# Phosphodiesterase-5 inhibitors, but not calcium channel blockers, improve peripheral vascular function in systemic sclerosis

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## Abstract

### Objective

*Systemic sclerosis (SSc) is a rare autoimmune disease associated with vasculopathy. Raynaud's phenomenon is a common symptom of SSc, and treatment guidelines support calcium channel blocker (CCB) and phosphodiesterase inhibitor-5 (PDE5i) as first- and second-line therapy, respectively. However, the impact of these drug classes on peripheral vascular function or haemodynamic outcomes in SSc is unknown.*

### Methods

*Flow-mediated dilation (FMD) was measured in patients with SSc (n=119) that were allocated into groups based on cardiovascular-acting medications usage within the previous 24 hours.*

### Results

*Clinical cardiovascular outcomes were unaffected by acute cardiovascular-acting medications, with the exception of PDE5i that resulted in lower diastolic blood pressure (CV Meds+PDE5i: 66±11 vs. No CV Meds: 74±8; CV Meds: 72±8; CV Meds+CCB: 73±7 mmHg, $p<0.05$). Patients on CCB had similar FMD to patients with and without cardiovascular-acting medication usage (No CV Meds: 7.6±4.0; CV Meds: 6.2±3.4: CV Meds+CCB: 5.8±3.1%, $p>0.05$), while FMD in patients on PDE5i (CV Meds+PDE5i: 8.9±4.4%) was greater than patients with cardiovascular-acting medication usage regardless of the presence or absence of CCB usage ($p<0.05$). A subset of patients (n=17) completed multiple testing visits with and without CCB usage in the previous 24 hours, CCB usage did not affect FMD (no CCB: 6.7±3.4 vs. CCB: 7.7±6.6, $p>0.05$).*

### Conclusion

*Acute CCB usage does not affect peripheral vascular function or haemodynamic outcomes in patients with SSc, whereas acute PDE5i usage results in lower diastolic blood pressure and greater FMD. These findings suggest that PDE5i improves vascular function in SSc, while CCB usage does not.*

**Key words**

endothelium, vascular function, flow-mediated dilation, scleroderma, Raynaud's phenomenon

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## Introduction

Systemic sclerosis (Scleroderma; SSc) is a rare autoimmune disease that results in debilitating fibrosis of the skin and internal organs with a median survival of ~11 years post diagnosis (1, 2). Although there is heterogeneity with organ involvement, vascular dysfunction is present in nearly all patients (3, 5). Indeed, a meta-analysis has reported that endothelium-dependent vasodilation, as determined by flow-mediated dilation (FMD), is impaired in patients with SSc (6). We have identified impaired FMD in patients with SSc as well (7-9), and have shown that acute tetrahydrobiopterin ($BH_4$) administration, an endothelium-targeted drug, augments brachial artery FMD in this population (10).

In patients with SSc, Raynaud's phenomenon (RP) is the most common symptom, and vasospasm is a critical component of SSc pathogenesis. RP is associated with increased cardiovascular-related death (11). While certain cardiovascular-acting medications, such as ACE inhibitors may alleviate symptoms of RP, these medications are contraindicated in SSc due to the potential to mask scleroderma renal crisis (12). Thus, with a recent focus on the discipline of cardio-rheumatology, there is a substantial interest in better understanding the treatment and mechanism of vasospasm in SSc (2, 13-15). Current guidelines for treatment of RP support calcium channel blocker (CCB) usage as first-line therapy in patients with SSc (2, 16-19). In severe RP or in patients failing first-line CCB treatment, prescription of a phosphodiesterase inhibitor-5 (PDE5i) is second-line therapy (20). We have previously reported that 75-92% of patients with SSc in our previous studies are actively prescribed CCBs, while upward of ~28% of patients with SSc are actively prescribed PDE5i (7, 9, 10, 21, 22). However, the impact of these drug classes on peripheral vascular function or haemodynamic outcomes in patients with SSc is unknown. Thus, we sought to determine the effects of cardiovascular-acting medication usage within the previous 24 hours on peripheral vascular function or haemodynamic outcomes, as determined by FMD, in a large cohort of patients with SSc that were allocated into groups based on cardiovascular-acting medications usage within the previous 24 hours.

## Methods

### *Patients*

119 patients with SSc were recruited from the University of Utah SSc Clinic. Patients were previously diagnosed with SSc by the 2013 classification criteria (23). All procedures were approved by the Institutional Review Board of the University of Utah and Salt Lake City VAMC (IRB# 00077934), which serves as the ethics committee, and were performed at the University of Utah SSc from April 2016 to August 2019. Written informed consent was obtained prior to participation after an explanation of the nature, benefits, and risks of the study.

