Concise Report

Vasodilator iontophoresis—a possible new therapy for digital ischaemia in systemic sclerosis?

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Objective. This study investigated whether whole finger vasodilator iontophoresis increases digital blood flow in patients with systemic sclerosis (SSc). If so, this might indicate a novel approach to therapy.

Methods. Eight patients and 8 healthy controls underwent whole finger iontophoresis using a specially designed chamber. Treatment was with 0.5% sodium nitroprusside (NaNP) or 1% acetylcholine chloride (ACh), and the procedure then repeated with the other vasodilator (randomly assigned order). Three treatments were carried out for each chemical; 2 min treatments were carried out bilaterally at 200 μA, a third was then carried out for 5 min on one digit only (randomly assigned to left or right). Blood flow increases were monitored with laser Doppler imaging (LDI). Maximum perfusion increase from baseline (MAX) and the area under the time perfusion curve (AUC), normalized for baseline, were calculated. Data were compared with a three-way analysis of variance test.

Results. Perfusion increased in both patients and controls, but significantly more so in controls (P_MAX = 0.001, P_AUC = 0.005, respectively). Values were significantly higher for the 5 min treatment compared with the 2 min treatment (P_MAX = 0.011 and P_AUC = 0.008 for both groups). No significant differences were found between the use of NaNP and ACh.

Conclusions. The increased perfusion with both ACh and NaNP in the patient group (albeit to a lesser degree than in the control group) indicates that this local approach to vasodilation is effective. Increasing iontophoresis time causes more sustained vasodilation. Further studies are indicated to investigate a possible therapeutic effect in patients with severe digital ischaemia.

KEY WORDS: Iontophoresis, Vasodilation, Ischaemia, Systemic sclerosis.

Introduction

Digital ischaemia is a key clinical feature of systemic sclerosis (SSc) and is associated with reduced skin blood flow [1, 2]. Ischaemia can be so severe as to result in digital ulceration that can be painful, slow to heal and can become infected, leading to gangrene and sometimes necessitating amputation. Approximately 40% of patients with SSc develop severe digital ischaemia and/or ulceration [3, 4]. Intravenous prostanoids, the standard treatment for severe SSc-related digital ischaemia/ulceration, require admission to hospital, may cause systemic vasodilatory side-effects and are not always effective. Therefore, a safe and effective treatment, that does not cause adverse effects, is badly needed.

Iontophoresis is the process of ‘driving’ ions into the skin by application of a low electric current and has been investigated as a technique for administering lidocaine [5], heparin [6] and antibiotics [7], and in diabetes management, as a method of extracting glucose for monitoring purposes [8].

There has been limited previous investigation of iontophoresis as a treatment for ischaemia. In the early 1950s and 1960s, hyaluronidase and histamine iontophoresis, respectively, were used in a small number of patients to treat SSc-related ischaemic ulceration [9, 10]. In the 1980s, zinc iontophoresis in a patient with diabetic peripheral vascular disease, who had a leg ulcer [11]. More recently, Gherardini et al. [12] carried out a study on venous stasis ulcers, iontophoresing calcium and iontophoresing calcium gene-related peptide and vasoactive intestinal polypeptide, and Sakurai and Yamamura [13] performed iontophoresis of prostaglandin E2 on a patient with peripheral vascular disease with an ischaemic ulcer. Iontophoresis was carried out on surrounding skin, rather than directly on the ulcer site; studies reported various degrees of improvement.

Many pathophysiological studies have been carried out using vasodilator iontophoresis techniques to assess endothelial dependent and independent cutaneous blood flow in, for example, diabetes, pregnancy and hypertension [14–16]. Iontophoresis of acetylcholine chloride (ACh, endothelium dependent) or sodium nitroprusside (NaNP, endothelium independent) result in dramatic increases in dermal blood flow. We and others have examined these vasodilatory responses in patients with SSc [17–21]. Vasodilation occurs even in patients with SSc with thickened skin, and this response is localized, occurring only at the site of iontophoresis; there is no systemic effect. The aim of these studies has been to assess whether vasodilation is impaired and if so, whether this is primarily endothelial dependent.

