Cyclooxygenase inhibition attenuates sympathetic responses to muscle stretch in humans

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Submitted 20 December 2007; accepted in final form 14 April 2008

Cui J, Moradkhan R, Mascarenhas V, Momen A, Sinoway LI. Cyclooxygenase inhibition attenuates sympathetic responses to muscle stretch in humans. Am J Physiol Heart Circ Physiol 294: H2693–H2700, 2008. First published April 25, 2008; doi:10.1152/ajpheart.91505.2007.—Passive muscle stretch performed during a period of post-exercise muscle ischemia (PEMI) increases muscle sympathetic nerve activity (MSNA), and this suggests that the muscle metabolites may sensitize mechanoreceptors in healthy humans. However, the responsible substance(s) has not been studied thoroughly in humans. Human and animal studies suggest that cyclooxygenase products sensitize muscle mechanoreceptors. Thus we hypothesized that local cyclooxygenase inhibition in exercising muscles could attenuate MSNA responses to passive muscle stretch during PEMI. Blood pressure (Finapres), heart rate, and MSNA (microneurography) responses to passive muscle stretch were assessed in 13 young healthy subjects during PEMI before and after cyclooxygenase inhibition, which was accomplished by a local infusion of 6 mg ketorolac tromethamine in saline via Bier block. In the second experiment, the same amount of saline was infused via the Bier block. KETOROLAC Bier block decreased prostaglandin synthesis to ~34% of the baseline. Before ketorolac Bier block, passive muscle stretch evoked significant increases in MSNA (P < 0.005) and mean arterial blood pressure (P < 0.02). After ketorolac Bier block, passive muscle stretch did not evoke significant responses in MSNA (P = 0.11) or mean arterial blood pressure (P = 0.83). Saline Bier block had no effect on the MSNA or blood pressure response to ischemic stretch. These observations indicate that cyclooxygenase inhibition attenuates MSNA responses seen during PEMI and suggest that cyclooxygenase products sensitize the muscle mechanoreceptors.

Exercise pressor reflex; passive exercise; autonomic nervous system; muscle afferents; regional intravenous anesthesia

Exercise is a potent stimulus to activate the sympathetic nervous system (36). Increases in muscle sympathetic nerve activity (MSNA) during exercise are caused, reflexively, by the stimulation of mechanosensitive and chemosensitive afferents within the contracting muscle (27). Groups III and IV afferent fibers in muscles are suggested to be involved in this reflex (28, 43). Whereas group III muscle afferents are predominantly mechanically sensitive, unmyelinated group IV muscle afferents are mainly chemically sensitive (1, 2, 22, 24).

A number of animal studies have shown that mechanoreceptor stimulation in cats activates sympathetic afferents to muscles (21) and kidneys (17, 42) and can evoke pressor responses to exercise (16, 25, 39). Recently, we demonstrated in healthy humans that passive stretch of leg or arm muscles evokes a significant increase in MSNA during the first few seconds of the muscle stretch; however, under freely perfused conditions, the magnitude of the response is small and transient, and the evoked hemodynamic consequences are limited (9, 10).

Animal studies suggested that the group III mechanosensory neurons are polymodal and may be sensitized by metabolites (2, 19, 35), which may in turn increase the sympathetic responses to mechanoreceptor stimulation during exercise. Previous human studies (3, 20) speculated that the mechanosensitive nerve endings were sensitized by the chemical products of the muscle contraction during active exercise. The study of Bell and White (5) showed that external pressure applied to the leg muscles during post-exercise circulatory occlusion evoked further increases in blood pressure and suggested that exercise metabolites sensitized a population of mechanosensitive afferents in human muscles. Recently, we demonstrated that the static passive stretch of muscles via the extension of the wrist (EOW) evoked significant increases in mean MSNA and blood pressure when the muscle metabolites were accumulated under post-exercise muscle ischemia (PEMI), whereas the static passive stretch of the muscles had no significant effects on mean MSNA and blood pressure under a freely perfused condition (10). Although these data suggest that muscle metabolites sensitize the mechanoreceptors in the muscles, the causative metabolite(s) was not tested in these reports (3, 5, 10, 20).

