

Tourniquet-Induced Limb Ischemia: A Neurophysiologic Animal Model

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A rat model of tourniquet-induced ischemia was created to observe the changes in sciatic afferent neuronal activity associated with prolonged tourniquet inflation on the hind leg. The sciatic nerve was divided in the proximal thigh and a two-electrode microfilament recording technique and signal averaging computer were used to survey afferent neuronal activity prior to and after tourniquet inflation. This method was able to determine both firing rate and conduction velocity of spontaneously active or mechanically sensitive nerve fibers. In 14 rats observed prior to tourniquet inflation there was much spontaneous activity. These fibers all had rapid conduction velocities (30 ± 6.9 m/s) (mean \pm SD) and firing rates (16.3 ± 1.9 H). All fibers could be stimulated by movement of distal joints or by probing the skin of the leg. After tourniquet inflation, a pressure-induced conduction block occurred stopping all spontaneous and mechanically induced activity. After a short interval, (55 ± 16 min) a different group of spontaneously active fibers were observed that had both slow conduction (2.04 ± 0.77 m/s) and firing rates (0.54 ± 0.9 H). These fibers did not respond to mechanical stimulation of the limb distal to the tourniquet, or local anesthetic or cold block of the nerve distal to the tourniquet. Blockade of the sciatic nerve just proximal to the tourniquet and deflation of the tourniquet did abolish activity in these fibers. In ten separate rats in which tourniquets were placed but no surgical incision made, mean arterial blood pressure rose significantly after tourniquet inflation. With tourniquet deflation, blood pressure fell significantly from levels observed during tourniquet inflation. This study showed the presence of a group of spontaneously active fibers with velocities in the C-fiber range that were not observed prior to tourniquet inflation. The receptive fields of these fibers were most likely in the ischemic tissue or axons directly under or just proximal to the tourniquet. The neurophysiologic changes noted in this experimental model could represent the physiologic basis of tourniquet pain. (Key words: Equipment, tourniquet; intraoperative use; ischemia; pain. Pain: tourniquet induced.)

WHILE PNEUMATIC tourniquets are widely used during limb operations, their use is associated with a number of adverse effects such as severe pain during otherwise adequate regional anesthesia and hypertension during general anesthesia.¹⁻⁴ The pain during regional blockade is

often difficult to control and frequently requires supplemental iv analgesics or even the induction of general anesthesia. The etiology of the discomfort associated with prolonged tourniquet inflation is unclear; however, several possible explanations have been proposed. The mechanism could involve the sensitization or spontaneous activation of small-diameter pain fibers such as a-delta or c-fibers.^{5,6} The triggering stimuli could include ischemia of the peripheral neuron or receptor distal to the inflated tourniquet or activation of the nerve fiber in the compressed area directly under or adjacent to the tourniquet. Alternatively, the nociceptive pathway could involve activation of large myelinated fibers that are somewhat resistant to local anesthetics and able to penetrate a region block.¹ The ability of such large-diameter myelinated fibers to contribute to the sensation of pain has been recently demonstrated by Campell *et al.*⁷ who has shown that certain peripheral neuropathic pain states are maintained by neural input carried on these large myelinated fibers. Because of the variety of unanswered questions about the basis of tourniquet-induced pain the following study was undertaken to better characterize and define the neurophysiologic changes that occur with prolonged tourniquet inflation.

Methods

After obtaining animal care committee approval, 20 male Sprague-Dawley rats weighing 350–400 g were used. After an intramuscular injection of pentobarbital a tracheostomy was preformed and left femoral arterial and venous catheters were inserted. Anesthesia was maintained by a continuous iv infusion of pentobarbital at approximately 10 mg/h to maintain a mean arterial pressure between 80–100 mmHg. Ventilation was controlled and supplemental oxygen given to maintain an arterial oxygen-hemoglobin saturation greater than 95%. Temperature was maintained at 37° C using a water-filled warming blanket. A 1-cm \times 7–9-cm pneumatic tourniquet (D. E. Hokanson Inc., Bellevue, WA) was placed around the distal right thigh above the knee joint but was not inflated. With the animal in the prone position the right sciatic nerve was exposed just distal to the sciatic plexus to a point just proximal to the location of the tourniquet. The nerve was then covered in a 37° C paraffin oil bath to prevent drying. A silver recording electrode, R2, was placed under the whole nerve just proximal to the tourniquet and a ground electrode was anchored in the nearby

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Received from the University of Washington Veteran's Affairs Medical Center, Seattle, Washington. Accepted for publication January 23, 1990. Supported by the American Society of Anesthesiologists Starter Grant and the Anesthesia Department, University of Washington, Seattle, Washington.

