Changes Resembling Complex Regional Pain Syndrome Following Surgery and Immobilization

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Abstract: The study of complex regional pain syndrome (CRPS) in humans is complicated by inhomogeneities in available study cohorts. We hoped to characterize early CRPS-like features in patients undergoing hand surgery. Forty-three patients were recruited from a hand surgery clinic that had elective surgeries followed by cast immobilization. On the day of cast removal, patients were assessed for vasomotor, sudomotor, and trophic changes, and edema and pain sensitization using quantitative sensory testing. Pain intensity was assessed at the time of cast removal and after 1 additional month, as was the nature of the pain using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS). Skin biopsies were harvested for the analysis of expression of inflammatory mediators. We identified vascular and trophic changes in the surgical hands of most patients. Increased sensitivity to punctate, pressure, and cold stimuli were observed commonly as well. Moreover, levels of IL-6, TNF-alpha, and the mast cell marker tryptase were elevated in the skin of hands ipsilateral to surgery. Moderate-to-severe pain persisted in the surgical hands for up to 1 month after cast removal. Exploratory analyses suggested interrelationships between the physical, quantitative sensory testing, and gene expression changes and pain-related outcomes.

Perspective: This study has identified CRPS-like features in the limbs of patients undergoing surgery followed by immobilization. Further studies using this population may be useful in refining our understanding of CRPS mechanisms and treatments for this condition.

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Complex regional pain syndrome (CRPS) is a painful, disabling, and often chronic condition principally affecting the extremities. While acute CRPS sometimes improves spontaneously or with aggressive physical therapy, CRPS present for a period of 1 year or greater seldom spontaneously resolves, and worsens in many patients from years 1 to 8 after onset. Trauma to the distal extremities is a frequent cause of CRPS. For example, the estimated incidence of CRPS after extremity surgery depends to a degree on the specific procedure, but by all accounts the problem is common. The rate of CRPS is 8.3% after carpal tunnel surgery and greater than 30% after distal radius fracture in some series. Immobilization in the setting of trauma is a widely recognized factor predisposing patients to the development of CRPS, with 47% of all CRPS sufferers in 1 study having a history of medically imposed limb immobilization. Moreover, the nature of the syndrome is dynamic. The affected limb often progresses through an acute phase in which the limb is sensitive and swollen and displays an elevated temperature, to a chronic phase in which the inflamed appearance has resolved, but the pain and disability remain.

The heterogeneous nature of CRPS in terms of both etiology and duration in available study populations has made the study of the syndrome and its treatments challenging. This has led to the assembly of clinical research networks, the identification of new animal models, and the development of new approaches to the use of human subjects. One innovative approach to
neurogenic inflammation.40 In neither published report
immediately following cast removal.

applied either during the early postsurgical period or
progression or resolution of changes in the surgical limb; under study; 3) the potential opportunity to study the circumstances leading to the pathophysiological features generate the model; 2) the homogeneity of the inconvenient or potentially harmful intervention to acute CRPS include 1) the lack of requirement for an immobilization model of CRPS.22,30 The advantages of using such a population to study specific features of CRPS, would in fact display vascular, trophic, and nociceptive changes at the time of cast removal similar to those with acute CRPS, and that some patients would exhibit persistent changes. Furthermore, we hypothesized that postsurgical patients would express elevated cutaneous levels of interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)α, nerve growth factor (NGF), and tryptase, based on previous studies looking at elevated inflammatory mediator expression in CRPS patient skin blister fluid and skin biopsies,17,20,28 and skin from a rat fracture/cast immobilization model of CRPS.22,30 The advantages of using such a population to study specific features of acute CRPS include 1) the lack of requirement for an inconvenient or potentially harmful intervention to generate the model; 2) the homogeneity of the circumstances leading to the pathophysiological features under study; 3) the potential opportunity to study the progression or resolution of changes in the surgical limb; and 4) the potential ability to study interventions applied either during the early postsurgical period or immediately following cast removal.