One possible group of muscle metabolites that may sensitize mechanoreceptors in humans is cyclooxygenase (COX) products of free arachidonic acid metabolism. Animal studies suggest that arachidonic acid and the metabolites of COX (i.e., prostaglandins) stimulate muscle afferents (32, 34). These COX products can sensitize mechanosensitive afferents in the exercising muscles (19, 34, 35) and evoke part of the exercise pressor reflex (40). In humans, Middlekauff and Chiu (30) reported that COX inhibition via intra-arterial indomethacin infusion eliminated the reflex sympathetic activation during low levels of dynamic exercise and postulated that the COX products could sensitize the muscle mechanoreceptors.

There are, however, several points about the aforementioned study (30) that bear comment. First, active muscle contraction was employed, and the effects of central command engagement could not be entirely excluded. Second, only low levels of dynamic exercise were performed under a freely perfused condition. Finally, the effects due to the systemic administration of COX inhibitors per se could not be excluded. Related to this final point, animal studies have shown that an administration of pharmacological substances into the isolated carotid sinus for reducing prostaglandins (products of COX) synthesis...
impairs both afferent baroreceptor and efferent baroreflex responses to baroreceptor activation and/or deactivation (6, 7). Thus the systemic effects of drug infusion could have a myriad of effects, which could preclude a precise assessment of the specific intramuscular effects of COX inhibition. Therefore, the roles of the COX products in sensitizing muscle mechanoreceptors have not been studied thoroughly in humans.

We have demonstrated that an infusion of a low dose of ketorolac into the exercising arm via Bier block, a regional intravenous anesthesia technique, significantly decreased the synthesis of the COX products in the local muscles and attenuated the MSNA response to fatiguing exercise (11). Therefore, the purpose of the present study was to examine the effects of local COX inhibition in exercising muscle on MSNA responses to passive muscle stretch. We hypothesized that local COX inhibition in exercising muscle would attenuate the MSNA responses to the passive muscle stretch under the PEMI condition. COX inhibition in the exercising forearm was accomplished by a local infusion of ketorolac via the Bier block technique.

METHODS

Subjects. Thirteen subjects [8 men and 5 women; age, 25 ± 1 yr (SE); height, 175 ± 3 cm; and weight, 72 ± 2 kg] participated in the study. All subjects were normotensive (supine blood pressures, <140/90 mmHg), were not taking any medication, and were in good health. The subjects refrained from caffeine, alcohol, and exercise 24 h before the study. The experimental protocol was approved by the Institutional Review Board of the Milton S. Hershey Medical Center and conformed with the Declaration of Helsinki. Each subject had the purposes and risks of the protocol explained to them before written informed consent was obtained.

Renal blood flow velocity data were obtained in 4 of these 13 subjects. The data from these four subjects, in addition to data from seven separate subjects, are presented in the companion article (30a). As opposed to measuring MSNA responses, the companion article (30a) examines renal blood flow velocity and the mechanisms responsible for renal vasoconstriction during muscle stretch in humans.

Measurements. Blood pressure was recorded on a beat-by-beat basis from a finger with a Finapres device (Finapres; Ohmeda, Madison, WI). Resting blood pressures obtained from the Finapres were verified by an automated sphygmomanometer (Dinamap; Critikon, Tampa, FL). A standard electrocardiogram was used to monitor heart rate. Respiratory excursions were monitored with pneumography. Multifiber recordings of MSNA were obtained with a tungsten microelectrode inserted in the peroneal nerve of a leg. A reference electrode was placed subcutaneously 2 to 3 cm from the recording electrode. The recording electrode was adjusted until a site was found in which muscle sympathetic bursts were clearly identified using previously established criteria (41). The nerve signal was amplified, passed through a band-pass filter with a bandwidth of 500–5,000 Hz, and integrated with a time constant of 0.1 s (Iowa Bioengineering, Iowa City, IA). The nerve signal was also routed to a loudspeaker and a computer for monitoring throughout the study. Heart rate, blood pressure, MSNA, and respiratory excursions were recorded throughout the studies. The forces of passive stretch and handgrip were measured with force transducers. Venous samples were collected at the antecubital fossa of the exercising arm. The samples were coded with numbers and sent to another laboratory at Hershey Medical Center to analyze thromboxane B2. Plasma thromboxane B2 was used to document the effectiveness of the COX blockade (13, 15, 31). Thromboxane B2 levels were quantified by enzyme immunoassay (Amersham Biosciences).