Following on from these studies of pathophysiology, we have successfully carried out a pilot study in healthy controls, iontophoresing a whole finger using ACh [22]. We designed a chamber to allow submersion of the whole digit into iontophoresis solution, in comparison with iontophoresis of a chemical at a single point (~1 cm²) as in earlier pathophysiological studies. This pilot study showed that the whole area/digit could be locally medicated, resulting in an increase in perfusion as measured by laser Doppler imaging (LDI), without systemic side-effects [22].

The small pilot study reported here aimed to expand upon these initial findings to (i) test the hypothesis that patients with SSc, with intact skin, would also respond to whole finger vasodilator iontophoresis and (ii) determine whether both patients and healthy controls would respond equally well to both ACh and NaNP. If this novel method of vasodilatory delivery is effective in increasing blood flow in patients with SSc, then this might provide an alternative route of vasodilator therapy that could reduce both treatment time and systemic vasodilatory side-effects compared with current therapy with intravenous prostanoids.

Patients and methods

Patients

Eight patients with SSc [six females, two males, median age 56 (range 39–73) yrs, median number of years since onset of
Raynaud’s phenomenon 16 (range 6–43 yrs) and since onset of first non-Raynaud’s manifestation of SSc 12 (range 5–27 yrs) and eight age-matched healthy controls [six females; two males; 62 (42–76 yrs) were recruited into the study. One of the patients but none of the controls were smokers. Five patients had limited cutaneous SSc (lcSSc) and three had diffuse cutaneous SSc (dcSSc) as defined by LeRoy et al. [23]. Five patients had severe ischaemia (defined as a history of previous admission for i.v. vasodilator therapy or of surgical debridement). Two patients were anti-centromere antibody positive, none was antitopoisomerase I (anti-Scl-70) positive. Four patients were on vasodilators (three on nifedipine and one on losartan and moxonidine). None of the patients was on steroid or immunosuppressant therapy. The degree of skin thickening at the digit was assessed at the last clinic visit, not longer than 1 yr prior to the study, by modified Rodnan skin score (mRSS) [24]; one patient had a score of 0 (clinically normal skin), one patient a score of 1 (minimally involved) and six patients a score of 2 (involved, but able to move). In all eight patients, the mRSS was the same on right and left digits. No subjects were known to suffer from cardiovascular disease and specifically none had confirmed pulmonary arterial hypertension. Capillaroscopy for all patients showed abnormal capillary structure. The study was approved by the Salford and Trafford Local Research Ethics Committee. Informed patient consent was obtained for this study.

### Equipment

The prototype iontophoresis chamber that has previously been described [22], allows the finger to be submerged in the iontophoresis solution up to the proximal interphalangeal joint (see supplementary figure 1, available as supplementary data at Rheumatology Online).

### Protocol

Following acclimatization for 20 min at 23°C, the finger to be iontophoresed was cleaned with an alcohol wipe and a baseline LDI scan of blood flow taken (dorsal aspect of finger, imaging distance of 30 cm, scanning speed of 4 ms/pix, 633 nm, Moor LDI-vr, Axminster, UK). LDI is a recognized technique of measuring cutaneous microvascular perfusion [25]. The chosen finger was usually the index finger (controls n = 7, patients n = 7); however, the middle or ring finger was used for one healthy control (due to a cut in the skin) and one patient (recent ulceration). The order of hands, left, right, was randomly assigned. The chosen finger was iontophoresed for 2 min at 200 μA by submersion in the solution within the iontophoresis chamber. Following treatment, the digit was promptly removed from the chamber and lightly dabbed dry. Repeat LDI scans were then performed to monitor the increase in perfusion. Each scan lasted ~1 min.