Methods

Participants
The study protocol was first approved by the local Institutional Review Board. Forty-three participants were recruited from the weekly hand surgery clinic at the Veterans Affairs (VA) Hospital in Palo Alto, CA. Five women and thirty-eight men were enrolled after giving written informed consent. The principal inclusion criteria were 1) ages 18 to 75; and 2) status post hand/wrist surgery and cast immobilization of ≥12 days and availability for testing within 36 hours of cast removal. The principal exclusion criteria were 1) ongoing infection in either hand; 2) anticoagulation with agents other than aspirin; 3) neurological deficits potentially interfering with pain testing, neuropathic pain, or a history of CRPS; and 4) history of inflammatory skin diseases (psoriasis, dermatitis, etc).

Study Setting
Participants were met in the hand surgery clinic after their cast removal clinic appointment and were escorted to a private clinic space for enrollment and testing. The room was uniformly lit and temperature controlled to 21°C. A single research coordinator (A.P.) interacted with the study participants, performed all testing procedures, and collected all subjective data. Participants were seated at a table across from the research coordinator for all testing. For participants who elected to have a skin biopsy, the procedure was performed immediately after the conclusion of sensory testing in the same room. Follow-up phone calls were arranged for 28 days following cast removal.

Surgical and Medical Information
After providing written informed consent, the date, type, and location of surgery were collected in addition to any complications since the surgery. Hand dominance was recorded. The patients were queried as to pre- and postoperative pain medication use and duration of use, and these results were checked against the electronic medical record. The medical record was also reviewed for ongoing use of angiotensin converting enzyme inhibitors. Histories of psychological disease were recorded.

Pain Intensity and Characteristics
The nociceptive versus neuropathic nature of the patient’s pain was assessed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS).4 For assessment upon phone follow-up, we used the short form of the LANSS (5-LANSS), which has similar sensitivity and discriminatory properties to the parent scale, and a specificity of approximately 80%.5 Pain intensity was assessed on the day of cast removal and 1 month later in both the surgical and contralateral hands.

Average Pain
At the time of cast removal and 1 month later, average pain from the preceding 7 days was assessed using a verbally administered 0 to 10 numerical rating scale (NRS). This scale is sensitive and has relatively robust statistical properties.34

Dynamic Pain
At the time of cast removal and 1 month later, pain experienced immediately after opening/closing the hand to make a fist 4 times, excluding movement of any digits involved in surgery, was assessed using the 0 to 10 NRS.

Physical Observations
Both distal forearms and hands were visually assessed for erythema, difference in hair growth, difference in nail texture, and sweating. All observational and pain testing measurements were conducted first on the contralateral hand followed by the surgical hand.

Temperature
The temperature at 3 locations (center of the dorsum, pulp of digit 3, and center of the palm) was recorded.
with an infrared thermometer (Exergen DT-1000 Infrared Dermal Thermometer; Exergen Corp, Watertown, MA).

**Edema**

Hands were assessed for edema using a flexible measuring tape and the figure-of-eight measurement technique to quantify circumference. This method has sensitivity and intertester reliability similar to that of standard volumetry.21

**Mechanical Allodynia**

To assess allodynia, a cotton ball was lightly brushed 3 times along the dorsum of the contralateral hand as described by Bennett.4 Participants were asked if this was a normal sensation. The cotton ball was then lightly brushed 3 times along the dorsum of the operative hand at least 4 cm distant from the surgical incisions, and participants were asked whether this was a normal sensation or unpleasant or unusual in any way, eg, by evoking tingling or nausea. Unpleasant sensation experienced in the surgical hand was recorded as allodynia.

**Quantitative Sensory Testing (QST)**

The QST modalities tested reflected some of those most robustly changed in reports involving large CRPS patient cohorts and in a previously reported human model of CRPS involving cast immobilization.14,39

**Punctate Mechanical Pain**

Punctate mechanical pain thresholds were measured on the dorsum of the hand at least 4 cm distant from the operative location. These measurements were accomplished using an electronic von Frey anesthesiometer (Electronic von Frey Anesthesiometer model 2390; IITC Inc. Life Science, Woodland Hills, CA) fitted with a supplied rigid tip. During testing, the palm of the hand rested on a solid surface. The von Frey anesthesiometer was pressed perpendicularly against the skin of the dorsum, and pressure was applied at a constant rate until pain was reported. The thresholds were determined by averaging 3 individual measurements on each hand assessed in matched locations.

