A Multielectrode Nerve Cuff for Chronic Velocity Selective Recording in a sheep model

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***Abstract*— Supra-sacral spinal cord injury (SCI) causes loss of bladder fullness sensation and bladder over-activity, leading to retention and incontinence respectively. Velocity selective recording (VSR) of nerve roots innervating the bladder might enable identification of bladder activity. A 10-electrode nerve cuff for sacral nerve root VSR was developed and tested in a sheep model during acute surgeries and chronic implantation for 6 months. The cuff performed well, with 5.90±1.90 kΩ electrode, and <~800 Ω tissue impedance after 189 days implantation with a stable device and tissues. This is important information for assessing the feasibility of chronic VSR.**

***Clinical Relevance*— This demonstrates the manufacturing and performance of a neural interface for chronic monitoring of bladder nerve afferents with applications in urinary incontinence and retention management following SCI.**

I. Introduction

Brindley and colleagues developed an implanted nerve stimulator for restoring bladder control to people with clinically complete spinal cord injury [1]. The device has been commercially available for 40 years. Usually, the sacral sensory roots (i.e., afferent nerves) are cut by the surgeon because this prevents detrusor over-activity and thereby incontinence, and improves voiding (by reducing detrusor-sphincter dyssynergia) but this destructive procedure deters some clinicians from recommending the device. Alternative methods could use on-demand high-frequency blocking [2,3] or afferent neuromodulation [4,5]. Aberrant bladder contractions could be detected using the afferent activity within the sacral nerves and used to instigate the on-demand stimulation or modulation. We investigated the use of multi-electrode nerve cuffs to enable velocity selective recording (VSR) of neural activity [6]. We developed a 10-electrode nerve cuff because 10 is the greatest number that can be connected using two standard helical wire cables in the anatomical space [7]. These were implanted in sheep, chosen because they are similar in size to humans and can be housed safely at little cost for months. To record afferent nerve signals in sacral nerve roots the nerve cuff must be implanted deep within the spinal canal of the sacrum while causing little nerve damage. The surgical approach to expose the sacral roots is a dorsal laminectomy from L6 to ~S3/4, exposure of the dural cone of the spinal cord, then careful dissection to expose the extra-dural sacral roots that are lateral to the dural cone. This paper presents the nerve cuff design and fabrication, the implantation method, and methodologically-important impedance measurements from the ewe with the longest implant duration to date.

II. Methods

A. VSR Nerve Cuff Design

The VSR nerve cuff was designed to be implanted on the ovine sacral nerve root by a practicable method. The cuff comprises 10 circumferential electrodes spaced equally with 1.5 mm interelectrode pitch. The cuff was 15 mm in length with an adjustable ~2 mm diameter nerve lumen.

The cuff (fig. 1) was formed from: a flexible electrode array and interconnect tracks manufactured by laser cutting silicone rubber and stainless-steel foil; a reinforced cast silicone block; and two 5-core Cooper Cables [7] exiting parallel to the nerve; and a metal "buckle" closure. The cuff cables were connected to a percutaneous connector placed on the head of the animal for impedance measurements or neural recording from awake animals.

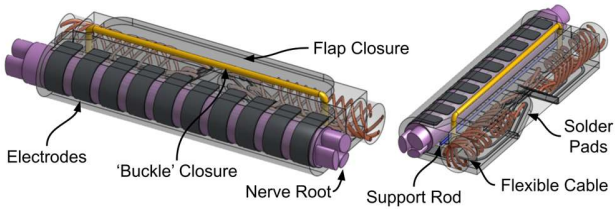

Figure 1. The 10-electrode Velocity Selective Recording Cuff.

B. VSR Nerve Cuff Manufacture and Assembly

The cuff electrode array and interconnections were manufactured as a planar structure by laser cutting silicone and metal foil laminates [8] (fig. 2 & 4). Arrays were manufactured on a glass slide carrier. Polystyrene sulfonate (PSS, Sigma Aldrich) release layer was spin coated onto the glass slide and dried at 100°C for 2 minutes. Medical grade two-part low-viscosity silicone elastomer (MED4-4220, NuSil) was mixed in 1:1 ratio, with coloured silicone added to improve laser cutting (MED-4800-2, NuSil). It was spin coated onto prepared slides and partially cured at 100°C for up to 5 minutes (fig. 4A). Stainless steel foil (AISI 304, 0.0125 mm thickness) was laminated to the partially-cured silicone with a roller. The foil was pattered with an Nd:YAG laser cutter and excess foil was removed (fig. 4B). A second layer of MED4-4220 was

*Research supported by UK EPSRC grant EP/P015999/1.

