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Authors

Dinsmoor, David
Usoro, Joshua
Barka, Noah
et al.

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Using evoked compound action potentials to quantify differential neural activation with burst and conventional, 40 Hz spinal cord stimulation in ovines

David A. Dinsmoor[a,*], Joshua O. Usoro[a], Noah D. Barka[a], Tina M. Billstrom[a], Leonid M. Litvak[a], Lawrence R. Poree[b]

Abstract

Introduction and Objectives: Unlike conventional dorsal spinal cord stimulation (SCS)—which uses single pulses at a fixed rate—burst SCS uses a fixed-rate, five-pulse stimuli cluster as a treatment for chronic pain; mechanistic explanations suggest burst SCS differentially modulate the medial and lateral pain pathways vs conventional SCS. Neural activation differences between burst and conventional SCS are quantifiable with the spinal-evoked compound action potential (ECAP), an electrical measure of synchronous neural activation.

Methods: We implanted 7 sheep with a dorsal stimulation lead at T9/T10, a dorsal ECAP sensing lead at T6/T7, and a lead also at T9/T10 but adjacent to the anterolateral system (ALS). Both burst and conventional SCS with stimulation amplitudes up to the visual motor threshold (vMT) were delivered to 3 different dorsal spinal locations, and ECAP thresholds (ECAPTs) were calculated for all combinations. Then, changes in ALS activation were assessed with both types of SCS.

Results: Evoked compound action potential thresholds and vMTs were significantly higher ($P < 0.05$) with conventional vs burst SCS, with no statistical difference ($P > 0.05$) among stimulation sites. However, the vMT−ECAPT window (a proxy for the useable therapeutic dosing range) was significantly wider ($P < 0.05$) with conventional vs burst SCS. No significant difference ($P > 0.05$) in ALS activation was noted between conventional and burst SCS.

Conclusion: When dosed equivalently, no differentially unique change in ALS activation results with burst SCS vs conventional SCS; in addition, sub-ECAPT burst SCS results in no discernable excitability changes in the neural pathways feeding pain relevant supraspinal sites.

Keywords: Evoked potentials, Neuromodulation, Pain, Sheep, Spine

1. Introduction

In conventional spinal cord stimulation (SCS), square pulses are delivered at a regular rate, such as 50 Hz with 300 μs pulse widths (PWs). This differs markedly from burst SCS waveforms where multipulse bursts of stimuli are delivered. BurstDR (Abbott Inc, Plano, TX), for instance, incorporates 5 1-millisecond pulses with an intraburst rate of 500 Hz delivered at 40 Hz,[6,29] with passive charge balancing (**Fig. 1**).[27] Burst SCS is generally programmed at lower amplitudes compared with conventional SCS, although its electrical charge per second is 3 times greater[29]; recent research has used burst SCS amplitudes at 60% of the perception threshold (PT).[2]

An accurate mechanistic understanding of any therapeutic intervention to treat pain, such as SCS, is essential to optimize clinical outcomes.[7] Mechanistic explanations for burst SCS commonly reference the pain-relevant, lateral and medial supraspinal pathways.[28] These pathways incorporate sensory input by

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[a] Medtronic plc, Minneapolis, MN, USA, [b] Department of Anesthesia, University of California San Francisco Pain Management Center, San Francisco, CA, USA

**Corresponding author. Address: Medtronic plc, 7000 Central Ave NE RCE470, Minneapolis, MN 55432. Tel.: (763) 526-8801. E-mail address: david.a.dinsmoor@medtronic.com (D.A. Dinsmoor).*

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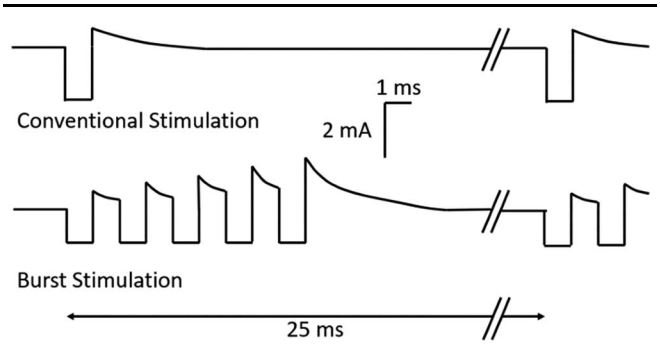

Figure 1. Conventional and burst spinal cord stimulation.

ascending tracts of the anterolateral system (ALS). The basis for these mechanistic explanations is findings from preclinical observations and small human samples.[18,25,26] However, these findings are not unique to burst SCS alone. For instance, modulation of the medial pain pathway is readily achieved with so-called "clustered tonic" or conventional SCS itself and not just burst SCS.[11,19] While direct electrophysiologic recordings with burst SCS have been made in the dorsal horns in rats[8]—and in 1 rat, from the dorsal columns[14]—it is as yet unclear whether the burst SCS waveform, when programmed with clinically relevant parameters, results in modulation of any neural signal transmitted by an ascending pathway.

One tool for directly assessing changes in neural response is the spinal-evoked compound action potential (ECAP). Typically described as the biopotential resulting from synchronous activation of dorsal column Aβ fibers in response to SCS, the ECAP has been incorporated in closed-loop SCS systems to compensate for motion between the SCS leads and the spinal cord.[31,34] The utility of ECAPs extends beyond just this application. Evoked compound action potentials may be used to quantify neural activation in other spinal targets, such as the dorsal root ganglia (DRG).[9] Furthermore, ECAPs may be used to assess changes in neural excitability resulting from a therapeutic intervention, such as a medication change; although the medication change does not result in an ECAP itself, it does result in easily detected changes in the amplitude of the ECAP elicited with SCS.[16]

In this work in anesthetized sheep, we use the ECAP to quantify changes in neural activation with both burst and conventional SCS. After placing the SCS leads using an anatomical placement scheme,[2] we set the SCS amplitudes relative to the sheep ECAP thresholds (ECAPTs); an approach previously demonstrated to relate SCS PTs to ECAPTs in both rodents (by the visual motor threshold) and humans.[3,23] Then, using a first-of-its-kind method, we used a separate lead to assess changes in ALS activation with swept amplitude burst and conventional SCS. We conclude with a discussion on the comparative dosing and mechanistic implications for both burst and conventional SCS.