**Joint Pressure Pain**

Joint pressure pain thresholds were tested in the metacarpophalangeal joints of digits 2 to 4 of the contralateral and surgical/immobilized hand. This was performed with a pressure algometer (Commander; JTECH Medical, Salt Lake City, UT). During testing, the palm of the hand rested on a solid surface. The rod with a curved fingertip attachment was pressed perpendicularly against the skin above the metacarpophalangeal joints, and pressure applied at a constant rate of 2 N/second until pain was reported. Three measurements per joint were made and all measurements averaged for each hand.

**Interdigital Skin Fold Pressure Pain**

The pressure algometer described above fitted with a 1-cm² rubber-tipped rod was used to assess pressure pain on a dermal fold between digits. The skin between digits 2 and 3 was used, as the larger first interdigital skin fold was often within a few centimeters of the surgical area. Participants’ palms rested against a solid surface with fingers slightly abducted. The pressure algometer was pressed perpendicularly against the skin between the digits at a constant rate (2 N/second) until pain was reported. Three measurements per hand were made and measurements averaged for each hand.

**Cold Hyperalgesia**

Cold pain threshold was assessed using a thermal sensory analyzer and a 32 × 32-mm probe (Medoc TSA 2001 Thermal Sensory Analyzer Probe; Medoc Instruments, Ramat Yishai, Israel). During testing the palm of the hand being tested rested on a solid surface while the research coordinator (A.P) held the probe against the dorsum. The participants’ contralateral hand operated a mouse to stop cooling when cold pain was first sensed. For determination of cold pain threshold, 5 successive stimulations starting from a baseline temperature of 32°C decreasing by 1°C per second were averaged for each hand.

**Skin Biopsy**

Participants were presented with the option of participating in the skin biopsy portion of the study. If the subject elected to undergo biopsies, the procedures were performed directly after completion of other testing. One 3-mm punch biopsy was collected from the dorsum of each hand with the surgical hand biopsy at least 4 cm from any incision using a commercially available kit (Acuderm Inc, Ft Lauderdale, FL). The biopsy sites were cleaned with alcohol, and a small amount of 1% lidocaine was injected via a 30-gauge needle. A 3-mm disposable punch biopsy instrument was used. Inward pressure was placed on the instrument while it was rotated. When subcutaneous fat was reached, the instrument was removed. The circular biopsy was elevated and the base freed using an Iris scissor. Pressure was applied to assure hemostasis. Topical antibiotic was applied and a small bandage placed. No sutures were necessary.

**Tissue Processing and Quantification of Gene Expression**

Immediately after harvest, the skin biopsies were stored in RNA later stabilization reagent solution (Qiagen, Valencia, CA) for 1 to 4 months at −80°C. Total RNA from the samples was then extracted using RNeasy Micro Kit (Qiagen) and quantified using a NanoDrop ND-1000 UV-Vis spectrophotometer (NanoDrop Technologies, Wilmington, DE). At that point, cDNA (20 μL final volume) was synthesized from 500 ng RNA using a QuantiTect Reverse Transcription Kit (Qiagen). Real-time polymerase chain reactions (PCRs) were performed with fluorescent probes using either Quantifast duplex PCR detection kits (Qiagen) or QuantiTect SYBR Green-based real-time PCR Kit (Qiagen) in ABI PRISM 7900HT Sequence Detection System (Life Technologies, Grand Island, NY) according to the manufacturers’
instructions. TNF-α, TPSAB-1 (tryptase), NGF, IL-1β, and IL-6 transcripts were individually subjected to duplex analyses with glyceraldehyde 3-phosphate (GAPDH) using 2 different fluorescent dyes, while IL-1β and GAPDH were detected by separate reactions with singleplex expression analyses for each dye. To validate the primer sets used, we performed dissociation curves to document single product formation. The data were analyzed by the comparative cycle threshold method, as described in the manufacturer’s manual. All assays were performed in triplicate for each sample.