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fascia (fig. 1). The entire sciatic nerve was then divided at its proximal end to prevent the propagation of efferent impulses from the spinal cord. Using a dissecting microscope, the epi- and perineurium were removed and small microfilaments were dissected from the whole nerve at the cut proximal end of the sciatic. The microfilaments could then be placed across a second pair of silver recording electrodes, R1. If spontaneous activity was seen in the microfilament, the microfilament was carefully dissected until only one or two active fibers could be clearly isolated on the oscilloscope. The recording and signal averaging protocol is as follows.

Both R1 and R2 were connected to High Z^o probes (Grass HIP 511E) configured for a common mode rejection and a Grass^o P511 AC amplifier. All activity was recorded on an eight-channel tape recorder. Impulses

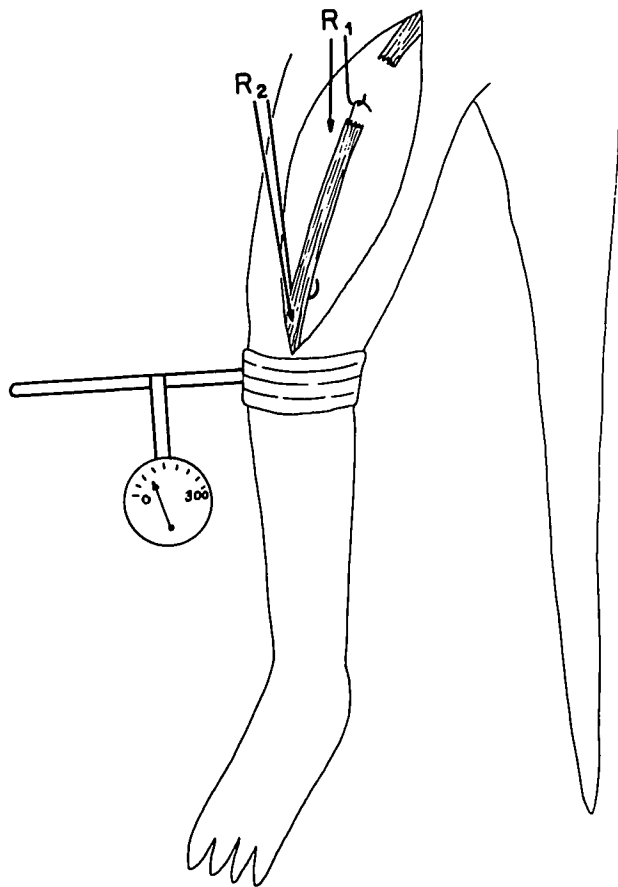


FIG. 1. Schematic of experimental preparation. Animal is prone with left sciatic nerve exposed in an oil bath. The sciatic nerve has been sectioned in the proximal thigh to prevent the propagation of efferent neural activity. A microfilament has been dissected from the whole nerve and placed over the bipolar electrode R1. A second bipolar electrode, R2, is under the distal sciatic just proximal to the inflated thigh tourniquet. Neural activity from recording electrodes is amplified and displayed on an oscilloscope.

from the distal electrode, R2, are fed to a digital delay line attached to a summation averaging computer (Nicolet^o 1072). By this method the signal delay can be varied from 2–40 ms. Signal averaging is triggered on the action potential of interest from the recording electrode R1 displayed on a Tektronix^o 565 oscilloscope with a Schmidt^o trigger. The sweep gate out signal from the Tektronix^o 565 is used to trigger signal averaging from the R2 whole nerve electrode that was displayed on a storage oscilloscope, (Tektronix^o 5103). The delay line is necessary because orthodromic action potentials will propagate from the distal area near the tourniquet prior to their appearance at the cut microfilament. Thus by continually triggering from a spontaneously active fiber from the microfilament contained on electrode R1, a signal average could be obtained from the distal whole nerve on the R2 electrode. With adequate averaging, two distinct peaks could be displayed on the oscilloscope that corresponded to R1, "time zero," and the impulse propagated through the whole nerve, R2. By electronically displaying the time between both peaks on the oscilloscope and measuring the distance along the sciatic nerve between the R1 and R2 electrodes the conduction velocity of the spontaneously active fiber can be determined without the need for external electrical stimulation. In addition, the firing rate of the fiber of interest could easily be measured.