### *Patient characteristics*

Body mass index (BMI) was measured from height and body mass. Clinical features of patients with SSc were recorded for blood pressure, disease duration, antinuclear antibody, SSc-specific antibody status, and cardiovascular-acting medications. Patients were included in this cross-sectional study after reviewing their cardiovascular and immunosuppressive medications used in the previous 24 hours and dividing them into one of four groups: 1) no cardiovascular-acting medications (No CV Meds), 2) cardiovascular-acting medications excluding CCBs and PDE5is (CV Meds), 3) cardiovascular-acting medications including CCBs (CV Meds+CCB), and 4) cardiovascular-acting medications including PDE5is (CV Meds+PDE5i). We identified 20 patients who had vascular testing performed under conditions in which they had or had not used a CCB within the previous 24 hours. 3 of these patients did not have consistent acute PDE5i usage between visits and were excluded. The remaining 17 patients were included in a quasi-interventional retrospective study to determine the effects of acute CCB usage on vascular function and haemodynamics.

*Peripheral vascular function and haemodynamics*

Endothelium-dependent dilation was assessed non-invasively with the FMD technique using a 5-min suprasystolic occlusion period, as described previously (7, 10, 24) and in accordance with published guidelines (25). Briefly, a blood pressure cuff was placed on the right arm, distal to the ultrasound Doppler probe on the brachial artery. Simultaneous measurements of brachial artery vessel diameter and blood velocity were performed using a linear array transducer operating in duplex mode, with imaging frequency of 14 MHz and Doppler frequency of 5 MHz (Logic 7, GE Medical Systems, Milwaukee, WI). All measurements were obtained with the probe appropriately positioned to maintain an insonation angle of ≤60°. The sample volume was maximised according to vessel size and was centred within the vessel on the basis of real-time ultrasound visualisation. The brachial artery was insonated approximately midway between the antecubital and axillary regions, and measurements of diameter and blood velocity were obtained continuously at baseline and for 2 minutes after cuff deflation. End-diastolic, ECG R-wave-gated images were collected via video output from the Logic 7 for off-line analysis of brachial artery vasodilation using automated edge-detection software (Medical Imaging Application, Coralville, IA). Heart rate was monitored from a standard 3-lead ECG. FMD was quantified as the maximal change in brachial artery diameter after cuff release. FMD is expressed as a percent increase in diameter from baseline. Shear rate was calculated according to the equation: shear rate ($s^{-1}$) = blood velocity · 8/vessel diameter. Forearm blood flow was calculated as per the equation: forearm blood flow (ml/min) = (blood velocity · π · [vessel diameter/2]$^2$ · 60). Forearm vascular conductance was calculated as per the equation: forearm vascular conductance (AU) = forearm blood flow/mean arterial blood pressure. Forearm vascular resistance was calculated as per the equation: forearm vascular resistance (AU) = mean arterial blood pressure / forearm blood flow. Peak reactive hyperaemia was identified as the highest post-occlusion blood flow.

**Table I.** Patient characteristics.

| | No CV Meds | CV Meds | CV Meds+CCB | CV Meds+PDE5i |
|---|---|---|---|---|
| Sample size, n (m/f) | 33 (5/28) | 35 (2/33) | 35 (6/29) | 16 (2/14) |
| Age, yr | 50.8 ±11.3 | 60.7 ±9.8* | 53.8 ± 14.2† | 62.6 ± 10.5*‡ |
| Height, cm | 168 ±7 | 164 ±9 | 166 ± 7 | 165 ± 8 |
| Body mass, kg | 74.2 ±22.4 | 73.9 ±16.1 | 72.7 ± 15.1 | 80.7 ± 16.9 |
| BMI, kg/m$^2$ | 26.1 ±6.7 | 27.5 ±5.4 | 26.6 ± 4.9 | 29.6 ± 5.6 |
| Systolic blood pressure, mmHg | 113 ±12 | 118 ±18 | 117 ± 13 | 116 ± 16 |
| Diastolic blood pressure, mmHg | 74 ±8 | 72 ±8 | 73 ± 7 | 66 ± 11*†‡ |
| Mean arterial pressure, mmHg | 87 ±8 | 88 ±10 | 88 ± 8 | 83 ± 11 |
| Heart rate, bpm | 78 ±14 | 75 ±12 | 78 ± 13 | 81 ± 14 |
| RP duration, yr | 13.2 ±11.3 | 12.6 ±11.1 | 11.4 ± 10.4 | 19.2 ± 14.8‡ |
| SSc disease duration, yr | 9.2 ±8.8 | 9.9 ±9.3 | 8.6 ± 6.3 | 14.2 ± 11.1‡ |
| Immunosuppression, n (%) | 6 (18%) | 13 (37%) | 15 (43%) | 8 (50%) |
| *Antibody presence* | | | | |
| ANA positive, n (%) | 27 (82%) | 27 (77%) | 29 (83%) | 13 (81%) |
| Centromere, n (%) | 12 (36%) | 13 (37%) | 14 (40%) | 7 (44%) |
| Sm, n (%) | 0 (0%) | 0 (0%) | 1 (3%) | 0 (0%) |
| RNP, n (%) | 2 (6%) | 2 (6%) | 3 (9%) | 1 (6%) |
| Ssa/Ro60, n (%) | 0 (0%) | 3 (9%) | 1 (3%) | 0 (0%) |
| SSb/LA, n (%) | 0 (0%) | 0 (0%) | 1 (3%) | 0 (0%) |
| Topol, n (%) | 1 (3%) | 3 (9%) | 3 (9%) | 3 (19%) |
| Ro-52, n (%) | 1 (3%) | 1 (3%) | 1 (3%) | 0 (0%) |
| RNA POL III, n (%) | 5 (15%) | 7 (20%) | 4 (11%) | 2 (13%) |
| PMSCL, n (%) | 0 (0%) | 4 (11%) | 2 (6%) | 1 (6%) |
| Fibrillarin, n (%) | 1 (3%) | 3 (9%) | 0 (0%) | 1 (6%) |
| Th/To, n (%) | 1 (3%) | 0 (0%) | 1 (3%) | 0 (0%) |
| Multiple, n (%) | 4 (12%) | 7 (20%) | 3 (9%) | 2 (13%) |
| *Cardiovascular-acting medications* | | | | |
| CCB, n (%) | 0 (0%) | 0 (0%) | 35 (100%) | 3 (19%) |
| PDE5i, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | 16 (100%) |
| ACE Inhibitor, n (%) | 0 (0%) | 10 (29%) | 3 (9%) | 2 (13%) |
| Alpha receptor blocker, n (%) | 0 (0%) | 3 (9%) | 4 (11%) | 2 (13%) |
| Beta-blocker, n (%) | 0 (0%) | 3 (9%) | 4 (11%) | 0 (0%) |
| Diuretic, n (%) | 0 (0%) | 4 (11%) | 7 (20%) | 8 (50%) |
| Endothelin receptor antagonist, n (%) | 0 (0%) | 1 (3%) | 1 (3%) | 8 (50%) |
| Statin, n (%) | 0 (0%) | 6 (17%) | 7 (20%) | 4 (25%) |

