Received: October 10, 2012 Revised: January 13, 2013 Accepted: February 11, 2013

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12053

Electrically Evoked Compound Action Potentials Recorded From the Sheep Spinal Cord

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Objectives: The study aims to **c**haracterize the electrical response of dorsal column axons to depolarizing stimuli to help understand the mechanisms of spinal cord stimulation (SCS) for the relief of chronic pain.

Materials and Methods: We recorded electrically evoked compound action potentials (ECAPs) during SCS in 10 anesthetized sheep using stimulating and recording electrodes on the same epidural SCS leads. A novel stimulating and recording system allowed artifact contamination of the ECAP to be minimized.

Results: The ECAP in the sheep spinal cord demonstrates a triphasic morphology, with P1, N1, and P2 peaks. The amplitude of the ECAP varies along the length of the spinal cord, with minimum amplitudes recorded from electrodes positioned over each intervertebral disc, and maximum amplitudes recorded in the midvertebral positions. This anatomically correlated depression of ECAP also correlates with the areas of the spinal cord with the highest thresholds for stimulation; thus regions of weakest response invariably had least sensitivity to stimulation by as much as a factor of two. The choice of stimulating electrode location can therefore have a profound effect on the power consumption for an implanted stimulator for SCS. There may be optimal positions for stimulation in the sheep, and this observation may translate to humans. Almost no change in conduction velocity (~100 ms) was observed with increasing currents from threshold to twice threshold, despite increased Aβ fiber recruitment.

Conclusions: Amplitude of sheep Aβ fiber potentials during SCS exhibit dependence on electrode location, highlighting potential optimization of Aβ recruitment and power consumption in SCS devices.

Keywords: chronic pain, compound action potential, neurophysiology, neuromodulation, neuropathic pain, neurostimulation, physiologic measurement, spinal cord stimulation

Conflict of Interest: The authors declare no conflict of interest.

INTRODUCTION

Direct electrical stimulation of the spinal cord stimulation (SCS) has been used to ameliorate the symptoms of chronic neuropathic pain for over 40 years (1,2). Despite its therapeutic use, the mechanisms are not well understood (3,4), and there have been few studies attempting to measure the electrophysiologic response of the dorsal column nerve fibers to electrical stimulation from SCS devices, although the response of dorsal horn neurons in animal models of neuropathic pain have been studied (5,6). A detailed understanding of the electrophysiology during SCS would provide valuable insight into stimulation mechanisms and enhance device algorithms and patient fitting strategies. The advent of a number of new potential applications of SCS (7–9) has further motivated us to study the electrophysiology of the spinal cord in response to electrical stimulation.

Activity in the spinal cord, generated in response to electrical stimulation, is routinely measured during decompression or scoliosis surgery (10). The supramaximal stimulation is applied to a peripheral nerve, motor cortex or a site along the cord, many vertebral segments away from the recording site. Monitoring of the electrically evoked compound action potential (ECAP) allows the surgical team to assess the risk of spinal cord injury during the procedure. In the cochlear implant field, measurement of the ECAP is routine, but is complicated by artifact (11,12). The origins of artifact are not well understood but can completely obscure the response. The artifact is proportional to the stimulation, whereby high stimulation currents and pulse widths result in high electrical artifact (13).

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Evoked responses can be detected when they appear later in time than the artifact, or when the signal-to-noise ratio (SNR) is sufficiently high. Depending on the stimulation and recording system, the artifact may be last for one, tens, or hundreds of milliseconds after the stimulus (13), but provided the neural response is detected after this window, neural evoked response data can be obtained. This is the case in surgical monitoring where there are large distances (tens of centimeters) between the stimulating and recording electrodes. Cochlear implants use small stimulation currents relative to the tens of mA sometimes required for SCS, and thus measured signals in these systems present a relatively lower artifact. To characterize the responses from the dorsal columns, high stimulation currents (~1–25 mA) and close proximity between electrodes (7–50 mm) are required, and therefore the measurement process must minimize the generation of artifact. This is in sharp contrast to existing surgical monitoring techniques.

We have recently reported the first measurements of the propagating action potentials in the human spinal cord with standard SCS leads, using a pair of electrodes for stimulation and the remainder for recording (14). We confirmed that the fibers recruited during stimulation for pain relief had a high conduction velocity consistent with Aβ fibers of the dorsal column. These studies were carried out in patients undergoing trial stimulation for SCS implantation where it is impossible to explore a complete set of stimulation parameters. To more completely explore the recruitment characteristics of dorsal column fibers, we have conducted measurements in anesthetized sheep with a novel stimulation and recording system to minimize artifact. Here we report the responses from dorsal columns in the sheep as an animal model and have characterized the electrophysiologic response of a population of fibers to further broaden understanding of the mechanisms of SCS for the relief of chronic pain.

METHODS

Animal Model

Sheep were chosen as an appropriate large animal. The sheep spinal canal dimensions (15) are smaller than in a human; however, it is still feasible to insert a standard epidural electrode array. Percutaneous leads were employed that are 1.4 mm in diameter and consist of eight cylindrical ring contacts (electrodes). In this study, electrodes with a spacing of 7 mm (3 mm long and a 4 mm interelectrode spacing) were used (Model 3086 Octrode, St. Jude Medical, St. Paul, MN, USA). The subjects were provided by and experiments were carried out at the Kearns Facility at Royal North Shore Hospital under the Animal Care and Ethics Committee approval. The study complied with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. The animals were injected with alfaxalone (Alfaxan CD-RTU, Jurox, Australia) slowly to effect (maximum expected dose of 1.5 mg/kg over 2 min, but halted on obtaining desired effect), to induce anesthesia, and were intubated with a portex-cuffed endotracheal tube and ventilated with an oxygen-air mixture to a minimum of 30% oxygen containing isoflurane as a maintenance agent. Ventilation peak pressures were limited to 18 cm H_2O, with I : E ratios of 1:2 giving tidal volumes of 10 mL/kg with resulting mean airway pressures of between 4 and 5 cm H_2O. Subjects were monitored by electrocardiogram, arterial blood pressure, arterial saturation, and end-tidal carbon dioxide. Isoflurane levels were controlled to maintain lack of surgical responsiveness and weak jaw tone, and passive dilation of pupils with slow response to light, as well as maintaining arterial blood pressures of between 120–140 mmHg (systolic) and 80–100 mmHg (mean). Gas flow was used at minimum flow rates to conserve heat and moisture and the patients were maintained with a heat and moisture exchanger and covered after surgical placement with drapes to prevent heat loss. Subjects were maintained on approximately 1.2 times maintenance fluid rates using compound sodium lactate with potassium added to 7 mM (i.e., +2 mM) and magnesium added to 3 mM.