Iontophoresis was carried out three times for each chemical. The 2 min treatment was repeated on the bilateral digit and the treatment was then repeated on the first finger for 5 min. Each iontophoresis treatment was carried out following a baseline scan, and following iontophoresis repeat LDI scans were performed for 10 min (for 2 min treatment) or for 25 min (5 min treatment) or until blood flow returned to baseline values (see supplementary figure 2, available as supplementary data at Rheumatology Online, for a typical set of LDI images).

Treatment was with 0.5% NaNP (pharmaceutical grade, Mayne Pharma Plc, Warwickshire, UK) or 1% ACh (Sigma). The order of the treatments was randomly assigned. The chamber and the return electrode (a saline-soaked wrist strap) were connected to an iontophoresis controller (MIC-1e, Moor Instruments Ltd). For ACh, the chamber was connected to the negative terminal and for NaNP to the positive terminal.

### Data analysis

Images were examined and the mean flux (measured in perfusion units PU), proportional to the mean speed of red blood cells multiplied by number per unit volume in the region of interest (distal phalanx, proximal to the nail) was determined for the digit, for each frame. This data was normalized for baseline, and flux values were plotted for the first 10 frames to provide a time perfusion curve for each subject, (see supplementary figure 3, available as supplementary data at Rheumatology Online) for each treatment. From this plotted data the maximum increase in blood flow from baseline (MAX) was determined and the area under the time perfusion curve (AUC) was calculated. For the 2 min treatment, the mean MAX and AUC data were taken for both digits.

### Statistical analysis

Data were compared with a three-way analysis of variance (ANOVA), to compare group, drug and dose (time). All analysis was carried out using SPSS v11.5, (Chicago, IL, USA).

### Results

Clinical details for patients with SSc are shown in Table 1.

One patient reported mild, tolerable discomfort during iontophoresis of one digit and chose not to discontinue the treatment; some patients and controls described a prickling feeling similar to ‘pins and needles’.

Values for MAX and AUC are shown in Table 2. MAX and AUC values were significantly higher for the control than the patient group (P_{MAX} = 0.001, P_{AUC} = 0.005). Values were significantly higher for the 5 min treatment compared with the 2 min treatment (P_{MAX} = 0.011, P_{AUC} = 0.008). No significant differences were found between results for NaNP and for ACh (see supplementary figure 4, available as supplementary data at Rheumatology Online).

### Table 1. Clinical details for SSc patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Duration of Raynaud's phenomenon (yrs)</th>
<th>Disease duration (yrs)</th>
<th>Disease subtype</th>
<th>mRSS total score</th>
<th>mRSS digital score</th>
<th>Antibody status</th>
</tr>
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<tbody>
<tr>
<td>F</td>
<td>54</td>
<td>19</td>
<td>19</td>
<td>lcSSc</td>
<td>4</td>
<td>1</td>
<td>ANA 1/10000</td>
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<tr>
<td>F</td>
<td>73</td>
<td>7</td>
<td>7</td>
<td>lcSSc</td>
<td>7</td>
<td>2</td>
<td>ANA 1/10000</td>
</tr>
<tr>
<td>F</td>
<td>39</td>
<td>17</td>
<td>8</td>
<td>lcSSc</td>
<td>0</td>
<td>0</td>
<td>ACA positive</td>
</tr>
<tr>
<td>M</td>
<td>51</td>
<td>14</td>
<td>13</td>
<td>dcSSc</td>
<td>10</td>
<td>2</td>
<td>ANA 1/1000</td>
</tr>
<tr>
<td>F</td>
<td>57</td>
<td>11</td>
<td>11</td>
<td>dcSSc</td>
<td>17</td>
<td>2</td>
<td>ANA 1/1000</td>
</tr>
<tr>
<td>M</td>
<td>52</td>
<td>6</td>
<td>5</td>
<td>dcSSc</td>
<td>14</td>
<td>2</td>
<td>ANA 1/1000</td>
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<tr>
<td>F</td>
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<td>43</td>
<td>27</td>
<td>lcSSc</td>
<td>7</td>
<td>2</td>
<td>Anti-RNP positive</td>
</tr>
<tr>
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<td>59</td>
<td>24</td>
<td>24</td>
<td>lcSSc</td>
<td>6</td>
<td>2</td>
<td>ACA positive</td>
</tr>
</tbody>
</table>