Values are means ± SD. Data were analysed using one-way ANOVA.
*$p$<0.05 *vs*. No CV Meds; †$p$<0.05 *vs*. CV Meds; ‡$p$<0.05 *vs*. CV Meds+CCB.
ANA: anti-nuclear antibody; BMI: body mass index; CCB: calcium channel blocker; CV Meds: cardiovascular-acting medications; PDE5i: phosphodiesterase type-5 inhibitor; RP: Raynaud's phenomenon; SSc: systemic sclerosis.

*Statistical analysis*

In the cross-sectional study, one-way ANOVA and ANCOVA (covariates: age; diastolic blood pressure) were used to compare differences between groups, and a least significant difference unpaired t-test identified values that were significantly different. In the quasi-interventional retrospective study, a paired t-test identified values that were significantly different. Statistical significance was set at $p$<0.05 for all analyses. Data are presented as means ± SD.

## Results

*Cross-sectional study*

*- Patient characteristics*

Patient characteristics for the cross-sectional study are presented in Table I. Patients in the No CV Meds and CV Meds+CCB groups were younger than the CV Meds and CV Meds+PDE5i groups ($p$<0.05). Height, weight, and BMI were similar between groups ($p$>0.05). RP and SSc disease duration were also greater in CV Meds+PDE5i *vs*. CV Meds+CCB ($p$<0.05). Antibody presence and cardiovascular-acting medication usage within the previous 24 hours are also presented in Table I. Systolic blood pressure was similar between groups ($p$>0.05). Diastolic

