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On biocompatibility and stability of transversal intrafascicular multichannel electrodes - TIME

Thomas Stieglitz, Tim Boretius, Paul Čvančara, David Guiraud, Thomas Guiho, Victor Manuel Lopez-Alvarez, Xavier Navarro

Abstract—Transversal intrafascicular multichannel electrodes (TIME) have been developed to interface with peripheral nerves after upper limb amputation. Intended use is the electrical stimulation of the median and ulnar nerve to deliver sensory feedback during phantom limb pain treatment and artificial hand control. Miniaturized electrode arrays were developed on polyimide substrates with thin film metallization using sputtered iridium oxide as electrode coating. Here, we report on the essential requirements including biocompatibility, mechanical and stimulation stability that have been investigated before permission was granted by the legal authorities to conduct subchronic first-in-man clinical trials. Explants have been investigated to identify possible first failure points and optimize the devices for chronic implantation.

I. INTRODUCTION

INTERFACES to peripheral are a research topic for more than 50 years in rehabilitation engineering. Only few approaches have been transferred from animal experiments in clinical trials or even in approved medical products. Upper limb interfaces are under investigation if hand grasp shall be restored after spinal cord injury or stroke or if sensory feedback shall be delivered after hand amputation in prosthetic hand control or phantom limb pain treatment. Different nerve interface concepts were recently investigated in subchronic and chronic clinical trials on the ulnar and median nerve: circumneural cuff-electrodes [1], micro-machined intraneural needle arrays [2] and flexible, polymer-based intrafascicular electrodes [3]. Our approach of a transversal intrafascicular multichannel electrodes (TIME) has been developed with a focus to treat phantom limb pain after hand amputation [3]-[5]. In this paper, we report on the investigations on device stability and biocompatibility that have been performed to meet the essential requirements of the active implantable medical device directive (90/385/EEC) as prerequisite to enter human clinical trials and results of a subchronic pilot study that led to some design changes

II. MATERIALS AND METHODS

An electrode concept has been developed and investigated up

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to human clinical trials for intrafascicular implantation.

A. TIME Electrode Design

Micromachining techniques have been used to develop a polymer-based electrode made of a polyimide-platinum sandwich with sputtered iridium oxide as electrode coating. The microsystem was assembled with an alumina interconnector to a helically wound cable made of MP35N that ended in a miniaturized plug (Omnetics Nano). 14 stimulation and two counter electrodes were placed on each device [9].

B. Mechanical and Electrochemical Characterization

Mechanical loading is supposed to occur mainly on the helically cable that will be routed percutaneously from the nerve through the muscles and the skin. Bending and stretching load cycles have been performed for 250,000 times on MP35N wires with polyesterimide insulation that have been helically wound to a cable and placed into a silicone rubber hose with a diameter of 1.8 mm. Stimulation pulses have been applied in phosphate buffered saline solution to determine the chemically safe maximum charge injection capacity. Test cycles ran for up to 250 million pulses for sputtered iridium oxide and electrode site diameters of 80 μm .

C. Biocompatibility and Biostability

According to ISO 10993 (Biological Evaluation of Medical Devices), several investigations have been performed. Cytotoxicity testing has been done with probes that have passed the whole manufacturing process. L929 cells have been chosen according to the standard. Direct contact and extract tests have been performed. Qualitative and quantitative assessment has been performed. Sensitivity and chronic reactivity tests have been performed in rodent models. Histology has been performed [7] as well as investigations on selectivity of the transversal implantation of the intrafascicular electrode concept [8].

Stability of the electrodes in the first-in-man-trial has been assessed by electrode impedance measurements during stimulation. Therefore, the magnitude of the voltage excursion of the cathodic phase was divided by the amplitude

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of the stimulation pulse.

Explant electrodes were investigated under light and scanning electron microscope. Focused ion beam was used to generate cross sectional views from the interfaces of the polyimide and the thin-film metallization.

Design and process changes have been applied based on the findings of the first human clinical trial. Modified TIME have been implanted in a second clinical trial.

III. RESULTS

Electrodes have been developed (Fig. 1) and characterized with respect to mechanical stability of the cable, stability of the thin-film under stimulation and biocompatibility in vitro and in vivo.

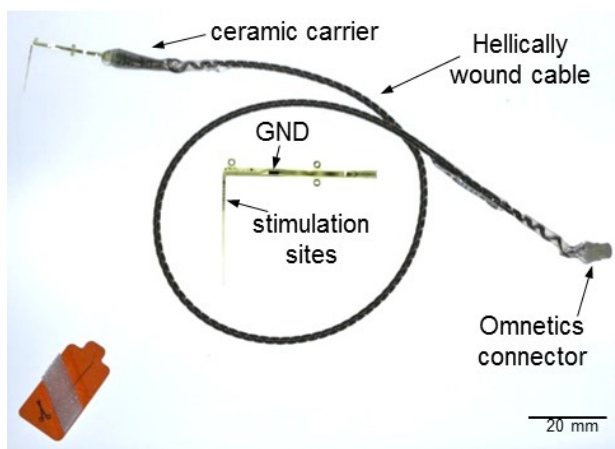


Fig. 1. TIME electrode consisting of micromachined electrode array, ceramic carrier, cable and connector. Inset shows details on arrangement of stimulation sites and counter electrode (GND).

Cables did not break over 250,000 bending cycles and stimulation sites did not show changes in charge injection capacity that was determined safe for up to 120 nC per stimulation site [9]. Only mild foreign body reaction was investigated in preclinical studies [7] with the electrodes in the nerve. Selectivity was superior to cuff and longitudinal intrafascicular electrodes [9]. The TIME was stable and established a reliable interface with the ulnar and median nerve in a human for 30 days [9]. Impedance measurements proved that 7 out of 8 counter electrodes and 50 out of 56 stimulation sites were working after 30 days.

Optical inspection after explantation showed intact electrode metal but delamination tendencies at large counter electrodes [10]. Redesign of TIME resulted in segmented counter electrodes and inclusion of silicon carbide /diamond like carbon adhesion layers [11] to improve metal to polyimide adhesion. The connector assembly has been modified to reduce the number of handling steps. Electrodes have been certified “MR conditional” for 3 T MR imaging of the head. Currently, impedance monitoring of electrodes in the second clinical trial shows well performing electrodes after more than five months now.

IV. DISCUSSION

Polymer-based devices made out of a polyimide-thin-film sandwich showed to be an alternative [9] to intraneural [2] and cuff-electrode [1] arrays to chronically interface peripheral nerves in humans in the upper extremity. Stability of thin-film metallization is the key parameter that limits long-term implantation of these neural interfaces. Implanted electrodes are currently working well for about 5 months in a second clinical trial (unpublished data). Neural implants with a large number of electrode sites still use percutaneous wires in lack of fully implantable pulse generators with high channel count connectors. This situation is still the largest hurdle to transfer these neural interfaces into implantable medical products for a large patient population.

V. CONCLUSIONS

Thin-film based multichannel electrodes proved to be able to establish a reliable and stable interface to peripheral nerves in human clinical trials. However, before commercialization into clinically approved devices can take place, fully implantable system solutions have to become available to make them attractive for chronic implantation.

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