Use of near infrared spectroscopy to detect impaired tissue oxygen saturation in patients with complex regional pain syndrome type 1

Utilisation de la spectroscopie proche de l’infrarouge pour détecter les troubles de la saturation en oxygène dans le tissu de patients atteints du syndrome douloureux régional complexe de type 1

Geoff A. Bellingham, MD • Ryan S. Smith, MD • Patricia Morley-Forster, MD • John M. Murkin, MD

Received: 11 October 2013 / Accepted: 4 March 2014 / Published online: 26 March 2014
© Canadian Anesthesiologists’ Society 2014

Abstract

Purpose Deep tissue hypoxia has been hypothesized in the pathogenesis of complex regional pain syndrome type 1 (CRPS 1) for some patients. The purpose of this study was to determine if near-infrared spectroscopy (NIRS) could detect differences in deep tissue oxygen saturation (StO2) and microcirculatory function in the hands of patients with CRPS 1.

Methods Tissue oxygen saturation was evaluated at baseline and during an ischemia reperfusion challenge using vascular occlusion testing (VOT) in affected vs unaffected hands of patients with unilateral upper limb CRPS 1. A non-randomized experimental study design was used with baseline StO2 as the primary outcome measure. Secondary outcome measures were occlusion and reperfusion slopes from VOT. Values were compared with the unaffected, contralateral hand and with the dominant and non-dominant hands of sex and age-matched volunteers. Correlations between values derived from NIRS and measures of pain and function from the Brief Pain Inventory (BPI) and the Disability of the Arm, Shoulder and Hand (DASH) questionnaires were explored.

Results Independent of handedness, the baseline StO2 of the affected hands of ten CRPS 1 patients was significantly lower than that of their unaffected hands (−5.8%; 95% confidence interval [CI] −10.6 to −1.0; P = 0.02). The baseline StO2 of affected CRPS 1 hands was also significantly lower than the non-dominant hands of ten volunteers (−7.3%; 95% CI −12.4 to −2.3; P = 0.007). Differences in VOT occlusion and reperfusion slopes did not reveal changes that could be uniquely attributed to CRPS 1. No significant correlations were detected between values derived from VOT and values for pain and function obtained from BPI and DASH questionnaires for patients with CRPS 1.

Conclusions Hands of patients affected by CRPS 1 of the upper limb showed significantly lower StO2 compared with their unaffected contralateral hand as well as the hands of control subjects. This trial was registered at: ClinicalTrials.gov: NCT01586377.

Résumé

Objectif L’hypoxie tissulaire profonde jouerait un rôle dans la pathogénie du syndrome douloureux régional complexe de type 1 (SDRC 1) chez certains patients. L’objectif de cette étude était de déterminer si la spectroscopie proche de l’infrarouge (NIRS) pouvait détecter des différences de saturation en oxygène (StO2)
dans les tissus profonds et de la fonction microcirculatoire dans les mains de patients atteints de SDRC 1.

**Méthodes** La saturation tissulaire en oxygène a été évaluée à la ligne de base et au cours d’un test d’ischémie-reperfusion utilisant une test d’occlusion vasculaire (VOT) sur des mains de patients atteints de SDRC 1 unilatéral d’un membre supérieur, comparativement à des patients indemnes de SDRC 1. Un plan d’étude expérimentale non randomisée a été utilisé en prenant la StO2 de la ligne de base comme mesure de référence du critère d’évaluation principal. Les critères d’évaluation secondaires étaient les pentes d’occlusion et de reperfusion de la VOT. Les valeurs ont été comparées à celles de la main contralatérale, non atteinte, et à celles de la main dominante et non-dominante de volontaires appariés pour le sexe et l’âge. Les corrélations entre valeurs tirées de la NIRS et les mesures de douleur et de fonctionnement provenant des questionnaires BPI (Court inventaire de la douleur) et DASH (Handicap du bras, de l’épaule et de la main) ont été explorées.

**Résultats** Indépendamment de la dominance de la main, la StO2 de référence des mains affectées chez dix patients atteints de SDRC 1 a été significativement plus basse que celle de leurs mains indemnes (−5,8 %; intervalle de confiance à 95 % [IC]: −10,6 à −1,0; P = 0,02). La StO2 de référence des mains atteintes par le SDRC 1 était également significativement plus basse que celle des mains non dominantes de dix volontaires (−7,3%; IC à 95 % −12,4 à −2,3; P = 0,007). Les différences dans les pentes d’occlusion et de reperfusion au cours du VOT n’ont pas révélé de modifications qui pourraient être exclusivement attribuées au SDRC 1. Aucune corrélation significative n’a été détectée entre les valeurs tirées du VOT et les valeurs pour la douleur et la fonction tirées des questionnaires BPI et DASH chez les patients atteints de SDRC 1.