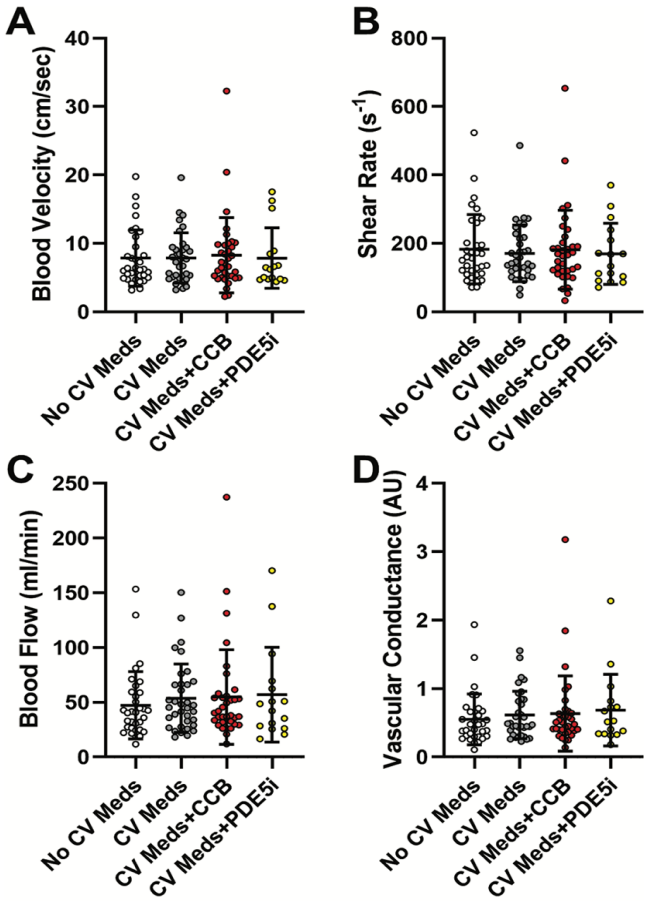


**Fig. 1.** Comparison of brachial artery blood velocity (**A**), shear rate (**B**), blood flow (**C**), and vascular conductance (**D**) in patients with systemic sclerosis with no cardiovascular-acting medications (No CV Meds), 2.) cardiovascular-acting medications excluding calcium channel blockers (CCBs) and phosphodiesterase-5 inhibitors (PDE5i; CV Meds), 3.) cardiovascular-acting medications including CCBs (CV Meds+CCB), and 4.) cardiovascular-acting medications including PDE5is (CV Meds+PDE5i) in the previous 24 hours. Data were analysed using a one-way ANOVA with a least significant difference unpaired *t*-test to identify values that were significantly different. Data are individual values and means ± SD.

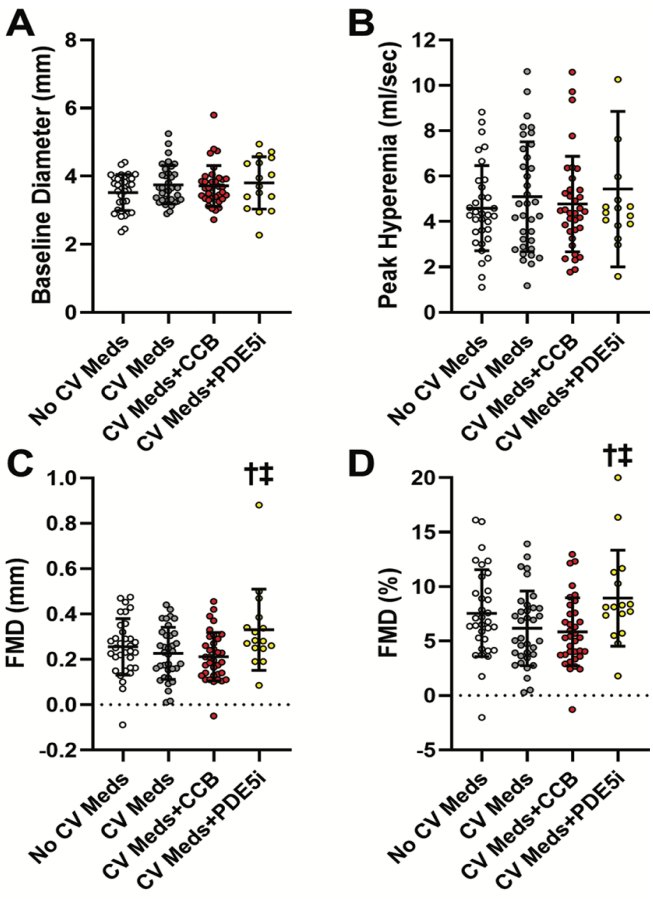


**Fig. 2.** Comparison of brachial artery baseline diameter (**A**), peak hyperaemia (**B**), and flow-mediated dilation (FMD), expressed as an absolute (**C**) and percent change from baseline (**D**) in patients with systemic sclerosis with no cardiovascular-acting medications (No CV Meds), 2.) cardiovascular-acting medications excluding calcium channel blockers (CCBs) and phosphodiesterase-5 inhibitors (PDE5i; CV Meds), 3.) cardiovascular-acting medications including CCBs (CV Meds+CCB), and 4.) cardiovascular-acting medications including PDE5is (CV Meds+PDE5i) in the previous 24 hours. Data were analysed using a one-way ANOVA with a least significant difference unpaired *t*-test to identify values that were significantly different. †$p<0.05$ *vs*. CV Meds. ‡$p<0.05$ *vs*. CV Meds+CCB.
Data are individual values and means ± SD.

blood pressure was lower in the CV Meds+PDE5i group *vs*. No CV Meds, CV Meds, and CV Meds+CCB groups ($p<0.05$). Mean arterial pressure was similar between groups ($p>0.05$). Resting heart rate was similar between groups ($p>0.05$).