**Data Handling and Statistical Analysis**

The patient database was kept on password-protected equipment in a locked room, and data files on portable devices were encrypted. The data security plan was approved by the Institutional Review Board. Statistical analysis of data and the preparation of data plots were performed using Prism 5 software (Graphpad Software, LaJolla, CA). Comparisons of mean values for parametric data were conducted using t-testing. Correlational analysis was conducted using the Pearson approach for parametric data and the Spearman approach for non-parametric data, eg, the LANSS scores. Data are presented as mean ± standard deviation or as box and whisker plots. The minimum level of significance was $P < .05$.

**Results**

**Demographics and Treatment Characteristics of the Study Cohort**

Our study cohort consisted of 43 patients attending a hand surgery clinic at a single medical center. Most patients were middle-aged, and strong bias existed toward male participants, characteristic of a Veteran’s Affairs medical center (Table 1). Approximately one-third of the patient cohort had a psychiatric diagnosis of depression or anxiety at the time of surgery. The most common procedures performed on the patients included carpo-metacarpal arthroplasty for degenerative disease, followed by stabilization of fractures involving the hand, bone fusion procedures, and soft tissue operations such as tendon transfers. The period of immobilization averaged between 4 and 5 weeks.

**Vascular, Sudomotor, and Trophic Changes in the Surgical Limbs**

On the day of cast removal the surgical and contralateral limbs were inspected. Table 2 and Fig 1 provide data demonstrating that differences between the limbs for each of these characteristics were found in many but not all patients. Erythema and trophic changes of the nails were relatively common, though abnormal sweating was seldom evident based on physical examination. Both edema, defined as a measured circumference at least .5 cm greater than that of the contralateral hand, and elevated skin temperature, defined as a temperature >1°C above the contralateral hand, were common as well. Most patients had multiple observable changes in the surgical limbs.

**Spontaneous and Dynamically Evoked Pain**

Patients were asked to rate the average pain in their surgical extremities over the preceding week using a 0 to 10 NRS. These assessments were made at the time of cast removal and 1 month following cast removal. For the week preceding cast removal the mean average pain intensity was 3.9, and 1 month later was 3.0 ($P = .08$, paired t-test). Even 1 month from the time of cast removal, 42% (18/43) of patients reported moderate-to-severe pain in the surgical hand (Fig 2A). Likewise, mean dynamic pain at the time of cast removal was 3.5, and 1 month later was 1.8 ($P < .001$, paired t-test). For this measure, 23% (10/43) continued to experience moderate-to-severe pain (Fig 2B).

**The Quality of the Pain in the Operative Hands at the Time of Cast Removal and 1 Month Later**

The LANSS helped differentiate the postoperative pain as primarily neuropathic versus nociceptive. This scale has been used to detect neuropathic contributions to pain after surgery and other forms of trauma. Use of this instrument indicated that 10/43 patients (23%) experienced pain, having a neuropathic versus nociceptive component.

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**Table 1. Demographic, Psychiatric, and Surgical Characteristics of the Patient Cohort (N = 43)**

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<th>Demographics</th>
<th>Psychiatric Diagnoses</th>
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<td>Sex (M/F)</td>
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<tr>
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<th>Total Findings</th>
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<td>None</td>
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<tr>
<td>Nail growth differences</td>
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<tr>
<td>Sweating in surgical hand</td>
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<tr>
<td>Warmth (≥1°C)</td>
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<td>2</td>
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<tr>
<td>Edema (≥ 5-cm increase)</td>
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NOTE. Demographic and psychiatric information was taken from the patients’ electronic medical records. Data pertaining to the surgical procedures, the hand-waxing of the patients, and the period of immobilization after the surgical procedures were collected at the time of cast removal.