2. Methods

2.1. Methods overview

We first implanted ovines with 3 octopolar, percutaneous, and epidural SCS leads. The first lead—used to deliver burst or conventional SCS and referred to as the dorsal stimulation lead—was placed at T9/T10. A second lead used for sensing ECAPs, referred to as the dorsal sensing lead, was placed more cranially at T6/T7. The third lead was placed opposite to the first lead, adjacent to the anterolateral system. This third lead is referred to as the anterolateral system lead. Then, we delivered either burst or conventional SCS with progressively increasing (swept) stimulation amplitudes up to the visual motor threshold (vMT) and measured the resulting ECAPs. This is referred to as the first test configuration. Then, we assessed the effects of burst and conventional SCS on ALS activation, both over swept stimulation amplitudes (the second test configuration) and with SCS amplitudes fixed to 60% of the ECAPT (the third test configuration). All data recorded were subsequently analyzed off-line. Unless indicated otherwise, we followed all methods identically among trials; no specific randomization or investigator blinding was used. We describe the details of these steps more fully below.

2.2. Subjects

All preclinical work was approved by the Medtronic Institutional Animal Care and Use Committee. The animals were cared for according to the USDA Animal Welfare Act standards and the eighth edition of "The Guide for Care and Use of Laboratory Animals." Female ovines (N = 7) of multiple breeds were used in this study. The animals were between 8 and 19 months of age and weighed between 52 and 72 kgs. Before experimental use, the animals were housed in a colony in a temperature and humidity-controlled environment with a 12 ± 1 hour light/dark cycle with water supplied ad libitum.

2.3. Surgical procedure

The sheep were premedicated with 400 μg of fentanyl, and total intravenous anesthesia (TIVA) with propofol was used for both induction (250–300 mg) and maintenance (0.3–1.0 mg/kg/h); prior research has suggested propofol TIVA results in no significant change in spinal ECAPs in sheep vs an awake state.[24] Three Tuohy epidural needles were positioned at the midlumbar level, with 2 on the left and 1 on the right of midline. Under fluoroscopic guidance, the 3 leads (Model #977D260, Medtronic plc, Dublin, Ireland) were introduced epidurally through the needles. The dorsal stimulation lead was placed so that electrodes 3 and 4 (with electrodes 0 and 7 cranial and caudal, respectively) were positioned midline over the T9/T10 intravertebral disc. We selected this lead location for consistency with prior work on anatomical placement procedures for clinical burst SCS.[2] The dorsal sensing lead was placed more cranially, with electrodes 3 and 4 centered midline over the T6/T7 intravertebral disc. This location was selected as it places the ECAP recording electrodes approximately 10 cm from the stimulating electrodes on the dorsal stimulation lead. Given the ovine ECAP conduction velocity of about 100 m/s,[21] this spacing allows for sufficient temporal separation between the stimulation artifact and the associated ECAP.[4]

The anterolateral system lead was steered ventrally and slightly right of midline but at the same axial level as the dorsal stimulation lead. We used this lead as a rough proxy for monitoring changes in spinothalamic tract excitability. We acquired a final set of images using intraoperative computed tomography (O-arm, Medtronic plc)—an example is included in **Figure 2**—or fluoroscopy. In some instances, we generated a 3D reconstruction (Mimics, Materialise NV, Leuven, Belgium) of the leads to assist with confirming lead location, with an example in the supplementary material (available at http://links.lww.com/PR9/A178). Finally, the Tuohy needles were removed, and the leads were

sutured to the animal. We then proceeded to the electrophysiology portion of the study.

2.4. Stimulation and recording equipment

We used a custom clinical-grade research system, as described elsewhere, for generating stimulation signals and recording the resultant ECAPs.[4] In brief, stimulation waveforms were generated using a custom software program (NeuroExp, Medtronic plc) and then passed through an isolated stimulator (Model# DS5, Digitimer Inc, Hertfordshire, United Kingdom) to the animal. Evoked compound action potentials were amplified (Model# D440, Digitimer Inc) and then digitized and processed with the custom software.

2.5. Electrophysiology

In our first test configuration (**Fig. 3**), we sought to characterize ECAPs over a range of clinically relevant burst and conventional stimulation amplitudes and locations. First, we delivered burst SCS to location #1 (noted in red in **Fig. 3**) on the dorsal stimulation lead. Here, we define location #1 as electrodes 3 and 4, location #2 as electrodes 1 and 2, and location #3 as electrodes 5 and 6. The leading cathodic phase of the stimulation pulses was delivered to the most cranial electrode (ie, electrode #3 with location #1) for the pair of electrodes at each location. We increased stimulation amplitudes in 25 μA steps in a single sweep with a 5 s dwell at each step until vMT was observed. After a stimulation sweep with burst SCS at a particular location was complete, the stimulation amplitude was reset to 0 μA and conventional SCS (40 Hz, 1 ms PW with passive charge balancing) was delivered with progressively increasing stimulation amplitudes to the same location. The dwell times and amplitudes step sizes used with the conventional SCS were identical to those used with burst SCS. Again, stimulation amplitudes were increased until vMT was observed. We recorded any ECAPs elicited with the burst and conventional SCS from electrodes 1 and 2 on the dorsal sensing lead; the anterolateral system lead was unused. After the conventional and burst SCS sweeps were delivered to location #1, the above process was repeated with location #2, and finally with location #3. In total, we assessed 42 different combinations (7 sheep, 3 stimulation sites per sheep, and 2 types of SCS [burst and conventional] per site).

In our second test configuration (**Fig. 4**), we used test pulses on the anterolateral system lead to assess changes in ALS excitability resulting from dorsal SCS. Here, we again delivered swept amplitude burst and conventional SCS serially to the 3 different locations on the dorsal stimulation lead. Between every fourth burst or conventional pulse (ie, a 10 Hz rate), however, we delivered a single balanced, biphasic, 100 μs PW, fixed amplitude test pulse to the 2 most caudal electrodes (E7/E6) of the anterolateral system lead with the resultant ECAP measured on the 2 most cranial electrodes (E1/E0) of the same lead. The amplitude of the test pulse was selected to generate an approximately 50 μV ECAP. We again recorded any ECAPs elicited with the burst and conventional SCS from electrodes 1 and 2 of the dorsal sensing lead. We assessed another 42 different combinations for this portion of the study.