**Conclusions** Les mains des patients atteints de SDRC 1 du membre supérieur ont présenté une StO2 significativement plus basse comparativement aux mains contralatérales indemnes et aux mains de sujets contrôles. Cette étude a été enregistrée sur le site ClinicalTrials.gov sous le numéro NCT01586377.

Complex regional pain syndrome type 1 (CRPS 1) is a clinical disorder in which an injury to a limb—without clinical verification of damage to a nerve—results in continuing pain disproportionate to the inciting event, accompanied by sensory, motor, vasomotor, and sudomotor changes. Injuries that have been known to lead to CRPS 1 include sprains, fractures, or crush injuries.

A precise mechanism explaining CRPS 1 pathophysiology has not been delineated, and investigations have been able to show pathological changes in the central nervous system induced at locations varying from the site of tissue injury.

Investigations by Coderre et al. have led to a microvascular injury hypothesis which proposes a mechanism that may lead to the initiation and maintenance of CRPS 1 symptoms in some patients. A rodent model of ischemia and reperfusion (I-R) injury in the hind limb leads a “slow-flow/no-reflow” phenomenon within the microvasculature which results in impaired oxygen delivery to deep tissues. This I-R injury model leads to post-ischemia pain with CRPS 1-like symptomatology. It is suggested that a cause of pain in some patients with CRPS 1 may be due to continued ischemia and resultant inflammation of deep tissues (i.e., muscle, bone, and nerve) consequent to microvascular changes taking place after an I-R injury.

Past studies have detected markers of impaired blood flow, such as low skin capillary hemoglobin oxygenation and elevated skin lactate, in the limbs of patients with CRPS 1. Nevertheless, these findings have been limited mainly to the skin surface; markers have not been detected that may indicate impaired nutritive blood flow to deeper tissues, which could be the driving force for these observed changes.

The use of near-infrared spectroscopy (NIRS) has been proposed to investigate the oxygenation status of the deeper tissues in patients with CRPS 1. Near-infrared spectroscopy is a noninvasive method of measuring oxygen saturation of hemoglobin within blood vessels less than 1 mm in diameter (arterioles, venules, and capillaries) at tissue depths of 2-6 cm, depending on probe design. Although tissue NIRS can detect the microcirculation of skin and subcutaneous fatty tissue with adequate probe placement, this has been estimated at less than 5% of the signal measured.

Use of NIRS has been investigated in other disease states to help diagnose or guide therapy. Examples include monitoring cerebral perfusion during carotid endarterectomy, assisting in the diagnosis of compartment syndrome, or evaluating resuscitative efforts during sepsis.

The purpose of this experiment was to determine if microvascular dysfunction could be measured using NIRS and a calibrated ischemia reperfusion challenge. This was accomplished using vascular occlusion testing (VOT) and comparing results in the affected hands of patients diagnosed with CRPS 1 with results in the contralateral unaffected hand and the hands of healthy controls. Given the results of past observational studies, we hypothesized that lowered tissue oxygen saturation (StO2) and abnormal vasoreactivity in response to an ischemia reperfusion challenge would be found in the affected hands of CRPS 1 patients. As such, the primary outcome measure was baseline StO2, and secondary outcome measures included occlusion and reperfusion slopes derived from VOT.
Methods

This study was approved by the University of Western Ontario, Health Sciences Research Ethics Board on August 12, 2011.

Study participants

Clinic staff identified and recruited volunteer patients in an outpatient chronic pain clinic at a tertiary care hospital from September 2011 through November 2012.

Patients were recruited if they had clinical signs of CRPS 1 and fulfilled the International Association for the Study of Pain (IASP) diagnostic criteria. Additional recruitment criteria included patients whose CRPS 1 symptoms were limited to one upper extremity and the duration of symptoms was greater than 16 weeks. The duration of CRPS 1 was defined as the time from the initial diagnosis to enrolment in this study.

