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Tourniquet Constriction Exacerbates Hyperalgesia-related Pain Induced by Intradermal Capsaicin Injection

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Background: **When capsaicin is injected intradermally, hyperalgesia develops around the injection site. The authors observed that volunteers report painful sensations in the skin remote from the injection site during tourniquet constriction of the affected extremity.**

Methods: **Each volunteer received an intradermal injection of capsaicin on the volar forearm, followed by intermittent tourniquet constriction of the extremity. In some participants, the tourniquet position was rotated between different sites on the upper extremities. Laser Doppler measurements were made in the skin to measure capillary blood flow during pain magnification.**

Results: **Hyperalgesia developed in the volunteers who were tested after the capsaicin injection. Blood flow increased three times in the dermal capillaries remote from the injection site after capsaicin injection. The tourniquet-induced pain reached peak intensity soon after tourniquet inflation. Tourniquet constriction of the arm on the affected side reliably induced painful exacerbation in each person tested. The quality of the sensation was described as burning and extended across the arm in most volunteers. Only when pinprick hyperalgesia was detectable did the volunteers experience the diffuse, immediate pain sensation. The pain initiated by the tourniquet constriction likely is related to changes in skin capillary blood flow.**

Conclusions: **Low cutaneous blood perfusion is related to the intensity of ongoing, spontaneous pain when secondary hyperalgesia is present. The specific trigger(s) have yet to be identified. (Key words: Cutaneous blood flow; ischemia; pain.)**

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HOT peppers have been used for centuries as a remedy for various ailments. Modern clinicians use the active ingredient capsaicin most commonly to relieve pain. Topical application of capsaicin to skin or mucus membranes and intrathecal administration causes the release and ultimate depletion of substance P and calcitonin gene-related peptide.[1–5] This response is thought to be the antecedent to pain relief when used for pain reduction. Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is a specific excitant of unmyelinated afferent fibers (C fibers). Because most C fibers conduct nociceptive impulses and produce acute symptoms that mimic some chronic pain syndromes, such as complex regional pain syndrome types I and II, capsaicin has been used as a probe to study the mechanisms of pain generation. An intradermal injection of a small amount of capsaicin evokes an intensely painful, burning sensation. The skin overlying the bleb raised by the injec-

tion is insensitive to noxious stimuli, but overlapping zones of hypersensitivity to heat, light touch, and punctate stimulation develop around it.[6] If the extremity is undisturbed, the subject will experience ongoing pain sensations that wax and wane in intensity. The location of the pain may be adjacent to or as far away as 15 cm from the injection site.[7] While conducting studies to further characterize these effects, we found that within 5 to 15 s of restricting blood flow to the extremity with a tourniquet, our participants experienced a painful sensation similar in quality to the initial injection but considerably more widespread. When the tourniquet was released, the symptoms were relieved immediately. The following psychophysical studies were conducted to characterize this phenomenon in regards to its latency, intensity, and reliability; to determine the optimal position of the tourniquet for creating the response; and to explore likely mechanisms, with particular emphasis on the relation between cutaneous blood flow and pain.

Methods

The studies were approved by the Clinical Research Institutional Review Board of the National Institute of Dental Research. Fifteen healthy volunteers participated in these experiments, which consisted of 10 men and 5 women, whose ages ranged from 21 to 49 yr. Two of the volunteers participated in experiments 1 and 2, which are described here. The exclusion criteria were (1) a predisposition to developing allergic responses to foods; (2) a history of illness after ingesting foods containing hot peppers; or (3) a history of a chronic pain condition or other medical condition. Before beginning the experiments, each volunteer was taught how to use the pain intensity rating scale and given a logistical summary of the experiment. They expected that severe pain would occur after injection of the capsaicin, but no specific information was given about the effects of the tourniquet. They were instructed to report as accurately as possible any change in sensation. Three sets of experiments were conducted to meet the objectives of the study.

General Sequence of Events for Experiments

All 15 participants reclined in the supine position throughout the testing. A tourniquet (Inflatomatic Pressure Tourniquet; Zimmer, Inc., Warsaw, IN) was positioned on the upper arm and prepared for the initial inflation. The participants were instructed that they would be asked to rate their pain repeatedly after the capsaicin injection and before, during, and after tourniquet inflation. Pain intensity ratings were obtained at 5- and 15-s intervals during the inflation period. Five minutes after the capsaicin injection, the skin surrounding the injection site was tested for the presence of allodynia and hyperalgesia by stroking the skin with a 2 × 2 piece of cotton gauze and touching the skin with a weighted punctate probe. The weight applied to the probe was chosen before we started the experiment and was heavy enough to stimulate a sharp, but nonpainful, sensation. The tourniquet was inflated 10 to 15 min after the capsaicin injection, and pain intensity was assessed repeatedly during the constriction period. There was a 3-min resting period between each constriction period.