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nociceptive character on the day of cast removal, while 1 month later 15/43 (35%) met LANSS criteria for pain of neuropathic character. Pain intensity for those experiencing pain of nociceptive versus neuropathic character was similar at the time of cast removal (3.6 versus 4.6, \( P > .05 \)), but significantly higher for those experiencing neuropathic symptoms 1 month after cast removal (2.1 versus 4.6, \( P < .001 \)). Of the 15 patients experiencing pain of neuropathic character 1 month after cast removal, only 6 had positive LANSS scores at the time of cast removal. Thus, in the month following cast removal, 9 patients experienced the emergence of pain having neuropathic characteristics, a trend similar to that previously reported for postsurgical patients.34

**Quantitative Sensory Testing**

Fig 3 presents data demonstrating robust decreases in punctate pain thresholds in hands ipsilateral to surgery versus the paired contralateral hands. The average decrease in punctate pain threshold was 36%. Significant reductions in pressure pain thresholds were also found when the stimulus was applied to either the interdigital skin folds (24%) or metacarpophalangeal joints (20%). Finally, an increase in the cold pain threshold was observed (6.1°C in surgical hands versus 4.3°C in the contralateral hands). Thus, multiple testing modalities demonstrated a relative pain sensitization of the hand on the operative side.

**Biochemical Markers in Skin Tissue**

Skin biopsies were harvested from both the surgical and contralateral hands at the time of cast removal from 19 patients willing to undergo the biopsy procedure. Processing this tissue for analysis at the mRNA level was conducted for the cytokines IL-1β, IL-6, and TNFα, the neurotrophin NGF, and the mast cell marker enzyme tryptase. Analysis revealed a statistical increase in IL-6, TNFα, and tryptase expression in the surgical hand skin versus the contralateral hand (Fig 4).

**Exploratory Analyses**

Our studies were designed primarily to describe physiological and sensory changes occurring in the hands of patients after surgery and immobilization. Our dataset did support, however, exploratory analyses of possible links between patient characteristics, biochemical alterations, and sensory changes and our selected pain outcomes.

We first examined correlations between QST parameters and pain outcomes. Supplementary Table 1 provides data demonstrating correlations between QST measurements and pain outcomes such as dynamic pain, NRS average pain intensity, and LANSS score at the time of cast removal and 1 month later. Potential correlations were observed between lower punctate pain thresholds in the hands of patients ipsilateral to surgery and higher dynamic pain ratings, and between lower punctate pain thresholds and higher LANSS scores at the time of cast removal. Likewise, experiencing cold pain at a higher temperature was associated with the same 2 pain-related outcomes.

Demographic factors may influence susceptibility to CRPS. Because of the nature of the sample (only 5 female patients), we were not able to examine the effect of sex on the outcome parameters. Correlations between age and QST measurements were, however, very suggestive. Inverse (age protective) correlations were observed.
between age and punctate pain \( (r^2 = -0.30, P < .05) \) as well as joint pressure \( (r^2 = -0.31, P < .05) \) and cold \( (r^2 = 0.37, P < .05) \) contralateral-ipsilateral differences at the time of cast removal. Age was poorly correlated with the pain outcomes, though advancing age had a marginal correlation \( (r^2 = -0.28, P = 0.07) \) with lower LANSS scores at the time of cast removal.

We also examined the relationship between skin levels of the measured inflammatory mediators and pain outcomes. For these analyses we attempted to correlate the ratio of mediator expression in the skin of surgical versus contralateral hands with pain outcomes at the time of cast removal and 1 month later. These revealed correlations between the skin NGF expression ratio and both dynamic \( (r^2 = 0.55, P < .05) \) and NRS \( (r^2 = 0.55, P < .05) \) pain at 1 month after cast removal along with the skin IL-1\( \beta \) ratio and LANSS at 1 month after cast removal \( (r^2 = 0.52, P < .01) \).