*- Peripheral vascular function and haemodynamics*

Brachial artery blood velocity, shear rate, blood flow, and vascular conductance were similar between No CV Meds, CV Meds, CV Meds+CCB, and CV Meds+PDE5i groups (Fig. 1A, 1B, 1C, 1D, respectively) ($p>0.05$ for all). Brachial artery diameter at baseline was similar between groups (Fig. 2A) ($p>0.05$). Peak reactive hyperaemia was similar between groups (Fig. 2B) ($p>0.05$). FMD expressed as an absolute and percent change from baseline was greater in CV Meds+PDE5i group *vs*. CV Meds, and CV Meds+CCB groups (Fig. 2C, 2D, respectively) ($p<0.05$). ANCOVA indicated that neither age or diastolic blood pressure had a statistically significant effect on absolute or percent FMD. We observed no effect of immunosuppression on markers of vascular function within groups, although there was a tendency for greater FMD in patients in the CV Meds+PDE5i with acute immunosuppression compared to those without immunosuppression (11.0±5.5 *vs*. 6.9±1.3%, respectively) ($p=0.055$). We observed no effect of endothelin receptor antagonist (ERA) usage on vascular function within groups ($p>0.05$). There were no effects of anti-centromere antibody status on vascular function ($p>0.05$).

*Quasi-interventional retrospective study*

*- Patient characteristics*

Patient characteristics for the quasi-interventional retrospective study are presented in Table II. The average time between visits was 0.8±0.5 years, with

**Table II.** Patient characteristics.

| | No CCB | CCB |
|---|---|---|
| Sample size, n (m/f) | 17 (1/16) | 17 (1/16) |
| Age, yr | 55.4 ± 13.2 | 55.3 ± 12.9 |
| Height, cm | 167 ± 8 | 167 ± 8 |
| Body mass, kg | 81.0 ± 21.0 | 81.3 ± 21.1 |
| BMI, kg/m$^2$ | 29.0 ± 6.5 | 28.9 ± 6.3 |
| Systolic blood pressure, mmHg | 117 ± 16 | 115 ± 8 |
| Diastolic blood pressure, mmHg | 74 ± 9 | 75 ± 7 |
| Mean arterial pressure, mmHg | 89 ± 9 | 89 ± 7 |
| Heart rate, bpm | 80 ± 15 | 78 ± 9 |
| RP duration, yr | 9.2 ± 7.3 | 9.2 ± 7.0 |
| SSc disease duration, yr | 8.3 ± 7.3 | 8.2 ± 7.1 |
| *Antibody presence* | | |
| ANA positive, n (%) | 14 (82%) | 14 (82%) |
| Centromere, n (%) | 8 (47%) | 8 (47%) |
| Sm, n (%) | 0 (0%) | 0 (0%) |
| RNP, n (%) | 1 (6%) | 1 (6%) |
| Ssa/Ro60, n (%) | 2 (12%) | 2 (12%) |
| SSb/LA, n (%) | 0 (0%) | 0 (0%) |
| Topol, n (%) | 2 (12%) | 2 (12%) |
| Ro-52, n (%) | 1 (6%) | 1 (6%) |
| RNA POL III, n (%) | 0 (0%) | 0 (0%) |
| PMSCL, n (%) | 1 (6%) | 1 (6%) |
| Fibrillarin, n (%) | 1 (6%) | 1 (6%) |
| Th/To, n (%) | 0 (0%) | 0 (0%) |
| Multiple, n (%) | 3 (18%) | 3 (18%) |
| *Cardiovascular-acting medications* | | |
| CCB, n (%) | 0 (0%) | 17 (100%) |
| PDE5i, n (%) | 2 (12%) | 2 (12%) |
| ACE Inhibitor, n (%) | 2 (12%) | 3 (18%) |
| Alpha receptor blocker, n (%) | 1 (6%) | 1 (6%) |
| Beta-Blocker, n (%) | 1 (6%) | 1 (6%) |
| Diuretic, n (%) | 2 (12%) | 1 (6%) |
| Endothelin receptor antagonist, n (%) | 1 (6%) | 1 (6%) |
| Statin, n (%) | 0 (0%) | 3 (18%) |

Values are means±SD. Data were analysed using paired t-tests.
*$p$<0.05 *vs*. No CCB.
ANA: anti-nuclear antibody; BMI: body mass index; CCB: calcium channel blocker; PDE5i: phosphodiesterase type-5 inhibitor; RP: Raynaud's phenomenon; SSc: systemic sclerosis.

7 patients having the No CCB condition first and 10 patients having the CCB condition first. We observed no differences in any patient characteristics between No CCB and CCB conditions ($p$>0.05 for all).

*- Peripheral vascular function and haemodynamics*

Brachial artery blood velocity, shear rate, blood flow, and vascular conductance were similar between No CCB and CCB conditions (Fig. 3A, 3B, 3C, 3D, respectively; $p$>0.05). Brachial artery diameter at baseline was similar between No CCB and CCB conditions (Fig. 4A; $p$>0.05). Peak reactive hyperaemia was similar between No CCB and CCB conditions (Fig. 4B; $p$>0.05). FMD expressed as an absolute and percent change from baseline were similar between No CCB and CCB conditions (Fig. 4C, 4D, respectively) ($p$>0.05).