The surgical procedure was as follows. L1 or L2 vertebrae levels were identified under fluoroscope and the tissue dissected away from its dorsal spinal processes and from that of the next vertebra caudal thereto. Hemostasis was achieved with electrocautery and local injection of bupivacaine and adrenaline (Marcain 0.5% plus adrenaline, 1:200,000, AstraZeneca (North Ryde, NSW, Australia)). The dorsal spinous processes of L1 and L2 were removed and a laminectomy was then performed at the dorsal midline cranial margin of L1. The periostium was exposed using bone nibblers and incised with a number 11 scalpel blade to expose the dura. Leads were inserted extradurally via an "epiducer" (St. Jude Medical), which was gently advanced superficial to the dura. The epiducer was used to provide reliable access to the epidural space for two leads. The first lead was advanced in the epidural space under fluoroscopic imaging to the T8–T9 level. The lead insertion followed a similar technique as has been described for humans with adjustment of the position of the electrode to achieve a midline placement with stylets of various shapes formed at the tip (16).

Equipment and Measurement

The stimulating and recording system was a Multi-Channel System MkII (MCS; Saluda Medical, Sydney, Australia). The system has 24 channels of continuous recording (with an amplifier noise floor of 0.2 μV) and multiple software programmable current sources. The MCS was designed specifically to minimize the generation of artifact during the stimulation phase and maximize rejection of artifact during the recording phase. The stimulation system consists of current sources that can be configured with software to produce arbitrary stimulation patterns. In this study, the current sources were configured to produce biphasic tripolar stimulation with a guarded cathode, comprising a central cathode connected to a current source (herein referred to as the stimulation electrode), with adjacent anodes on either side (connected to ground).

Each lead consists of eight equally spaced electrodes connected to individual recording channels. Two leads (16 electrodes) were inserted along the same axis, with the tip of the caudal lead positioned to be roughly 4 mm from the caudal electrode in the more rostral lead so that all 16 electrodes were equally spaced. Both leads were connected to the stimulating and recording system, which allowed all 16 electrodes on the two leads to be used for stimulation (on three electrodes) or recording (on 13). As such, ECAP responses could be measured propagating rostrally from the stimulation electrode (orthodromic or normal direction of propagation) and/or caudally (antidromic or opposite to normal direction). All signals were measured relative to an indifferent electrode (titanium plate, ~25 × 80 × 2 mm) inserted intramuscularly at the surgical site.

The stimulation current was increased in small steps from 0 mA to threshold for ECAP responses and then increased further to about 5× threshold current. This was repeated for each stimulation electrode (E2–E15) and for varying pulse widths (40, 80, 120 μsec). Between each parameter change (stimulation electrode, current, or pulse width), 50–200 stimulus pulses were delivered. Stimulation frequency was set to standard SCS values of 30–40 Hz.

Responses were filtered at 4 kHz and sampled at 30 kHz with a United Electronic Industries data acquisition system (Walpole, MA, USA), which also passes the data through anti-aliasing filters at the