Although neither burst nor conventional SCS use the kHz rates that typically necessitate a wash-in to realize a therapeutic effect,[22] we were nevertheless interested in any changes in ALS excitability that may exhibit a delayed onset. Accordingly, in our third test configuration, we delivered 10 minutes of burst SCS to location #1 in 6 of the sheep (the testing was inadvertently missed in the seventh sheep). The burst SCS amplitude was set to 60% of the ECAPT for consistency with current clinical practice. We continuously delivered ALS test pulses as described above during the 10 minutes that the burst SCS was provided, while simultaneously recording ECAPs from the ALS. The sheep were euthanized at the end of the experiment. The test configurations are summarized in **Table 1**.

2.6. Data analysis

We analyzed the recorded data offline using custom software developed previously to isolate stimulation artifact from the neural response.[5] For both stimulation configurations, we first removed the stimulation artifact—concurrent with the passive charge recovery phase for the SCS—using an exponential modeling method and then averaged the resulting responses acquired at each stimulation amplitude step in the sweep. We determined the ECAP amplitude by calculating the difference between the N1 and P2 features of the averaged ECAPs. For burst SCS, we

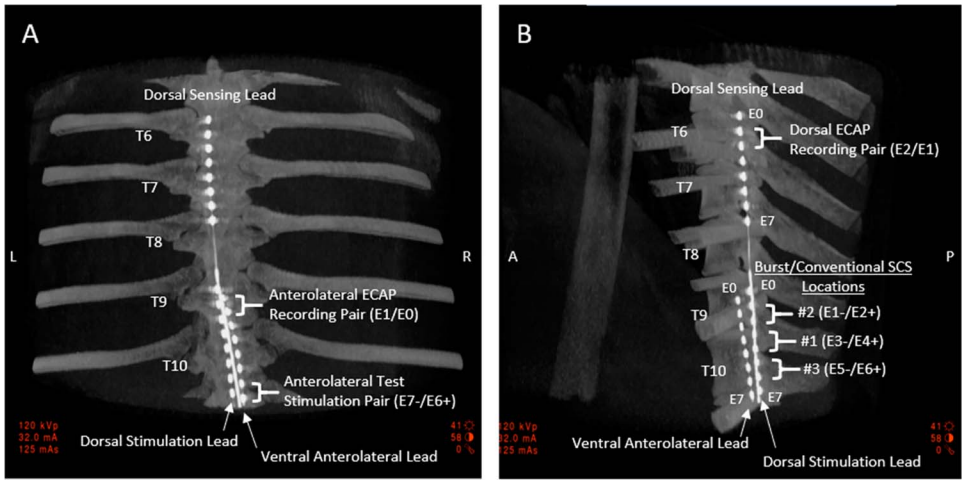

Figure 2. Example lead placement intraoperative computed tomography reconstructions. Both A/P (A) and lateral (B) views for sheep #1, showing the dorsal stimulation lead centered on the T9/T10 intravertebral disc and the dorsal sensing lead centered at the T6/T7 intravertebral disc. The ventral anterolateral lead is on the opposite side of the cord from the dorsal stimulation lead. ECAP, evoked compound action potential; SCS, spinal cord stimulation.

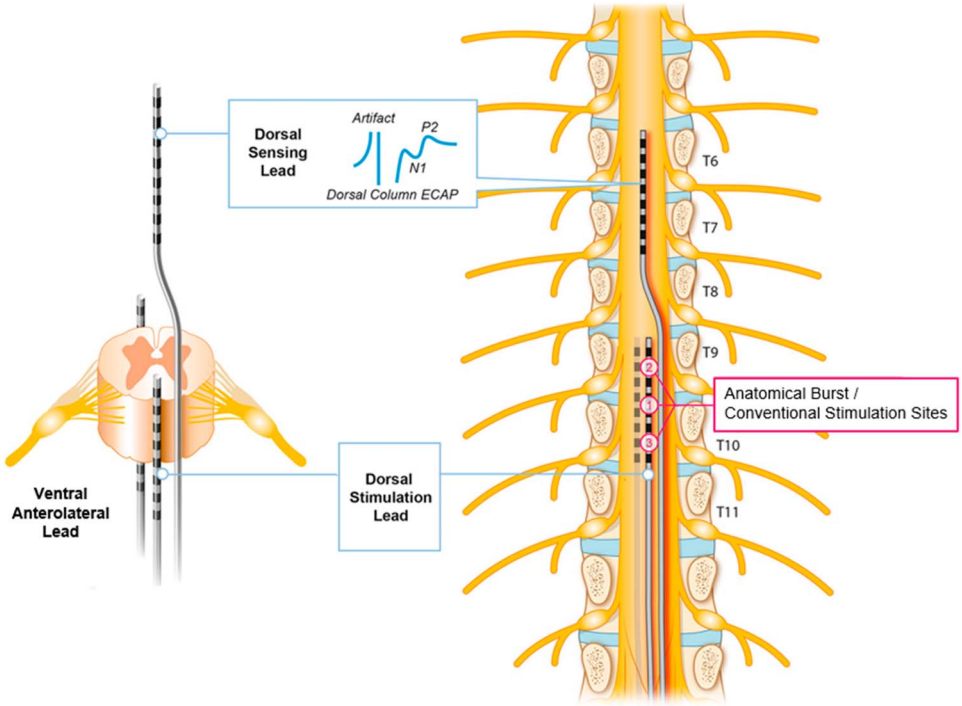

Figure 3. Lead locations for burst and conventional spinal cord stimulation (SCS), dorsal-evoked compound action potential (ECAP) sensing, and anterolateral system (ALS) neural activation measurements. Conventional or burst SCS is delivered to 1 of 3 locations on the dorsal stimulation lead centered at the T9/T10 disc. Evoked compound action potentials elicited with this SCS are sensed on the dorsal sensing lead, centered approximately at the T6/T7 disc. The ventral ALS lead (shown here for completeness) is used in a later portion of the experiments.

measured the amplitude of the ECAP elicited with the last pulse in the 5-pulse burst.