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spin coated on top of the foil and fully cured at 150°C for 15 minutes (fig. 4C). Electrode pads and solder pads were exposed in the top silicone layer by laser cutting (fig. 4D). The electrode array was released from the glass slide by dissolving PSSA in deionized water (fig. 4E). A released electrode array is shown in Fig. 2.

The manufactured electrode array part was cleaned by repeated ultrasonication in Leslie's soup [9], isopropyl alcohol (IPA), acetone, and deionized water.

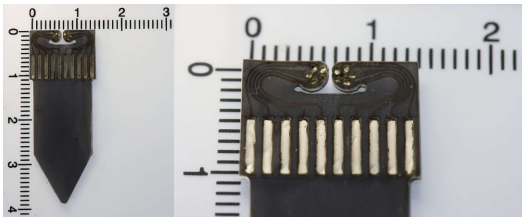

Figure 2. Planar 10-electrode array. Left: the full array with a flap for "buckle" closure. Right: a magnified view with the electrodes (below) and two circular arrays of 5 solder pads (above).

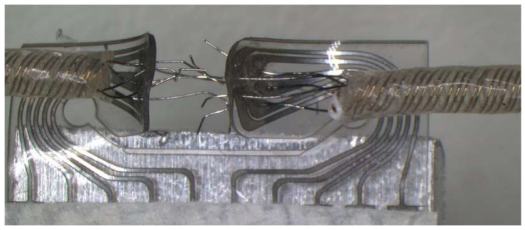

Figure 3. The cable connection arrangement with solder pads at to 60° to aid connection and parallel Cooper Cables. Jig not shown.

The cleaned array was placed in a custom jig for solder connections to the 5-core Cooper Cable. Array solder pads were elevated to 60° to aid connection (fig. 4F), and de-insulated, pre-tinned Cooper Cable wires were inserted into the through-hole pads (fig. 3 & 4G). Solder connections were formed using a phosphoric acid flux (85%) and solder with water soluble flux (Hydro-X Multicore Loctite 60EN 5C). Solder joints were cleaned with deionized water.

The cast silicone block was formed in a three-part polytetrafluoroethylene (PTFE) mould. The mould was cleaned by ultrasonication with acetone, IPA, and deionized water. A fine stainless steel support rod, to stiffen the block, was held inside the mould using monofilament nylon thread. Two-part silicone elastomer (Sylgard 184, DowSil) was mixed in a 10:1 ratio, degassed under vacuum, injected into the mould, and cured at 150 °C, 2 bar pressure, for 10 minutes.

The block and the metal buckle were attached to the soldered array and cables with one-part silicone adhesive (DOWSIL 734). The solder joints were encapsulated with MED4-4220 to protect against corrosion and to prevent electrical short circuits (fig. 4H). The assembled nerve cuff was cured at room temperature, 2 bar pressure, for at least 24 hours (Fig. 5). Figure 4 shows the manufacturing process schematically.

B. Implantation Tool

A special tool was developed to facilitate cuff implantation onto the extradural sacral root without stretching the root, improve apposition of the nerve and cuff along their length and standardize the process of implantation. Cuff implantation was extremely difficult using only standard surgical instruments. The implantation tool held the cuff in place while the electrode flap was passed round the root (note that a suture was attached to the tip of the flap (see fig. 6); the flap was passed under the buckle; the right amount of silicone glue was applied to the cuff mating surfaces; the flap was pulled in using the tool until the root was snug but with little tension; and the tool clamped the flap during silicone curing. Figure 6 shows the cuff in the implantation tool; figure 7B shows the clamp in use

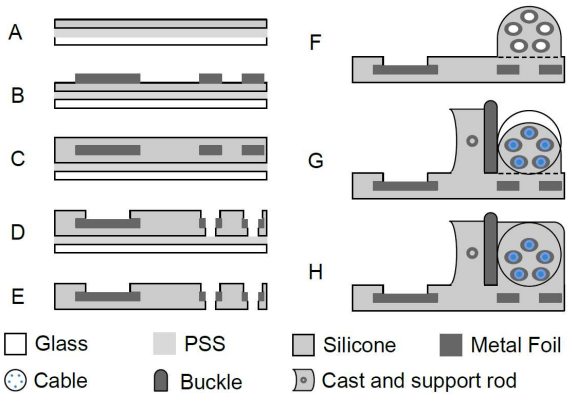

Figure 4. Manufacturing Process for the VSR Nerve Cuff.

