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## Pressure and Activity-Related Allodynia in Delayed-Onset Muscle Pain

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### Abstract

**Objectives**—Muscle pain from different activities was tested with the muscle pain expected to vary in ways that may clarify mechanisms of activity-induced exacerbation of myofascial pain.

**Methods**—Participants ( $N = 20$ ; 45% women; 23 years old ( $SD = 2.09$ )) consented to participate in a six session protocol. Bilateral muscle pain ratings and pressure pain thresholds (PPTs) were collected before and for 4 days after lengthening (i.e., eccentric) muscle contractions were completed with the non-dominant elbow flexors to induce delayed-onset muscle pain. The muscle pain ratings were collected with the arms in several conditions (e.g., resting, moving, contracting in a static position) and PPTs were collected with the arms.

**Results**—In the ipsilateral arm, muscle pain ratings at rest and during activity significantly increased while PPTs significantly decreased after the eccentrics ( $\eta^2s = .17 - .54$ ). The greatest increases in pain occurred during arm extension without applied load, in which there was more stretching but less force than isometrics. In the contralateral arm, neither muscle pain nor PPTs changed from baseline.

**Discussion**—These results resemble previous electrophysiology studies showing differential sensitization across stimuli and support that increased depth of information about aggravating activities from clinical patients is needed.

### Keywords

delayed-onset muscle soreness; stretch injury

### Introduction

Pain can occur during activity in healthy adults.<sup>1–7</sup> Activity can also exacerbate the preexisting pain of clinical patients. For example, patients with osteoarthritis,<sup>8,9</sup> low back pain,<sup>10,11</sup> chronic regional myalgia,<sup>12</sup> fibromyalgia syndrome,<sup>13–17</sup> migraine,<sup>18</sup> neuropathic pain,<sup>19,20</sup> neuromuscular disease,<sup>21</sup> and post-surgical pain<sup>22</sup> have reported acute exacerbations of pain with activity. Thus, activity should be investigated as a potential source of spikes in patients' pain.

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Along with ratings of clinical pain, activity has been reported to stimulate nociceptors in basic electrophysiology studies. A classic investigation by Mense and Meyer<sup>23</sup> found that Group III and IV muscle nociceptors were activated by noxious pressure, noxious stretch, and noxious contraction force. Further, after muscle inflammation, nociceptors started to respond to innocuous levels of these stimuli. Also, a more recent investigation by Ro and colleagues<sup>24</sup> reported that the number of *c-fos* containing cells in trigeminal brainstem nuclei increased with masseter muscle inflammation and further increased with jaw movement. Thus, the nociceptors innervating muscle sensitize after inflammation and this sensitization is manifested as an enhanced response to joint movement and muscle stimulation.

Pain and nociceptor activation vary with both the intensity<sup>1,23,7</sup> and type of activity<sup>25,26,23,27</sup> so the activity's characteristics need to be considered. For example, recalled knee pain from weight bearing activities was more strongly associated with radiographic severity of arthritis than recalled knee pain from non-weight bearing activities.<sup>28</sup> Therefore, examination of different activities may advance our understanding of the mechanisms of activity-induced exacerbation of pain.

Activity-induced exacerbations of pain can be investigated by comparing pain from activities that differ in controlled ways. For example, Sullivan and colleagues<sup>29</sup> have developed an innovative canister lifting task for patients with low back pain, in which the canister weight and canister distance from patients are varied. An alternative and novel approach is to induce delayed-onset muscle pain in healthy participants with controlled exercise and then investigate how controlled activities affect the pain. Such an approach is clinically-relevant because induced delayed-onset muscle pain interferes with normal daily activities outside of the laboratory and generates self-care behaviors such as stretching and massaging the muscles.<sup>30,31</sup>

The purpose of this investigation was to test the hypothesis that delayed-onset muscle pain would vary across activities even when the activities differ in simple ways. The delayed-onset muscle pain was induced with lengthening (i.e., eccentric) contractions of the non-dominant elbow flexors and the activities assessed were normal movements and contractions of the elbow. The identification of activities that most increase pain in temporarily damaged muscles may lead to insights into the mechanisms of activity-induced exacerbations of pain in patients with myofascial pain.