**Discussion**

CRPS is a problematic condition. The condition has its peak incidence in middle age, particularly in women,\(^{11,31}\) though children can be affected as well.\(^{37}\) Disability is very common in the setting of CRPS and can be progressive.\(^{36,42}\) The condition itself is enigmatic in its etiology and frequently changes in its clinical characteristics over time.\(^{8}\) Though significant progress has been made using newer rodent CRPS models\(^{15,27}\) and by applying carefully designed experimental paradigms to human volunteers in pain laboratories,\(^{39}\) translating these findings into clinical populations has been difficult due to the limited availability of subjects and the heterogeneity of the assembled cohorts in terms of etiological factors, duration of the symptoms, and histories of treatment. In the present set of studies we characterized the limbs of patients who underwent hand and wrist surgery followed by several weeks of immobilization, a set of factors known to predispose patients to developing CRPS. Many of the postsurgical patients exhibited CRPS-like changes immediately after cast removal in terms of surgical extremity warmth, edema, pain sensitization, and the production of inflammatory mediators in the skin (Figs 1 and 2, Table 2). These postsurgical patients may be useful in CRPS research as well as in understanding the broader issue of the transition from acute to chronic postoperative pain.

Pain-related changes occurring after distal upper extremity surgery and cast immobilization were assessed using several approaches. At the time of cast removal most patients had at least mild movement-induced pain in the hand and experienced at least mild pain over the preceding week (Fig 2). This pain decreased over the first month for many patients, but it is remarkable that 42% of patients (18/43) persisted in showing moderate-to-severe levels of pain (4/10 or greater) 4 weeks after cast removal, or about 8 to 9 weeks on average from the time of surgery. Though the LANSS questionnaire has important limits in terms of sensitivity and specificity, scores indicated that many patients experienced neuropathic-like pain characteristics more than 1 month after cast removal. Nociceptive-type pain was less severe on average. Evidence of neuropathia was associated with more severe pain in a recent population-based study of persistent postoperative pain.\(^{18}\) Importantly, 9 patients appeared to convert from a primarily nociceptive to a primarily neuropathic-type pain by 1 month after cast removal. This observation is similar to the increasing neuropathic symptoms observed in patients in the months following thoracotomy.\(^{34}\) The Budapest CRPS diagnostic criteria include the evaluation of patients for signs related to sensory, vasomotor, sudomotor/edema, and motor/trophic changes.\(^{16}\) All of our patients showed sensory changes in at least 1 of the QST tests, and almost all patients had 1 or more additional signs consistent with the Budapest CRPS criteria (Table 2). Importantly, our study was not designed to determine the incidence of CRPS itself after surgery, particularly at the 1 month post-cast-removal time point. However, the location of pain in
nonsurgically involved tissues, the neuropathic character of the symptoms, and the observation of trophic and vascular changes in the limbs of many of the patients suggest that pain occurring after cast removal in surgical limbs may arise from causes other than those involved in the primary healing process.

The QST testing performed on areas of the hand ≥4 cm removed from the surgical site demonstrated pain sensitization in the limbs ipsilateral to surgery in comparison to the contralateral limbs (Fig 3). The testing modalities were selected based on the results of testing performed on humans with CRPS in previous studies. While no single testing modality shows profound changes in every CRPS patient, mechanical allodynia, cold hyperalgesia, and pressure hyperalgesia are found in approximately 30 to 70% of CRPS patients, and most patients show a combination of modes of sensitization. Our measurements demonstrating lateralized decreases in punctate mechanical pain thresholds were clear and demonstrated a 36% decrease on average. Likewise our pressure pain measurements in joints and interdigit skin folds showed thresholds reduced 24 and 20%, respectively, in the ipsilateral versus contralateral hands, with most patients showing sensitization in the surgical hand for both these traits. Interestingly, pressure pain threshold was the QST parameter most frequently found to be changed in patients with CRPS type 1 in a review of 298 patients with this diagnosis.