## Discussion

In the cross-sectional study, we classified 119 patients with SSc into four groups based on acute cardiovascular-acting medication usage within the previous 24 hours. These groups included: 1) No CV Meds, 2) CV Meds, 3) CV Meds+CCB, and 4) CV Meds+PDE5i groups. At rest, we found similar peripheral vascular and haemodynamic outcomes between groups, although patients in the CV Meds+PDE5i group had lower diastolic blood pressure than the other groups, suggesting that acute PDE5i usage may lower systemic vascular resistance. Moreover, we observed that patients with acute PDE5i usage had greater FMD compared to patients in the CV Meds and CV Meds+CCB groups. We observed similar FMD in No CV Meds, CV Meds, and CV Meds+CCB groups, suggesting that acute CCB usage does not improve endothelium-dependent vasodilation. In a follow-up quasi-interventional retrospective study, we classified 17 patients with SSc who had completed multiple FMD visits into two conditions based on the presence or absence of acute CCB usage. At rest and during assessment of FMD, we observed similar peripheral vascular and haemodynamic outcomes between No CCB and CCB conditions, providing further evidence that CCBs do not improve endothelium-dependent vasodilation in patients with SSc. Taken together, these data suggest that acute CCB usage does not affect any peripheral vascular function or haemodynamic outcome in patients with SSc. On the contrary, acute PDE5i usage results in greater FMD, suggesting that PDE5i usage improves endothelium-dependent vasodilation.

*Acute calcium channel blocker usage does not alter peripheral vascular function and haemodynamics*

In our previous studies, we have reported that 75-92% of patients with SSc are actively prescribed CCBs (7, 9, 10, 21, 22). Thus, in the present study, we sought to determine if acute CCB usage alters peripheral vascular function and haemodynamics in patients with SSc. CCBs inhibit L-type voltage-gated calcium channels, leading to vascular smooth muscle vasodilation, which should result in increased peripheral blood flow at rest. In patients with SSc, CCBs are prescribed as a therapeutic for symptoms of RP. RP is the most common symptom in patients with SSc, and vasospasm is a critical component of disease pathogenesis. Guideline based care for RP is included in European Union League Against Rheumatism (EULAR) 2023 recommendations for the treatment of SSc (16), the European Society for Vascular medicine (ESVM) 2017 recommendations for the diagnosis and management of RP (17), the 2018 Treatment Algorithms by Consen-

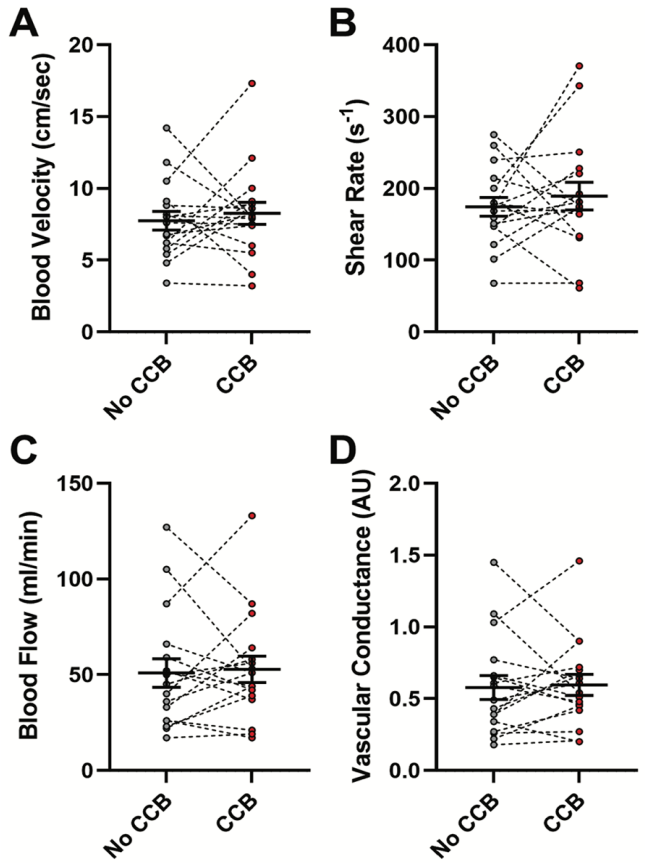


**Fig. 3.** Comparison of brachial artery blood velocity (**A**), shear rate (**B**), blood flow (**C**), and vascular conductance (**D**) in patients with systemic sclerosis under conditions in which they had or had not used a calcium channel blocker (CCB) in the previous 24 hours. Data were analysed using a paired *t*-tests to identify values that were significantly different. Data are individual values and means ± SD.