Prior to tourniquet inflation, several microfilaments from each sciatic nerve were surveyed to determine baseline spontaneous activity. Conduction velocity, firing rate, and the effect of manipulation of lower-extremity joints on the firing rate were determined. The tourniquet was then inflated to 1.5–2 times systolic blood pressure while continually observing the spontaneously active fiber(s). In all 20 animals the presence of a cyanotic limb distal to the tourniquet after inflation was confirmed and the absence of bleeding to a small puncture in the foot pad was used to confirm adequate tourniquet placement and inflation. After all spontaneous and mechanically induced activity had stopped, the microfilament was continually observed for the new onset of spontaneous activity. If no spontaneous activity occurred by 30 min other microfilaments were surveyed for activity. Once an active fiber was found, the conduction velocity, firing rate, and tourniquet time to discovery were recorded.

After the above parameters were determined the animals were divided into several subgroups and a variety of tests were performed prior to termination of the experiment. In an attempt to determine the origin of the impulse or receptive field of the spontaneous fiber, in all animals the skin was probed, a surgical incision made, and lower-extremity joints moved to determine the effect, if any, on the firing rate of the isolated fiber. In all animals the nerve distal to the tourniquet was exposed and the area packed with ice or infiltrated with 2% lidocaine (2

ml). Finally, in an attempt to assure complete denervation of the leg distal to the tourniquet, all muscle, nerve, and connective tissue in five animals was surgically severed to expose the bare femur. If these maneuvers distal to the tourniquet failed to effect the firing of the spontaneous fiber, ice or 2% lidocaine (0.5 ml) was placed on the sciatic nerve just proximal to the tourniquet to determine if a proximal block was effective in abolishing the activity when placed proximal to the tourniquet. Finally, in five animals the effect of deflating the tourniquet on the spontaneous fiber was recorded.

In an effort to better characterize the hemodynamic effects of prolonged tourniquet inflation in this model, ten additional rats were observed using the following protocol. All animals underwent tracheostomy with controlled ventilation of their lungs, insertion of femoral venous and arterial catheters, and had tourniquets placed but not inflated on the lower extremity. To minimize blood and third-space fluid shifts, the sciatic nerve was not exposed. The animals received an iv bolus of pentobarbital (50–100 mg/kg) and a continuous infusion at 25–40 mg · kg⁻¹ · h⁻¹. After a 45 min period of hemodynamic stability, the mean arterial pressure was continuously recorded prior to tourniquet inflation for an additional 1 h. The tourniquet was then inflated and the animal observed for 90 min at which time the tourniquet was deflated and the hemodynamic parameters recorded for 1 h. At the end of each study the animal was killed with iv pentobarbital. Data analysis of mean arterial blood pressure was done using the Wilcoxon's rank sum test with Bonferroni's correction for multiple comparisons. An overall *P* value of less than 0.01 was considered significant.

Results

There was much spontaneous activity identified prior to inflation of the tourniquet. Twenty fibers identified had conduction velocities that ranged from 20–44 m/s (30 ± 6.9 m/s) (mean \pm SD), with firing rates from 11–25 H (16.3 ± 1.9 H). In all fibers identified prior to tourniquet inflation the firing rate increased in response to movement of the foot, ankle, or knee. Typically, inflation of the tourniquet caused an increase in the firing rate of these fibers, but by 20 min of tourniquet inflation in 18 of 20 animals all spontaneous activity had ceased and remained silent to even mechanical stimulation of the lower extremity. From 24–90 min (55 ± 16 min) after tourniquet inflation in 14 of the 20 animals other spontaneously active fibers were identified that displayed conduction velocities in the range from 0.89–3.3 m/s, (2.04 ± 0.77 m/s) with firing rates from 0.2–1 H (0.54 ± 0.9 H). In the remaining six of 20 animals, four were observed to have slowly firing fibers after tourniquet inflation but a signal average was unable to be obtained due to technical difficulties in isolating a clear signal from which to trigger. In two animals, spontaneous activity never stopped after tourniquet inflation.