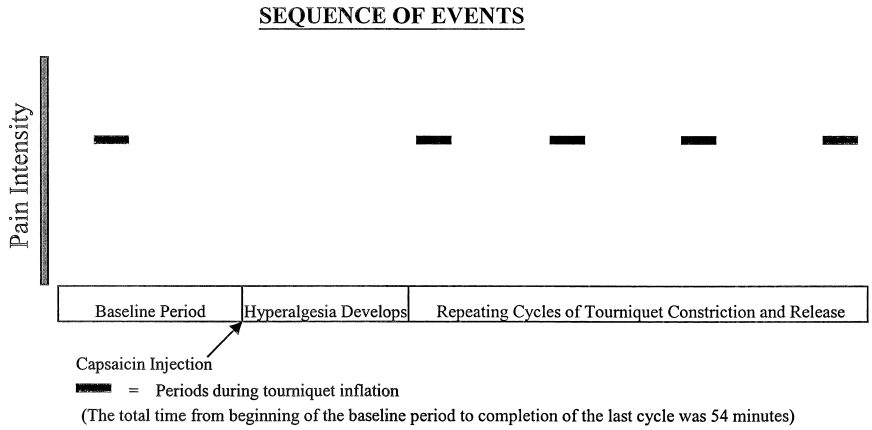

Fig. 1. The general sequence of events during each of the experiments. Pain intensity assessments were recorded before, during, and after tourniquet constriction and after capsaicin injection during the hyperalgesic development period. The cycle of tourniquet inflation and deflation was repeated at least four times during the experiments.

The sequence was repeated thereafter for several cycles. Spontaneous pain assessments were taken 15 s before the beginning of tourniquet inflation. The time line shown in figure 1 depicts the general sequence of events during the experiments.

Intradermal Capsaicin Injection

A single dose of 250 μg capsaicin in 25 μl of a polyoxyethylene (20) sorbitan monooleate (Tween 80) vehicle was injected intradermally midway between the wrist and elbow on the volar forearm using a 1-ml hypodermic syringe attached to a 26-gauge needle. The entire volume of capsaicin was injected rapidly, which produced a wheal within the dermis.

Pain Intensity Assessment

To assess pain intensity, the participants used a verbal analog scale.[8] This scale consisted of a 20-cm vertical bar. Adjacent to the right of the bar were pain descriptors ranging from "No Pain Sensation" at the bottom to "Extremely Intense" near the top. Each term (Extremely Intense, Very Intense, Intense Strong, Slightly Intense, Barely Strong, Moderate, Mild, Very Mild, Weak, Very Weak, and Faint) had an associated arrow pointing to a specific region of the bar. This pain rating scale was displayed on a single 11 $\times$ 8 inch white sheet. Participants were instructed to draw a single horizontal line through the bar to indicate their pain intensity for each measurement. A new sheet was shown at each time point.

Experiment 1

Tourniquet Response Characterization. Five persons participated in experiment 1, which was conducted to establish the reliability, latency, and intensity of the response. The control condition for these experiments was the baseline ongoing pain intensity just before tourniquet inflation. The tourniquet cuff pressure was set at 100 mmHg for each cuff inflation, with the cuff positioned on the arm just proximal to the elbow. The sequence of events were described before and are depicted in figure 1.

Experiment 2

Determining Optimal Tourniquet Position. Six persons participated in experiment 2, which was conducted to determine the optimal location of the tourniquet placement that induced the painful response. The control condition for this experiment was the baseline ongoing pain intensity just before tourniquet inflation. The tourniquet was inflated on the distal aspect of the contralateral upper arm for the initial test. Subsequent inflations were rotated between the proximal upper arm (just below the axilla), wrist, and distal upper arm on the ipsilateral side of the capsaicin injection. Because 100 mmHg cuff pressure induced minimal mechanical stimulation at the wrist, the tourniquet pressure was increased to 150 mmHg for each of these tests. A smaller cuff size was used at the wrist to accommodate its circumference. Aside from changing the location of the tourniquet site and the tourniquet pressure, the sequence of events proceeded as in experiment 1.