Exclusion criteria included age less than 18 or greater than 75, pregnancy, history of peripheral vascular disease requiring angioplasty or bypass surgery, type 1 or 2 diabetes, history of systemic vasculitis, and the use of vasoactive medications.

Characteristics of the CRPS 1 syndrome were collected, including the side of the affected limb, handedness, duration of the syndrome, and a description of the inciting event. The presence or absence of allodynia, hyperalgesia, swelling, sudomotor change, temperature change, colour change, weakness, tremor, paresis, and trophic change (hair, nails, and skin) was also documented.

A control group without history of CRPS 1 was recruited from staff working at the same hospital from which patients were recruited. This group consisted of females who were within the same age range as the patients.

Baseline demographic data were collected, including age, sex, weight, height, and handedness, for both patients and members of the control group.

Variables

Tissue oxygen saturation and VOT

An InSpectra™ StO2 monitor (model 650) (Hutchinson Technology, Hutchinson, MN, USA) with 15 mm probe spacing was applied to the thenar eminence on both hands of each participant. The NIRS probes used in the study were validated for use only at this location; therefore, probes were not placed at any other location on the upper limbs. Study participants were placed in a seated position with their hands positioned at heart level. Ambient room temperature was controlled at 20-23°C.

An InSpectra™ VOT research system, which automated the measurement of all values, was used to perform all StO2 measurements and VOT.

Vascular occlusion testing was performed for each limb, and the starting limb was randomized to mitigate confounding variables, such as any anxiety or pain elicited by the VOT, which could increase sympathetic activity, thus affecting vascular function.

The cycle for the VOT research system began with a measurement of baseline blood pressure. After a subsequent period of 2.5 min of stable baseline StO2 (< 2% variability), VOT was then started, and a baseline average StO2 was calculated. The VOT was performed by inflating a pneumatic tourniquet over the brachial artery to a pressure of 50 mmHg greater than systolic blood pressure. The tourniquet was released once a StO2 value of 40% was obtained or after a period of five minutes tourniquet inflation without having reached a StO2 of 40%. All data were displayed and recorded by the system following a five-minute period of recovery with continued StO2 measurement.

Testing cycles for each individual were separated by 20 min. During this time, patients remained seated with no adjustments to the testing environment.

The InSpectra™ clinical research software (Hutchinson Technology, Hutchinson, MN, USA) was used to calculate the baseline StO2 (%), occlusion slope (change in StO2 per minute during tourniquet inflation, %/min), and reperfusion slope (change in StO2 per second after tourniquet deflation, %/sec) from the VOT. To measure the temperature of the participants’ hands, an AR300 infrared thermometer (resolution 0.1°C, accuracy ± 1.5°C) (Polarich Industries Ltd, Hong Kong) was placed over the thenar eminence of each hand prior to the application of the NIRS probes.

Tissue hemoglobin index

Tissue hemoglobin index (THI), a measure of the hemoglobin signal strength detected by the NIRS probe, was measured for each study participant’s hands. This measurement acts as a guide to determine if the sensor is optimally positioned over muscle tissue. A signal measurement greater than 5.0 is indicative of sufficient hemoglobin to obtain an adequate signal.

Questionnaires

All patients and healthy volunteers completed the Brief Pain Inventory (BPI) and the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaires prior to applying NIRS probes and performing VOT.

Statistical analysis

All data are presented as mean (SD). Comparison of means for values obtained from CRPS 1 patients and volunteers was performed using Student’s paired t test for within-person
comparisons and Student’s two-sample t test for between-person comparisons. Correlation between values derived from the BPI and DASH questionnaires and values from the NIRS probes was performed using Spearman’s rank-order correlation. \( P < 0.05 \) was considered statistically significant; all tests are two-sided. All analyses were performed using SPSS™ version 21 (SPSS Inc., Chicago IL, USA).

We were unable to undertake a sample-size calculation for this study as data regarding use of this specific technology for StO2 in CRPS 1 patients are lacking. Instead, a convenience sample of ten patients and ten volunteers was employed to generate estimates that would be useful for future sample-size calculations. This number is comparable with previously published studies investigating CRPS tissue hypoxia markers.

