CTD [32,33]. This distinction of painful blanching of the skin guiding prescribed therapies is important contextually for understanding guideline-based care for RP treatment [2,9,34].

How might this impact clinical practice or future developments?

Including pain-related mechanisms for RP allows expansion of studies on the mechanism of action of therapies prescribed for RP. RP is considered a disorder of vascular thermoregulatory control. In non-CTD related RP, where nailfold capillaroscopy is normal, vasospasm of the digital and cutaneous vessels is believed to occur because of an increased alpha2c-adrenergic response located on vascular prejunctional terminals and smooth muscle, and does not result in vascular pathology [35]. As such, a drug targeting vascular thermoregulatory control mechanisms is important for RP symptomatic modification. In CTD-related RP, where vascular structural and functional changes combination therapies may be needed.

Pre-clinical models of CTD-related RP and SSc delineate the relative contributions of specific ligands, receptors, their signaling pathways and feedback mechanisms and have been challenged by lack of fidelity for features of vasculopathy, fibrosis, and autoimmunity. Skin biopsies support the importance of abnormal endothelium and microvascular pericytes in CTD-related RP, which are not present in primary RP. Unbiased spatial proteomics with single-cell resolution in skin biopsy tissues further support the role of the endothelial cell in patients with SSc that expresses markers for endothelial-to-mesenchymal transition and is located in close proximity to immune cells and myofibroblasts [36]. Specifically, pericytes are a perivascular mesenchymal stem cell with macrophage-like properties embedded within the endothelial basement membrane and are found primarily around blood capillaries, precapillary arterioles, postcapillary venules, and collecting venules to facilitate and assimilate cell communication. The contribution of pericytes to the total alpha 2-adrenoceptor number of the micro-vessels are proposed in animal models to be substantial [37]. The potential of vascular therapeutic targets that can target the pericyte is intriguing. It is critically important to understand the role of immune-mediated vascular dysregulation in CTD-related RP pain.

Therapeutics for RP can target the vascular lumen, barrier function, smooth muscle, or surrounding connective tissue (Figure 2). The wall to lumen ratio of the radial artery in primary RP and SSc-related RP is reduced and functionally impaired [38,39]. Treatment with an essential co-factor for endothelial nitric oxide (NO) can improve endothelial function in SSc [40,41], however accumulating evidence supports that the interplay between carbon monoxide (CO), generated by heme oxygenase (HO) and NO plays a crucial role in vascular homeostasis and regeneration by improving endothelial cell communication with neighboring cells, including smooth muscle cells, immune cells, pericytes [42]. Nifedipine, first-line therapy and one of the most widely used pure L-type calcium channel blockers (CCB) for treatment of patients with RP is hypothesized to reduce osteoblastic differentiation of pericytes, thus reducing vascular calcification that may be important for calcinosis. Of note, cilnidipine is a newer fourth-generation calcium channel blocker (CCB) with both L-type and N-type Ca2+channel blockade that has renoprotective, cardioprotective and neuroprotective effects through direct effect on sympathetic nerve endings [43]. Cilnidipine has potentially clinically relevant activity at Nav1.7, a target in pain treatment, and is effective as a combination therapy with a phosphodiesterase 5 inhibitors (PDE5i) [44]. Cilnidipine is currently under investigation for SSc-RP efficacy, safety, and SSc-RP related pain.

In severe RP or failing first-line CCB treatment, prescription of a PDE5i, which protects cyclic guanosine monophosphate (cGMP) from degradation mediating vascular smooth muscle relaxation through nitric oxide signaling is considered second-line therapy for RP [45]. Of interest the mechanism of action of pentoxifylline, which can be consider in RP, may be related to phosphodiesterase inhibition in addition to platelet sensitivity to the anti-aggregatory action of

endogenous prostaglandin I2 (PGI2), which is an unstable cyclooxygenase metabolite detected first in vascular endothelial cell , an is associated with the amelioration of pericytes reduction and the transition to myofibroblasts [46]. While PDE4i has not been specifically studied in RP, the PDE4 subfamily (PDE4A, PDE4B, PDE4C, and PDE4D) selectively degrades cAMP and plays a vital role in regulating the balance of second messengers in various tissues [47]. PDE4 is the major subtype of PDE enzyme expressed in immune and inflammatory cells and is under investigation in SSc interstitial lung disease for the potential effect of reversibility of vascular-mediated fibrosis [48].