## Materials and Methods

### Participants

Participants ( $N = 20$ ; 45% women) with an average age of 23 years ( $SD = 2.09$ ) consented to participate in a six session protocol that was approved by the University of Missouri's Health Science Institutional Review Board. The restrictions for participation were the following: (a) had not engaged in upper body strength training on a regular basis (i.e., two times per week) for consecutive weeks within the previous six months, (b) were not currently experiencing arm pain, (c) had no history of upper arm injury within the previous six months, and (d) no chronic pain conditions. In addition, participants were screened by questionnaire for potential risk factors to the exercise protocol (e.g., excessive swelling, loss of range or motion, exertional rhabdomyolysis). Furthermore, participants were restricted from the following behaviors: smoking 3 hours prior to a session, consuming any food or drink except water 8 hours prior to a session, and taking analgesics throughout the study period.

## Measures

**Muscle pain ratings**—In order to evaluate the multidimensional nature of pain,<sup>32</sup> ratings of muscle pain intensity and muscle pain unpleasantness in both arms were assessed before and after lengthening (i.e., eccentric) muscle contractions with 0–100 numeric scales. More specifically, ratings were collected while the participants' arms were (1) stationary at approximately 90° of elbow flexion, (2) moving through active range of motion without applied load to full elbow flexion, (3) moving through active range of motion without applied load to full elbow extension, and (4) during five repetition maximal strength tests (5 RM) at 90° of elbow flexion. The anchors of the pain intensity scales were “no pain” and “most intense pain sensation imaginable.” The anchors of the pain unpleasantness scales were “no unpleasantness” and “most unpleasant imaginable.” Numeric pain scales have been found to be reliable and valid.<sup>33</sup>

**Pressure Pain Threshold**—Pressure pain threshold (PPT) was defined as the point at which a pressure stimulus first became painful. The pressure stimulus was applied at 25% of the distance from the cubital fossa to the greater tuberosity of the humerus while both arms were stationary at approximately 90° of elbow flexion. Using a hand-held 10 kg dolorimeter with a 1 cm rubber tip (Pain Diagnostics Inc.), pressure was increased at a rate of about 1 kg/s until the participant first reported feeling pain. The average of two repeated measurements was analyzed for each arm.

## Procedures

After a familiarization session, participants visited the laboratory for five consecutive days. Muscle pain ratings were collected for both arms during rest, flexion, and extension and pressure pain thresholds were assessed for both arms at rest. Lastly, participants were positioned in a muscle testing apparatus (Biodex System 3; Biodex Medical Systems, Shirley, NY) so that muscle pain could be measured during maximal isometric (i.e., static) contractions by both arms. For the isometric contraction test, the participants completed a 5 repetition maximal (5 RM) test with 2 minutes of rest in between each repetition at 90° of elbow flexion.

Following the isometric tests, eccentric contractions of the participants' non-dominant elbow flexors were completed with the muscle testing apparatus to induce delayed-onset muscle pain. (The non-dominant arm was defined as the contralateral arm to the arm with which the participants wrote.) More specifically, the participants performed 3 sets of 12 maximal eccentric repetitions with a rest period of 60 s in between each set. Eccentric contractions were completed at a velocity of 90°/s through the participants' active range of motion.

It is important to clarify how the state of the elbow flexor muscles varied across the conditions within the study. The elbow flexors were agonists during flexion and isometrics with less force produced and more shortening during the unloaded flexion than the isometrics. The elbow flexors were also agonists during eccentrics with more force produced and more lengthening than during the unloaded flexion and isometrics. In contrast, the elbow flexors were antagonists during unloaded extension with less force produced and similar lengthening to eccentrics.<sup>34</sup>

After the eccentric exercise, participants were given a rest period of about 1 hour. During this time, they were instructed to continue adherence to the pre-session restrictions, but they were allowed to leave the laboratory if they desired. After the rest period, muscle pain and pressure pain thresholds were assessed again in the same manner as before the eccentric exercise. Then the session was terminated and participants were reminded of the schedule

and restrictions for the subsequent sessions, which included avoiding any self-care behaviors for muscle pain (e.g., ice or heat application, stretching, massage, etc.).

Participants returned to the laboratory at one, two, three, and four days after the eccentric contractions in order for us to evaluate changes in muscle pain across time. These sessions were held either in the morning or afternoon hours in congruence with the previous session so that all the sessions of a single participant were either in the morning or afternoon. During each laboratory session, the muscle pain measures were repeated. Muscle pain ratings and pressure pain thresholds were completed as previously described.

