Nerve Conduction Velocity During Hypothermia in Man

Rudolph H. de Jong, M.D.,* William N. Hershey, M.D.,† Irving H. Wagman, Ph.D.‡

Alterations in peripheral nerve impulse conduction during cooling were investigated in 7 surgical patients. A significant association between maximum conduction velocity and mean nerve temperature was found for peroneal nerve. Conduction velocity fell from 49.6 m./sec at 35.5° C. to one-half (25.9 m./sec) at 23.5° C. and to one-fourth (12.1 m./sec) at 21.5° C. Conduction velocity decreased linearly at a rate of 1.84 m./sec/degree centigrade between 36° and
23° C. (P < 0.001). Below 23° C. nerve threshold rose rapidly and conduction velocity fell sharply. Results obtained in this investigation are in good agreement with findings obtained from other species over a comparable temperature range.

In vitro animal studies 1, 2, 3, 4 have demonstrated a linear relation between nerve conduction velocity and temperature. Results however have been variable, depending upon animal species, diameter of nerve fibers and temperature range studied. Furthermore, current data describing the relationship between conduction velocity (or conduction time) and temperature in man cover a limited temperature range; only presumptive evidence of a linear correlation between conduction velocity and temperature has been found between 36° and 30° C. 5, 6

Since we had the opportunity to study surgical patients during hypothermia as part of a continuing investigation of the action of general anesthetics on the human nervous system,

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* Associate Professor, Department of Anesthesiology, University of Washington, Seattle, Washington.
† Research Trainee, Department of Anesthesia, University of California, San Francisco.
‡ Professor, Department of Animal Physiology and Research Physiologist, National Center for Primate Biology, University of California, Davis, California.

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we decided to measure conduction velocity in greater detail and over a wider temperature range than heretofore possible. These data afford a more detailed comparison with those obtained by others in animals and in man. Results obtained from the present investigation provide evidence that conduction velocity relates linearly to temperature, above 23° C.

Methods

Seven otherwise fit patients (mean age 39.1 years, range 22–48 years) underwent operation for ligation of intracranial vascular aneurysms under hypothermia. Subjects selected for study demonstrated normal peripheral neuromotor function on neurologic examination. Prior to operation informed patient consent was obtained for the study. Only patients cooled by means of circulating refrigerant blankets were included because we felt that nerve temperature equilibration would not be achieved during rapid cooling by immersion.

Patients were lightly premedicated with pentobarbital and atropine. Anesthesia was induced with thiopental and succinylcholine and the trachea intubated. Anesthesia was initially maintained with nitrous oxide-halothane. Respiration was manually assisted with periodic hyperinflation of the lungs. The electrocardiogram and femoral arterial pressure were continuously monitored. Cooling was achieved by placing the patient from neck to toes between blankets with internal refrigerant coils. Shivering was controlled by deepening of anesthesia during induction. Upon reaching an esophageal temperature of 32°–33° C., nitrous oxide was discontinued and the inspired halothane concentration reduced to 0.2 to 0.5 per cent in a 5 liter oxygen flow until esophageal temperature reached 28.5°–30.5° C. Warming was started upon ligation of the aneurysm.
Following induction of anesthesia, but prior to cooling, stimulating electrode pairs were placed at two separate sites close to the course of the peroneal nerve. One pair of 26 gauge, 1.5 cm. metal needles (Grass EEG needle electrodes) was inserted at the neck of the fibula (proximal stimulus site) the other pair at the dorsum of the foot near the anterior tibial nerve (distal stimulus site). Electrodes of each pair were 1–2 cm. apart and the cathode was always distal. The conduction distance between proximal and distal stimulating electrodes was measured on the surface of the leg between each cathode. Excitation of proximal and distal stimulus sites was accomplished with two Grass S-1 stimulators, delivering square waves of 0.2–0.3 msec. duration which were isolated from ground by transformers. The muscle action potential of the extensor digitorium brevis was recorded with a pair of discs, one placed over the muscle belly, the other over the tendon. Following conventional preamplification of cathode follower input, the muscle action potential was displayed on a Tektronix 502 oscilloscope. The oscilloscope screen was directly photographed on 35 mm. film by a Grass camera. The film was read at 15-fold magnification to measure directly latency and amplitude of the action potential.