Experimental design. All subjects were tested in the supine position. An intravenous catheter was inserted in the antecubital fossa of the nondominant arm. The maximum voluntary contraction (MVC) of the nondominant hand was tested during each visit. To ensure the strength of the stretch was as vigorous as possible without evoking pain, the stretch strength for each subject was tested before the study. A specifically designed brace with a joint at the wrist was used to support each subject’s forearm and hand. After the study paradigm was explained to the subject, the hand portion (at the level of fingers) of the brace was pulled in the dorsal direction by a segment of rope connected to a weight via a pulley. This action flexed the wrist in the dorsal direction (EOW) as the force was measured with a digital force gauge (DPS-220; Imada, Northbrook, IL). During EOW, the position of the forearm and wrist remained fixed. The EOW stretched the flexor carpi radialis in the forearm and flexor digitorum superficialis in the hand. The weight for EOW was increased gradually until the subject reported any pain/discomfort. The maximal weight used to stretch the muscles without inducing pain was obtained during the first visit and was used for all stretch protocols performed on the 2 study days. The average force used in these subjects was 5.6 ± 0.3 kg. No subjects complained of pain with EOW on day 2.

Pre-ketorolac Bier block control trial. After instrumentation, 6 min of baseline measures of heart rate, blood pressure, MSNA, and

![Pre-BierBlock trial](Image)
respiratory excursion were collected with the subject in the resting condition. A baseline blood sample was also obtained. Each subject then performed static isometric handgrip at 30% MVC to fatigue followed by 4 min of PEMI by inflating a cuff on the upper arm to 250 mmHg. After the cuff was inflated, a second blood sample was drawn. After 2 min of PEMI, EOW was performed for 2 min. Subjects did not complain of any additional pain caused by the EOW during PEMI.

**Bier block.** After 10–15 min of recovery from the control trial, the Bier block procedure was utilized to regionally administer ketorolac tromethamine (marketed as Toradol), a nonselective COX inhibitor (8), into the forearm. The clinical applications for ketorolac are described in the companion article (30a). To drain the forearm vasculature, the arm was elevated and bandaged with a tight elastic wrapping beginning at the hand. The pneumatic cuff on the upper arm was then inflated to 250 mmHg, and the bandage was removed. Thereafter, 6 mg ketorolac tromethamine in 40 ml of saline were infused into the occluded arm via the catheter (11). This allows the ketorolac to distribute in the previously emptied vascular system and to diffuse into the forearm tissue. After 20 min, the cuff was deflated and the subjects rested for an additional 15–20 min.

**Ketorolac Bier block trial.** Following ketorolac blockade, another 6 min of baseline data were collected, and a blood sample was drawn. The handgrip exercise at the same intensities as those employed before the Bier block trial followed by 4 min of PEMI was repeated. One blood sample was drawn during PEMI. After 2 min of PEMI, EOW was performed for 2 min. The time line of the protocols is shown in Fig. 1.

To separate the effects of ketorolac from the Bier block procedure itself, a control study was performed on a second visit to the laboratory about a month after the first experiment. All parameters were recorded in the same fashion as the first visit. The pre-saline Bier block trial (control trial) in the second visit was the same as the pre-ketorolac Bier block trial performed in the first visit. During the Bier block procedure, 40 ml saline (no ketorolac) were infused into the arm. The handgrip exercise and PEMI protocol was repeated for the saline Bier block trial.