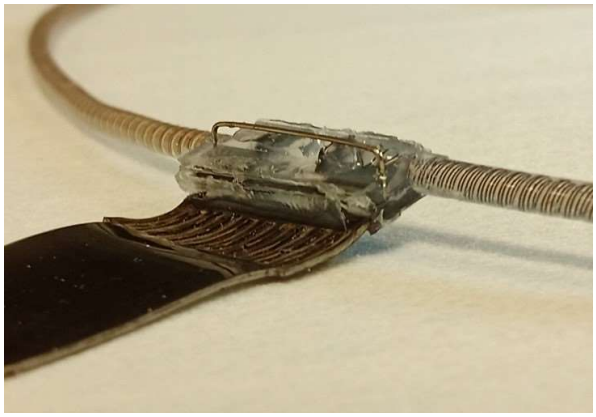

Figure 5. An assembled 10-electrode nerve cuff.

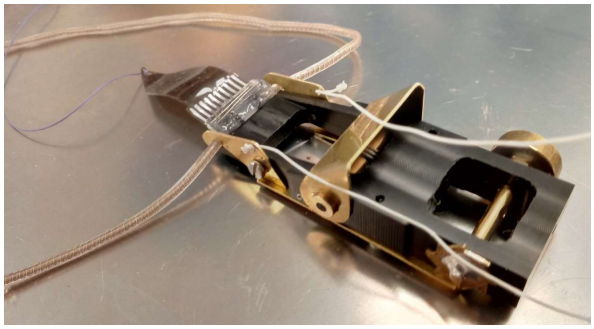

Figure 6. Cuff in implantation tool. Note the suture thread in the flap. The white clamp is added after tensioning the flap round the root.

C. Electrode Impedance

Electrode impedance was measured at 1 kHz between adjacent electrodes with a 10mV p-p sinusoid using LCR

Meters (including LCR-6200, GW Instek). Implanted impedances was compared with explanted electrode impedances measured in isotonic saline.

D. Chronic Sacral Nerve Root Implantation

All the experimental procedures detailed in this paper were performed in accordance with the United Kingdom Animals (Scientific Procedures) Act 1986 under Home Office regulations (Project Licence P302A3B70).

Adult ewes underwent general anaesthesia involving: a pre-medication from a transdermal fentanyl patch placed 12-hours prior to surgery, an induction with IV ketamine (7.5 mg/kg) and midazolam (0.5 mg/kg), intubation and maintenance on sevoflurane mixed in oxygen. Intraoperative fentanyl and ketamine analgesia was provided as required. A lumbosacral dorsal laminectomy was performed through the midline to expose the extradural sacral roots and each root was identified based on anatomical landmarks (e.g., lumbosacral ligamentum flavum) and identification of the sciatic nerves. A cuff was implanted on a sacral root (exact root determined by response to electrical stimulation and concomitant bladder cystometry recording), the cables were tunnelled to the head using a trocar and connected to a percutaneous head connector.

Impedance measurements and neural recordings were made while the ewes were conscious but constrained in a crate or on a treadmill. At the end of each study the ewes were re-anaesthetised and the cuffs and the roots were explanted for further study. At the end of the experiment each animal was terminated by overdose of pentobarbital.

III. RESULTS

Four VSR nerve cuffs were implanted acutely and four chronically for durations up to 6 months. The results shown here are from a single ovine subject (body weight: 73kg) that was implanted for 189 days on the right S3 sacral root.