Proper placement and fixation of the stimulating and recording electrodes was of the utmost importance to insure consistent results over many hours. Desired location of stimulating electrodes in proximity to be peroneal nerve was achieved when the threshold stimulus was below 25 volts. Maximal stimulus strength was then determined and was increased by 50 per cent to attain supramaximal intensity. The results of the present study are based on responses to supramaximal stimuli and deal only with conduction velocity of the fastest conducting fibers in the peroneal nerve supplying the extensor digitorium brevis muscle. However during the course of every session, threshold and submaximal responses were continually recorded to further insure that stimulating and recording conditions remained reasonably constant.

Nerve temperature was measured with a 22-gauge, 7.5 cm. long needle thermistor probe (Yellow Springs; model 513) which was in-
serted into the anterior tibial compartment with its recording tip in proximity to the midportion of the peroneal nerve, between knee and ankle. Although nerve temperature may vary somewhat along its length, we chose this portion to be representative of mean nerve temperature. Temperature measurements were based upon comparable portions of the nerve. A wide temperature gradient, at times exceeding ten degrees, was found between nerve and esophageal recording locations.

Determination of conduction velocity of the fastest fibers in the nerve segment lying between proximal and distal stimulating cathodes was made in a standard manner. The motor nerve was excited at the two separate sites and latencies of the electrical response of the innervated muscle to proximal and distal stimulation, were measured separately to the point where the action potential just leaves the base line (fig. 1). Since the delay in terminal conduction pathway time is identical for either site of stimulation, subtraction of latency of response to distal stimulation from latency of response to proximal stimulation yields the conduction time for an impulse traveling from proximal to distal stimulus (cathode to cathode) along the inter-electrode nerve segment. The measured conduction distance in meters (D) divided by the measured difference in conduction time in seconds (T) yields the conduction velocity ($V = D/T$) in meters per second.

Results

A total of 130 observations were made on 7 subjects at nerve temperatures ranging from 36.0° to 20.1° C. Latency and duration of muscle action potential became progressively prolonged with drop in nerve temperature. Below 24° C, latency and duration were so increased and amplitude so much decreased, that precise measurements of the magnified record, even when made at high gain, became progressively more difficult. However by choosing identical inflection points on the rising potential slope for proximal and distal responses, uncertainty of latency measurement was reduced to an acceptable level. Above 23° C, the nerve threshold to stimulation remained constant. Below 23° C, the threshold rose suddenly and steeply, and at approximately 20° C, muscle action potentials could no longer be detected even at maximal stimulator output. This could mean that the nerve-muscle system became inexcitable at this temperature, although it is more likely that these methods were not sufficiently sensitive to detect the resultant action potentials (see below).

An interesting observation was that the mechanical muscle twitch became increasingly attenuated and slow as temperature was lowered. Above 28° C, each proximal volley gave rise to a brisk movement of sufficient force to be noticeable to the surgeon. At lower temperatures the leg muscles made a very slow, gradual, prolonged and weak movement. Muscle function recovered rapidly as the leg was warmed.

To facilitate presentation of data, conduction velocities have been grouped at intervals of one degree between 36.0° and 20.1° C. (table 1). Means and the standard errors are representative of the midpoint of each temperature group (e.g., 33.5° C.). The mean velocity at 35.5° C was 49.6 m./second; this fell to approximately one-half at 23.5° C. (25.9 m./second) and to one-fourth at 21.5° C. (12.1 m./second). Above 23° C, the relation between conduction velocity and temperature was linear (see below). Below 23° C, conduction velocity fell suddenly, sharply, and

Table 1. Mean Peroneal Nerve Conduction Velocity (Grouped Data)

<table>
<thead>
<tr>
<th>Temperature Range (°C)</th>
<th>n</th>
<th>Mean Velocity (m/sec)</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.1-36.0</td>
<td>5</td>
<td>49.6</td>
<td>0.9</td>
</tr>
<tr>
<td>34.1-35.0</td>
<td>8</td>
<td>48.0</td>
<td>0.3</td>
</tr>
<tr>
<td>33.1-34.0</td>
<td>11</td>
<td>44.5</td>
<td>0.9</td>
</tr>
<tr>
<td>32.1-33.0</td>
<td>12</td>
<td>43.1</td>
<td>1.0</td>
</tr>
<tr>
<td>31.1-32.0</td>
<td>11</td>
<td>41.8</td>
<td>1.0</td>
</tr>
<tr>
<td>30.1-31.0</td>
<td>12</td>
<td>39.7</td>
<td>1.0</td>
</tr>
<tr>
<td>29.1-30.0</td>
<td>14</td>
<td>37.1</td>
<td>0.9</td>
</tr>
<tr>
<td>28.1-29.0</td>
<td>10</td>
<td>37.3</td>
<td>1.1</td>
</tr>
<tr>
<td>27.1-28.0</td>
<td>14</td>
<td>35.2</td>
<td>0.7</td>
</tr>
<tr>
<td>26.1-27.0</td>
<td>10</td>
<td>32.5</td>
<td>0.6</td>
</tr>
<tr>
<td>25.1-26.0</td>
<td>9</td>
<td>30.6</td>
<td>0.9</td>
</tr>
<tr>
<td>24.1-25.0</td>
<td>3</td>
<td>29.0</td>
<td>2.3</td>
</tr>
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<td>12.1</td>
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<tr>
<td>20.1-21.0</td>
<td>3</td>
<td>7.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>
irregularly, apparently approaching zero at approximately 18° C. The findings obtained below 23° C. may or may not have represented actual physiologic conditions because of the above mentioned problems of measurement and are therefore not included in the statistical analysis.