Experiment 3

Capillary Blood Flow and Pain Intensity. Six persons participated in experiment 3, which was conducted to determine if there was a difference between high and low capillary blood flow in the skin of the hyperalgesic arm and the level of pain intensity. The sequence of the experiment was as described for experiment 1. However, for the first two cycles of tourniquet constriction, 100 mmHg pressure was used to inflate the tourniquet. For the second two cycles, 150 mmHg pressure was used to inflate the tourniquet. Throughout the tourniquet constriction testing, the capillary blood flow in the skin was measured continuously using laser Doppler flowmetry (periflex). The probe was attached distal to the zone of secondary hyperalgesia on the skin near the wrist, to avoid exciting pain and to maximize the signal-to-artifact ratio. The tracings were stored on computer for analysis after completion of the experiment. Markings were made along the time axis to indicate the beginning and end of each manipulation.

Statistical Analyses

The baseline, ongoing pain measurements before each cuff inflation were averaged for comparison with the average peak pain intensity during tourniquet constriction. The data in experiments 1 and 2 were analyzed using a two-way repeated-measures analysis of variance. The *post hoc* comparisons used for experiments 1 and 2 were the Bonferroni and Tukey methods, respectively. The results from experiment 3 were analyzed using a paired Student *t* test to determine if there was a significant difference between peak pain

intensity ratings during high and low blood perfusion (SAS software; SAS Institute, Cary, NC).

Results

Capsaicin Injection

The initial pain induced after intradermal injection was described as a very intense, localized, burning sensation much like a bee sting. The latency to peak pain intensity was less than 5 s, and the pain diminished to 50% of peak within 10 min after injection. During the initial 5 min after injection, the location of the spontaneous pain changed from localized at the injection site to a diffuse zone of pain surrounding the injection site. The sensation was described as burning and superficial by all the participants, with some experiencing additional pain in deeper structures (muscles, tendons, and joints). Five minutes after injection, 13 of 15 participants had evidence of pin prick hyperalgesia and light touch allodynia. The pin prick was described as intensely sharp and moderately painful. The light touch allodynia was only mildly painful. A flare developed around the bleb site in each volunteer.

Experiment 1

Figure 2 shows the increase and decrease in pain intensity after the capsaicin injection and responses to the tourniquet constriction of the ipsilateral distal arm with 100 mmHg pressure. Tourniquet constriction of the arm before the capsaicin injection did not induce pain in any of the persons tested. After the capsaicin injection, each inflation of the tourniquet increased the pain intensity by more than 50% of the baseline ongoing pain. The pain induced by the tourniquet was described as a burning sensation, confined to the superficial surface of the volar forearm, extended from the distal edge of the cuff to the wrist. Unlike the rapid increase in pain after the capsaicin injection, there was a delay of 5 to 30 s before the onset of pain. For several participants, the tourniquet had to be released prematurely because the pain intensity was intolerable.

Experiment 2

Figure 3 shows the effect on pain intensity when the tourniquet position was altered. The tourniquet was first positioned on the arm contralateral to the injection site. Thereafter the tourniquet was positioned ipsilateral to the injection site and was rotated between the wrist and