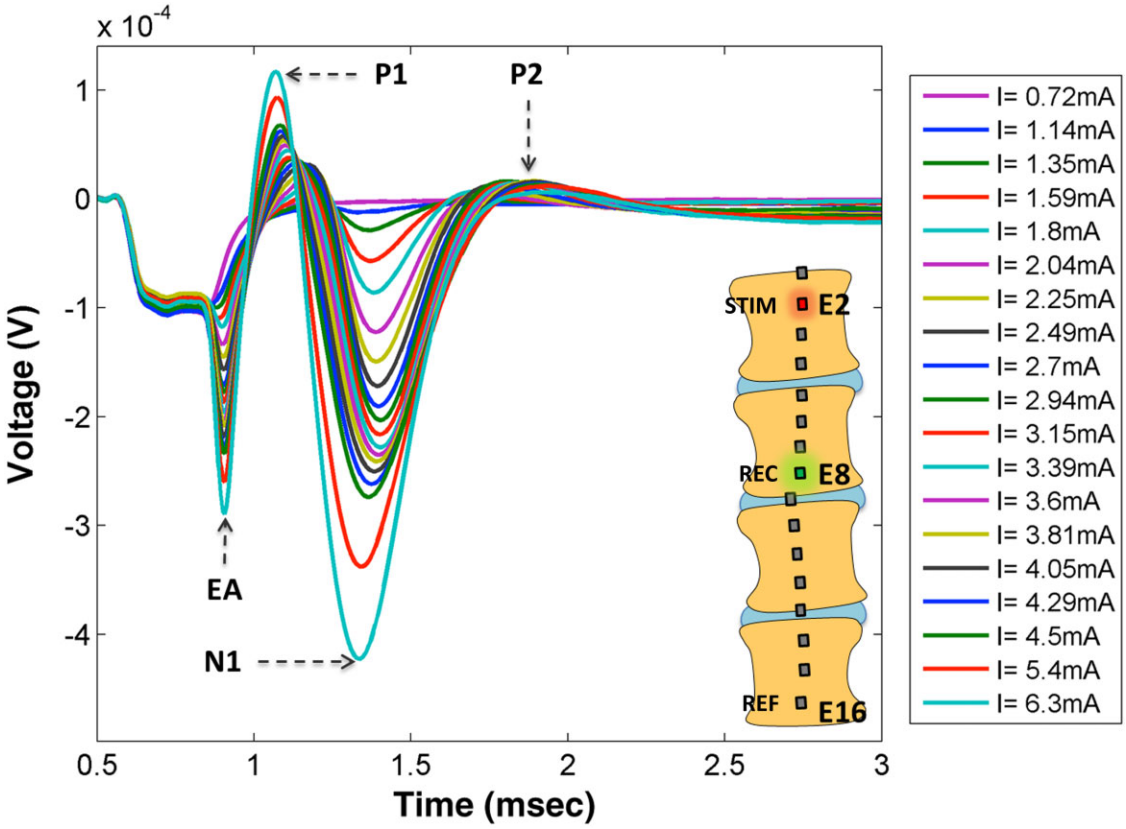

Figure 1. Measurement of the compound action potential in the sheep spinal cord from a dorsal mid-line epidural electrode for currents from 0.72 mA (just below threshold) to 6.3 mA. A diagram of the lead and electrode placement is shown in the inset. The responses were generated from tripolar biphasic (40 μs per phase) stimulation between electrodes 1, 2 and 3 with electrode 2 the second phase cathode ("STIM" electrode; see methods for explanation) measurements are recorded on electrode 8 ("REC" electrode; antidromic recording). The recording is initiated prior to the delivery of the stimulus. The stimulus duration is indicated on the graph. An "electrode artifact" is present labeled EA on the figure. The P1 N1 and P2 peaks are also labeled.

Nyquist frequency (15 kHz). The data were averaged between parameter changes.

Analysis

Custom software was developed for analysis (MATLAB, Natick, MA, USA). The recorded data were interpolated by a factor of 5 and low pass filtered with a −3 dB cutoff frequency of 7.5 kHz. ECG signal is present on the epidural electrodes and contaminates the ECAPs. The ECG from subcutaneous needles was also recorded on a separate channel. The response recordings were averaged to improve the SNR using only responses from isoelectric phases of the ECG where contamination from the ECG was minimal. Each sweep of averaged data used for measurement started ~200 μs before the stimulation pulse, and latencies reported in the following are relative to this recording initiation point.

RESULTS

Experiments were performed in ten animals and ECAP recordings were successfully obtained in all. The magnitude of the responses varied from animal to animal as expected given the variability in individual anatomy and physiology, and electrode placement with respect to the spinal cord.

The surgical placement of epidural leads in the sheep is more challenging than in humans. Percutaneous placement is not possible as the gap between spinous processes was too small to introduce a Tuohy needle. Laminectomy provides access to the dural surface enabling lead insertion; however, steering the electrode to maintain a midline dorsal placement requires considerable care. Changes in position of the animals resulted in rotation of the vertebrae at different levels. Even so, differences in responses correlated strongly with electrode placement.

The recorded signals consist of the neural response and a small electrode artifact (EA) (Fig. 1). The neural response is triphasic, consisting of a positive P1 peak followed by a negative N1 peak and then a secondary positive P2 peak. Figure 1 shows the amplitude of the ECAPs at one antidromic recording site with increasing current. The neural response morphology is characteristic of extracellular recordings of axonal compound action potentials (17,18). As described in these studies: The first phase P1 is dominated by the capacitive current due to the initial membrane depolarization; phase 2 is dominated by Na^+ ion current and is negative due to the influx of Na^+ ions during the neuronal membrane action potential; and the third phase is positive due to the K^+ ion conduction during repolarization.

The vertebral canal and epidural space, in which the lead is placed, is much smaller in sheep than in the humans and so the electrode is expected to be closer to the neural tissue of the spinal cord. The threshold for activation is correspondingly lower in the sheep than humans (14; 50 vs. 700 nC, respectively).

Care must be taken in interpretation of the ECAP recordings due to the presence of EA, which is the result of residual charge from the

