Recruitment Selectivity of Single and Pairs of Transverse, Intrafascicular, Multi-channel Electrodes (TIME) in the Pig Median Nerve

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Abstract

When applied in the rat model the Transverse Intrafascicular Multi-channel Electrode (TIME) showed selective nerve fascicle recruitment. But results from the larger and poly-fasicular median nerves in pigs indicated that a single TIME could not reach the entire nerve and could only selectively recruit a subset of the nerve fasicles. The use of multiple TIME structures could offer a means to achieve highly selective fascicular stimulation while reaching a larger percentage of the fascicles in the nerve. This work investigates this approach using pairs of TIMEs implanted in the median nerves of anesthesized pigs (n=6). TIME structures were implanted at different angles relative to each other or in parallel with one another. Electrical stimuli was passed through each contact of each TIME and the resulting electromyograms were recorded from seven muscles innervated by the median nerve. The ability to recruit these muscles was used to assess the stimulation selectivity of each contact using a selectivity index comparing the root-mean-square of the the evoked EMG of individul muscles.

Results showed a signifcant increase in the selectivity index, when using two TIMEs compared to one. The optimal improvement was obeserved when TIMEs were placed in parallel to each other in such a way that they interfaced non-overlapping nerve regions.

Keywords: TIME, pig model, median nerve, stimulation, electrode

Introduction

Selective peripheral neural electrodes may be used as means to restore sensory and motor functions. Advanced prosthetic limbs with sensing abilities have been developed for amputees [1]. However, the lack of reliable, safe and selective interfaces to intuitively link the user to the multiple degrees of freedom and control in these prosthetics device is currently hindering their use.

Designers of peripheral nerve electrodes face a trade-off between selectivity and invasiveness. The result is an array of different neural interfaces which have been under development. These include the multipolar cuff electrode, the thin-film longitudinal intra-fascicular electrode (tfLIFE), transverse intra-fascicular multi-channel electrode (TIME) and the Utah Slanted Electrode Array (USEA). All have different selectivity / invasiveness ratios[2-4].

The TIME consists of a flexible polyimide substrate loop, which holds 6 iridium oxide coated contact sites on each side of the loop[2]. Being transversely implanted into the nerve, the TIME is considered to be more invasive than the cuff electrode; but since its substrate is flexible and penetrates the nerve only once, it is considered less invasive than the USEA. A recent study in the sciatic nerve of rats showed that the TIME could selectively recruit three muscles innervated by this nerve, thus showing both intra- and inter-fascicular selectivity [5]. However, recent studies in the median nerves of pigs have found that a single TIME is capable of selectively reaching only a subset of a large poly-fascicular nerve[6,7].

In a poly-fascicular nerve, fascicles adjacent to the TIME are most likely to be selectively recruited. By implanting several TIMEs within the same peripheral nerve, more fascicles will be located adjacent to an electrode and, thus, a larger part of the nerve can potentially be selectively recruited. This study aims to investigate the ability to selectively recruit muscles innervated by the median nerve of the pig, when pairs of TIMEs are inserted in different configurations.

Material and Methods

Experimental procedures

Acute pig experiments were carried out in 6 domestic pigs (25-40 kg). Under full anaesthesia the pigs were intubated and positioned in the supine position. The median nerve was exposed and two or four TIMEs were implanted either through the middle of the nerve at different implantation angles (Group A, 5 pigs, 16 TIMEs, with 45º between TIMEs) or parallel to each other with different offsets from the midline of the nerve (Case B, 1 pig, 2 TIMEs; see Fig 1 a & b). Seven muscles innervated by the median nerve were exposed and epimysial electromyographic (EMG) patch electrodes were attached. The muscles were: Pronator teres, Palmaris longus, Flexor carpi radialis, Flexor digitalis superficialis, Flexor digitorium profundus, Abductor pollicis brevis and Humeral head of deep digital flexor.

Electrical stimulation consisting of rectangular, cathodic current pulses (100 µs duration) of increasing current intensities was presented at 2 Hz to each contact of the individual TIMEs, and the EMG responses from the seven muscles were simultaneously recorded. For Group A: 40 µA to 800 µA (40 µA steps), each current level was repeated five times (STG2008, Multichannel systems, Germany). In Case B, stimulation current was increased from 20 µA to 800 µA (20 µA steps) and each level was repeated three times (Stim'ND, Neuromedics, France [8]). A stainless steel needle placed subcutaneously on the thorax served as anode.