For the first stimulation configuration of burst and conventional SCS with concurrent ECAP measurement on the dorsal sensing lead, we generated growth curves for each stimulation amplitude sweep by plotting the measured ECAPs vs the delivered stimulation current. Growth curves are common graphically relating ECAPs to the stimulation current.[1] We then calculated

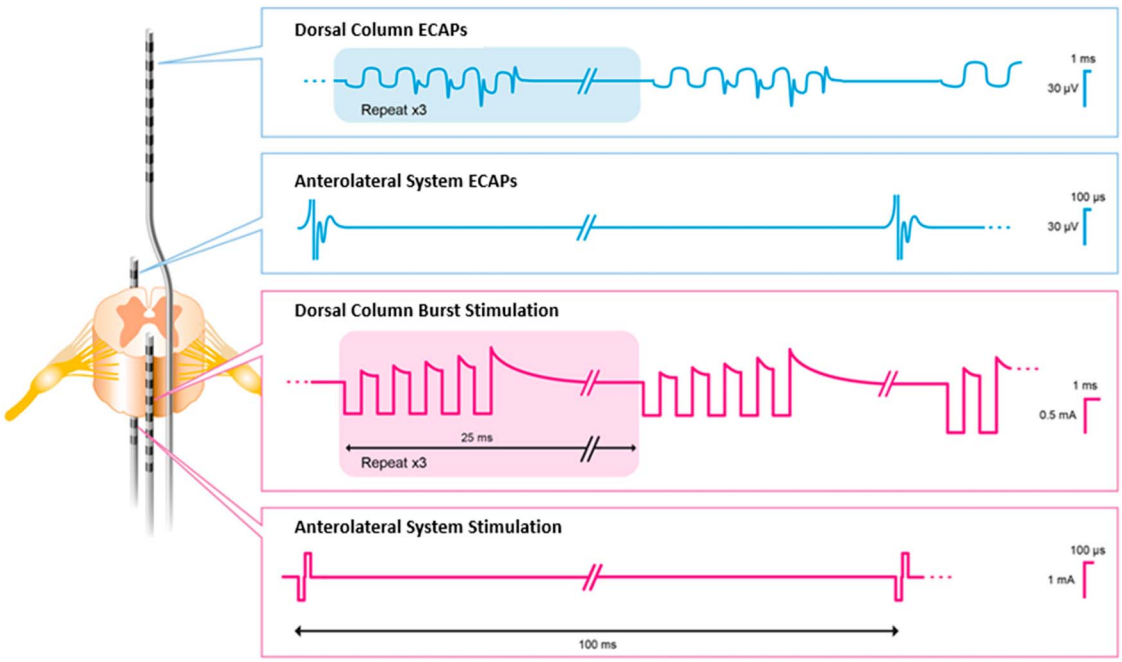

Figure 4. Time interleaving of the burst or conventional spinal cord stimulation (SCS) with the anterolateral system (ALS) test pulses. Burst or conventional (not shown in this illustration) SCS is delivered to 1 of 3 locations on the dorsal stimulation lead. Evoked compound action potentials (ECAPs) elicited (if any) with the burst or conventional SCS are sensed on the dorsal sensing lead. Every 100 milliseconds, a test pulse is delivered on the ventral ALS lead with the resultant ECAP assessed to characterize any change in ALS activation.

Table 1

Experimental design configurations.

	Configuration #1	Configuration #2	Configuration #3
Site(s) of conventional/burst SCS	Dorsal midline lead over T9/T10 disc, using electrodes: 1. 3−/4+ 2. 1−/2+ 3. 5−/6+	Dorsal midline lead over T9/T10 disc, using electrodes: 1. 3−/4+ 2. 1−/2+ 3. 5−/6+	Dorsal midline lead over T9/T10 disc, using electrodes 3−/4+
Burst (and conventional, if used) SCS parameters	1. Burst (5 1-ms PW, 500 Hz pulse bursts, at 40 Hz) 2. Conventional (1 ms PW, at 40 Hz)	1. Burst (5 1-ms PW, 500 Hz pulse bursts, at 40 Hz) 2. Conventional (1 ms PW, at 40 Hz)	Burst (5 1-ms PW, 500 Hz pulse bursts, at 40 Hz) for 10 min
Burst (and conventional, if used) charge balancing	Passive	Passive	Passive
Burst (and conventional, if used) amplitude	Starting at 0 μA, increased in 25 μA steps in a single sweep with a 5 s dwell at each step until vMT was observed (all waveforms)	Starting at 0 μA, increased in 25 μA steps in a single sweep with a 5 s dwell at each step until vMT was observed (all waveforms)	Fixed at 60% of ECAPT
Site of ECAP recording	Dorsal midline lead over T6/T7 disc, using electrodes 1/2	Dorsal midline lead over T6/T7 disc, using electrodes 1/2	N/A
Site of anterolateral test pulse	N/A	Ventral lead aligned with T9/T10 disc, electrodes 6+/7−	Ventral lead aligned with T9/T10, electrodes 6+/7−
Anterolateral test pulse parameters	N/A	100 μs PW balanced biphasic pulse at 10 Hz rate at fixed amplitude that generates ~50 μV ECAP	100 μs PW balanced biphasic pulse at 10 Hz rate at fixed amplitude that generates ~50 μV ECAP
Site of anterolateral ECAP recording	N/A	Ventral lead aligned with T9/T10 disc, electrodes 0/1	Ventral lead aligned with T9/T10 disc, electrodes 0/1
Number of animals tested	7	7	6

ECAP, evoked compound action potential; ECAPT, evoked compound action potential threshold; PW, pulse width; SCS, spinal cord stimulation; vMT, visual motor threshold.

the ECAPT from each growth curve using a method described by Pilitsis et al.[23] As this work demonstrated a highly significant correlation in humans between the ECAPT and the PT, we assume here that the ECAPT represents the stimulation current at which the sheep would perceive the SCS as well. We used paired *t* tests to assess the significance between burst and conventional SCS ECAPTs, vMTs, and the SCS amplitude range between vMT and the ECAPT (referred to as the vMT–ECAPT window). We assessed these differences separately for all 3 stimulation locations. For comparisons across the 3 stimulation locations within either conventional or burst SCS, one-way analysis of variances were used.