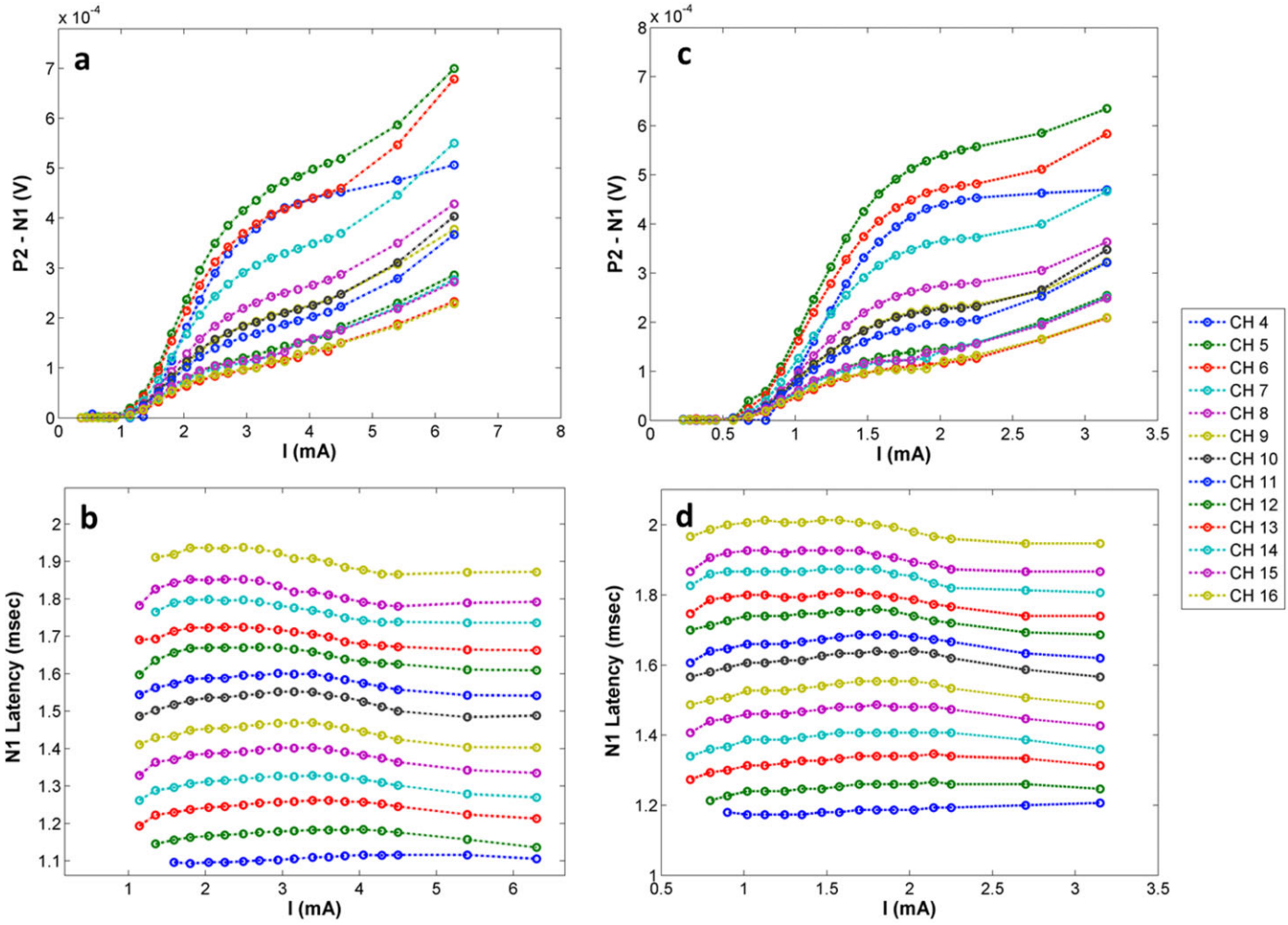

Figure 2. Peak-to-peak amplitude P2-N1 (a, c) and N1 latency (b, d) relative to recording initiation recorded on electrodes 4–16 for all stimulation currents. The stimulus employed the same parameters as used in generation of the data in Figure 1, with pulse width = 40 μs (a, b) or 80 μs (c, d).

stimulation current in the electrode or recording system being measured. The artifact labeled EA in Figure 1 may be distinguished from a neural responses because 1) the artifact is expected to increase from 0 mA, whereas the neural response displays a threshold and is present only above a threshold current; 2) unlike the artifact, the neural ECAP responses propagate along the spinal cord such that the latency to the response increases with distance from the stimulation electrode; 3) the responses are extinguished when the animal is euthanized, while the artifact remains. The artifact manifests as a decaying exponential potential immediately after the stimulus pulse. It has its most profound effect on the ECAP P1 peak so in this paper the amplitude, P2-N1, is measured as the N1 and P2 peaks are less affected by artifact.

The amplitude of the ECAP potentials (P2-N1) from Figure 1 is plotted along with amplitudes from all the measurement electrodes (E4–E16) against the current in Figure 2a. For a given current, the ECAP amplitude decreases with distance from the stimulation electrode (e.g., at 2 mA, ECAP amplitude decreases from ~250 to 50 μV for a distance of 3–14 electrodes from the stimulation). However, the potential for the electrode closest to the stimulating electrode, E4, is lower than the successive electrode, E5, due to the amplitude measurement being affected by artifact. The amplitudes of the responses at the five most distal electrodes (E12–E16) cluster together demonstrating a decreasing variation in amplitude with distance from the stimulus source (see also Fig. 7). The growth of the ECAP potential with increasing current is linear from threshold to over twice threshold.

Figure 2c displays the amplitude variation (P2-N1) with increasing current for a longer pulse width of 80 μs, exhibiting a behavior similar to the shorter pulse width. Neural activation is a function of the charge delivered to the nerve (integral of the current over the pulse width). For a given activation (measured here by P2-N1 amplitude) the charge required is linearly related to pulse width (19, see also 20), with greater pulse widths requiring greater charge. The amplitude as a function of the delivered charge at three different pulse widths is shown in Figure 3. Although the curves follow a similar shape, the charge required for a given amplitude is slightly larger at longer pulse widths as would be expected from the charge vs. pulse width relationship.

ECAP Conduction Velocity

The N1 peak position in time, or latency, (relative to the recording initiation) is plotted against the stimulation current in Figure 2b,d. The N1 latency increased by <0.1 ms as the stimulus current was increased to about 2× threshold, and then decreased at higher cur-

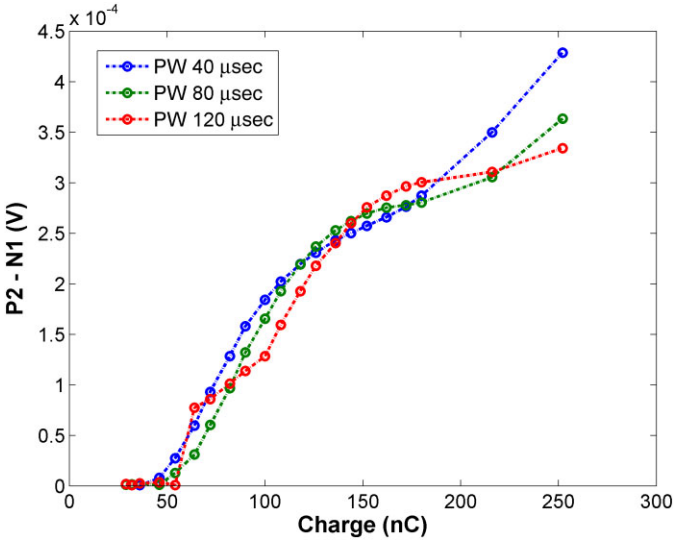

Figure 3. Amplitude P2-N1 plotted against the charge delivered for three different pulse widths of 40, 80, and 120 µs. Stimulation was tripolar using electrode 2 as center cathode; the recordings were made on electrode 8.