### Results

#### Patients

Thirteen patients with CRPS 1 were confirmed as eligible participants. Three patients elected not to participate for fear that testing of their affected limb would increase their pain. Ten CRPS 1 patients completed the study protocol and had their results analyzed. Ten healthy control subjects were confirmed eligible and all completed the study protocol. All CRPS 1 patients who volunteered and satisfied inclusion criteria for the study were female. Baseline patient and volunteer demographics are provided in Table 1. Characteristics of patient CRPS 1 syndrome are described in Table 2.

#### Vascular occlusion testing measured values

Table 3 describes the baseline StO2, occlusion slope, and reperfusion slope values for CRPS 1 affected and unaffected hands of patients and the dominant and non-dominant hands of healthy controls. Baseline StO2 values of patients’ and healthy control volunteers’ hands are plotted in the Figure.

Mean differences in VOT measured values within groups and between CRPS 1 affected and non-dominant control volunteer hands are provided in Table 4. A statistically significant difference was detected between the affected and unaffected hands of CRPS 1 patients. A significant difference in baseline StO2 was also detected between CRPS 1 affected hands and the non-dominant hands of healthy control volunteers. The non-dominant hand was used as a comparison in an attempt to help mitigate any difference that increased activity of dominant hands could play in changing VOT measured values.

Significant differences in within-group occlusion slopes were identified between affected and unaffected hands of patients and between dominant and non-dominant hands of control volunteers. There was no significant difference in occlusion slope between CRPS 1 affected hands and non-dominant hands of healthy controls. No significant differences were identified in reperfusion slopes.

#### Brief Pain Inventory, DASH, and StO2

Baseline StO2 did not show any significant correlations with BPI average pain, worst pain, or least pain.
Additionally, no significant correlation was found for either the BPI interference scores or the DASH questionnaire scores. A summary of results are provided in Table 5.

Discussion

The present study detected a significantly lower NIRS-derived StO2 in the affected hands of CRPS 1 patients when compared with their contralateral unaffected hands and the non-dominant hands of volunteers. Diminished baseline StO2 may be a unique feature of CRPS 1 that could serve as a novel quantifiable factor for the diagnosis or monitoring of this syndrome.

Prior studies have identified markers of hypoxic conditions in the affected limbs of patients with CRPS 1; however, these findings have been determined predominantly at the skin surface. The distinguishing

### Table 2 Patient CRPS 1 descriptive characteristics and baseline StO2 values

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Inciting event</th>
<th>Duration (days)</th>
<th>Medications</th>
<th>Baseline StO2 affected/healthy hand</th>
<th>Sensory changes</th>
<th>Sudomotor changes</th>
<th>Vasomotor changes</th>
<th>Motor/trophic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>F</td>
<td>Radial head fracture</td>
<td>766</td>
<td>Gabapentanoids, Acetaminophen, Tramadol</td>
<td>74.4/74.2%</td>
<td>A, Ha</td>
<td>Sl, St</td>
<td>T, C</td>
<td>W, P, D</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>F</td>
<td>Ligament reconstruction for scapholunate tear</td>
<td>768</td>
<td>Opioids, TCA, Gabapentanoids, Cannabinoid, SNRI</td>
<td>68.5/77.9%</td>
<td>A, Ha</td>
<td>Sl</td>
<td>T, C</td>
<td>W, Tr, D</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>F</td>
<td>Distal radial fracture</td>
<td>3,815</td>
<td>Acetaminophen, Tramadol, SSRI</td>
<td>68.9/81.0%</td>
<td>A</td>
<td>Sl</td>
<td>T, C</td>
<td>W, Tr</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>F</td>
<td>STT fusion and distal radial bone graft</td>
<td>568</td>
<td>NSAIDs, Acetaminophen, SSRI</td>
<td>59.2/77.5%</td>
<td>A, Ha</td>
<td>T, C</td>
<td>W</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>F</td>
<td>Carpel tunnel release</td>
<td>325</td>
<td>TCA, Gabapentanoids</td>
<td>79.0/82.0%</td>
<td>Ha</td>
<td>Sl</td>
<td>T, C</td>
<td>Tr, D</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>F</td>
<td>Third finger amputation to distal phalanx</td>
<td>1,682</td>
<td>Opioids, Gabapentanoids, SNRI</td>
<td>77.0/80.7%</td>
<td>A, Ha</td>
<td>Sl, St</td>
<td>T, C</td>
<td>W, Tr, D</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>F</td>
<td>Excision trapezial implant and open median nerve release</td>
<td>3,650</td>
<td>NSAIDs, Opioids, Gabapentanoids, Muscle relaxant, SSRI</td>
<td>68.5/74.7%</td>
<td>A, Ha</td>
<td>Sl, St</td>
<td>C, T</td>
<td>W, P, Tr, D</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>F</td>
<td>AC joint Grade 1 sprain</td>
<td>781</td>
<td>NSAIDs, Opioids, Gabapentanoids, Tramadol, SNRI</td>
<td>81.2/77.2%</td>
<td>A, Ha</td>
<td>Sl</td>
<td>T, C</td>
<td>D</td>
</tr>
<tr>
<td>9</td>
<td>46</td>
<td>F</td>
<td>Burn on dorsum of hand</td>
<td>154</td>
<td>NSAIDs, Gabapentanoids, Tramadol</td>
<td>68.0/77.8%</td>
<td>A, Ha</td>
<td>Sl, St</td>
<td>T, C</td>
<td>W, Tr</td>
</tr>
<tr>
<td>10</td>
<td>52</td>
<td>F</td>
<td>Distal radial and scaphoid fracture</td>
<td>245</td>
<td>Gabapentanoids</td>
<td>78.9/78.8%</td>
<td>A</td>
<td>Sl, St</td>
<td>T, C</td>
<td>W, P, Tr</td>
</tr>
</tbody>
</table>