For the second stimulation configuration—burst and conventional SCS with interleaved delivery of test pulses on the anterolateral system lead—we generated another set of growth curves. These growth curves depict the amplitude of the ECAP elicited with the test pulse to the anterolateral system lead vs the amplitude of the SCS delivered to the dorsal stimulation lead. We then used paired *t* tests to assess the significance of averaged ALS ECAP amplitude differences between burst and conventional SCS in 3 different "bins": sub-ECAPT, within the vMT–ECAPT window, and supra-vMT. The bin boundaries were specific to the SCS type (conventional or burst) delivered to the dorsal stimulation lead and were defined once the ECAPTs and vMTs for all the test conditions were acquired. Again, we assessed these differences separately for all 3 stimulation locations.

Finally, when delivering burst SCS at 60% of the ECAPT (our third test configuration), we assessed the ALS ECAP for any change in amplitude, morphology, or latency over the 10 minutes we delivered the SCS. We assessed amplitude changes in each sheep by averaging the ALS ECAPs over the first 30 seconds of recording to calculate an ECAP baseline. Then, we averaged the ECAP amplitudes for each subsequent minute of recording and plotted the difference between each minute and the baseline.

3. Results

3.1. Dorsal-evoked compound action potentials

With burst SCS, the ECAP manifested first with the fifth pulse in the burst before progressively manifesting with earlier pulses as the stimulation amplitude was increased. Example ECAPs are shown in the top window of **Figure 5A, B**, with the associated growth curves in the bottom window. As shown in **Figure 6A**, the ECAPTs for conventional SCS were significantly higher than those for burst SCS at all 3 stimulation locations (paired *t* test, $P < 0.05$). In addition, ECAPTs were not statistically different across the 3 locations within either conventional or burst SCS (ANOVA, $P > 0.05$).

When assessing the vMT–ECAPT window (**Fig. 6B**), we observed a significantly wider range of SCS amplitudes that could be delivered between the ECAPT and the vMT with conventional vs burst stimulation (paired *t* test, $P < 0.05$). Here, the averaged vMT–ECAPT windows ranged between 0.37 and 0.43 mA for conventional SCS vs 0.11 to 0.15 mA for burst SCS (**Fig. 6B**). These differences were driven by the far higher vMTs noted with conventional SCS vs burst SCS. As mentioned earlier, ECAPTs were significantly higher with conventional (0.18–0.25 mA) vs burst SCS (0.08–0.12 mA); however, these differences were overshadowed by the comparatively larger differences in vMT between conventional (0.55–0.63 mA) and burst (0.22–0.26 mA) SCS. In addition, vMTs were not statistically different across the 3 locations within either conventional or burst SCS (ANOVA, $P > 0.05$). Evoked compound action potential thresholds, vMTs, and vMT–ECAPT windows for all 3 stimulation sites—along with all paired statistical comparisons—are included in **Table 2**.