We extended our observations to the biochemical level. Several studies have found that inflammatory mediators, including IL-6 and TNFα, are elevated in the venous blood, skin blister, and skin of CRPS-affected limbs. These cytokines have been linked to pain or pain sensitization in numerous human and animal studies. We found that IL-6 and TNFα expression was significantly increased in the skin of the surgical compared to contralateral limbs, though the range of the increases for these mediators was broad (Fig 4). It was concluded that keratinocytes are the major, but not necessarily only, source of these mediators in a rat tibia fracture/cast immobilization CRPS model. Prior studies using this rat model of CRPS also demonstrated elevated levels of IL-1β and NGF in the skin after 4 weeks cast immobilization. While we did observe trends toward increases of these mediators, they were not significantly changed. Lastly, prior skin studies in CRPS patients and in the rat fracture/cast CRPS model indicate that mast-cell-derived tryptase is elevated in the injured extremity. Mast cells may act through the liberation of any of a number of mediators in addition to tryptase itself to support pain sensitization, including histamine, prostaglandin E2, leukotrienes, and TNFα. The skin biopsies collected after removal of the casts from the surgical patients showed an increase in tryptase expression. Collectively, these results suggest that the biochemical changes in the skin of patients after hand/wrist surgery and immobilization are similar to those observed in CRPS patients.

While this study was designed primarily to examine the physiological, sensory, and biochemical changes in the limbs of patients undergoing surgery and extended immobilization, we did perform exploratory analyses attempting to identify interrelationships between the traits and factors we assessed. Limitations in study power restrict our ability to rely on the negative results, and the multiple comparisons intrinsic to performing correlative analysis on large data matrices suggest caution in interpreting positive findings. However, our findings do suggest that QST measures such as punctuate and cold pain thresholds may be related to pain, particularly the neuropathic contributions to that pain experienced in the immediate postimmobilization period. Potentially highly significant for mechanistic studies, the changes in the levels of IL-1β and NGF in skin measured at the time of cast removal appeared to be related to pain experiences up to 1 month later. Correlations involving NGF may be especially important as they were identified between skin levels of this mediator and dynamic pain as well as average NRS pain over the preceding week. This neurotrophin has been linked strongly to multiple forms of pain including CRPS using a fracture/cast pain model involving 4 weeks of immobilization, an immobilization

**Figure 4.** Lateralized differences in skin mediator levels 1 month after hand surgery. For these analyses, 3-mm skin biopsies were collected from skin at least 4 cm distant from surgical incisions on the dorsal surfaces of the hands at the time of cast removal and sensory measurements. Samples were processed for mRNA analysis, and target mRNAs were quantified using real-time quantitative PCR. For the purposes of data display the data were normalized to a contralateral side mediator level of 1. The data are displayed as mean ± SD, *P < .05, **P < .01. (A) IL-1β mRNA levels; (B) IL-6 mRNA levels; (C) TNFα levels; (D) NGF mRNA levels; (E) Tryptase mRNA levels.
period similar to the average immobilization imposed on our patients (33 days). Moreover, anti-NGF agents have proven beneficial in controlling pain in clinical populations, although concerns over the consequences of long-term use have arisen. More broadly, it has been suggested that immunotherapies of various types might be helpful in controlling CRPS. If future studies are consistent with the current results, it may be reasonable to determine if perioperative or short-term postoperative suppression of cytokine or NGF signaling, or perhaps inhibition of mast cell activity, could reduce subacute postoperative pain, reduce the occurrence of CRPS, or enhance the functional outcomes of limb surgeries.

In this report we provide data demonstrating that the study of patients undergoing distal limb surgery with subsequent immobilization might provide a useful pain model. These patients exhibit CRPS-like changes at least around the time of cast removal, and many experience moderate-to-severe pain for at least a month afterward. It seems plausible that this model could be used to study approaches to reducing persistent postoperative pain and other CRPS-like changes, if not CRPS itself. On the other hand, the diversity of sensory and biochemical changes after this type of surgery and the correlations that likely exist between some of these factors suggest that larger studies or studies focused on specific factors might enlighten us about fundamental mechanisms supporting or suppressing the development of CRPS or persistent postoperative pain. It should be recognized that our study population was predominantly male, distinct from the overall sex distribution of CRPS sufferers, and psychological disease was common. Though a recent report suggests a lack of effect of sex on the propensity to develop CRPS, caution should be used in generalizing our observations. While this model is unlikely to be suitable to address all questions, it is our hope that this or similar approaches may allow fundamental biological and therapeutic discoveries to be made by combining experimental investigations with standard clinical care.

Supplementary Data
Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.

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