Prostacyclin analogs, most commonly intravenous (IV) iloprost, are reserved for severe RP, usually after failing CCB and PDE5-I treatments, but have cost-prohibitive prescription restrictions in the US, when used for the primary indication of RP [45]. Fluoxetine, a serotonin reuptake uptake inhibitor, is a cost-effective alternative treatment for mild RP when side effects limit vasodilators. Experimental data suggest that serotonin drives fibrosis in the skin and visceral organs, promotes platelet aggregation, induces vasoconstriction and increases pulmonary vascular resistance thus remains an interesting therapeutic target for CTD-related RP [49,50]. Local therapies such as injected digital Botox injections may prevent the oxidant-induced intracellular accumulation of reactive oxygen species (ROS) in vascular endothelial cells and is considered an important management strategy [51,52]. The identification of neuropathic pain may benefit from adjuvants such as gabapentinoids and antidepressants, with temporary use of opioids sometimes required in severe cases with digital ischemia [53].

Opportunities for clinical trials for RP

It is critical to study primary and CTD-related Raynaud's concurrently to clarify medication effectiveness, but it is important to stratify patients based on capillaroscopy, disease severity and duration. The FDA defines a basket trial as a master protocol study designed to test a single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics. This design allows a strong response signal seen in a sub-study (i.e., SSc-RP) to allow for expansion to generate further data to support regulatory approval [54]. The use of platform clinical trial design may be possible in unique populations, such as the Veterans Hospital Administration (VHA). Our previous study data from the Veterans Health Administration (VHA) suggests that CCB medications are potentially being under-utilized for RP and systemic sclerosis (SSc) treatment [55]. Furthermore, well-defined disease populations, such those in the Collaborative National Quality and Efficacy Registry (CONQUER) for SSc allow integration of disease duration into outcome assessments, such as pain related to RP and DU [56].

Conclusions

Treatment of pain related to RP is a challenge for healthcare providers in the US due to diagnostic and training limitations and therapeutic access to guideline-based vasodilator medications, such as cost-prohibitive prostanoids. The use of capillaroscopy can allow the identification of CTD patients that require medication therapy. Advances in outcome measures, such as the ASRAP, will allow improved clinical trial design for RP that can meet FDA rigor for significant impact on feel and function. Preclinical models and secondary outcomes, which focus on pericyte biology and mechanism of fibrotic reversal offer hope to SSc patients with painful DU. Clinical trial design should include both primary and CTD-related RP to clarify therapeutic

effect and the mechanism of painful skin blanching to best understand patterns of pain-related to RP in the US.

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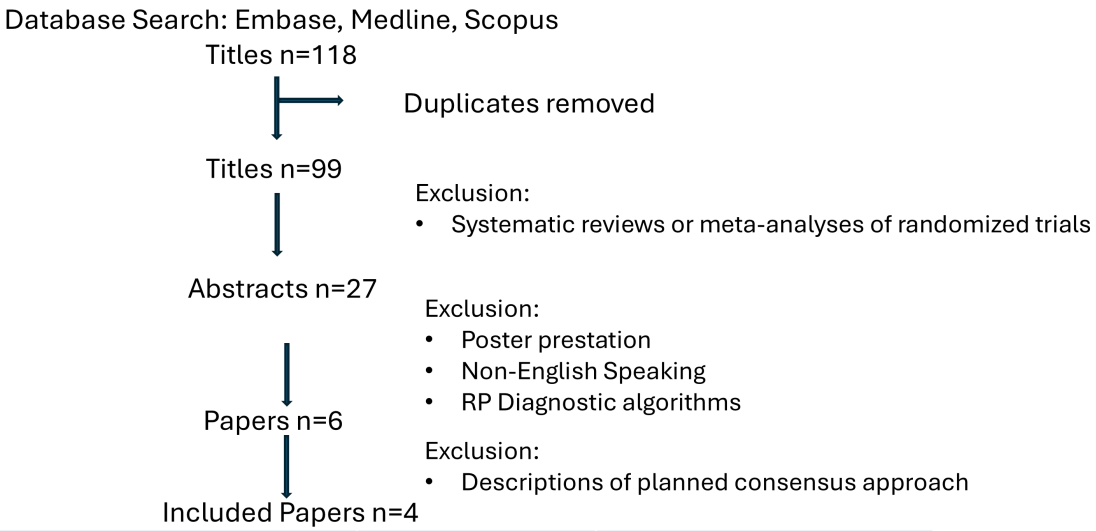
Figure 1: Narrative Review of Published Treatment Guidelines for RP