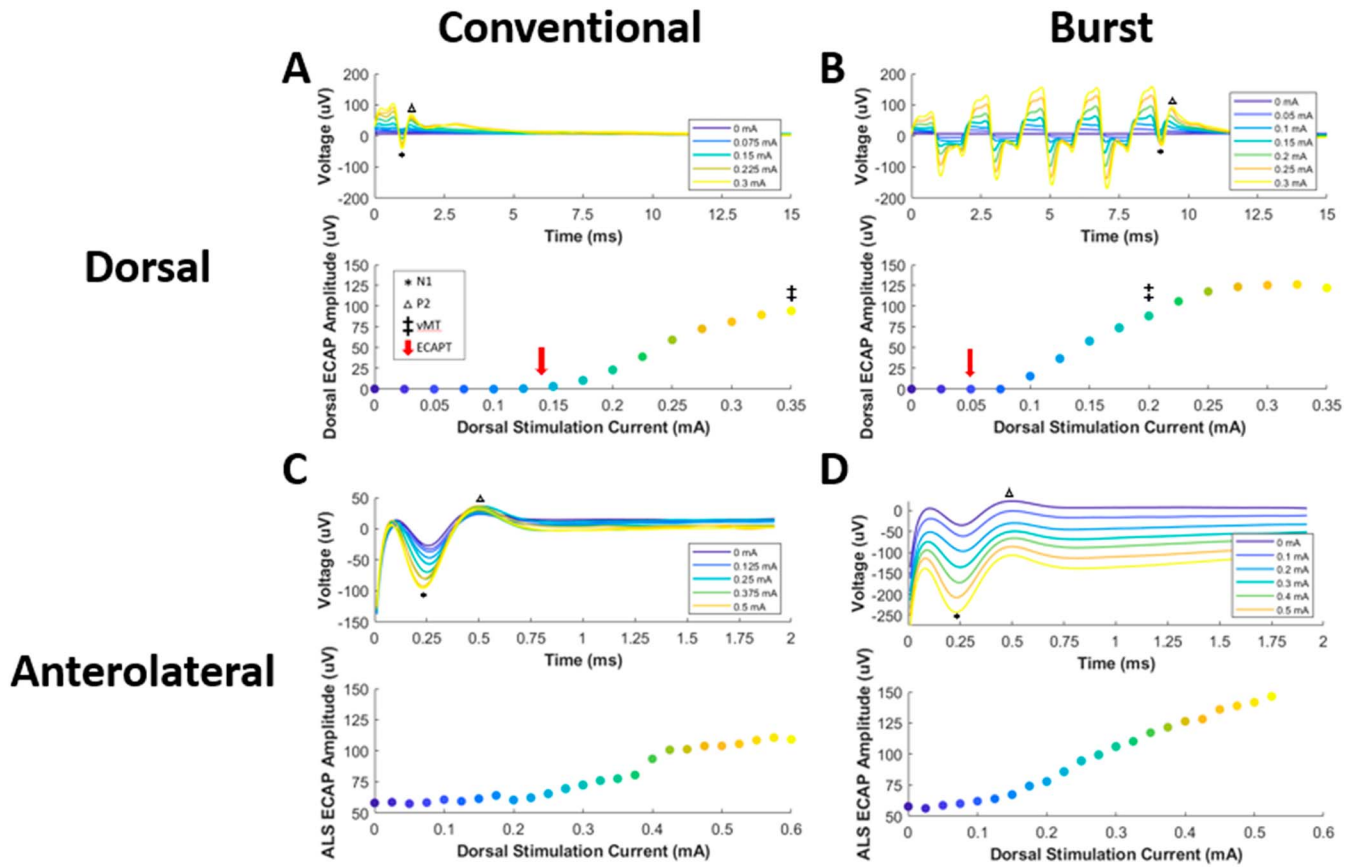

Figure 5. Representative (sheep #6, location #3) evoked compound action potentials (ECAPs) and growth curves for conventional and burst stimulation at dorsal and anterolateral locations. Evoked compound action potentials recorded from the dorsal columns (DCs) as a result of dorsal conventional or burst spinal cord stimulation (SCS) are shown in panels (A and B), respectively. Panels (C and D) show ECAPs recorded from the anterolateral system (ALS) immediately after an anterolateral test pulse while conventional or burst SCS is applied dorsally, respectively. Here, the stimulation current refers to the amplitude of conventional or burst stimulation not the ALS test pulse. The top window in each panel displays a subset of individual ECAP recordings, whereas the bottom panel shows the resultant growth curve as stimulation amplitude is increased. The calculated ECAP threshold (ECAPT, red down arrow) and visual motor threshold (vMT, ‡) are displayed on the growth curve, whereas the N1(*) and P2 (Δ) ECAP trough and peak are indicated in the top window.

3.2. Anterolateral system-evoked compound action potentials

Stimulation and recording on the anterolateral system lead resulted in ECAPs (**Fig. 5C, D**) with amplitudes and triphasic morphologies similar to those noted previously with dorsal spinal ECAP recordings in sheep.[4,21] When either conventional or burst SCS was applied concurrently to the dorsal stimulation lead with our second test configuration, we observed changes (**Fig. 7**) in the ALS ECAP amplitude that trended with increasing stimulation amplitudes (sub-ECAPT, vMT–ECAPT window, and supra-VMT) on the dorsal stimulation lead. As appreciated in **Figure 7**, there was a minimal change in ALS ECAP amplitude for both conventional and burst SCS in the sub-ECAPT bin across all 3 stimulation locations. When dorsal stimulation amplitudes fell within the vMT-ECAPT window or supra-vMT bins, however, there was a considerable increase in the ALS ECAP amplitudes compared with baseline. No significant differences (paired *t* test, $P > 0.05$) were seen between conventional and burst SCS at any location or bin, suggesting no differential impact on the ALS ECAPs between conventional and burst SCS.

When burst SCS was continuously applied with an amplitude of 60% of the ECAPT for a 10-minute interval (**Fig. 8**) with our third test configuration, the average ALS ECAP amplitudes for all 6 sheep increased negligibly by 6.2 ± 0.44 μV (mean ± SD) at the end of the 10-minute period. These changes varied between sheep; after calculating the minute-by-minute ALS ECAP amplitude change from baseline for each sheep (**Fig. 8B**), we noted a slight decrease in 2 sheep (#1 and #2), a slight increase in 2 sheep (#4 and #5), and negligible change in the remaining 2 sheep (#3 and #6). No changes were seen in ALS ECAP morphology or latency.

4. Discussion

As evidenced above, our results do not support the hypothesis of neural activation changes that would result in a differentially unique supraspinal effect with burst vs conventional SCS; we postulate that any differences noted previously[28,36] may result from the confound of nonequivalent dosing between the 2 types of SCS. Furthermore, we suggest any therapeutic effect realized with burst SCS—when configured with clinically relevant parameters—may stem from a mechanism local to the stimulation electrodes (such as the gate control theory of pain), vs a supraspinal process. We elaborate on these points, among others, below.

4.1. The dorsal-evoked compound action potential threshold and dosing considerations for burst and conventional spinal cord stimulation: clinical implications

In all instances, we note a lower ECAPT with burst vs conventional SCS. At location #1, for instance, the ECAPT—and presumably

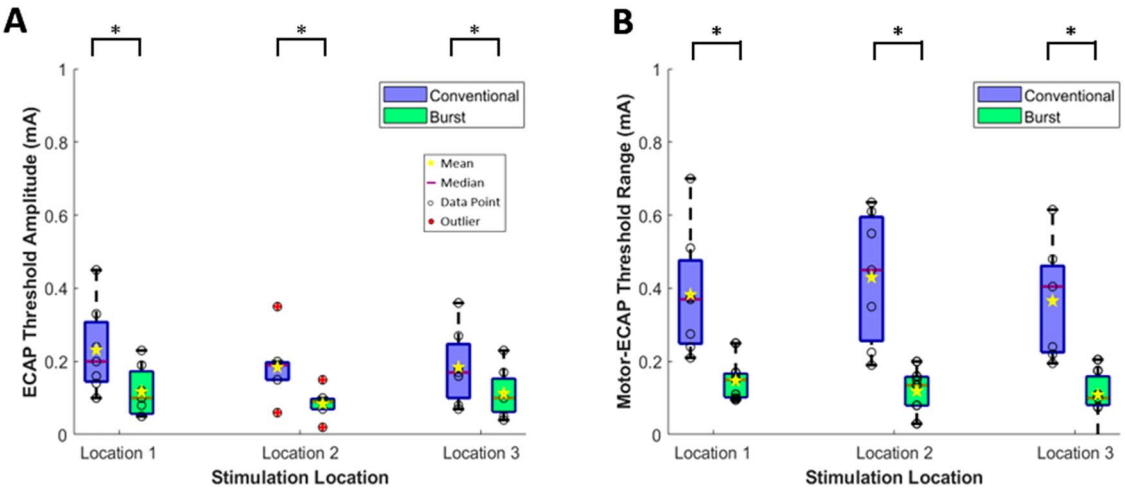

Figure 6. Dorsal-evoked compound action potential threshold (ECAPT) and visual motor threshold–evoked compound action potential threshold (vMT-ECAPT) window comparisons between conventional and burst spinal cord stimulation (SCS). Panel (A) shows box and whisker plots summarizing the ECAPT across all 7 sheep. The horizontal red line indicates the median, whereas the yellow star indicates the mean. The bottom and top edges of the box reflect the 25th and 75th percentile of data, respectively, whereas the whiskers indicate the range. Individual data points are shown with the black circles, whereas red circles indicate outliers. There were no experimental considerations to confirm them as outliers and were therefore included in statistical analysis (paired *t* test, * indicates $P < 0.05$). Panel (B) shows box and whisker plots of the vMT-ECAPT window for conventional and burst SCS at the 3 stimulation locations.