**Data analysis.** Data were sampled at 200 Hz via a data acquisition system (MacLab; AD Instruments). MSNA bursts were first identified in real time by the visual inspection of data, coupled with the burst sound from the audio amplifier. These bursts were further evaluated by computer software that identified bursts based on fixed criteria, including an appropriate latency following the R-wave of the electrocardiogram (9, 12). Integrated MSNA was normalized by assigning a value of 100 to the mean amplitude of the largest 10% of the bursts during the 6-min baseline period (9, 12). Normalization of the MSNA signal was performed to reduce variability between subjects attributed to factors including needle placement and signal amplification. Total MSNA was identified from the burst area of the integrated neurogram (9, 12). Mean arterial pressure (MAP) was calculated from the Finapres waveform during handgrip exercise and PEMI, whereas the baseline MAP was verified by an automated sphygmomanometer from an upper arm. These data analyses were performed by two independent investigators.

**Statistics.** Differences in the mean values of hemodynamic parameters between the baselines before the four exercise trials were evaluated via post hoc analysis after repeated-measures one-way ANOVA. Differences in the mean values of hemodynamic parameters between the baselines and exercise and between the drug infusion conditions were evaluated via post hoc analysis after repeated-measures two-way ANOVA. Differences in the mean values of hemodynamic parameters between the PEMI and PEMI + EOW and between before and after Bier block were evaluated via Tukey’s post hoc analysis after repeated-measures two-way ANOVA. All values are reported as means ± SE. P values of <0.05 were considered statistically significant.

**RESULTS**

The infusion of ketorolac via Bier block significantly decreased resting plasma thromboxane B2 (Table 1). Because both prostaglandin and thromboxane synthesis are COX dependent, the decrease of thromboxane B2 suggests that the synthesis of COX products including prostaglandins was inhibited in the present study (13, 15, 31). Before the ketorolac Bier block, thromboxane B2 rose with exercise; after the ketorolac Bier block, thromboxane B2 did not increase with exercise. In contrast, the saline Bier block had no similar effect on thromboxane B2 levels (Table 1).

Baseline values for MSNA, MAP, and heart rate obtained before the four trials did not differ (Table 2). Isometric handgrip evoked increases in MSNA, heart rate, and MAP in the four trials (Table 3). After the ketorolac Bier block, MSNA responses during the last minute of handgrip before fatigue were significantly lower than that before the blockade (Table 3). In contrast, the saline Bier block had no similar effect on the MSNA response to the exercise. Thus, after the ketorolac Bier block, the MSNA responses to exercise were significantly lower than those after the saline Bier block. There was no significant difference in heart rate between the ketorolac Bier block and saline Bier block trials.

**Table 1. Effects of ketorolac on thromboxane B2 levels**

<table>
<thead>
<tr>
<th></th>
<th>Before Ketorolac Block</th>
<th>After Ketorolac Block</th>
<th>Before Saline Block</th>
<th>After Saline Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexercise</td>
<td>192±3</td>
<td>39±3</td>
<td>175±30</td>
<td>173±28</td>
</tr>
<tr>
<td>Postexercise</td>
<td>338±56*</td>
<td>31±2*</td>
<td>256±53*</td>
<td>324±54*</td>
</tr>
</tbody>
</table>

Values are means ± SE. The blood samples for thromboxane B2 measurements were drawn during preexercise baseline and pre-exercise muscle ischemia conditions. Thromboxane B2 units are picromilliters per milliliter. *P < 0.05 vs. the respective preexercise baseline; †P < 0.05 vs. the respective control trial condition.