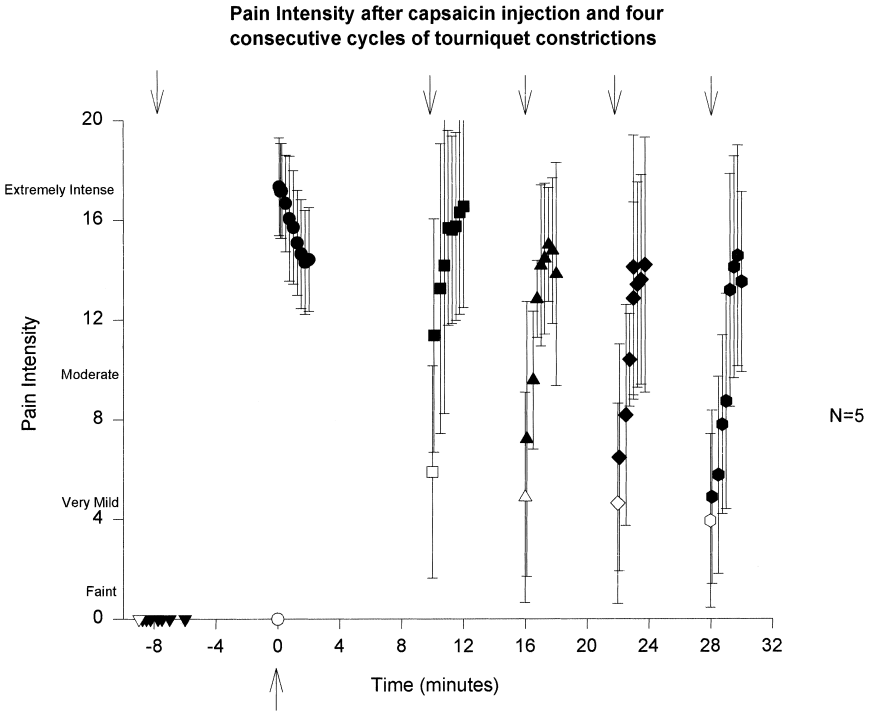

Fig. 2. The effects of tourniquet constriction and capsaicin injection on pain intensity. Downward-pointing arrows indicate the time of tourniquet inflation. The upward-pointing arrow indicates capsaicin injection. The closed circles indicate mean pain intensity (mean ± SD)

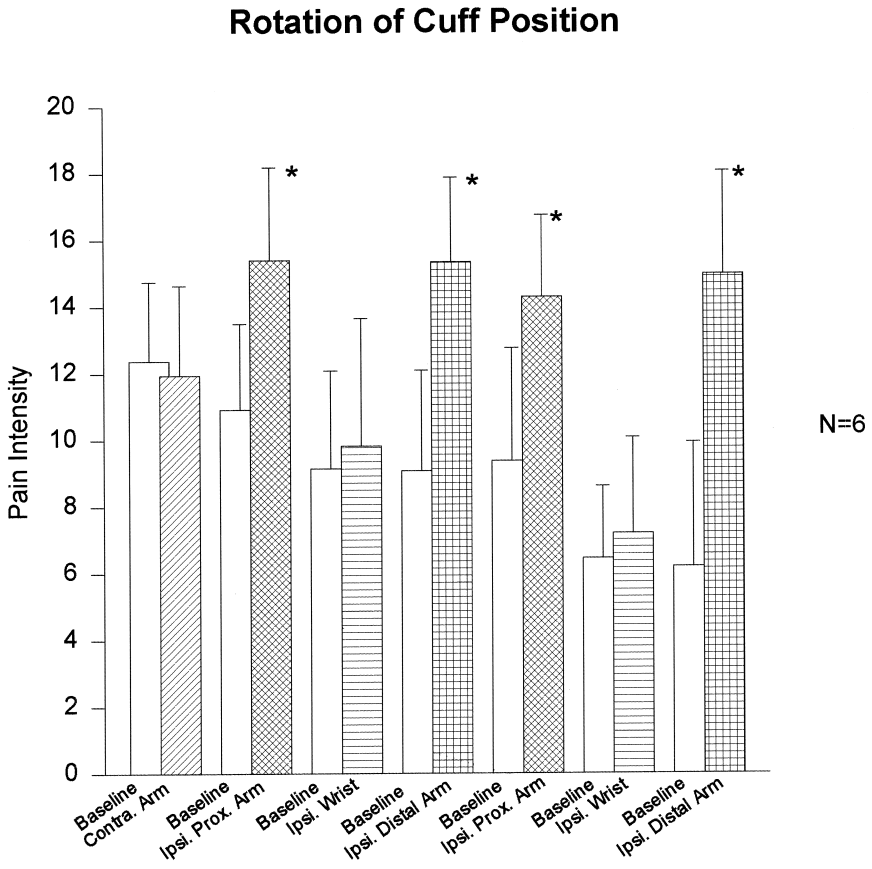

Fig. 3. The pain intensification effect on the capsaicin-injected extremity after tourniquet constriction of the affected (ipsilateral arm) and unaffected (contralateral arm) upper extremity. The effect of altering the location of the tourniquet position on the ipsilateral arm (proximal arm, distal arm, and wrist) is also shown. The mean baseline pain intensity ratings (white bars) are compared with the peak pain intensity ratings (filled bars) during tourniquet constriction. * $P < 0.002$.

the distal and proximal arm. The spontaneous pain intensity decreased steadily during the experiment. Constriction of the contralateral arm or the ipsilateral wrist failed to induce any increases in pain. Applying the tourniquet to the ipsilateral distal and proximal arm induced the greatest response. Two of the participants failed to develop secondary hyperalgesia. They experienced their pain in a much smaller localized area around the injection site, and more time was required for their pain to reach intense levels. Descriptions of the pain for all the volunteers matched those given in experiment 1.