## Data Analyses

In order to test our hypotheses for changes in muscle pain ratings, we conducted repeated measures analyses of variance (ANOVAs) with three factors: ARM (ipsilateral – eccentric contractions - and contralateral), CONDITION (resting, flexing, extending, and maximally contracting in static position), and TIME (pre-exercise, 1-hr post-exercise, 1 day, 2 days, 3 days, 4 days) with pain intensity or pain unpleasantness as the dependent variable. Significant 3-way interactions were followed up with CONDITION by TIME repeated measures ANOVAs within each arm, which were followed up with CONDITION repeated measures ANOVAs within each time point.

In order to test our hypotheses for changes in pressure pain thresholds, we conducted repeated measures ANOVAs with two factors: ARM (ipsilateral – eccentric contractions - and contralateral) and TIME (pre-exercise, 1-hr post-exercise, 1 day, 2 days, 3 days, 4 days). Significant 2-way interactions were followed up with TIME repeated measures ANOVAs within each arm and pairwise comparisons.

All analyses were conducted using SPSS software (SPSS, Inc., Chicago, IL) with Greenhouse-Geisser correction of degrees of freedom to adjust for violations of sphericity. Statistical significance was defined as  $p < .05$  and eta squared ( $\eta^2$ ) was calculated to determine the meaningfulness of the results. Eta squared values of .01, .06, and .14 corresponded to small, medium, and large effect sizes, respectively.<sup>35</sup>

## Results

### Muscle Pain Ratings

Pain intensity and unpleasantness were affected by a large interaction among the factors of arm, arm condition, and measurement time point (ARM by CONDITION by TIME:  $F_{15, 255} = 8.35$ ,  $p < .001$ ,  $\eta^2 = .33$  and  $F_{15, 240} = 7.44$ ,  $p < .001$ ,  $\eta^2 = .32$ ). Follow-up analyses within the ipsilateral arm, revealed that the ratings changed differently across time depending upon the arm condition. However, in general, both pain intensity and pain unpleasantness increased significantly by large amounts to a peak at 2 days post-exercise with the largest increases occurring during arm extension, next largest during flexion and isometrics, and smallest at rest. (See Table 1.)

Additional analyses comparing arm condition within each time point showed that before exercise, both pain intensity and unpleasantness were higher during the isometric maximal contraction than at rest and during flexion and extension. However, this pattern changed after the eccentric contractions. One hour after the exercise, there were non-significant and small differences among the arm condition for pain intensity or unpleasantness. One to four days after the exercise, both pain intensity and unpleasantness were the highest during extension, followed by flexion and isometrics, and were lowest at rest. (See Table 2 and Figures 1 and 2.)

A different pattern of results was observed for the contralateral arm. The muscle pain ratings for the contralateral arm were unaffected by the ipsilateral arm's eccentric contractions so that the pain in the contralateral arm remained highest during maximal contractions as was found in the ipsilateral arm before the eccentric contractions. (See Table 3.)

### Pressure Pain Thresholds

Pressure pain thresholds after the eccentric contractions changed across time differently in the ipsilateral and contralateral arms (ARM by TIME:  $F_{5,90} = 10.74$ ,  $p < .001$ ,  $\eta^2 = .37$ ), but the pressure pain thresholds were generally lowest at 1 and 2 days post-exercise (TIME effect  $F_{5,90} = 4.33$ ,  $p = .007$ ,  $\eta^2 = .19$ ) and lower in the ipsilateral arm than the contralateral arm (ARM effect  $F_{1,18} = 7.44$ ,  $p = .014$ ,  $\eta^2 = .29$ ). More specifically, within the ipsilateral arm, pressure pain thresholds decreased significantly by a large amount and were lowest at 1 day, 2 days, and 3 days after exercise ( $F_{5,90} = 8.99$ ,  $p < .001$ ,  $\eta^2 = .33$ ). Within the contralateral arm, non-significant and small changes from baseline were detected. ( $F_{5,90} = 2.53$ ,  $p = .068$ ,  $\eta^2 = .12$ ). (See Figure 3.)