**Table 2. Preexercise baseline measurements**

<table>
<thead>
<tr>
<th></th>
<th>Before Ketorolac Block</th>
<th>After Ketorolac Block</th>
<th>Before Saline Block</th>
<th>After Saline Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>123±3</td>
<td>126±3</td>
<td>120±3</td>
<td>121±3</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>62±1</td>
<td>62±1</td>
<td>62±2</td>
<td>63±2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>82±2</td>
<td>83±2</td>
<td>81±2</td>
<td>82±2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60±2</td>
<td>59±2</td>
<td>59±2</td>
<td>60±2</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>11.9±1.3</td>
<td>12.0±1.3</td>
<td>11.1±1.4</td>
<td>11.5±1.4</td>
</tr>
<tr>
<td>MSNA, units/min</td>
<td>182±25</td>
<td>158±18</td>
<td>160±22</td>
<td>179±28</td>
</tr>
<tr>
<td>Respiration, cycles/min</td>
<td>16.6±0.7</td>
<td>16.1±0.7</td>
<td>17.2±0.7</td>
<td>17.0±0.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. SBP, DBP, and MAP are systolic, diastolic, and mean arterial blood pressure, respectively, which were measured by an automated sphygmomanometer from an upper arm. MSNA, muscle sympathetic nerve activity. There is no significant difference in the measurements between the trials.
MSNA and MAP during PEMI in all of the four trials were significantly greater than those of the preexercise baselines (all \( P < 0.001 \); Figs. 2 and 3). MSNA total activity during PEMI after ketorolac Bier block was significantly lower than before the ketorolac Bier block (\( P < 0.03 \)); however, the MSNA burst rate during PEMI after ketorolac Bier block only tended to be lower than that before the ketorolac Bier block (\( P = 0.08 \); Fig. 2). MSNA responses to PEMI did not decrease after saline Bier block (Fig. 2). Neither ketorolac Bier block nor saline Bier block had any significant effect on MAP or heart rate responses to PEMI (Fig. 3).

Before ketorolac Bier block, MSNA during the PEMI + EOW was significantly greater than that during the PEMI alone condition (\( P < 0.005 \)). After ketorolac Bier block, MSNA during PEMI + EOW was not significantly different from that during the PEMI alone condition (Fig. 2). Before ketorolac Bier block, MAP during the PEMI + EOW was also significantly greater than that during the PEMI alone condition (\( P < 0.02 \)). After ketorolac Bier block, the EOW did not cause an increase in MAP (Fig. 3). Both before and after saline Bier block, EOW during the PEMI caused significant increases in MSNA and MAP (Figs. 2 and 3). EOW had no significant effects on heart rate in all trials. Recordings of EOW force, heart rate, integrated MSNA, and blood pressure during the PEMI and EOW in a representative subject are shown in Fig. 4.

### DISCUSSION

The main findings from the present study are that the MSNA and blood pressure responses to passive muscle stretch during PEMI are attenuated by the local administration of a COX antagonist into the circulatory system of the exercising muscles. These results confirmed our hypothesis and suggest that...
COX products in exercising muscles sensitize the mechano-sensitive afferents during muscle contraction.

Although previous studies demonstrated that anesthetized cat triceps surae group III muscle afferents are predominantly mechanically sensitive, whereas unmyelinated group IV muscle afferents are chemically sensitive (1, 2, 16, 22–24), a significant proportion of both afferent types exhibits polymodal characteristics and is capable of responding to both mechanical and metabolic stimuli (1, 22, 24). Animal studies have suggested that the response seen with mechanical stimulation is influenced by the prevailing local metabolic conditions (2, 19, 34, 35). In humans, a compression of the calf muscle in the PEMI condition evoked further increases in blood pressure, and the magnitude of the increase was dependent on the intensity of the preceding bout of contraction (5). A progressive increase in MSNA was seen during low-level rhythmic handgrip (3) or during later cycles of intermittent quadriceps contractions (20). We have shown recently that the responses in MSNA and blood pressure to passive muscle stretch were increased along with the increase in the accumulation of muscle metabolites (10). Consistent with this observation, the EOW under PEMI conditions in the present study caused significant increases in MSNA and MAP in the control trials (before Bier block) and after saline Bier block. It should be noted that PEMI alone caused pain/uncomfortable sensations in some subjects. However, no subject complained of any additional pain or discomfort during any of the EOW trials. Thus the accentuated MSNA responses to EOW in the control trials should not be caused by the pain sensation. Although these observations (3, 5, 10, 20) suggested that the mechano-sensitive nerve endings could be sensitized by accumulating metabolites, the causative metabolite(s) was not identified in these human studies.