Individual data for conduction velocity and temperature have been plotted in the form of a scatter diagram (Fig. 2). A linear regression analysis of 123 points lying between 36.0 and 23.1 degrees was performed, excluding observations below 23.1° C. The best-fitting straight line over the 36°-23.1° C. temperature range was represented by \( Y = 1.84X - 16.82 \), where \( Y \) is conduction velocity in m./sec. and \( X \) is temperature in °C. The 95 per cent confidence limits for the temperature correction factor were 1.65-2.01 m./second/degree centigrade. The linear association between conduction velocity and temperature was highly significant by \( t \)-test (\( P < 0.001 \)) between 36° and 23° C.

Discussion

The important effect of temperature on nerve conduction velocity has been recognized since the turn of the century. In the present investigation, the maximal mean motor conduction velocity of the peroneal nerve at 35.5° C. was found to be 49.6 ± 0.9 m./second in man, a value in good agreement with previously reported results (51.8 m./second;* 51.5 m./second;* and 49.6 m./second).9 This fell linearly at a rate of 1.8 m./second per degree drop in temperature to 23° C. Conduction velocity was reduced to one-half normal value at 23.5° C. The exact point at which the nerve presumably became inexcitable could not be determined with precision, although apparent inexcitability was recorded at approximately 18° C. This value is probably too high owing to technical problems of measurement; extrapolation of the regression line to 0 m./second, although of course speculative, yielded a temperature of 9.1° C. at which conduction would presumably cease.

Comparison of our findings with those obtained by others in animals and in man shows good agreement on the whole. Lucas10 found that the maximal conduction velocity of frog's sciatic nerve fell at a rate of 1.8 m./second/degree centigrade in the 18°-5° C. temperature range and obtained an identical value for molluscan nerve. Gasser2 also found the conduction velocity of frog's sciatic nerve to fall linearly with temperature in the 24°-12° C. range. Similarly, other investigators have found a linear rate of fall of 1.6-1.9 m./second/degree centigrade for frog sciatic nerve. Rosenberg and Sugimoto1 investigating the problem over a wider temperature range (25 degrees) found that as temperature was lowered below 12° C. the rate of fall in conduction velocity of frog nerve increased and became 4.2 m./second/degree centigrade in the vicinity of 5° C., more than twice that at room temperature. An apparent trend to more rapid fall at temperatures below 23° C. was observed in our study and is consistent with the above findings.

Our results, however, are somewhat different from at least 2 other studies performed on the ulnar nerve of man. Carpendale5 found that a decrease in perineural temperature from 35° C. to 25° C. approximately doubled conduction time in the ulnar nerve of 3 subjects. Henriksen6 observed an average decrease in ulnar nerve conduction velocity of 2.4 m./second/degree centigrade over the 35–30° C. range. The above values are higher than those obtained in the present investigation on pero-
neral nerve. The reason for this discrepancy is not entirely clear, but might be attributable to the higher conduction velocity of ulnar nerve (59.1 m./second) versus peroneal nerve (51.5 m./second) found by these investigators and the fact that all myelinated fibers cease impulse conduction at the same temperature. Until recently it has been assumed that cold differentially affects impulse conduction in fibers of different diameter and conduction velocity. Douglas and Malcolm,11 for example, found that in the cat delta fibers were blocked at 22° C. while alpha fiber conduction, though slowed, was still intact. They concluded that in the myelinated A group the smaller fibers were blocked at higher temperatures than were the larger fibers. More recent evidence, obtained by direct recording from cat nerve fibrils, has cast doubt on this concept. Paintal12 found that observed differences in temperature conduction block between alpha and delta groups were attributable to greater temporal dispersion of the delta elevation in the compound action potential. This author convincingly demonstrated that all myelinated fibers, regardless of size, cease to conduct at the same temperature (range 7.6°-9.1° C.). If this is indeed the case, then the greater the conduction velocity of a fiber at body temperature, the greater is the rate of fall of its velocity during cooling.