Experiment 3

Capillary blood flow was measured using the laser Doppler throughout the experiment, beginning before the capsaicin injection. Figure 4 shows the change in blood flow in nonhyperalgesic skin, distal to the site of capsaicin injection and secondary hyperalgesia. Beginning immediately after the acute increase in pain from the capsaicin injection, the blood flow steadily increased on average three times or more.

Figure 5 shows the average pain intensity ratings and corresponding capillary blood flow measured using the laser Doppler. Each of the four cycles of tourniquet constriction tests performed resulted in a 50% or more reduction in capillary blood flow after tourniquet constriction. The pain assessments at least doubled in intensity within 30 s after inflation and reached peak intensity within 75 s. When the cuff was released, the capillary blood flow rebounded immediately to at least baseline levels and the pain decreased to 50% of peak intensity within 30 s and approached baseline intensity within 80 s. The difference between the peak pain intensity during high perfusion (1.43 ± 0.76, mean ± SD) and low perfusion (11.76 ± 3.25, mean ± SD) was significant at $\alpha = 0.05$ ($T = -8.5$, $P < 0.05$). There was a 5-s time lag after tourniquet inflation before significant pain intensity changes could be detected, compared with an immedi-

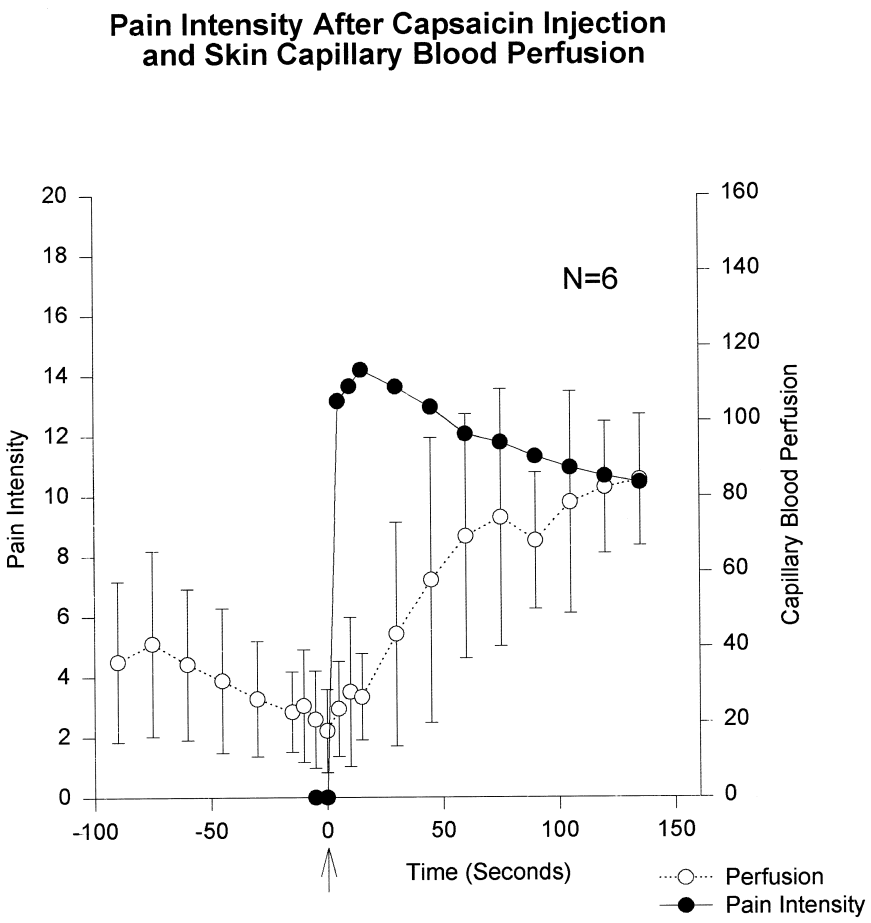

Fig. 4. Simultaneously obtained measures of mean skin perfusion and mean pain intensity after capsaicin injection. The upward-pointing arrow indicates the time of capsaicin injection.

ate change in perfusion after tourniquet inflation and deflation.