A. *Implantation & post-mortem examination*

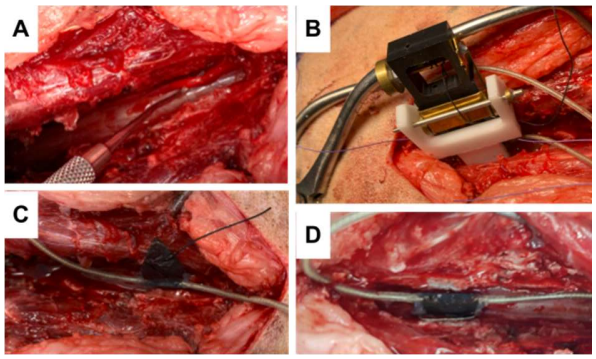

Figure 7. Nerve cuff implantation. A: S3 right root exposed and held by a nerve root retractor, next to the dural cone. B: The implantation tool in place while glue cures. C: After curing and removing the tool, the flap, which can be seen here, is cut off. D: The cuff in place before tunneling the cables.

Fig. 7 and Fig. 8 are from a single ovine subject. The implantation tool successfully enabled nerve cuff implantation (fig. 7). At post-mortem examination (189 days post implantation) the nerve cuff remained intact and the tissue appeared healthy. The implanted and contralateral nerve roots were excised for histological analysis (fig. 8). Macroscopic nerve root evaluation showed indentations on the surface of the nerve from the electrodes (fig. 8B) suggesting possible mild nerve constriction due to the nerve cuff. The root inside the cuff appeared to have increased vascularization compared to the contralateral root.

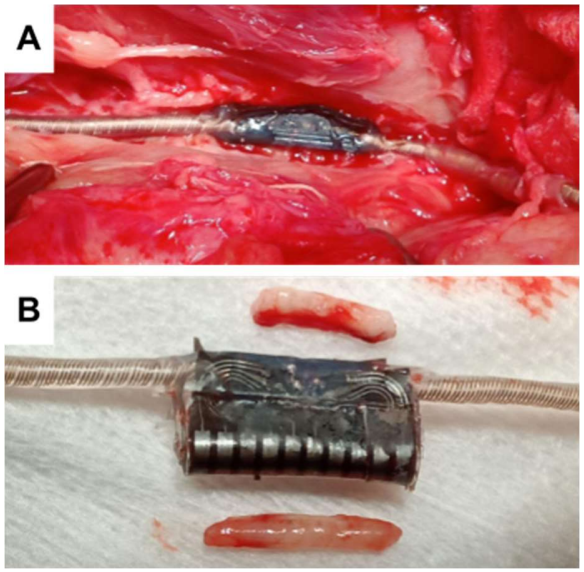

Figure 8. A: Cuff exposed at post-mortem. B: After dissection, showing the contralateral root (top), and the root from within the cuff (bottom).

B. *Electrode Impedance*

2-electrode impedances from this one animal at 1kHz are shown in Fig 9. These are between adjacent electrodes (1 to 2, 2 to 3, etc) except for 6 to 7 which were short-circuit at the head connector. Mean was 5.19±1.03 kΩ after 96 days implantation, increasing to 5.90±1.90 kΩ after 189 days implantation. Following explant, mean impedance in isotonic saline was 2.00±0.21 kΩ. Impedance of electrode 9 increased to a greater extent than all other impedances, $Z_{e8,e9,189days}$ = 8.70 kΩ, $Z_{e9,e10,189days}$ = 8.80 kΩ, $\bar{Z}_{e1\ldots e7}$= 4.95±0.88 kΩ, however electrode 9 impedance was not different from other impedances following explant $Z_{e8,e9,explant}$ = 1.93 kΩ, $Z_{e9,e10,explant}$ = 2.42 kΩ.

From 118 days post-implantation, 4-electrode impedance measurements were taken with an LCR meter, current being injected between electrodes 1 and 10, while voltages were sensed at 2 to 3, 3 to 4, etc, again except 6 to 7. These transimpedances (fig. 10) are the volume impedances along the lumen and are relevant because they determine the amplitude of the neural voltages between the electrodes.

IV. DISCUSSION

The cuff described above allows the use of highly durable helical cables, to achieve ten connections to the multi-electrode cuff for chronic recording of sensory nerve signals. The method enables the cables to emerge parallel to the nerve root which suits the location in the spinal canal, and the glued flap allows the nerve cuff circumference to be adjusted to fit the root. Using glue to seal the cuff requires time to cure but the tool makes holding the cuff shut during this time easier. After six months, the tissue round the cuff appears healthy and

the internal root is well vascularised, with no observable neurological deficits and a functional dermal response.