MRSS: modified Rodnan skin score; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ANA: anti-nuclear antibody; ACA: anti-centromere antibody; RNP: ribonucleoprotein.
Discussion

The control group’s more marked vasodilation confirms that microvascular function is impaired in patients with SSc, and the fact that the response to both ACh and NaNP was attenuated indicates that dysfunction is not solely endothelial.

Previous pathophysiological (small area) iontophoresis studies with ACh and NaNP involving comparisons between healthy controls and patients with SSc have revealed inconsistent results. La Civita et al. [18] and Anderson et al. [21] found impaired responses to iontophoresis of both ACh and NaNP in the fingers of patients with SSc compared with the control group. Khan and Belch [20] found decreased response to ACh but not NaNP in the digits of patients with SSc compared with the control group. Marasini and Conciato [26] testing only ACh, on the forearm, also found an impaired response in patients. In contrast, Anderson et al. showed no differences in groups for either ACh or NaNP with either forearm [17] or digital [19] iontophoresis at higher doses. Anderson et al. [21] hypothesised that the variability of these results most likely stems from differences in protocol, with lower currents providing more sensitivity to group differences, and higher currents possibly ‘saturating’ vasodilation. Despite some inconsistencies in results between these studies, a key point to emerge is that whether or not impaired vasodilation was observed in patients with SSc, the patient group did always show an increase in blood flow, even if lower and sometimes delayed compared with controls. Our study confirmed this and extended the observation to the whole finger.

In examining responses to different ‘doses’ of iontophoresis (2 min and 5 min at 200 μA) we aimed to identify a suitable regimen for patients, which would be easily tolerable and could be administered several times a day if necessary. Although longer durations of iontophoresis could have been examined, for practical purposes (patient tolerability in holding the hand still) 5 min was thought to be a feasible maximum. Our study demonstrated a definite local blood flow increase with both ACh and NaNP in patients with SSc, indicating that this local approach to vasodilation was effective in increasing digital blood flow without significant adverse effects. NaNP has the added advantage that it is available in pharmaceutical grade for administration.

Patients were not followed up for a long term, as this was not intended to be a treatment study, but rather a pilot study to demonstrate feasibility in patients with thickened skin and ischaemia. It may be possible to increase the blood flow response to iontophoresis in patients with SSc in a number of different ways:

(i) Our previous study compared iontophoresis with a placebo procedure of placing the digit in room temperature liquid with no current applied. The placebo caused significant vasoconstriction [22]. Therefore, the first improvement could be to use warmed ionic solutions.
(ii) Using a pulsed current to drive the iontophoresis unit, as this may allow longer treatment periods (thus increasing the dose).
(iii) By iontophoresing several times a day, over sequential days. These modifications will be built in to future studies. In the Longer term, we also aim to validate other vasodilators, which may have longer-lasting effects.

In conclusion, we have demonstrated that whole finger vasodilator iontophoresis is an effective method of increasing blood flow in the fingers of patients with SSc, without systemic adverse effects. The next step will be an open study to investigate a possible therapeutic effect in patients with severe digital ischaemia and/or ulceration. If our initial open studies are successful, then this will pave the way for randomized trials that will monitor the longer-term effects of iontophoresed vasodilators on both digital ulceration and ischaemia. Our ultimate aim is to develop a transdermal treatment that is effective, free from systemic adverse effects and that can be administered without the need for hospitalization.

Supplementary data

Supplementary data are available at Rheumatology Online.

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References