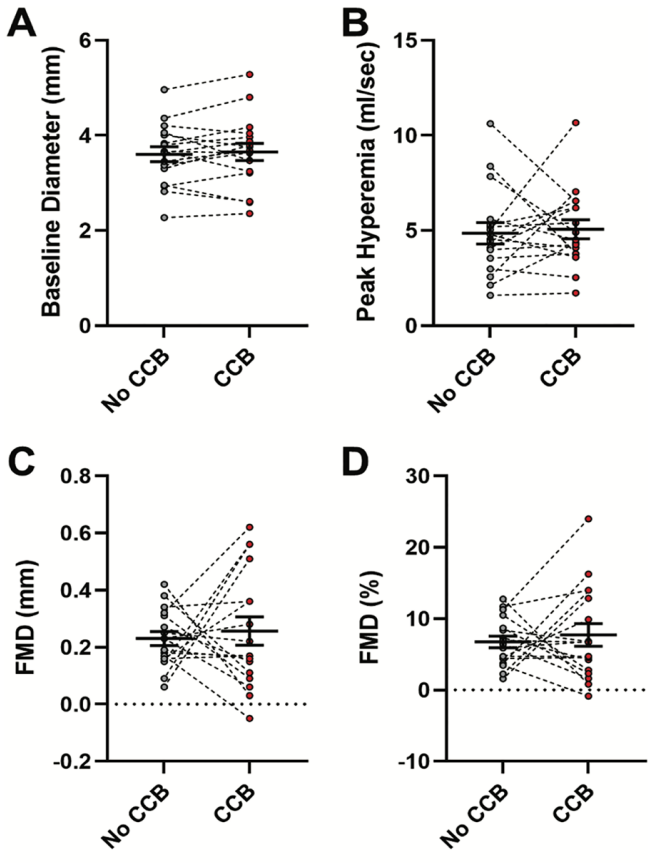


**Fig. 4.** Comparison of brachial artery baseline diameter (**A**), peak hyperaemia (**B**), and flow-mediated dilation (FMD), expressed as an absolute (**C**) and percent change from baseline (**D**) in patients with systemic sclerosis under conditions in which they had or had not used a calcium channel blocker (CCB) in the previous 24 hours. Data were analysed using a paired *t*-tests to identify values that were significantly different. Data are individual values and means ± SD.

sus of SSc Experts (18), and the British Society for Rheumatology/British Health Professionals in Rheumatology (BSR/BHPR) 2016 guideline for treatment of SSc (19) and supports CCB usage as first line therapy. CCBs inhibit L-type voltage-gated calcium channels, leading to vascular smooth muscle relaxation and vasodilation. Thus, based on these guidelines and mechanism of action, we hypothesised that acute CCB usage would result in greater peripheral vascular function or haemodynamic outcomes. Surprisingly, these outcomes appeared to be unaffected by acute CCB usage. In a subgroup of patients with SSc that had multiple testing visits in which they had or had not acutely used CCBs, we also observed no difference in any peripheral vascular function or haemodynamic outcomes. These findings suggest that acute CCB usage is not effective at improving endothelium-dependent vasodilation in patients with SSc.

In the cross-sectional study, we also observed similar blood pressure in those patients on No CV Meds, CV Meds, and CV Meds+CCB, as well as in No CCB and CCB conditions in the quasi-experimental interventional study. CCBs are often prescribed to treat hypertension. While the patients in the study were normotensive, their resting brachial artery blood flow was diminished compared to healthy age-matched controls from previous studies (7, 9). Our group has previously reported on the ability of FMD as a characteristic of vasculopathy in SSc (26). Despite the use of vasodilators, patients with SSc have attenuated brachial artery blood flow that is associated with elevated oxidative stress, especially in patients with severe RP with digital ulceration (8, 9). It is important to note that while we observed no apparent benefit of CCB usage on peripheral vascular function and haemodynamics at rest and during assessment of FMD in this large sample of patients with SSc, these results do not exclude the possibility that there are long-term vascular benefits of CCB usage in SSc. Longitudinal studies of vasculopathy in SSc are critical for understanding cardiovascular outcomes in this patient population.

### *Acute phosphodiesterase inhibitor-5 usage results in greater FMD in patients with SSc*

In patients with severe RP or in patients failing first-line CCB treatment, prescription of a PDE5i is considered second-line therapy (20). In our previous studies, we have reported that 0-28% of patients with SSc are actively prescribed PDE5i (7, 9, 10, 21, 22). Although the prevalence of PDE5i usage