**CRPS 1** = complex regional pain syndrome type 1; **NSAID** = non-steroidal anti-inflammatory drug; **SNRI** = serotonin norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **STT** = scaphotrapezotrapezoidal; **TCA** = tricyclic antidepressant

A = allodynia; Ha = hyperalgesia; Sl = swelling; St = sweating; T = temperature; C = colour; W = weakness; P = paresis; D = dystonia; Tr = trophic changes

### Table 3 Measured VOT values represented as mean (standard deviation); 95% confidence interval

<table>
<thead>
<tr>
<th></th>
<th>CRPS 1 affected</th>
<th>CRPS 1 unaffected</th>
<th>Dominant control</th>
<th>Non-dominant control</th>
</tr>
</thead>
<tbody>
<tr>
<td>StO2 (%)</td>
<td>72.4 (6.9); 67.5 to 77.3</td>
<td>78.2 (2.6); 76.4 to 80.0</td>
<td>80.3 (4.4); 77.2 to 83.4</td>
<td>79.7 (3.2); 77.4 to 82.0</td>
</tr>
<tr>
<td>Occlusion slope (%)/min</td>
<td>-10.3 (2.4); -12.0 to -8.6</td>
<td>-12.9 (2.7); -14.9 to -10.9</td>
<td>-13.6 (2.4); -15.3 to -11.9</td>
<td>-11.5 (1.8); -12.7 to -10.2</td>
</tr>
<tr>
<td>Reperfusion slope (%)/sec</td>
<td>5.5 (2.5); 3.7 to 7.3</td>
<td>6.4 (1.2); 5.6 to 7.2</td>
<td>6.6 (1.7); 5.3 to 7.8</td>
<td>6.6 (2.9); 4.5 to 8.7</td>
</tr>
</tbody>
</table>
feature of this study was the use of NIRS, which allowed for evaluation of deep StO\textsubscript{2} of the microvasculature. Observations from this study may lend support to the hypothesis that, in some patients, endothelial dysfunction of deep tissues may drive the syndrome’s pathophysiology.

Notably, diminished StO\textsubscript{2} in the affected limbs of CRPS 1 patients did not correlate with any clinical measures of pain or disability obtained from the BPI or DASH questionnaires. Consequently, the clinical relevance of lowered tissue oxygenation remains uncertain at present. A possible explanation for this finding is that patients were being treated with a variety of analgesic modalities that may have served to reduce nociceptive input from hypoxic conditions or even to influence microvascular function. The heterogeneity of analgesic use among patients in this study is a significant confounding variable.

Another notable facet of this study is that all patients recruited were female. This most likely reflects the fact that females are two to four times more likely to suffer from CRPS 1 than males.\textsuperscript{12} There is no concern that the lower muscle mass of females would have affected the results of the measured NIRS values. The THI of all participants fell well above the cutoff threshold for adequate signal strength published by the manufacturer. Furthermore, THI values did not differ significantly between affected and unaffected hands of CRPS 1 patients and between dominant and non-dominant hands of volunteers. This indicates that any atrophy of muscle mass is unlikely responsible for the observed changes.