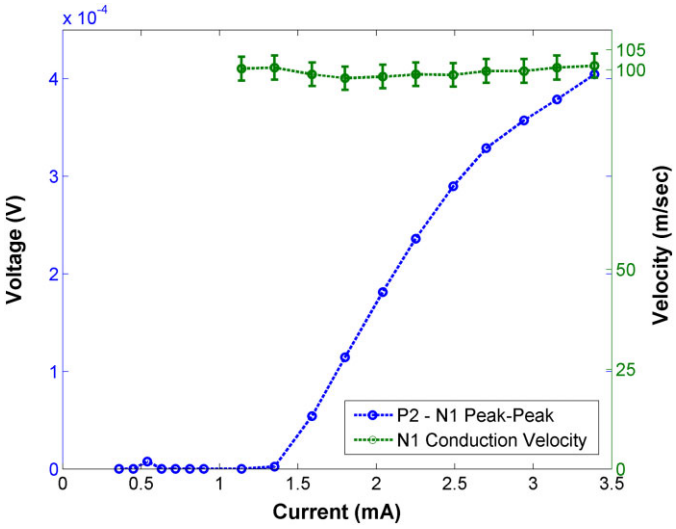

Figure 4. The conduction velocity calculated from the N1 latencies as a function of the stimulating current (right abscissa). The velocity is shown along with the P2-N1 amplitude growth curve (left abscissa).

rents to a plateau level. The conduction velocity can be calculated from the N1 positions along a number of electrodes knowing the spacing between successive electrodes (7 mm, center to center), plotting distance from the stimulus electrode vs. N1 latency and finding the slope (slope = V = D/T or conduction velocity = distance between electrodes/difference in N1 latency). The velocities estimated in this manner are shown in Figure 4. It is expected that as the stimulation current is increased the velocity of the observed potentials should drop, as slower, smaller diameter fibers are recruited. However, the figure shows velocity only decreasing from 101 to 98 ms from threshold to ~1.5× threshold and then increasing again to 101 ms, a change of less than 3%.

Conduction velocity was estimated from measurements from the two electrodes adjacent to the stimulus and the last three electrodes (caudal to stimulus). The measurement error in estimation of the conduction velocity is related to the accuracy of the N1 latency. The data is sampled at 30 kHz giving a timing resolution of 33 µs. These data are then further upsampled, by a factor of 5; providing an improved timing resolution of 6.67 µs (error of ±3.33 µs). The interelectrode spacing for the electrodes used is 7 mm, so assuming a conduction velocity of 100 msec for Aβ fibers in a sheep spinal cord this gives a 0.07 ms time of travel between two electrodes (Δd = 1). Taking the conduction velocity (V = D/T) using a difference method: D = 7 mm * (Δd), T = 0.07 ms * (Δd) with an error of ±3.33 µs; then over six electrodes this corresponds to a velocity error of ±2 ms. The small changes of ~2% in conduction velocity observed (Fig. 4) are within the experimental error of the measurement method.

Using a tripolar, biphasic stimulation pulse complicates this conduction velocity estimate. The two guarding anodes deliver half the current of the central cathode, so at threshold only the central cathode activates the spinal cord axons as anodes have much higher activation thresholds (21). During the charge recovery phase of these biphasic pulses the anodes have a cathodic polarity and are therefore able to activate the spinal cord axons when they reach threshold current. When the guarding anodes activate some axons at currents greater than twice threshold there will be a shift in the ECAP N1 latency as these axons are activated 7 mm closer to the recording electrode.

Despite this complication, the current work is motivated by seeking to improve an understanding of the mechanisms of SCS. The therapeutic level for SCS in pain relief lies somewhere between just under one and a half to two times the ECAP threshold (22). That threshold is defined, for humans, as a point at which they first feel a sensation, and not the electrophysiologic response, which is determined via direct measurement. We have recently shown that electrophysiologic threshold and perception threshold in humans are close (14). The conduction velocities measured between threshold and twice threshold, which covers the therapeutic range for SCS, are remarkably constant (98–102 ms ± 2 ms) for the sheep.

Such consistency indicates that measurements are either being made from a relatively narrow distribution of fiber diameters, that the relative proportion of small to large fibers does not change with increasing current, or that smaller diameter fibers responses are not be observable with the current methods as smaller fibers have smaller responses. As current increases, axonal recruitment occurs from larger to smaller fibers and from closer to more distant fibers. If the proportion of small to large fibers is not changing with increased current, then it suggests that recruitment may be preferentially occurring over increased distance from the electrode.

ECAP Amplitude

As the ECAPs propagate along the dorsal columns, the recordings of distal electrodes contain the same triphasic morphology observed on the electrodes adjacent to the stimulus electrodes; only delayed in time, as a result of the conduction velocity, and with a variation in amplitude. The amplitude of the responses depends on the anatomic location of the recording electrode. This is illustrated in Figure 5 where the responses from all electrodes are measured at a stimulation current of 2.75 mA. In general, the electrodes positioned over the midvertebral segments show larger measured potentials than do the electrodes positioned over the intervertebral discs. The propagation direction is antidromic and a diagram indicating the anatomic placement of the electrodes is shown in Figure 5. The amplitude of the response decays with increasing distance from the recording electrode in a nonuniform manner. Those