PT—is significantly lower ($P < 0.05$) with burst (0.12 ± 0.07 mA) vs conventional SCS (0.25 ± 0.11 mA, mean ± SD). These lower ECAPTs, however, come at the expense of more charge required with burst vs conventional SCS to generate an equivalent response. In the previous example, a burst of five 1 millisecond pulses delivered at the ECAPT of 0.12 mA requires 0.6 μC of total charge from the battery. A single, 1 millisecond conventional pulse at an equivalent ECAPT of 0.23 mA requires 0.23 μC. The ratio of 0.6 μC to 0.23 μC noted in this example approximates well the 3-fold higher charge per second (as described by De Ridder et al.[29]) required by burst vs conventional SCS. Said another way, both burst and conventional SCS generate the same ECAPs that result in the perception of stimulation; with burst SCS, however, these ECAPs occur at lower stimulation amplitudes yet draw down the battery 3 times faster than conventional when programmed to an electrophysiologically equivalent point.

Burst SCS also exhibits—again using the response at location #1 as an exemplar—a significantly lower ($P < 0.001$) vMT vs conventional SCS (0.26 ± 0.09 mA vs 0.63 ± 0.20 mA, mean ± SD). This finding is consistent with clinical reports of EMG hyperexcitability with burst vs conventional SCS.[12] If we consider vMT a proxy for a maximally tolerable SCS amplitude in sheep, the tolerable dosing window (defined here as vMT-ECAPT) is significantly narrower ($P < 0.05$) with burst vs conventional SCS (0.15 ± 0.05 mA vs 0.38 ± 0.16 mA, mean ± SD). This effect may represent a tacit motivator for recent trends towards lower stimulation amplitudes with burst SCS.[15] Although some reports suggest research subjects achieve better pain relief with lower amplitude burst SCS, these reports may simply represent misattribution of fewer overstimulation related side effects (such as an exhausted affect or stabbing sensations) associated with burst SCS as better pain relief.[15] Unfortunately, turning the stimulation amplitude down to compensate for the narrower dosing window of burst vs conventional SCS may not represent the best means to provide effective therapy; at a certain point, the stimulation field is insufficient to affect any physiologic response.

4.2. Influencing anterolateral system excitability with dorsal spinal cord stimulation

The potentiating influence of both burst and conventional SCS on ALS excitability (as assessed with ECAPs) is a highly novel feature of this work, and the gate control theory serves well as a framework for understanding the mechanistic basis of this phenomena.[17] Particularly in neuropathic pain, the DRG exhibit a level of spontaneous firing[20,33,35]; this in turn increases the probability that fibers in a pain relevant ascending pathway on which the DRG synapse—such as the spinothalamic tracts—will fire. Electrical activation of Aβ fibers with dorsal column SCS is believed to exhibit an analgesic effect by inhibiting excitatory input on these ascending pathways.[32] Accordingly, one might assume

Table 2

The mean and SD of the evoked compound action potential threshold (ECAPT), visual motor threshold (vMT), and vMT−ECAPT window at all 3 locations for all animals in response to conventional or burst spinal cord stimulation (SCS).

Stimulation modality and location	ECAPT (mA)	*P*	vMT (mA)	*P*	vMT − ECAPT (mA)	*P*
Conventional, location 1	0.25 ± 0.11	0.002	0.63 ± 0.20	0.001	0.38 ± 0.16	0.005
Burst, location 1	0.12 ± 0.07		0.26 ± 0.09		0.15 ± 0.05	
Conventional, location 2	0.18 ± 0.09	0.002	0.61 ± 0.24	0.001	0.43 ± 0.17	0.001
Burst, location 2	0.08 ± 0.04		0.20 ± 0.09		0.12 ± 0.05	
Conventional, location 3	0.18 ± 0.10	0.015	0.55 ± 0.24	0.005	0.37 ± 0.14	0.002
Burst, location 3	0.11 ± 0.07		0.22 ± 0.08		0.11 ± 0.06	

Stimulation and sensing occurred along the dorsal columns. *P* values are indicated for significance testing between conventional and burst SCS configurations of those 3 parameters.

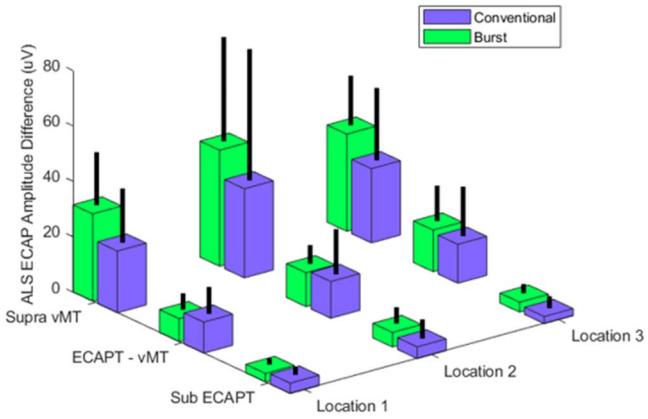

Figure 7. Anterolateral system (ALS)-evoked compound action potential (ECAP) amplitude difference comparisons between conventional and burst spinal cord stimulation (SCS) for each stimulation location and range. Evoked compound action potentials were recorded from the ALS after an ALS test pulse and the difference in ECAP amplitude from baseline (conventional/burst stimulation = 0 mA) was calculated as either conventional or burst stimulation was increased. The average ECAP amplitude difference was calculated over the entire stimulation ranges of sub ECAP threshold (ECAPT), therapeutic window, and supra visual motor threshold (vMT) across 7 sheep. Standard deviation error bars are indicated in black. Paired *t* tests between conventional and burst SCS were conducted at each combination of location and stimulation range; none of which were observed as significant.

fewer ascending pathway fibers would be in refractory state with suprathreshold dorsal column SCS than without. Since the stimulation pulse encounters fewer refractory fibers, a larger amplitude ECAP is elicited as more fibers are available to contribute to the ECAP.