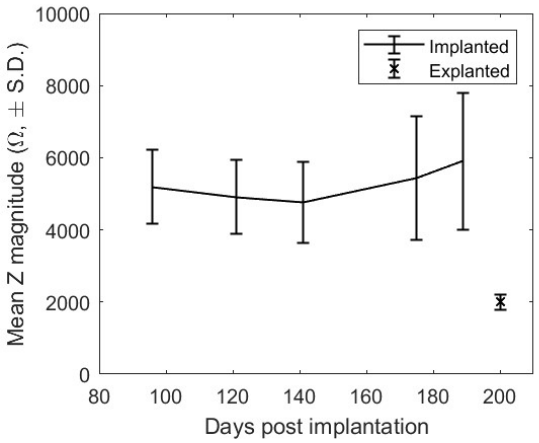

Figure 9. Mean ± standard deviation 1 kHz impedance magnitude with implantation time, average of adjacent electrode impedances. Explant impedance in isotonic saline is shown at 200 days.

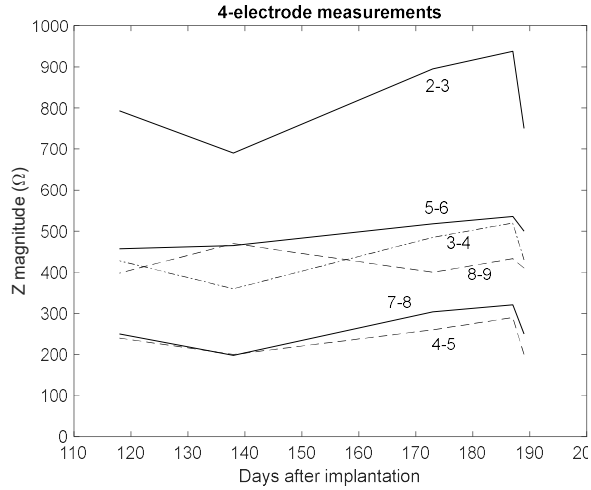

Figure 10. Transimpedances of the tissues within the cuff measured between the respective electrodes by the 4-electrode method.

The laminectomy site used in our model is presented to replicate what could be done in humans because of the recognized anatomical similarities between sheep and humans, in particular the spine length and spinal canal width [10]. The extra-dural location we have chosen is advantageous because it removes the need to work around the fragile intra-dural rootlets prone to iatrogenic damage. It also offers stability to the implant that can be secured to the soft tissue around the bone. The sheep model is relevant because of the comparable size of the ewes (~70 to 100kg) to humans. These docile animals can also be maintained easily and free to move in fields for extended periods of time or studied indoors on treadmills [10] while we interrogated non-invasively and awake the multielectrode nerve cuff.

Normally, impedances are measured between electrodes which means that the electrode interface impedances and the volume impedance through the nerve tissue are in series. For this cuff, the values were about 5 kΩ. But the 4-electrode measurements show that the axial impedance along the lumen was relatively small with a wide range from about 200 Ω to 800 Ω. Since the amplitude of the neural signal is proportional to this axial impedance, we should expect a similar range of amplitude and variation of the amplitude with time, as shown in Figure 10. This will affect the VSR processing in which the multiple signals are added after time delays: specifically, it will spoil the use of double-differential amplifiers to remove artefact due to potential gradients outside the cuff.

Fig. 9 and fig. 10 show that the impedance, measured between 2 adjacent electrodes is about three times higher in neural tissue than in isotonic saline. The impedance of electrode 9 was not high in saline after explantation, though it had been high in the body, suggesting that electrodes can be masked, perhaps by fatty or connective tissue or a fibrotic foreign body reaction, which can spoil the uniformity of the impedances.

This paper demonstrates chronic nerve cuff function. Chronic neural recordings and head-connector performance will be published in future reports.

ACKNOWLEDGMENT

We thank the anesthetists, the Biological Services Unit and staff at the Royal Veterinary College, UK, for facilitating the animal study.

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