Discussion

Using various pain models, including mechanical trauma and mustard oil application to skin, Lewis and Hess reported in 1933 that painful sensations were formed in the area of inflammation during occlusion of arterial blood flow.[9] In an investigation of postischemic parathesias, Merrington and Nathan[10] also noticed that during periods of ischemia any small nonpainful cutaneous lesions became painful during the tourniquet construction. Nathan then published results from experiments in which ischemia to the limb was induced using a sphygmomanometer cuff to a pressure of 200 mmHg.[11] Pain could be induced in the zone of tissue injury with occlusion of capillary blood flow (tourniquet constriction). On average, the pain became noticeable to the volunteers approximately 3 min after occlusion of the blood flow, and the pain was located in the area of injury. More recently, Drummond reported on the independent effects of ischemia on hyperalgesia in capsaicin-treated skin.[12] In these experiments, the capsaicin was painted on the skin instead of being injected intradermally. A tourniquet cuff was used to occlude blood flow after hypersensitivity had developed from the application of capsaicin. His results showed that arterial occlusion increased thermal hyperalgesia, but his participants did not describe increased spontaneous pain.

Our findings differ from the related studies noted before because there was minimal or no primary hyperalgesia present during our tourniquet constriction testing. The lack of primary hyperalgesia is evidenced by the size of the skin wheal produced from the capsaicin injection (2 to 3 mm in diameter) and the

