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Flexible multichannel vagus nerve electrode for stimulation and recording for heart failure treatment

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ABSTRACT

Vagus nerve stimulation is an emerging bioelectronic medicine to modulate cardiac function, as the nerve provides parasympathetic innervation to the heart. In this study, we developed a polyimide based 2D cuff electrode to wrap around on the vagus nerve. Thanks to the tiny size and bendable protruding structure of the contact tips of the device, the electrode sites are able to flexibly bend to touch the nerve, selectively record and stimulate the vagus nerve. Gold, platinum and platinum black materials were chosen to compose the electrodes for nerve stimulation and recording, respectively. Since the platinum black has ~30 times larger charge delivery capacity (CDC) than gold, Pt black electrode is used for nerve stimulation. The electrochemical impedance spectroscopy and cyclic voltammetry measurement of the three materials were conducted *in vitro*, revealing the results of 405 kΩ, 41 kΩ, 10.5 kΩ, @1 kHz and 0.81 mC/cm^2, 4.26 mC/cm^2, 25.5 mC/cm^2, respectively (n = 3). The cuff electrodes were implanted into the right-sided vagus nerve of rats for *in vivo* experiment. Biphasic current configuration was implemented for nerve stimulation with frequency of 10 Hz, pulse during of 300 μs and various currents stimulus. The result shows the heart beat frequency drops up to 36% during the stimulation and was able to return the regular frequency as stimulation was removed. Subsequently, the vagus nerve signals were recorded with the four channel cuff electrodes. The magnitude of the compound nerve action potentials (CNAPs) is ~10 μV and the signal to noise ratio (SNR) is ~20.

1. Introduction

Electroceuticals is a recently developed therapy *via* the modulation of the electrical signal in the nervous system bidirectionally to acquire the nervous signal and stimulate the nerves in particular (Bouton, 2015; Neren et al., 2016; Chunchai et al., 2016). This strategy is a rapidly growing new research field that focuses on the development of implantable electrical devices and shows significant potential to treat many stubborn and chronic diseases and pathological conditions, sometimes accompanied by pharmaceutical treatment (Smith et al., 2016; Famm et al., 2013; Bouton et al., 2016). Nerve electrodes are the essential components as interface between biological tissue and machines. The electroceuticals aims for both central nerve and peripheral nerves prosthetics, such as deep brain stimulation for control of Parkinson's disease (Howell and Grill, 2014), bladder prostheses (Navarro et al., 2005), cochlear prostheses (Shannon, 2012), retinal visual prostheses (Pezaris and Eskandar, 2009), vagus nerve stimulation (Giulioni et al., 2012) and motor paralysis to recover the function of limb movement (Xue et al., 2015). Among the peripheral nerve electrodes, apart from the intraneural nerve electrodes that are typically invasively inserted into the nerve and reach the small group of nerve bundles, the extraneural interfaces such as cuff electrodes and spiral electrodes are able to externally encircle or contact the nerve surfaces to reduce the risk of nerve damage and good for chronic performance, but sacrificing the spatial nerve signal recording resolution (Stieglitz et al., 2000; S.H. Lee et al., 2016; Y.J. Lee et al., 2016).

Among the peripheral nerves, the vagus nerve controls multiple health-promoting effects (Couck et al., 2017). The most commonly used vagus nerve stimulation (VNS) therapy are the treatment of epilepsy. In 1985, the electrical stimulation of the vagus nerve has been proved as benefits in seizure prevention (Zbara, 1985). In its anatomical structure, the vagus nerve is from cranial nerve containing 80% afferent sensory fibres from the heart, aorta, lungs and gastrointestinal tract and 20% efferent motor fibres, bridging the nucleus amiguus and nucleus

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dorsalis nervi vagi in the brain stem and the visceral organs (Tracey, 2009). VNS is associated with treatment of epilepsy, obesity, arthritis, blood pressure control and depression (Boon et al., 2007; Walsh and Kling, 2004). Moreover, it has been reported that the VNS applying on right-sided vagus nerve has greater effect than left-sided stimulation to regulate the heart beating as it innervates the sinoatrial node which functions as the heart activity. VNS is known to slow down the heart beat to reduce the incidence of ventricular arrhythmias and mortality during ischemia and prevent sudden cardiac death (Brack et al., 2013).

As researchers are dedicated to improving the cardiac function and heart failure symptoms from VNS, there is a significant need to selectively activate a particular portion of the nerve fibres in the vagus nerve by multi-channel systems. For example, the acute cardiac responses of VNS generally requires mostly B fibre (a branch of vagus nerve) stimulation (Peclin and Rozman, 2013). The selective stimulation may also avoid the side effect of VNS, such as coughing, difficult swallowing, nausea and indigestion (Libbus et al., 2017). Multi-channel electrode devices allow to selectively record an autonomic nerve activity in particular. The closed-loop control by involving both multi-channel recording and stimulation activates a neural pathways to control and treat the heart failure in the selective nerve branch. Unfortunately, seldom literature reported on the vagus nerve signal recording, needless to say such multi-channel vagus nerve signal recording and stimulation closed-loop system.