One intriguing analogue to our findings is noted with ECAPs recorded from the auditory nerve. Furosemide inhibits the hair cell function that results in auditory nerve excitation,[30] and auditory nerve ECAPs were indeed elevated in a preclinical model of hearing loss with furosemide vs a control group.[13] Just as burst and tonic SCS inhibit excitatory input to the pain relevant ascending pathways of the anterolateral system, the furosemide inhibits the excitatory electrical input from the hair cells to the auditory nerve—in both cases, a larger amplitude ECAP is the result.

4.3. Mechanisms of action and clinical outcomes with burst and conventional spinal cord stimulation

In recent work by Al-Kaisy et al.,[2] SCS amplitudes were programmed at about 60% of PT, presumably to avoid burst SCS-associated paresthesias (experienced by approximately 40% of subjects receiving burst SCS) or other overstimulation phenomena.[10] Recognizing that the PT approximates the ECAPT in humans for a given posture,[23] burst SCS with an amplitude of 60% of the ECAPT would likely result in no paresthesia as no signal propagates through the dorsal columns to any supraspinal site. However, our results demonstrate no activation or excitability changes in the ALS feeding the lateral or medial supraspinal pathways, either. Stimulation amplitudes below the ECAPT/PT are simply too low to influence any of the supraspinal pathways implicated in prior mechanistic hypotheses for the therapeutic benefit of burst SCS. Importantly, both conventional and burst SCS *can* influence the ascending pathways, and they do so similarly when dosed in an equivalent manner (**Fig. 7**). However, these effects only manifest at stimulation amplitudes that would be perceptible by the patient and not with the subperception amplitudes ostensibly used with burst SCS.

Given our finding of no demonstrable change in neural activation that could influence the lateral or medial pathways with burst SCS programmed in a clinically relevant manner, one might naturally ask which mechanism is truly responsible for the modest clinical benefit (a 31.2 mm reduction in the Visual Analogue Scale vs baseline) previously described with burst SCS.[10] This work does not answer that question. However, subperceptual pain relief has now been reported with nonburst SCS frequencies down to 10 Hz; the putative mechanism explanation for this pain relief is dorsal horn modulation local to the stimulation electrodes.[22] The clinical benefit of burst SCS might simply be realized through a mechanistic process identical to this or other conventional SCS approaches.

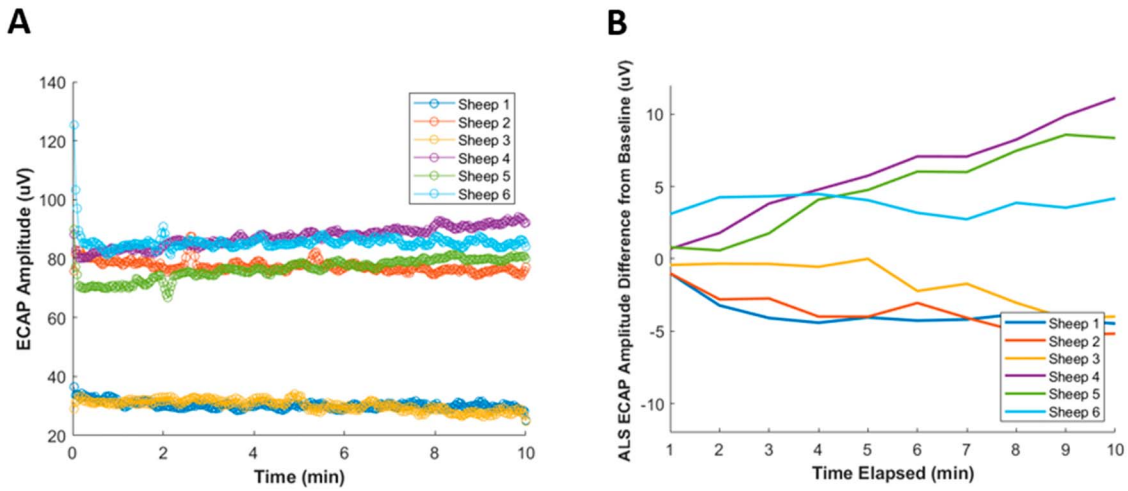

Figure 8. Anterolateral system (ALS)-evoked compound action potential (ECAP) amplitude trends over time with burst spinal cord stimulation (SCS). Panel (A) shows that burst stimulation (dorsal column [DC]) and a test pulse (anterolateral system [ALS]) were applied at a constant current amplitude, whereas ECAPs were recorded on the ALS lead over a 10-minute period. Traces from all 6 sheep are included. In panel (B), an initial baseline ECAP amplitude average was taken from the first 30 seconds of recording. Afterwards, for each sheep, the average ECAP amplitude was taken for each subsequent minute of recording and the difference between each minute and baseline was calculated for all 6 sheep.

4.4. Limitations

The primary limitation of this study is that we used normal physiology sheep on TIVA. Outcomes different than those we report here might be noted in awake sheep with an appropriate pain model. Furthermore, other differentially unique changes in anterolateral system activation with burst vs conventional SCS may be noted with anterolateral system leads at other locations (ie, more cranial to account for dorsal horn fibers ascending multiple segments before decussating), with longer intervals of stimulation (multiple days instead of 10 minutes with configuration #3), or with subthreshold amplitudes in configuration #3 set to amplitudes other than 60% of the ECAPT. Finally, there may be as-of-yet unknown neurophysiologic differences between sheep and humans that could influence the clinical relevance of our findings.

5. Conclusions

Spinal ECAPs are an important tool for generating electrophysiologic insight into all manner of SCS therapies. By incorporating these novel ECAP sensing methods into mechanistic preclinical research, pain researchers can quantify how SCS does—or does not—influence the neural circuitry responsible for pain relief. We hope that a better understanding of the SCS mechanisms of action afforded by ECAPs translates to more optimal therapy for patients with chronic pain.

Disclosures

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A178.

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