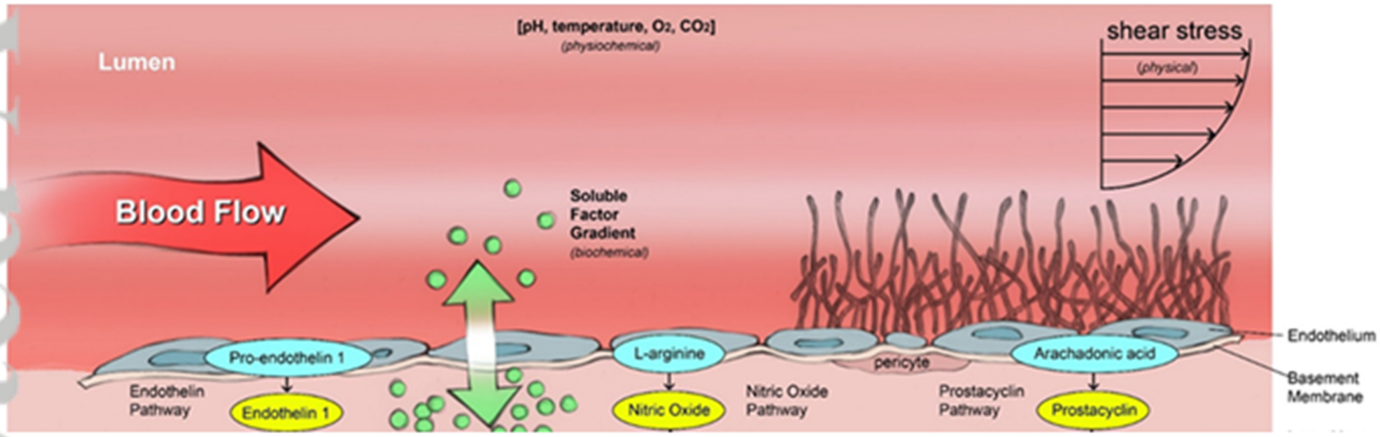
Figure 2: Mechanism of Action Should Address the Role of Barrier Function of Vascular Endothelium with Connective Tissue



EULAR	SSc Expert Consensus	ESVM	BSR/BHRP
CCB	CCB	CCB	CCB
Prostanoid	PDE5I	ARB	ARB
PDE5I	ARB	SSRI	SSRI, alpha blockers, ACE inhibitors, and statins
SSRI	Prostanoid	Prostanoid	Prostanoid