is much lower than that of CCB usage in our patient population, it is the most prevalent among other cardiovascular-acting medications. Thus, we also sought to determine if acute PDE5i usage would result in greater peripheral vascular function and haemodynamics in patients with SSc. In the current cohort, we identified 16 patients with acute PDE5i usage in the 24 hours prior to assessment of FMD. Similar to acute CCB usage, we observed similar vascular function and haemodynamics at rest to the other groups, although diastolic blood pressure was lower in patients with SSc with acute PDE5i usage compared to the other groups. Importantly, we found that patients with acute PDE5i usage had higher brachial artery FMD than patients in the CV Meds and CV Meds+CCB groups, indicating that PDE5i usage may improve endothelial function in patients with SSc. It is likely that greater FMD and lower diastolic blood pressure in patients with PDE5i usage are due to a reduction in vascular resistance as a result of elevated vascular smooth muscle cGMP. Patients with SSc have endothelial dysfunction that is likely due to impaired nitric oxide (NO) production or bioavailability. Thus, PDE5i enhance the action of NO by preventing breakdown of cGMP, which should lead to improved FMD and lower diastolic blood pressure. In contrast, CCBs improve peripheral blood flow by inhibiting calcium channels, thereby promoting vascular smooth muscle relaxation. Thus, the lack of a benefit of CCBs suggests that peripheral vascular dysfunction may be due to endothelial dysfunction rather than vascular smooth muscle dysfunction. Still, this does not discount the long-term benefits of CCBs on vasospasm and other vasculopathy in SSc. Future studies are warranted to directly test the acute *versus* long-term effects of these drugs on vascular structure and function in patients with SSc.

Notably, we observed similar FMD in patients with acute PDE5i usage and patients who had not taken any cardiovascular-acting medications. While ANCOVA demonstrated that age had no effect on FMD between groups, it is important to note that No CV Meds and CV Meds+PDE5i groups differed in age. Indeed, patients with acute PDE5i usage were ~10 years older than patients in the No CV Meds group, and it is well-established that FMD declines with advancing age (27-31). Thus, had these groups been age-matched, it is possible that patients with acute PDE5i usage may have had greater FMD compared to patients in the No CV Meds group. Unfortunately, we lacked the sample size to perform a quasi-interventional retrospective study with acute PDE5i usage similar to the study performed with acute CCB usage. PDE5i usage is a second-line therapy to CCB usage in patients with SSc. However, surprisingly, only 19% of patients with acute PDE5i usage also used CCBs. In other vasculopathy disease manifestations of SSc, such as pulmonary arterial hypertension, upfront combination therapy of CCB and PDE5i have gained traction as important for disease modification, possibly due to the mechanistic impact of combination therapeutic management (32). FMD can be used to assess the acute effects of therapeutic intervention (10, 14), as we have shown that acute $BH_4$ administration in patients with SSc improves FMD (10), as well as exercise-induced blood flow (22). In the current study, our sample size was too small to determine if combined CCB+PDE5i therapy resulted in further augmentation of FMD. Thus, future studies are warranted to determine the acute effects of both PDE5i and combined CCB+PDE5i therapy on FMD in patients with SSc.

## Limitations

This study is not without limitations. Our study population is mostly white, and there are racial differences in CCB usage, as well as race-specific hypertension guidelines and clinical practice (33). Additionally, patients in the CV Meds+PDE5i group were older and had longer disease duration than patients in other groups. It is well-established that FMD decreases with advancing age (27, 30, 31), although it is currently unknown if SSc accelerates the rate of decrease in FMD across the lifespan. Nevertheless, based on age and disease duration it would be expected that patients in the CV Meds+PDE5i would have lower FMD. Future studies are warranted to determine if FMD is decreased when these patients have not acutely taken PDE5i medications, as well as to determine if the rate of decline in FMD with age and SSc diagnosis are affected by PDE5i medication usage. Half of patients in the CV Meds+PDE5i group were on immunosuppressants and we observed a tendency for greater FMD in patients with immunosuppression, suggesting that immunosuppression may enhance the efficacy of PDE5i. Indeed, coadministration of PDE5i and immunosuppressants in patients that received kidney transplants resulted in elevated serum concentrations of sildenafil, a PDE5i drug, suggesting immunosuppression could increase the efficacy of PDE5i drugs (34). In addition to immunosuppression, 50% of patients in CV Meds+PDE5i group acutely used ERA. While we observed no difference between FMD based on ERA usage, this was a fairly small cohort (n=16) and could be confounded by immunosuppression, which may improve the efficacy of PDE5i. Future studies are warranted to determine the efficacy of these drugs in combination with PDE5i for patients with SSc. We cannot conclude that combination PDE5i or combined CCB+PDE5i therapy would result in better outcomes based on the study design and sample size. Nonetheless, our data supports further mechanistic studies of combined cardiovascular-acting medications for RP. Moreover, newer fourth-generation CCBs with both L-type and N-type calcium channel blockade, which exhibit reno-protective, cardioprotective, and neuroprotective effects through direct effects on sympathetic nerve endings, may be more effective than first-line pure L-type CCB therapy, which was used in this study (35). Future studies on these fourth-generation CCBs in patients with SSc are warranted.

## Conclusions

In summary, the results of the present study indicate that acute CCB usage in the previous 24 hours does not improve vascular function or haemodynamic responses at rest or during assessment

of FMD in a large sample of patients with SSc. Conversely, acute PDE5i usage results in greater FMD in patients with SSc, possibly through reductions in vascular resistance, as we also observed lower diastolic blood pressure in patients with acute PDE5i usage. Collectively, these findings suggest that acute PDE5i usage improves endothelial function in patients with SSc, while CCB usage does not.

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