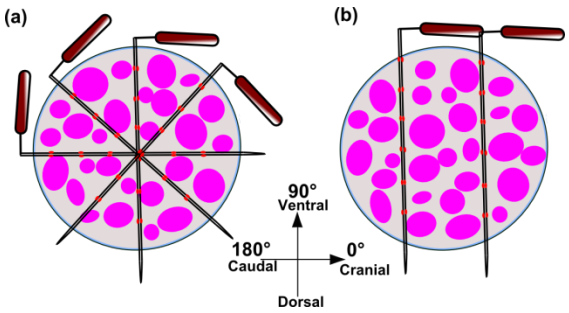

Fig. 1. Illustration of insertion schemes. (a) Example of four TIMEs which are placed in a nerve with a 45º angle in between. Based on the results from individual TIMEs, the SI_{DD} and RC could be calculated for TIMEs implanted at different angles (45º and 90º) relatively to each other. (b) TIMEs were implanted in parallel through the nerve, thus minimizing overlapping regions of recruitment.

Offline analysis

The EMG was bandpass filtered (0.1 – 2 kHz, Matlab, R2011a, MathWorks, USA). The root-mean-square value of the evoked EMG (time window: 2-12 ms after stim. pulses) was used for assessing nerve recruitment. To obtain the recruitment level of individual muscles (EMG_{RL}), root-mean-square values obtained for the same stimulation intensity were median filtered and normalized to the maximal evoked amplitude (100 %) obtained in individual muscle of each pig. Recruitment curves were linearly interpolated to 1 µA resolution. The selectivity index of an individual muscle (SI_M), j, was defined as:

(eq. 1) $$SI_{M,j} = max\left\{\frac{EMG_{RL,j}}{\sum_{i=1}^{N} EMG_{RL,i}} \mid EMG_{RL,j} > EMG_{RL30\%}\right\}$$

$SI_{M,j}$ was set to zero if the EMG_{RL} did not reach 30 %. The device selectivity for each individual TIME devices (SI_D) and for pairs of TIMEs (SI_{DD}) were defined as:

(eq. 2) $$SI_D = \frac{\sum_{j=1}^{N} SI_{M,j}}{N}$$

(eq. 3) $$SI_{DD} = \frac{\sum_{j=1}^{N} \max\{SI_{M,j,D1}, SI_{M,j,D2}\}}{N}$$

SI_{DD} was calculated for TIME devices implanted with a 45º angle (SI_{DD45}), a 90º angle (SI_{DD90}) or in parallel ($SI_{DD|}$, see Fig 1.). In general, SI values near 0 indicate no selectivity or a lack of recruitment, and a value close to 1 indicate good selectivity (muscles can be individually recruited). The recruitment correlation (RC) for pairs of TIMEs was defined using the Pearson correlation coefficient (PCC).

(eq. 4) $$RC_{DD} = PCC\left(\overline{SI_{M,D1}}, \overline{SI_{M,D1}}\right)$$

$\overline{SI_{M,Dx}}$ refers to a seven dimensional vector containing the SI_M for all muscles monitored. Values close to -1 indicate that each of the TIMEs in a pair selectively recruit different muscles, whereas, values close to 1 indicate that the same muscles are selectively recruited by the two TIME devices. The latter would imply that little is gained by implanting more than one TIME.

Statistics

SI_D results from each TIME was regarded as one group ($SI_{D,All}$) of single TIMEs, no matter if implanted at an angle or in parallel. To illustrate the separation between SI and RC, results for the different groups were compared using a t-test ($p <$

0.05 was regarded as statistical significant). No corrections were made for multiple comparisons.

Results

The SI_D for single TIMEs were similar no matter whether they were implanted at an angle or in parallel (0.27 ± 0.02 & 0.36 ± 0.04, respectively, p = 0.23, mean ± standard error of mean) and so they were pooled together in $SI_{D,All}$ (0.28 ± 0.02). The SI_{DD} for all three types of paired TIME configurations (SI_{DD45} = 0.38 ± 0.03 , SI_{DD90} = 0.41 ± 0.03, $SI_{DD||}$ = 0.56) show a significant improvement compared to $SI_{D,All}$, see Fig. 2 a.