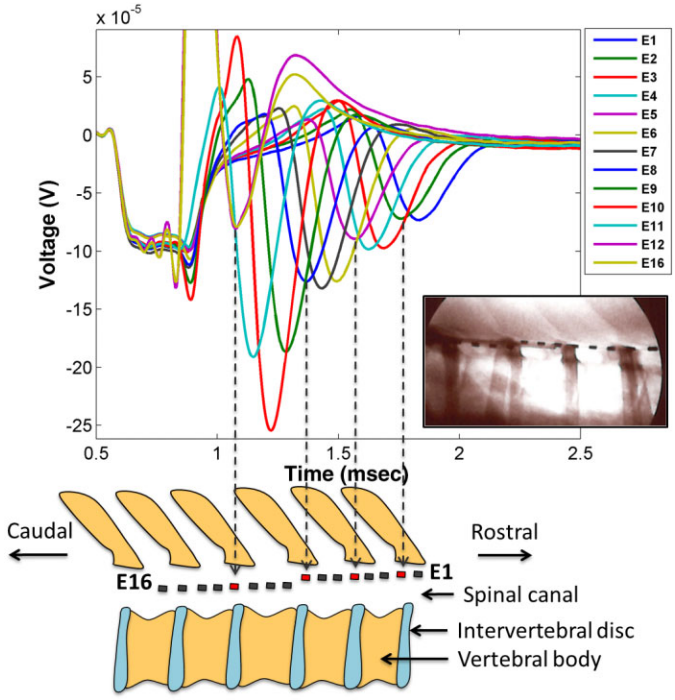

Figure 5. Propagating orthodromic potentials measured from stimulation of electrode 14 (top) and the relationship between the electrode position and responses. Arrows indicate ECAPs recorded on electrodes over intervertebral discs (bottom).

electrodes located in the areas where there are intervertebral discs demonstrate a pronounced reduction in amplitude in comparison with their neighbors.

The reduction in amplitude of measurement also corresponds to a reduction in efficiency of recruitment (greater current for a given ECAP response). Figure 6 shows stimulation on electrodes 2, 9, and 15 at the same stimulation current, and electrode placement as traced from a fluoroscope image. The responses of stimulation on channel 9 are less than half the amplitude of the responses recorded when stimulating on the other aforementioned electrodes. To further illustrate this phenomenon, the P2-N1 amplitude (at a fixed stimulation current and pulse width of 40 μs) for all stimulation sites along the electrode array is presented in Figure 7, in which orthodromic data (Fig. 7b) are separated from antidromic data (Fig. 7a) for all recording electrodes. The amplitudes of the responses reduce with distance from the stimulation electrodes, but the responses at electrodes 13 and 9 are further reduced from this trend line (Fig. 7a). Similarly stimulation at electrodes 13 and 9 generated the weakest overall responses (Fig. 7b).

DISCUSSION

Electrical stimulation of the spinal cord is used routinely for pain relief. The implantation of SCS electrodes requires considerable care. The position of the electrodes is adjusted at the time of surgery with feedback from the patient. A stimulus current is applied to an electrode and the patient reports the location and percept to the surgeon who in turn adjusts the position of the lead. Selecting the appropriate electrodes to stimulate and the intensity of stimulation can only be achieved through feedback from a conscious patient. We were motivated to study the compound action potential (ECAP) in response to electrical stimulation to determine if it can provide useful insight into the mechanism of SCS and provide further insight into how to optimize SCS electrode position. Measuring the ECAP amplitude, while varying electrode position, provides a useful tool for the optimization of stimulator programming parameters.

The amplitude and conduction velocity of the ECAP depends on many factors:

- the number and density of fibers in the electrically excited neural tissue
- the diameter of the fibers
- the distance of the fibers from the sensing electrode
- the impedance of the tissue between the electrode and the responding fibers
- the degree of synchronization between the responding fibers.

ECAPs measured from the sheep spinal cord via the epidural space behave in some ways as might be expected but are surprising in others. The triphasic response of the ECAP, the amplitude growth of the ECAP with increasing current and the consistency of the ECAP responses with applied charge with different pulse widths, could all be expected from the basic electrophysiology. Unexpected are the observations that the conduction velocity is not dependent on the current (at least from threshold to twice threshold), and the variation in ECAP amplitude along the spinal cord.

Large diameter myelinated fibers are easier to recruit than small diameter fibers (23), but the distribution of fiber diameters in the dorsal column is skewed toward small fibers, such that 95% of fibers are <8.7 μm (24). Large fibers have higher conduction velocities and so, as the current is increased, smaller, slower fibers are recruited, and the average conduction velocity would be expected to decrease. The evoked response is larger for larger diameter fibers and the reduction in response magnitude may mask contributions from the smaller fibers. The changes in impedance throughout the layers of tissues and fluids separating the responding fibers from the electrode may also have the effect of filtering the responses from the smaller diameter fibers. Another possible explanation is that the proportion of small to large fibers remains constant, as increasing current has the effect of recruiting fibers that are more distant from the electrode, while keeping the diameter proportion (and hence velocity) constant. A similar experiment with a peripheral nerve would have a much smaller distance effect on recruitment because the diameter of the nerve is much smaller than the extent of the dorsal columns. With the data presented here alone, the observation that the conduction velocity remains relatively constant is insufficient to conclude whether a narrow range of fiber diameters is recruited during SCS, or whether a relatively constant proportion of fiber diameters are recruited within therapeutic current limits.

The amplitude P2-N1 decreases as measurements are performed further away from the stimulus electrode. This is consistent with either a change in position of the fibers in the dorsal column (i.e., increasing separation from the recording electrode) or smearing of the ECAP due to the individual responses from a population of fibers becoming increasingly out-of-phase with each other because of their different conduction velocities. This important point is subject to further experiments and analysis.