Animal studies suggested that arachidonic acid (35) and COX products (19) might sensitize the mechanosensitive afferents. COX plays a critical role in the transformation of free arachidonic acid to prostaglandins and thromboxanes (37, 38). To inhibit the synthesis of COX products, ketorolac was used in the present study. Ketorolac is a powerful nonsteroidal anti-inflammatory drug available for intravenous administration that antagonizes COX (8). Because both prostaglandins and thromboxane synthesis are COX dependent, the thromboxanes (i.e., thromboxane B₂) were used as a bioassay of COX antagonism (i.e., prostaglandin synthesis inhibition) (13, 15, 31). In the present study, the local infusion of 6 mg ketorolac via the Bier block procedure greatly decreased thromboxane B₂ levels. Moreover, there was no increase in the thromboxane B₂ level after exercise, whereas the thromboxane B₂ level rose

![Fig. 3. Effects of EOW on heart rate (HR) and mean arterial blood pressure (MAP) during PEMI. A: before (pre-Bier block) and after ketorolac Bier block (keto Bier block). B: before (pre-Bier block) and after saline Bier block (saline Bier block). *P < 0.05 vs. the respective PEMI only (prior EOW) condition.](http://ajpheart.physiology.org/)

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PROSTAGLANDINS SENSITIZE MUSCLE MECHANOSENSORS

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after exercise during the control condition, a finding that supports prior observations (44). Thus the data indicate that the synthesis of COX products was inhibited in the exercising muscles, and this effect was maintained during exercise (11). Consistent with our previous observation (11), both the MSNA burst rate and total activity responses to fatiguing handgrip were significantly attenuated after ketorolac Bier block, whereas the saline Bier block had no similar effect. Moreover, the MSNA total activity response to PEMI was significantly attenuated after the COX inhibition. This result suggests that prostaglandins stimulate muscle afferents, a finding consistent with previous animal studies (19, 33, 35, 40). However, the observation of attenuated MSNA responses to muscle contraction after COX inhibition (11) does not prove that prostaglandins sensitize mechanoreceptors, since prostaglandins also directly stimulate muscle afferents. The present study was designed to identify the role prostaglandins play in sensitizing muscle mechanoreceptors in humans.

Before Bier block, static passive stretch under the PEMI condition caused significant increases in MSNA and MAP. After ketorolac Bier block, there was no significant difference in MSNA or MAP between the passive stretch and the PEMI only conditions. Saline Bier block had no similar effect. These data indicate that the MSNA response to mechanoreceptor stimulation, which is seen when the metabolites are accumulated in the muscles in the control trials, is attenuated after the COX inhibition. Moreover, static passive stretch under the PEMI condition also induced pronounced increases in renal vasoconstriction, as outlined in the companion article (30a). Therefore, the results suggest that COX products (i.e., prostaglandins) sensitize muscle mechanoreceptors in humans. The data also indicate that prostaglandins may play a role in the mediation of muscle afferent activity during exercise and recovery.
glandins) in the exercising muscles sensitize mechanosensitive muscle afferents.

The present results support previous observations in animals showing that arachidonic acid and prostaglandins can stimulate muscle afferents and alter the pressor response to muscle contraction (19, 32, 33, 35, 40). For example, the pressor responses to muscle contraction in decerebrate cats were attenuated after the topical application of a trolamine salicylate-based analgesic balm, which inhibits the synthesis of COX products (prostaglandin formation) (32). In decerebrate cats, the increases in group III and IV afferent activity during dynamic muscle contraction while the circulation to the muscles was occluded were greater than those during exercise while the muscle were freely perfused. COX inhibition by indomethacin significantly reduced the responses to dynamic exercise of the group III afferents, while the circulation to the muscles was occluded, and the group IV afferents during post-exercise circulatory occlusion (19). In anesthetized cats, COX blockade by indomethacin significantly inhibited sympathetic activation during dynamic muscle contraction (35). These findings support the concept that COX metabolites sensitize mechanosensory neurons.