### Discussion

This investigation detected that the eccentric muscle contractions successfully induced spontaneous pain (i.e., pain at rest) and allodynia to movement and pressure. Few investigations of eccentric contractions have reported muscle pain at rest. Of those that have assessed muscle pain at rest, one study detected increased resting pain<sup>36</sup> while two other studies did not.<sup>37,38</sup> Thus, the literature is currently mixed and more research is needed because pain at rest is clinically relevant due to its occurrence with clinical pain in humans and peripheral and central sensitization in animals.<sup>39-41</sup>

The movement and pressure allodynia that we detected are consistent with numerous studies of post-exercise muscle pain, but the novel pain measurement methodology in this study enabled comparison of specific types of movements and/or contractions. The muscle pain ratings differed depending upon the activity with lengthening producing the greatest pain in the damaged muscles. These findings resemble Mense and Meyer's<sup>23</sup> observation that inflammation-induced sensitization of Group III and IV fibers differed across stimuli (e.g., stretch, contraction, etc.). Thus, the findings support the potential of Mense and Meyer's findings with induced muscle inflammation in cats to translate to temporary endogenous muscle damage in humans.

As stated previously, the elbow flexors were agonists and shortening during unloaded flexion and isometrics and antagonists and lengthening during unloaded extension. Because the movement allodynia was highest during extension when the damaged muscles are antagonists and lengthening, it appears that stretch sensitive peripheral afferents were particularly sensitized by the eccentric contractions. , low threshold stretch receptors may be behaving as nociceptors and/or high threshold stretch sensitive nociceptors may have lowered activation thresholds. In fact, inflammation can make low threshold mechanoreceptors act like nociceptors<sup>42-46</sup> and can lower the stimulation thresholds of nociceptors,<sup>39,41</sup> which is important because inflammation does occur with muscle damage from eccentric muscle contractions.<sup>47,48</sup> It may be possible to use animal models of eccentric contractions, such as the one developed by Taguchi and colleagues,<sup>49,50</sup> to compare the activation level of stretch sensitive peripheral afferents to different types of activities before and after the eccentric contractions.

Our findings confirm that assessments of activity-related pain are affected by relatively simple differences among the activities. Detailed information about the characteristics of aggravating activities from clinical pain patients beyond "least, usual, worst, and current"

pain ratings may enable important biomechanical modifications to how activities are performed and improved prescriptions for therapeutic exercise. For example, patients with myofascial pain may benefit from incorporation of assistive devices (e.g., reaching tools) and/or strengthening exercises that minimize muscle lengthening. Reducing activity-related pain may reduce activity avoidance and deconditioning because numerous studies have found that pain impairs adherence to therapeutic exercise in patients with chronic pain.<sup>51–59</sup>

Unique strengths of this study's methodology were measuring bilateral muscle pain responses across 4 days post-exercise and our assessment of muscle pain ratings when both arms were performing different activities. Limitations of the investigation were the generally low levels of induced muscle pain and the absence of additional sensory tests such as temporal summation to heat or pressure. Future studies could easily address these limitations and further advance our understanding of the mechanisms and treatments for activity-related pain.

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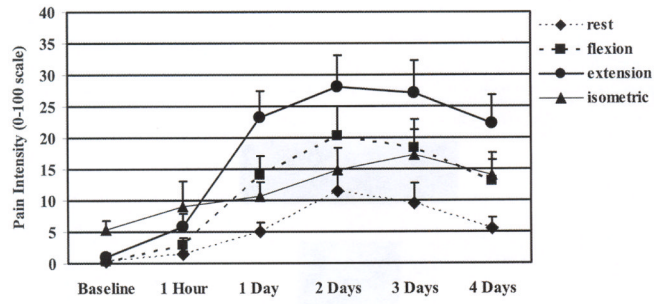


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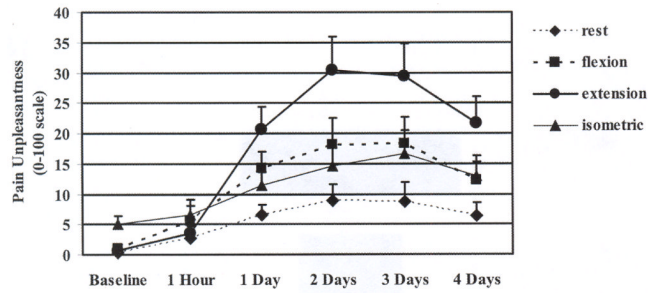
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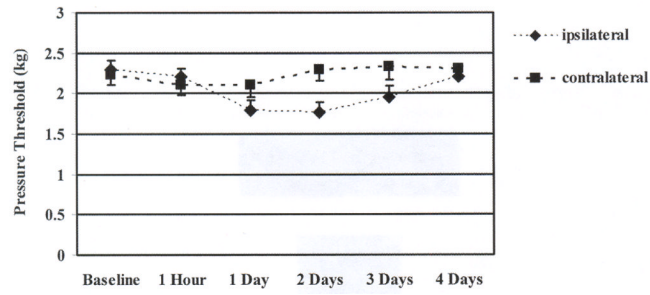
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**Figure 1.** Means and standard errors for the ratings of muscle pain intensity in the ipsilateral arm before and across 4 days after the eccentric contractions. Ratings at all time points increased from baseline when the ipsilateral arm was resting, flexing, and extending ( $p < .05$ ). Ratings did not change significantly from baseline when the ipsilateral arm was maximally contracting in a isometric position.