The conduction velocity and firing rates of fibers surveyed before and after tourniquet inflation are plotted in figure 2. The conduction velocity and firing rate of spontaneously active fibers observed after tourniquet inflation are markedly slower than the fibers surveyed prior to inflation of the tourniquet. Figure 3 shows a rate firing plot of a representative spontaneously active fiber. Inflation of the tourniquet causes a temporary increase in the firing rate of the fiber that gradually slows and eventually ceases

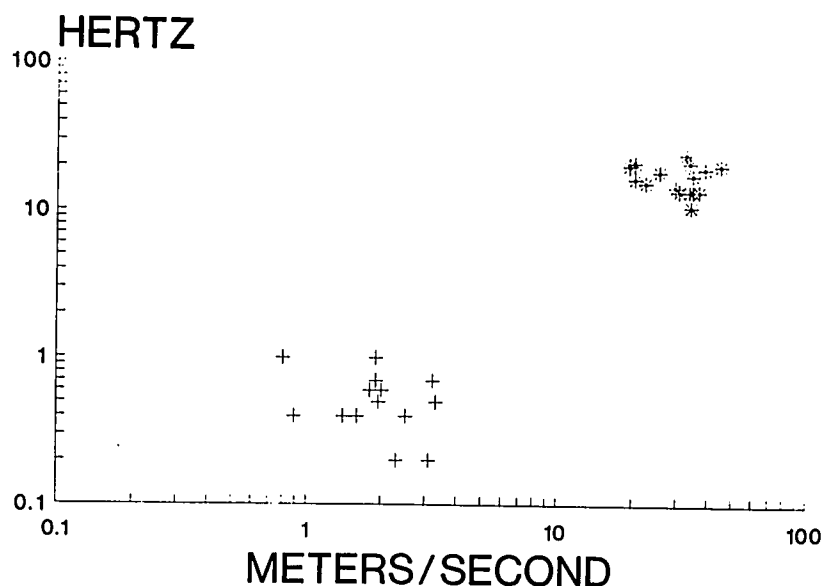


FIG. 2. Conduction velocity *versus* firing rate of spontaneously active fibers isolated before (*) and after tourniquet inflation (+). Data are presented on a logarithmic scale. The firing rate and conduction velocity of fibers isolated after tourniquet inflation were significantly slower than that observed in fibers prior to inflation.

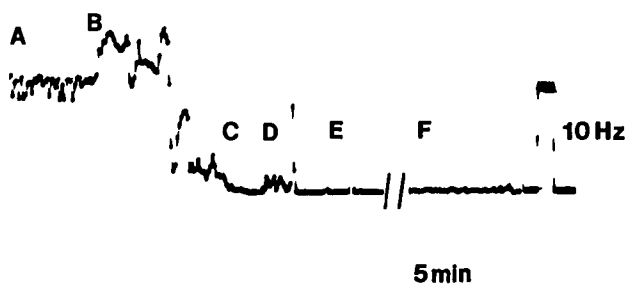


FIG. 3. Firing rate plot of a spontaneously active fiber illustrating a representative example of changes that occurred in neuronal activity prior to and after tourniquet inflation. *A* Firing rate of the fiber prior to tourniquet inflation. *B* Increase in firing rate seen immediately after tourniquet inflation. *C* Gradual decrease and cessation of spontaneous activity. *D* Mechanical stimulation of joint distal to tourniquet is still able to stimulate the fiber but with increased tourniquet inflation time further stimulation of the joint *E* does not cause the fiber to fire. *F* Low voltage, slowly firing fiber is found in a nearby microfilament. The waveform is displayed in figure 4.

over several minutes. The fiber can still be mechanically stimulated to fire, but after several more minutes of tourniquet inflation the fiber is unable to be stimulated by manipulation of the distal extremity. Eventually a slowly firing spontaneous fiber is found in a neighboring microfilament. The waveform of this fiber with a conduction velocity of 0.9 m/s is shown in figure 4.