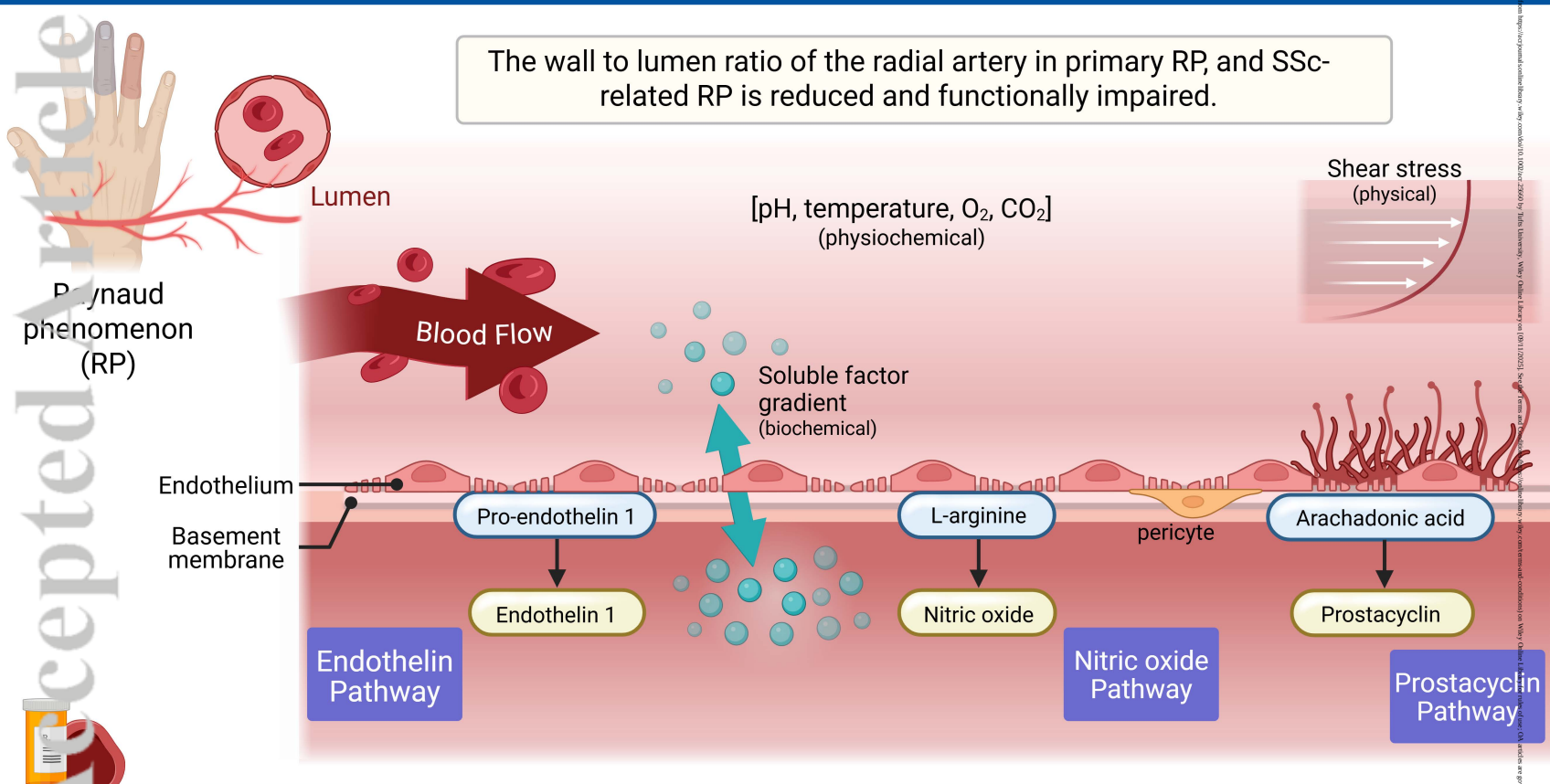
CCB: Calcium channel blocker, PDE5I: phosphodiesterase-5 inhibitor, SSRI: serotonin reuptake inhibitor, ARB: angiotensin receptor blocker; ACE: acetylcholine esterase

FINAL Figure 1.TIF



RP FINAL Figure 2.TIF

Re-thinking Strategies for a Pharmaceutical Approach to Pain-related to Connective Tissue Related Raynaud Phenomenon in the United States



Mechanism of action of pharmaceutical intervention for RP should address the role of barrier function of vascular endothelium with connective tissue.

Frech TM, Frech CG, Merryman WD, et al. Re-thinking strategies for a pharmaceutical approach to pain-related to connective tissue related Raynaud phenomenon in the United States. Arthritis Care Res (Hoboken) 2025.

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