**Figure 2.** Means and standard errors for the ratings of muscle pain unpleasantness in the ipsilateral arm before and across 4 days after the eccentric contractions. Ratings at all time points increased from baseline when the ipsilateral arm was extending ( $p < .05$ ). Ratings at 1 to 4 days increased from baseline when the ipsilateral arm was resting, flexing, and maximally contracting in a static position ( $p < .05$ ).



**Figure 3.**

Means and standard errors for the pressure pain thresholds before and across 4 days after the eccentric contractions. Pressure pain thresholds at 1 to 3 days were significantly decreased from baseline for the ipsilateral arm. Pressure pain thresholds did not change significantly from baseline for the contralateral arm.

Follow-up CONDITION  $\times$  TIME mixed repeated measures ANOVA results within each arm. Shaded results were statistically significant ( $p < .05$ ).

**Table 1**

Source	Arm	Pain Intensity			Pain Unpleasantness				
		df	F	p	$\eta^2$	df	F	p	$\eta^2$
CONDITION $\times$ TIME	ipsilateral	15,255	8.72	<.001	.34	15,255	8.67	<.001	.34
	contralateral	15,270	1.15	.339	.06	15,255	1.95	.141	.10
CONDITION	ipsilateral	3, 51	15.00	<.001	.47	3, 51	14.09	<.001	.45
	contralateral	3,54	11.06	.003	.38	3,51	6.74	.018	.28
TIME	ipsilateral	5,51	10.40	.002	.38	5,51	12.62	<.001	.43
	contralateral	5,90	1.56	.214	.08	5,85	1.81	.164	.10

**Table 2**

Follow-up CONDITION repeated measures ANOVA results within each time point for the ipsilateral arm. Shaded results were statistically significant ( $p < .05$ ).

Source	Pain Intensity			Pain Unpleasantness			
	df	F	p	η <sup>2</sup>	F	p	η <sup>2</sup>
Baseline	3,54	8.01	.010	.31	9.08	.006	.26
1 Hour	3,57	2.41	.111	.11	0.86	.433	.04
1 Day	3,57	13.75	<.001	.42	12.85	<.001	.40
2 Days	3,57	14.64	<.001	.44	14.55	<.001	.43
3 Days	3,57	19.54	<.001	.51	17.04	<.001	.47
4 Days	3,57	13.66	<.001	.43	12.56	<.001	.41



**Table 3**

Means and standard errors for the ratings of muscle pain intensity and unpleasantness in the contralateral arm before and across 4 days after the eccentric contractions.

	Baseline		1 Hour		1 Day		2 Days		3 Days		4 Days	
	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE
Pain Intensity												
Rest	0.26	0.19	0.30	0.18	0.52	0.44	0.48	0.43	0.26	0.22	0.30	0.23
Flexion	0.11	0.06	1.17	0.54	1.00	0.68	1.30	0.89	0.30	0.23	0.39	0.27
Extension	0.85	0.52	0.91	0.42	0.87	0.48	1.04	0.52	0.43	0.25	0.35	0.23
Isometric*	5.30	1.42	6.33	1.74	6.52	1.82	5.25	1.57	5.02	1.49	4.96	1.70
Pain Unpleasantness												
Rest	0.39	0.27	0.35	0.23	0.43	0.43	0.26	0.22	0.22	0.22	0.35	0.25
Flexion	0.22	0.15	0.87	0.50	0.73	0.50	0.61	0.34	0.35	0.24	0.52	0.37
Extension	0.70	0.34	0.83	0.48	1.00	0.52	0.91	0.40	0.39	0.25	0.39	0.27
Isometric*	6.09	1.92	5.55	1.83	6.35	2.14	3.98	1.35	5.05	1.71	3.87	1.50

\* Pain ratings when the contralateral arm was maximally contracting in a static position were higher than when resting, flexing, and extending ( $p < .05$ ).