There is a weak trend for SI_{DD90} to be higher than SI_{DD45} (p = 0.34), whereas, the $SI_{DD||}$ is higher than both SI_{DD45} and SI_{DD90}. However, this does not reach a level of significance (p = 0.06 and p = 0.11). The $SI_{DD||}$=0.56 obtained for the single case, was greater than any single SI_{DD} obtained in the two groups of TIMEs paired at an angle (max{SI_{DD45}}= 0.47 & max{SI_{DD90}} = 0.52).

The mean RC for TIMEs paired at an angle are close to zero (0.03 ± 0.10 and -0.01 ± 0.14). The $RC_{DD||}$ seems to be lower than that for RC_{DD45} and RC_{DD90}, however, this did neither reach a level of significance (p = 0.10 and p = 0.21). The one pair of TIMEs evaluated in parallel, resulted in a $RC_{DD|||}$ = -0.59, which was lower than any value obtained in the two other groups (min{RC_{DD45}} = -0.39 & min{RC_{DD90}} = -0.58).

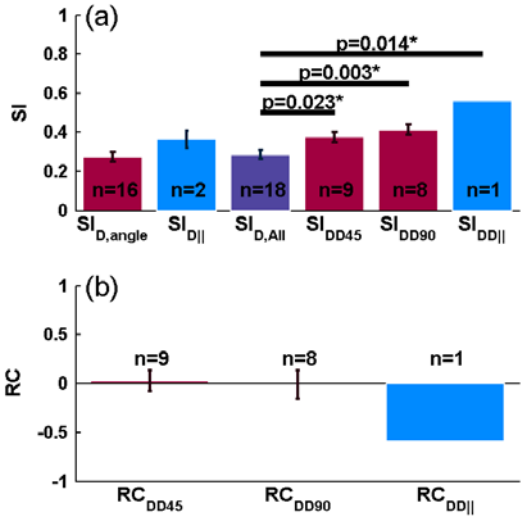

Fig. 2. (a) SI results of individual and pairs of TIME devices. (b) Results of RC for the pairs of TIME configurations. Errors bars indicate standard error of mean.

Discussion

The ability to selectively innervate the median nerve of a pig was significantly improved by using two TIMEs compared to a single TIME. There was a trend for 45º separation to provide the least improvement, 90º separation to provide intermediate improvement and for TIMEs implanted in parallel to show the highest improvement. Thus, as expected, results indicate that the more spatially separated TIMEs were within the nerve, the higher was the gain in selectivity.

A single TIME may be sufficient to selectively recruit the whole sciatic nerve of the rat[5]. However, in the poly-fascicular nerve of pig, results indicated that single TIMEs could only selectively recruit a subset of the nerve[9,10]. These results indicate that implantation of several TIMEs, ideally interfacing different non-overlapping nerve regions may be an approach to interface a whole poly-fascicular human size nerves.

The drawback with implantation of several TIMEs will obviously be an increase in the invasiveness of the combined nerve interface. An alternative to the implantation of several TIMEs might be to implant a single USEA. However, in relation to distributing a number of contact sites inside the nerve, the USEA approach is less effective and more invasive than the TIME, as each USEA contact site entail a needle to penetrate the nerve[4]. In contrast, the TIME distributes 12 contact sites inside the nerve when penetrating it only once. In addition, the TIME consists of a flexible polyimide substrate as compared to the stiff silicon structure of the USEA. Thus, several, TIMEs might still be preferred over an USEA.

The current study has been limited by having only one pair of TIMEs for the parallel configuration. In this configuration the Stim'ND prototype stimulator was used for the first time in a mammal model. Although, this stimulator produced results consistent with the commercial STG2008 stimulator, more experiments have to be performed to validate the performances of this stimulator under *in-vivo* conditions. Therefore results from the parallel TIME configurations should be interpreted with care. However, our initial hypothesis is consistently supported by the results, i.e. that less spatial overlap between paired TIMEs inside the nerve (Fig. 1) will result in less redundancy in the selectively recruited muscles (Fig. 2b) and, thus, result in the highest selectivity gain (Fig. 2a).

Conclusions

This study investigated the use of pairs of TIMEs to interface a large poly-fasicular nerve. The ability of the TIME to selectively recruit such nerves was significantly improved by using pairs of TIMEs as

compared to using one single TIME. Results indicate that the optimal improvement occur when TIMEs are placed in parallel to each other in such a way that they interfaced non-overlapping nerve regions.

Acknowledgements

The work was funded by European Union under the 7th Framework program (grant CP-FP-INFSO 224012/TIME**)**. We wish to thank the staff at Aalborg Biomedical Laboratory for their generous help during our experiments.

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