In spontaneously active fibers identified after tourniquet inflation, no change in firing rate occurred with movement of the foot, ankle, or knee, surgical incision of the skin, infiltration of the tissues distal to the tourniquet with local anesthetic, or cutting the tissues distal to the tourniquet. Placing ice or lidocaine on the sciatic nerve just proximal to the tourniquet stopped activity in five of five animals. An example of one such fiber is shown in figure 5. Movement of the distal extremity, placing ice on the exposed tissue, and severing all structures distal to the tourniquet failed to change the baseline firing rate. Placing ice on the sciatic nerve just proximal to the tourniquet stopped the firing of the fiber which restarted several minutes after the ice was removed. Deflation of the

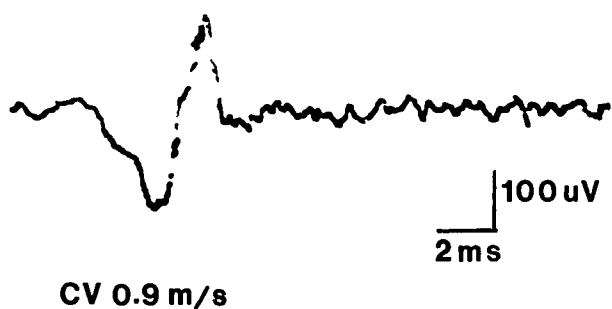


FIG. 4. Waveform of fiber isolated 90 min after tourniquet inflation. Conduction velocity was 0.9 m/s.

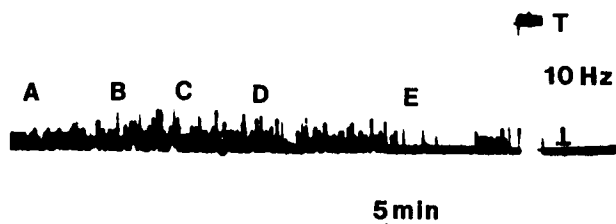


FIG. 5. Firing rate plot of a spontaneously active fiber, conduction velocity 0.99 m/s isolated after 80 min of tourniquet inflation. Baseline firing rate *A* is unaffected by moving the limb distal to the tourniquet, placing the distal extremity in ice *B*, infiltrating the deep tissue distal to the tourniquet with local anesthetic *C*, or by severing all tissue distal to the tourniquet *D*. Ice placed on the sciatic nerve just proximal to the tourniquet temporarily stops the spontaneous activity *E*.

tourniquet caused the spontaneously active fiber to decrease or cease to fire within several minutes in four of five animals. No spontaneously active fibers with slow conduction velocities were identified prior to tourniquet inflation.

In the ten separate animals studied to evaluate the effects of tourniquet inflation on blood pressure, inflation of the tourniquet caused a significant increase in the mean arterial blood pressure from preinflation control values (figure 6). Deflation of the tourniquet caused a significant decrease in mean arterial pressure from the levels observed when the tourniquet was inflated.

Discussion

Dull aching pain associated with prolonged tourniquet inflation during surgery was first described by Cole⁸ in

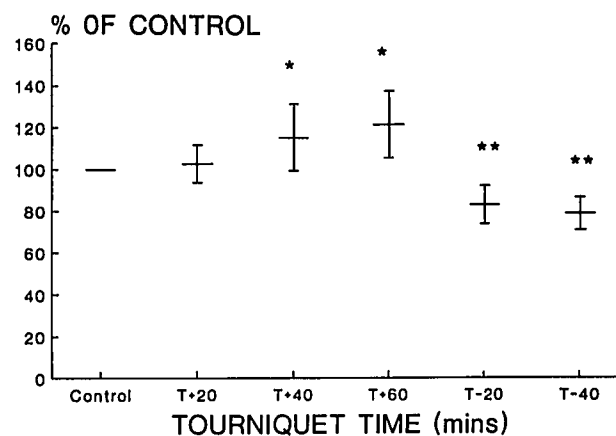


FIG. 6. Mean arterial pressure (MAP) during the control period prior to tourniquet inflation in ten animals, at 20, 40, and 60 min after tourniquet inflation, and at 20 and 40 min after tourniquet deflation. Mean arterial pressure and one standard deviation obtained during tourniquet inflation are expressed as a percent of the control MAP prior to tourniquet inflation. *Significant difference from control MAP. Mean arterial pressure obtained after tourniquet release is expressed as a percent of MAP at 60 min of tourniquet inflation. **Significant difference from T + 60.