Despite lower StO\textsubscript{2}, occlusion and reperfusion slopes derived from VOT failed to show changes that were unique to affected hands of CRPS 1 patients. Although the occlusion slopes were significantly steeper in the non-affected hands compared with affected hands of patients, a similar significant difference was identified between the dominant and non-dominant hands of volunteers. Furthermore, comparisons of slope measurements between non-dominant hands of volunteers and affected hands of CRPS 1 patients failed to reveal significant differences. This may suggest that the vasoreactivity of the microcirculation of affected hands in the patients was unchanged by CRPS 1. Alternatively, microcirculatory vasoreactivity could have been initially impaired at the onset of the syndrome but then recovered. This would have been missed in the present study since all patients recruited were in the chronic phase of CRPS 1. Future investigations recruiting acute phase CRPS 1 patients will be required to determine if this temporal relationship may exist.

It is intriguing to speculate that the lowered StO\textsubscript{2} observed with NIRS relates to the pathogenesis of CRPS 1. Nevertheless, there are several important limitations of this experiment that do not permit us to make this causal inference. These limitations may also help to explain the lack of correlation with BPI or DASH questionnaire scores. Nonetheless, observations from this study and the limitations identified are noteworthy as they can inform the design of future studies investigating the relationship between these variables.

The results of this study may have been influenced by the heterogeneity of CRPS 1 pathophysiology. The nature and location of the injuries resulting in CRPS 1 were variable between patients. NIRS probes used in this investigation are validated for placement over the thenar eminence and provide measurements solely of local tissue oxygenation. If the probe were not placed over the region of the original tissue injury that may have incited the

![Figure](https://example.com/figure.png)

**Figure** Baseline StO\textsubscript{2} of study groups. StO\textsubscript{2} is significantly less in CRPS 1 affected hands when compared with the contralateral unaffected hands as well as with the non-dominant hands of healthy controls. *P < 0.05. StO\textsubscript{2} = tissue oxygen saturation; CRPS 1 = complex regional pain syndrome type 1

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Differences in VOT measured values within groups and between CRPS 1 affected and non-dominant control hands, represented as mean difference (95% confidence interval); P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>StO\textsubscript{2} (%)</td>
</tr>
<tr>
<td>CRPS 1 affected vs unaffected</td>
<td>−5.8 (−10.6 to −1.0); 0.02</td>
</tr>
<tr>
<td>Control Dominant vs non-dominant</td>
<td>0.6 (−1.7 to 2.9); 0.57</td>
</tr>
<tr>
<td>CRPS 1 affected vs non-dominant control</td>
<td>−7.3 (−12.4 to −2.3); 0.007</td>
</tr>
</tbody>
</table>

CRPS 1 = complex regional pain syndrome type 1; StO\textsubscript{2} = tissue oxygen saturation; VOT = vascular occlusion testing

 Springer
disorder, it is possible that changes in the microvasculature from I-R injuries may not have been detected. Although this study captured tissue hypoxia in the thenar eminence of some patients, tissue hypoxia at other anatomical locations away from probe placement may have been missed. It is important to point out that those patients who had the most profound decreases in StO₂ seemed to be those whose original injuries were in the vicinity of the thenar eminence. This observation may highlight the significance of NIRS probe placement when evaluating microvascular perturbations and CRPS 1 symptomology.

Variation in NIRS values found in the hands of CRPS 1 patients may also represent the dynamic nature of the disease process. Commonly, patients will report that their affected limbs will go through cycles of pain, colour, and temperature changes, in addition to becoming more or less swollen. Since patients in this observational study were studied at only one time point, there is a possibility that changes in NIRS values were missed depending on the state of the tissues at the time of measurement. Patients in this study had a mean (SD) duration of symptoms lasting 1,255.4 (1,076.2) days, leaving them in the chronic phase of the disease process. This study did not evaluate patients in the acute phase of CRPS 1, which may have produced different results. Furthermore, tissue oxygenation was not measured during use of the thenar muscles. As such, dynamic tissue oxygenation was not evaluated, and deficiencies in StO₂ from impaired blood flow may have been overlooked. Dynamic muscle testing could lead to novel findings for this patient population as patients typically report increasing pain with increased hand use.