Determination of the temperature at which human nerve ceases to conduct would be of interest in establishing the temperature range in which cryoanaesthesia occurs. Extrapolation of the calculated regression line to 0 m./second conduction velocity yields a temperature of 9.1° C. at which impulse conduction presumably ceases. In the absence of data below 20° C. extrapolation is only presumptive evidence, nevertheless, the extrapolated temperature corresponds very closely with temperatures at which other mammalian nerves cease to conduct.5,12 Comparison of data obtained in man with those obtained in other mammals is made more creditable by noting that: (1) the Q10 (ratio of highest to lowest mean velocity over a 10° range) in the present study was 1.6 (28°-36° C. range), a value identical with that obtained by Paintal12 for cat saphenous nerve (27°-37° C.), and (2) the rate of fall of conduction velocity during cooling is the same in man as for other species (see above). Obviously, further studies are needed to determine the temperature at which impulse conduction in man ceases completely. Nevertheless, it is probable that this temperature will fall somewhere between the extremes of 9° C. and 18° C.

We have assumed that observed changes in nerve conduction velocity are attributable to changes in temperature alone, but in the present study the effect of the anesthetic must be considered. Halothane at inspired concentrations up to 2.5 per cent has insignificant effect on motor nerve conduction velocity between 35°-38° C. in man or cat (personal observations). While tissue solubility of halothane increases as temperature decreases, the relatively far greater reduction in inspired halothane concentration during cooling probably more than compensated for its increased solubility. It has been shown, moreover, that the earliest evidence of anesthetic action on nerve impulse conduction is an elevation of threshold to excitation.12,14 Since the nerve threshold remained stable over the entire 36°-23° C. temperature range it is unlikely that anesthetic action contributed to reduction in conduction velocity during cooling. A relative decrease in peripheral blood flow during hypothermia was evidenced by the large temperature gradient between nerve and body core temperature. This could possibly account for the changes in conduction velocity observed. However in vitro nerve without a blood supply is capable of transmitting thousands of impulses and shows identical behavior in conduction velocity during cooling and rewarming; the same was observed in the present study. Although rigid proof is lacking it is probable that changes in conduction velocity observed during cooling and rewarming in man are largely the result of thermal effects on metabolism of neural membrane.

Since the effect of temperature on nerve conduction velocity is significant, knowledge of this relation is of obvious importance for the proper comparison and interpretation of data obtained in normal man. For example, the average temperature of human forearm muscles was found to be 36° C., but a consider-
able drop, at times to 30° C., occurred after several hours exposure in an air-conditioned room. Gilliatt and his colleagues, especially, have pointed out the importance of making conduction velocity measurements in man under reproducible temperature conditions of the limb. Furthermore knowledge of normal values is important to determine the presence of alterations in nerve conduction. Reduction in conduction velocity of ulnar or peroneal nerve has been demonstrated for example in diabetic neuropathy, a neuromuscular disorders, nerve injury and old age. The results of the present study emphasize the importance of these considerations in man as well as of the continued investigation of other characteristics such as refractoriness of nerve and muscle, the reactions of the smaller fibers (especially those related to pain) and transmission at the myoneural junction during cooling.

Summary and Conclusions

Conduction velocity was determined for the fastest conducting fibers of the peroneal nerve supplying the extensor digitorium brevis muscle of 7 surgical patients during hypothermia. Mean nerve conduction velocity prior to induction of hypothermia was 49.6 ± 0.9 m./second at a mean nerve temperature of 33.5° C. The association between conduction velocity and temperature was linear above 23° C. (P < 0.001). Conduction velocity fell 1.84 m. second per degree fall in temperature between 36° and 23° C.

Threshold stimulus strength remained constant down to 23° C. Below this temperature, stimulation threshold rose sharply and the nerve-muscle system became apparently inexcitable between 15° and 20° C. Conduction velocity could therefore not be studied below 20° C., although extrapolation of the data to 0 m./second indicated that complete conduction block presumably occurred at 9° C.

Changes observed in conduction velocity during cooling and rewarming are attributable to thermal effects on the neural membrane.

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References