There are significant differences in the relative sensitivities of different areas along the spinal cord. The electrodes on which the lowest magnitude responses were recorded also generated the lowest evoked responses when used as the stimulating electrodes. This may be due to the separation between the electrode and the dorsal column fluctuating between the vertebrae as a natural con-

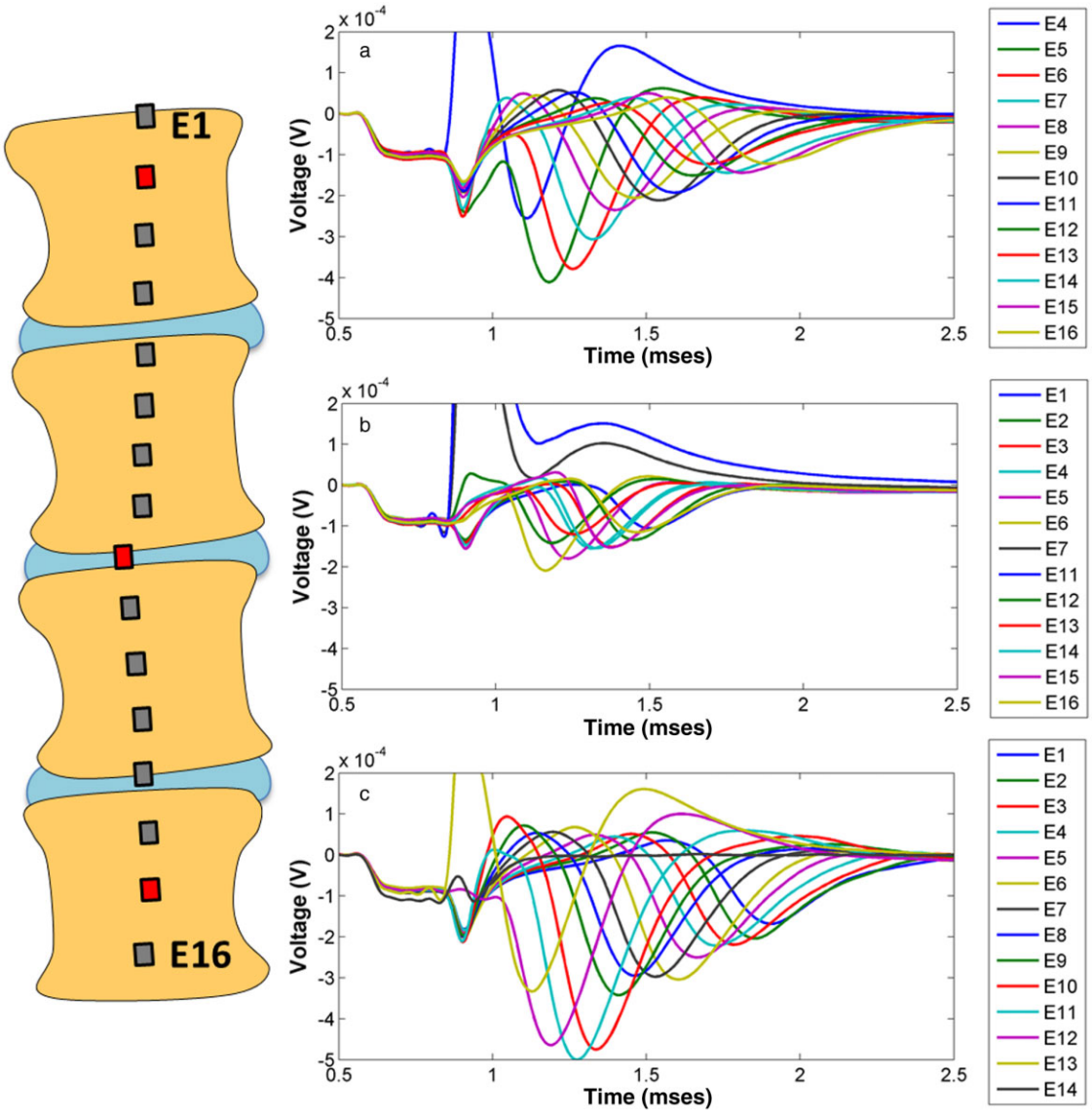

Figure 6. Illustration of the position of electrodes, stimulation electrodes highlighted, with respect to vertebral bodies (left) and the responses recorded from stimulation at electrodes 2 (a), 9 (b), and 15 (c). The propagation direction is orthodromic with stimulation on electrode 15 and antidromic with stimulation on electrode 2; while stimulation at the center of the array produces both antidromic and orthodromic responses.

sequence of the anatomy, although there is no direct evidence for this anatomic variation. The distance between the dorsal columns and the electrode is inversely proportional to its effectiveness. The increase in separation also reduces the response amplitude.

The amplitude and the excitability may also be affected by changes in the conductivity of the medium immediately surrounding the stimulating and recording electrode. Bone resistivity is more than twice that of the intervertebral discs that sit between the vertebral bodies (25,26), but existing models of SCS do not take this into account (27). As a result of this difference in resistivity, the current spread from the stimulating electrodes may make recruitment less efficient and consequently smaller responses are observed.

Another alternative explanation for the modulation in the response is due to the arrangement of the fibers within the dorsal columns. Each vertebra marks the introduction of new fibers from the corresponding dorsal roots. The excursion that these fibers take, as new laminae are laid down in the dorsal columns, will affect the position of fibers that entered the dorsal columns at lower segments. This will result in a change in the position of the fibers within the column and may manifest as a variation in the response amplitudes.

The present data collected in an anesthetized, but otherwise normal sheep may have differences compared to an animal with neuropathic pain. It is known in animal neuropathic pain models that there are excitability changes in dorsal column afferents that mediate allodynia (28,29). Similarly, in human neuropathic pain there are excitability changes in peripheral sensory axons (30,31). Electrophysiologic studies of dorsal column fibers comparing normal and neuropathic pain animal models may help understanding of mechanisms of SCS and provide potential diagnostic information.