In humans, Middlekauff and Chiu (30) showed that COX inhibition with an intra-arterial infusion of indomethacin eliminated the reflex sympathetic activation during low levels of dynamic exercise and concluded that COX products sensitize muscle mechanoreceptors. The present observation supports this conclusion. However, the experimental approach and the conditions of the present study were different from those in that study, as discussed in the Introduction. In the present study, selective stimulation (passive stretch) was employed. Moreover, only a small dose of the drug was infused in the present study. Although a small amount of ketorolac might enter the systemic circulation after upper arm-cuff deflation, the local administration of a small dose of this drug should have a far smaller systemic effect than the effects observed during intravenous and/or intra-arterial infusions. This point is supported by the observation that there were no differences between baseline MSNA, heart rate, and blood pressure values seen before the four trials.

Passive stretch had no effect on heart rate under either control or COX inhibition conditions. The observation under control conditions is consistent with previous work (4, 5, 10, 14). Static stretch (4, 10, 14) or muscle compression (5) during PEMI does not induce a significant response in mean heart rate. Under COX inhibition conditions, the present result is consistent with the observations of Middlekauff and Chiu (30). They reported that the heart rate response to low-level exercise after COX inhibition by intra-arterial indomethacin was not significantly different from that in the control (saline) trial.

**Perspective.** Although COX inhibition attenuated the MSNA response to passive stretch, the mean value of MSNA during the passive stretch was still higher (nonsignificant) than that during the PEMI only condition (see Fig. 2). In some of the subjects, a rise in MSNA was still observed during the passive stretch after ketorolac Bier block. This could be caused by the individual differences in the effects of COX inhibition. Alternately, this observation may hint that other metabolites, which might not be decreased by the ketorolac, could also be involved in sensitizing the muscle mechanoreceptors. Besides prostaglandins, animal studies have suggested that bradykinin (29) and ATP (26) might sensitize the mechanosensitive afferents. Thus the role of other potential substances in humans need to be evaluated in future studies.

**Limitations.** In the present study, the EOW was performed by flexing the wrist in the dorsal direction. The mass of stretched muscles with this maneuver was not large. Moreover, to avoid pain, the stretch force was not high. Both the small muscle mass and the low level of force generated could be important factors why the evoked responses under control conditions were of relatively small magnitude. However, when the muscle mass and the tension generated are increased during activities such as lifting heavy weights, etc., mechanoreceptor input could contribute in a much greater fashion to the exercise pressor reflex. Second, all afferent nerve fibers engaged by stretch are not engaged during contraction, and all fibers engaged by contraction are not engaged by stretch (18). Thus the results of the described muscle stretch experiments must be viewed with some caution.

Because the half-life of ketorolac is ~7.6 h, the ketorolac Bier block trial was always performed after the control trial. Thus we cannot exclude some order effect. Moreover, the Bier block procedure itself could influence the observed responses. To separate these factors, the saline Bier block trial was performed. Thus we believe this study design employed decreased the influences of trial order and the Bier block procedure per se.

In conclusion, the present results show that local COX inhibition in exercising muscle attenuates the MSNA and blood pressure responses to passive muscle stretch while the circulation to the muscles was occluded. These observations suggest that COX products may sensitize muscle mechanosensitive afferents and contribute to sympathetic activation seen during exercise.

**ACKNOWLEDGMENTS**

We acknowledge the technical assistance of Natalia Gonzalez and are grateful to Jennifer L. Stoner for secretarial help in preparing this article.

**GRANTS**

This work was supported by National Institutes of Health Grants P01-HL-077670 (to L. I. Sinoway), M01-RR-010732 (GCRC Grant), and C06-RR-016499 (Construction Grant) and the American Heart Association Grants 0565399-U and 0635245-N (to J. Cui).

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