1952. Since that report a number of investigators have attempted to define the incidence of tourniquet pain during operations performed under regional anesthesia. Egbert and Deas reported 64% of 55 patients given a spinal anesthetic with 12 mg of tetracaine complained of tourniquet pain even though the mean level of anesthesia to pinprick was the fifth dermatome level.¹ If, however, the dose of tetracaine was increased to 16 mg, (mean pinprick level T-4.6), the incidence of tourniquet pain decreased to 33%. The incidence of tourniquet pain seems to be greater in patients given spinal anesthesia with tetracaine (60%) than a similar group of patients receiving bupivacaine (25%) even though the group treated with tetracaine achieved a higher dermatomal level of spinal anesthesia.⁹ Finally, in similar groups of patients the addition of glucose to spinally administered bupivacaine caused the incidence of tourniquet pain to increase from 13–36% when compared with patients treated with bupivacaine alone.⁴ The quality of tourniquet pain is described as a dull, tight, aching, pain that may involve the entire extremity distal to the tourniquet.¹⁰ With regional anesthesia, tourniquet discomfort will usually start by 45 min following tourniquet inflation.¹⁰ In unmedicated unanesthetized volunteers, pain will occur within minutes of tourniquet inflation and gradually increase with time. In all cases, the related discomfort is abolished within minutes of deflation of the tourniquet.¹⁰

In patients undergoing an operation under general anesthesia the use of an intraoperative tourniquet is associated with increased mean arterial blood pressure and systemic vascular resistance.^{2,3,11,12} The time course of these hemodynamic changes parallels the increase in reported pain in patients with regional anesthesia. In unmedicated, unanesthetized volunteers, the changes in both blood pressure and reported pain occur simultaneously within minutes of tourniquet inflation.¹⁰

The neurophysiologic basis of tourniquet pain has been a subject of some debate. Various theories have proposed that peripheral receptors distal to the tourniquet originate impulses in response to ischemia, surgical stimulation, or metabolic products^{5,6,13} and these discharges propagate under the tourniquet mediating the sensation of pain. The origin of the neural discharges could also be from the distal ischemic axon itself or the axon or receptors in tissue directly under or just proximal to the tourniquet. The fiber type involved in the transmission of tourniquet pain remains unclear. Some have implicated activated large myelinated fibers that are resistant to local anesthetic block and thus able to convey impulses through even a regional anesthetic.^{1,8} The use of somatosensory evoked potentials have demonstrated that at least with epidural anesthesia, transmission through large fibers remains resistant to blockade and is able to convey evoked impulses

through the anesthetic.^{14,15} § The ability of large myelinated fibers to transmit nociceptive information has recently been reevaluated by Campell *et al.*⁷ who has found that in at least some peripheral nerve injury states the report of pain correlated very well with the function of these large traditional “nonpain” fibers and not to the that of the smaller diameter traditional a-delta or c pain fibers. Others have felt that tourniquet pain is carried by a-delta or c-fibers that become activated and are able to penetrate a local anesthetic block¹⁶ or perhaps enter the sympathetic chain and join the central nervous system at a point cephalad to the regional anesthetic.^{5,6}