The evoked neural responses recorded in sheep demonstrate the feasibility of evoked potential measurements in the spinal cord from

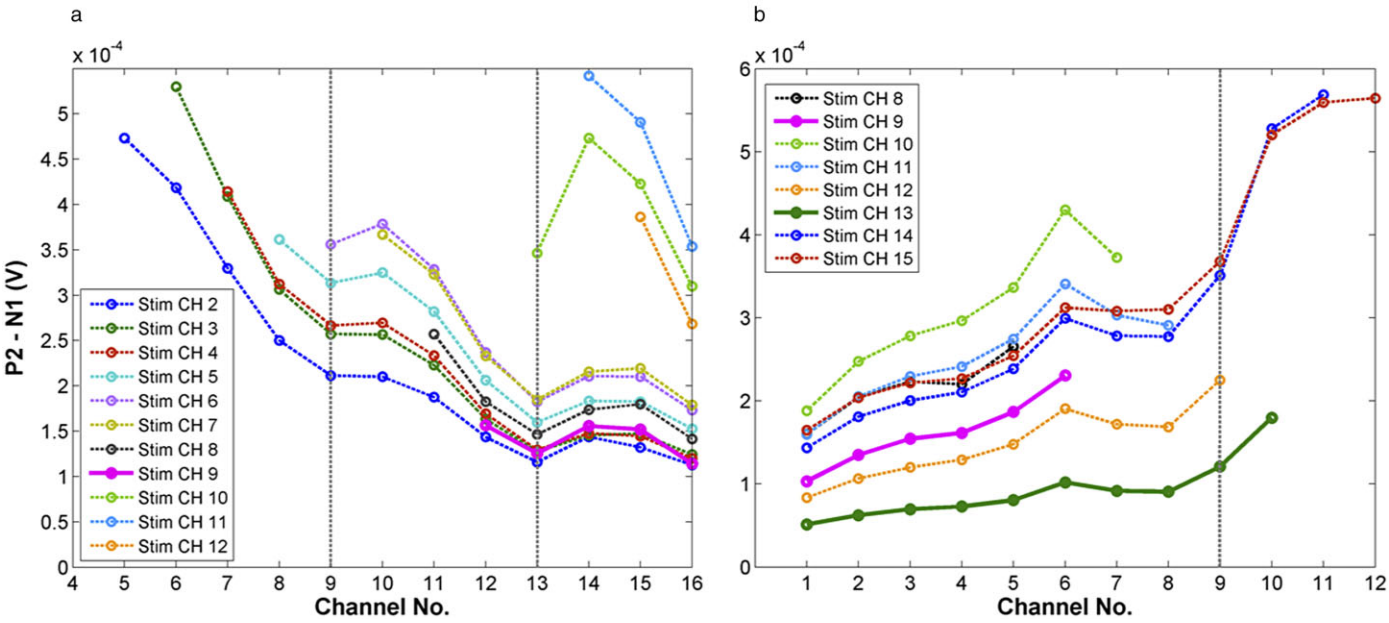

Figure 7. Amplitude P2-N1 measured at constant current stimulation on all electrodes in the antidromic direction (a) and orthodromic direction (b). Responses to stimulus on channels 9 and 13 are labeled with a vertical line, showing reduced responses compared with other stimulation electrodes; stimulation on channels 9 and 13 is represented with a thicker line.

the epidural space. The results indicate that there are different areas of "sensitivity" along the spinal cord where the evoked response measured for a given stimulation in midvertebral segments is almost double that with electrodes placed in the intervertebral gaps.

CONCLUSIONS

The variation in amplitude with anatomic position, if observed in humans, may provide useful indication of optimal areas to place electrodes and provide a means to select between different electrodes for programming. Lead migration is a common problem in SCS. The "signature" response of the amplitude variation could be used to determine the longitudinal change in the electrode position. The conduction velocities determined from N1 latency are remarkably constant over the stimulation range from threshold to twice threshold. This may indicate that a relatively narrow distribution of fiber sizes is recruited; however, confirmation of this requires further experiments and analysis.

Acknowledgements

Thank you to Linda Critchley for assistance in preparation of the animal study protocol and execution of the experiments, and Mark Bickerstaff for assistance in collection and analysis of data.

National Information and Communications Technology (NICTA) is funded by the Australian Government as represented by the Department of Broadband, Communications and the Digital Economy and the Australian Research Council through the Information Communication Technology Centre of Excellence program. NICTA holds pending patents related to the recording and stimulation system described in the manuscript.

Authorship Statements

Drs. Parker, Karantonis, Obradovic, Gorman, Mr. Single and Mr. Laird contributed to experiment design, conduct, and analysis. Mr. Single and Dr. Karantonis designed the stimulation and recording system. Drs. Ladd and Cousins conducted the animal anesthesia and surgery. Dr. Parker prepared the manuscript, Dr. Obradovic prepared the figures, and all authors reviewed the manuscript. Dr. Cousins provided background specialist knowledge on SCS.

How to Cite this Article:

Parker J.L., Karantonis D.M., Single P.S., Obradovic M., Laird J., Gorman R.B., Ladd L.A., Cousins M.J. 2013. Electrically Evoked Compound Action Potentials Recorded From the Sheep Spinal Cord.
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COMMENT

The authors of this study recorded and characterized electrically evoked compound action potentials (ECAP) from epidural stimulating and recording electrodes in anesthetized sheep. They found that the amplitude of the ECAP recorded from electrodes positioned over each inter-vertebral disc was far more less than that recorded in the mid-vertebral positions. Also, this anatomically correlated depression of ECAP correlates with the areas of the spinal cord with the highest thresholds for stimulation. Based on these findings, the authors suggest "Amplitude of sheep Aβ fiber potentials during SCS exhibit dependence on electrode location, highlighting potential optimization of pain suppression and power consumption in SCS devices." This is a well-designed and carefully performed study. The subject is interesting, the methods are sound, the results are well presented in the text with great details and are convincing.

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Comments not included in the Early View version of this paper.