Pooling the measured values for statistical analysis also assumes a uniform mechanism of pathology among all patients. Nevertheless, CRPS 1 is likely a clinical entity that encompasses a broad range of pathophysiological processes, some of which may or may not be maintained by tissue hypoxia. Consequently, detected changes in StO₂ may be seen in only a particular subset of patients. Analyzing the results and assuming homogeneity of the pathophysiological process is possibly a mistaken assumption.

A key issue preventing a causal relationship between StO₂ and CRPS 1 in this study is the lack of a temporal relationship between these two factors. The StO₂ of patients’ hands were unknown prior to the initiation of the signs and symptoms of CRPS 1. Therefore, comments cannot be made regarding any sequence of diminished oxygen saturation leading to CRPS 1. Future studies to help elucidate this temporal association will be needed to make a stronger case for the microvasculature injury hypothesis of CRPS 1 using NIRS.

A causal relationship between the reduced tissue oxygenation and CRPS 1 is further confounded by the presence of alternate explanations that may lead to this study’s findings. The patients with CRPS 1 who were tested had a high proportion of surgical procedures performed in the vicinity of the NIRS probe placement. There is a possibility that tissue changes imposed by surgical dissection may be responsible for some of the differences in oxygen saturation detected. A separate study investigating NIRS values with VOT in patients with and without surgery would be warranted to determine if this is a significant confounding factor.

Microvascular changes can also be induced in tissue that is immobilized. It is plausible that the painful hands of patients with CRPS 1 were not being used as often as the non-painful hands, thereby altering microvascular function. Investigations have revealed that disused skeletal muscle shows evidence of capillary degeneration and loss, reduced blood flow, and reduced arteriolar responsiveness. Using NIRS to evaluate patients who have been immobilized, such as patients requiring casting, may help to clarify this confounding variable.

Near-infrared spectroscopy technology was used in one study to compare the oxygenation in the affected upper limbs of CRPS 1 patients with the unaffected arm and healthy control subjects. Contrary to our study’s findings, the investigators found no signs of hypoxia in the forearm muscles of 30 patients at rest and during isometric handgrip exercises. This discrepancy cannot be readily explained; however, the location of the inciting injury in relation to the location of probe placement was not described. As our study suggested, probe placement may be of importance when looking for aberrations in oxygenation.

There are a number of uncertainties that have arisen from this study that require further examination. Consequently, future investigations should address the following issues: whether NIRS probes must be placed close to the site of

| Table 5 | Spearman’s rank-order correlations between baseline StO₂ of CRPS 1 affected hands and measures of pain and interference from the BPI and DASH questionnaire scores |
|-----------------|-----------------|-----------------|
| Correlation coefficient | 95% Confidence interval | Significance |
| BPI average pain | 0.07 | -0.7 to 0.8 | 0.9 |
| BPI least pain | 0.45 | -0.03 to 0.4 | 0.2 |
| BPI worst pain | -0.1 | -0.7 to 0.6 | 0.8 |
| BPI interference score | 0.3 | -0.5 to 0.9 | 0.3 |
| DASH questionnaire score | 0.2 | -0.7 to 0.7 | 0.9 |

CRPS 1 = complex regional pain syndrome type 1; StO₂ = tissue oxygen saturation

BPI = Brief Pain Inventory questionnaire; DASH = Disability of Arm, Shoulder and Hand questionnaire
initial injury to detect oxygen saturation changes, whether reduced StO2 can be found in other painful hand conditions (such as carpal tunnel syndrome), whether oxygen saturation changes in CRPS 1 are dynamic, whether immobilization of muscle can change NIRS values, and finally, whether there is a difference between NIRS and VOT values in acute vs chronic CRPS 1.

In summary, hands of patients affected by CRPS 1 of the upper limb showed significantly lower StO2 compared with their unaffected contralateral hand as well as the hands of control volunteers. The present study may lend further support to the theory that deep tissue hypoxia from microvascular pathology may drive the pathogenesis of CRPS 1 for some patients.

Acknowledgements The authors appreciate the assistance of Dean Meyer and Hutchinson Medical for support and provision of the tissue oximetry device for our research. The authors also thank Yves Bureau for statistical support and Cathy Rohfritsch for assistance with patient recruitment and testing.

Funding Research funding was obtained from an Internal Research Fund provided by the Department of Anesthesia and Perioperative Medicine, University of Western Ontario. The project was also supported in part by grant #11-41 from the Physicians’ Services Incorporated Foundation.

Conflicts of interest None declared.

References