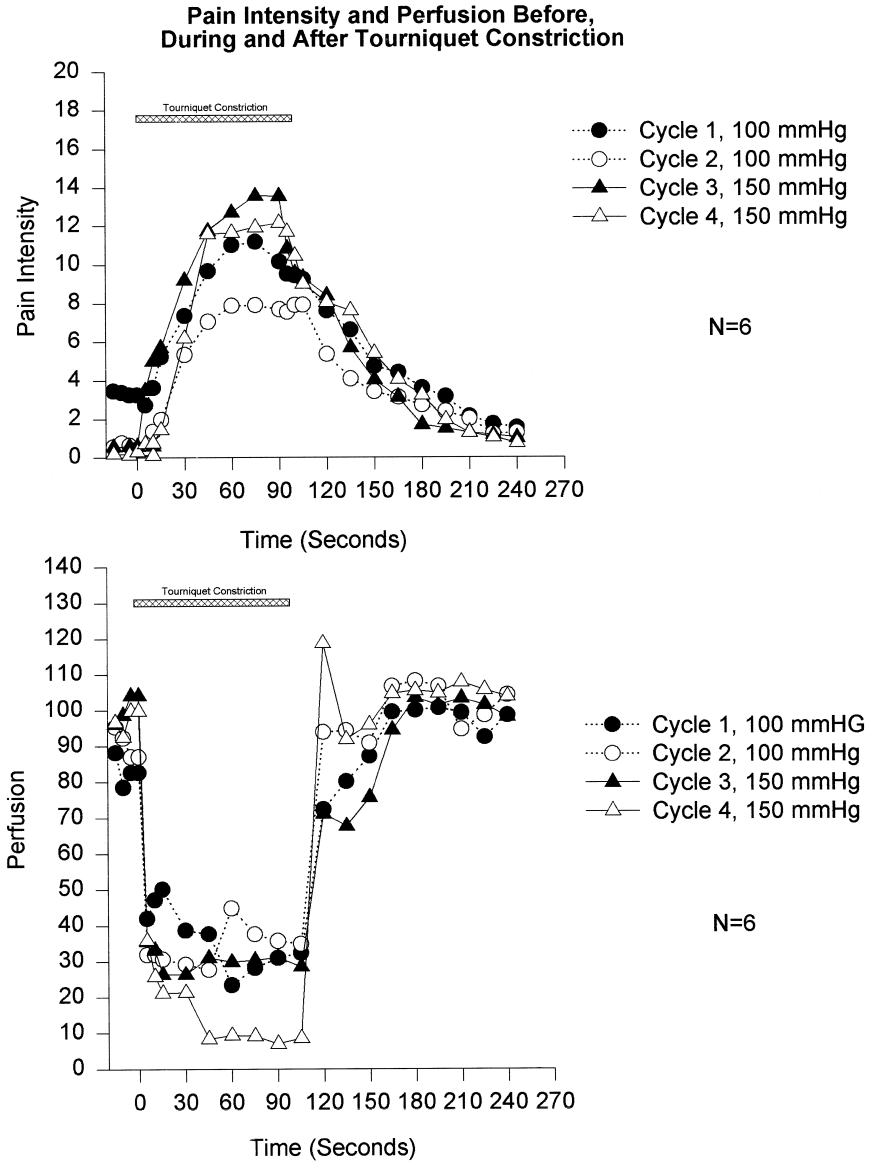

Fig. 5. (*Top*) The mean pain intensity before, during, and after cycles of tourniquet constriction. The graphs of each are overlaid to observe an effect of varying tourniquet constriction pressure. (*Bottom*) Mean skin perfusion distal to the zone of secondary hyperalgesia before, during, and after cycles of tourniquet constriction measured simultaneously with the pain intensity data shown in the top panel.

fact that this area of primary hyperalgesia becomes nearly insensitive to mechanical stimuli shortly after injection.[7,13] This is not true of the primarily inflammatory models where the skin is abraded or a chemical is painted on the skin. The contribution of primary hyperalgesia to the discomfort experienced with the inflammatory models is more than trivial. Quite to the contrary, the painful sensory phenomena present 10 to 15 min after a small intradermal capsaicin injection is mostly, if not primarily, secondary hyperalgesia. The tourniquet induced vascular changes, and pain reports occurred beyond the zone of primary hyperalgesia and visible flare response. We concluded that reduced capillary blood flow precipitates painful symptoms in the presence of secondary hyperalgesia. This hypothesis is supported by experiments from our laboratory that show that firm digital pressure over the brachial artery will induce the response, whereas partial con-

striction of the extremity without interrupting blood flow does not induce the painful response.

It is possible that the compression of the nerve fibers, particularly A-β fibers, is solely responsible for initiating the painful response to tourniquet constriction. However, we found that tightly constricting the hyperalgesic extremity was insufficient to induce the expected increase in pain, if A-β activation is all that is required. The tourniquet must be applied to the injured extremity proximal to the injury site. This suggests that the critical effect of the tourniquet constriction is related to factors other than intense A-β activation from the constricting tourniquet.

These studies were not designed to identify the specific underlying mechanisms that would explain a relation between tourniquet constriction and rapid exacerbation of pain during secondary hyperalgesia. Similarly, we cannot discern the role of central or peripheral pain mechanisms from the data we obtained in these experiments. However, this model offers a convenient means to extend our exploration of these issues.

Evidence exists that central changes contribute to the development of secondary hyperalgesia.[14,15] Changes in central processing are not sufficient to maintain intense, ongoing, diffuse pain equivalent to that induced by the tourniquet constriction. The tourniquet constriction adds another component. Because the major effect of this intervention is circulatory occlusion, we evaluated local blood flow and correlated alterations with the subjective effects. This study suggests that the tourniquet constriction interacts significantly with the local or central effects of capsaicin injection. The pain evoked during the experimental application of the tourniquet in the standard models of ischemic pain does not match the characteristic effects observed in this study.[16,17] However, similar components of nociception mechanism may be at work (*e.g.*, inflammatory mediators, protons, hypoxia, Aδ-fiber and C-fiber activation).[18–20]

We can conclude that tourniquet constriction of the extremity proximal to the capsaicin injection site causes an intensely painful sensation that is reliably reproducible among volunteers. The painful sensation extends beyond the zone of secondary hyperalgesia. The reduced response from the two participants who had very little secondary hyperalgesia suggests that there is a positive relation between the area of hyperalgesia and the degree of pain induced by the tourniquet constriction. Finally, we observed that a very small area of injury can induce vascular changes and sensory disturbances much farther away from the injury site than previously reported.

The secondary hyperalgesia produced by the injection of small amounts of intradermal capsaicin is unique in the ratio of primary to secondary hyperalgesia. However, some measure of secondary hyperalgesia is likely to be manifested after tissue injury. Similarly, the symptoms of the capsaicin intradermal injection model mimic various chronic pain syndromes, including allodynia (pain caused by light touch) as a common finding. Once we identify the precise mechanism of this tourniquet-induced response, we are hopeful that this addition to the capsaicin injection model will lead to improved evaluation and treatment of hyperalgesic and neuropathic pain conditions.

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