The experimental model presented in this paper has attempted to examine the neurophysiologic changes that occur during tourniquet-induced ischemia. The two electrode signal averaging technique allows for the recording and determination of both conduction velocity and firing rate of an isolated spontaneously firing neural fiber without the need to electrically stimulate the fiber. This technique has been used successfully to measure multiple c- and a-delta fibers in previous experiments.^{17–20} The findings of a conduction block of both spontaneous and mechanosensitive activity after 15–20 min of tourniquet inflation and the increase in activity after tourniquet deflation has been reported by others.^{21–23} The marked increase in activity recorded by percutaneous microneurography after a short period of tourniquet inflation has correlated with the perception of parathesias in humans.²⁴ In our study, after a period of relative quiet, low-voltage slowly firing fibers were noted. These fibers were often difficult to isolate due the low signal-to-background noise ratio or due to several low-level fibers occurring in the same microfilament. The conduction velocity after signal averaging was in the c-fiber to slow-conducting a-delta fiber range. This was in marked contrast to the fibers surveyed prior to tourniquet inflation. Because of the low signal-to-noise ratio, the time taken to obtain a clear signal average, the need to often survey multiple microfilaments, and presence of much spontaneous activity in the interval after tourniquet inflation, it was impossible to obtain with certainty the exact onset of activity of the isolated slowly conducting slowly firing fibers. It did appear however that there was a period of inactivity prior to the start of firing of these fibers. Because a variety of maneuvers distal to the tourniquet failed to affect the firing rate of these slow conducting fibers, it appears that the origin of activity is the axon or peripheral receptors located in the tissue directly under or in the “perischemic” area at the proximal edge of the tourniquet. Whether the etiology is ischemia or mechanical distortion of the axon or receptor is un-

§ Wilson PR, Wedel DJ, Daube JR: Evoked potential changes during epidural local anesthesia (abstract). *Regional Anesthesia* 12:98A, 1987.

certain. If the activation of these slowly conducting fibers plays a role in the transmission of tourniquet-induced pain, it is uncertain whether the fibers follow conventional afferent somatic nerves centrally to the spinal cord or if they enter the sympathetic chain and join the spinal cord at a rostral location. The slow firing rate of the isolated fibers do not conform to the isolated nerve preparation model in which c-fibers were able to conduct through a weak local anesthetic block if stimulated at a rapid rate. The firing rate of our isolated fibers were less than 1 H while those used by Stewart *et al.*¹⁶ were stimulated at rates from 9–15 H.

In an attempt to examine if hemodynamic changes similar to those noted in humans occurred in response to tourniquet inflation, ten animals were studied with tourniquet inflation alone alleviating the problems associated with blood loss and fluid shifts from surgical exposure of the sciatic nerve. There was a significant increase in mean arterial blood pressure with inflation of the tourniquet that increased with tourniquet time. Blood pressure also decreased after deflation of the tourniquet. These hemodynamic changes observed are similar to those seen in humans under general anesthesia. The use of a continuous infusion of barbiturate was selected to achieve a steady depth of anesthesia, and in all animals a second control period after tourniquet deflation was performed to assure that the changes in blood pressure were not simply due to an inadequate depth of anesthesia. If the hypertension observed was due solely to inadequate anesthesia, one would not expect to see a decrease in blood pressure with tourniquet inflation. In patients invasively monitored during operations in which tourniquets were used, hypertensive changes can not be explained on the basis of fluid shifts alone. Without behavioral data it is uncertain if the changes observed in our model are due to pain; however, the changes in blood pressure that occur after tourniquet inflation may eventually serve as a marker for screening administered agents or treatments for tourniquet-induced ischemia.

In summary, we have described an animal model of tourniquet-induced ischemia. A microfilament recording technique coupled with a signal averager has disclosed a group of spontaneously active fibers with slow firing rates and conduction velocities in the c-fiber range that were not seen prior to tourniquet inflation and differ markedly from fibers isolated in the control period. If these slowly conducting fibers are associated with the perception of tourniquet pain, it would be consistent with the observation that tourniquet-induced pain can be successfully treated by intrathecal or epidural opioids.^{25–28} The slow firing rate is not consistent with reports of isolated c-fibers impulses breaking through a weak local anesthetic block as a firing rate from 9–15 H was needed to overcome this

block.¹⁶ The model has also displayed changes in blood pressure that have commonly been seen in humans. Questions remain whether the etiology of this spontaneous activity is due to ischemic receptors under the tourniquet or from mechanically distorted or ischemic axons. In addition, the afferent pathways of these fibers are unknown and could follow conventional somatic nerves or enter and traverse the sympathetic chain. It is hoped that continued examination of this model will provide answers to some of these questions.

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