The materials to compose the peripheral nerve electrode interface including polyimide, parylene, SU-8 or polydimethylsiloxane (PDMS) as flexible biocompatible structure, and Pt, Au, PtIr, IrO_x, or some conductive polymers as conductive contact electrode sites to conduct electrical signal from or to the nerve (Geddes and Roeder, 2003). Polyimide is the most commonly used substrate material with demonstrated biocompatibility with Young's modulus from 2 to 8 kPa and furthermore polyimide material is not vulnerable during bending and torque. Cuff electrodes are considered so far the best compromise between invasiveness and signal quality (Navarro et al., 2005; S.H. Lee et al., 2016; Y.J. Lee et al., 2016). However, due to the variation in the nerve sizes, cuff electrodes have to be customized for each specific applications. The nerve size varies not only between individuals of the same specie but also along time in the same subject. Interaction with a foreign body by the electrodes will produce tissue inflammation, scarring formation, and other chronic changes that will affect the nerve diameter. For this reason, cuff electrodes need to be designed somewhat larger in diameter than the target nerve in order to account for these changes and prevent nerve constriction. However, this has the consequence of a looser contact and poorer signal quality.

In this paper, we developed a non-invasive, multi-channel, polyimide based flexible cuff neural interface electrode device for vagus nerve signal recording and stimulation. The electrode device has four protruding metal contact tips that allows the contact remains consistent after device implantation. The design permits the dynamic adaptation of the nerve interface to the chronic changes in the nerve and allows the use in a different species.

2. Experimental

2.1. Design and fabrication of the nerve electrode

The device consists of a polyimide-metal-polyimide sandwich structure with metal contacts and pads opened. A two dimensional (2D) ring frame containing four extended electrodes contact sites are the nerve interface region. Each contact sites has area of 12,000 μm^2. Device with this structure is able to encircle the nerve to record and stimulate the small nerve branch across the vagus nerve (Fig. 1a). The inner diameter of the ring frame is 300 μm and the outer diameter of the ring frame is 600 μm. The length of each electrode contact tip is 100 μm. Thus, the device is able to implement on the nerves with size of 100–300 μm. The reference electrode is located at the inner edge of the ring frame to cancel the surrounding noise and work with the working electrode as a pair. A 2 cm-length of ribbon cable is to extend the signal interconnection into the connection pads, where the Omnetics connector is installed. The polyimide ring frame is able to open up by applying a twisting force. The ring frame is subsequently closed by suturing through the holes on the top frame after device implantation on the nerve.

MEMS technology was employed to fabricate the multi-channel polyimide nerve electrode device. The fabrication starts with a 6-in. silicon wafer. The fabrication process flow is demonstrated in Fig. 1(b-f). First, a 1-μm-thick Al layer was deposited onto the silicon substrate as a scarification etching layer for final release of the flexible nerve electrode on the silicon wafer (Fig. 1b). A 6-μm-thick polyimide film (PI-2611, HD microsystem) was then spin-coated on Al layer and hard cured under 300 °C for 30 min at 4 °C/min ramping rate. A 200-nm-thick Al layer was evaporated on the polyimide as hard etching mask. After the first lithography step, the bottom polyimde structure was patterned on the thin Al surface. The exposed Al was wet etched followed by removal of the exposed polyimide by a reactive plasma etching (RIE) process. Next, the remaining thin Al layer was removed. The bottom polyimide pattern was formed as shown in Fig. 1c. Layers of Ti (20 nm thick)/Au (300 nm thick) or Ti (20 nm thick)/Au (300 nm thick)/Pt (200 nm thick) metal were deposited by metal evaporation. The electrode contacts, traces and pads were subsequently patterned by lift-off process (Fig. 1d). Next, a second 6-μm-thick polyimide layer was coated and fully cured under 350 °C for 30 min. The second top polyimide layer was etched and the structure was formed by following the same process as the first polyimide layer patterning (Fig. 1e). Subsequently, the polyimide chip was released from Al sacrificial etching by an electrochemical anodic dissolution process (Fig. 1f). Lastly, the released chip was rinsed by 5% HCl acid to remove the suspended Al_2O_3 on the device surface.

The pad opening of the device was designed for fixture of an Omnetics nano strip connector. As demonstrated in Fig. 1g, the dual row Omnetics connector with male end inserts into the flexible pads, electrically connected and glued by conductive epoxy (H20E, EPO-Tek, USA). Lastly, biocompatible UV epoxy (OG116-31, EPO-Tek, USA) was applied and covered the connection region between pads and connectors for electrical insulation. A customized Omnetics cable was used as further extension to the signal recorder or stimulator. The photo image of the fabricated cuff nerve electrode is shown in Fig. 1h.

To increase the charge delivery capacity, a set of Pt electrode devices were adopted to deposit Pt black by electrochemical plating method. The electrolyte was prepared by dissolving 1 g hexa-chloroplatinic acid (H_2PtCl_6) in 72 ml ultrapure water and by adding 14.4 mg lead(II)-nitrate ($Pb(NO_3)_2$) (Sigma Aldrich, USA) (Boretius et al., 2010). The packaged Pt nerve electrode were immersed into the solution and a two-electrode setup was employed, where the sample is as cathode electrode, a Pt mesh is used as anode electrode. Pt-black was electrochemically deposited on the Pt surface with 1 V DC voltage for 30 s. The scanning electron microscope (SEM) image of the Au, Pt and Pt black materials were exhibited in Fig. 1(i-k). The Au and Pt surface were reflective and smooth. The Pt black surface showed a dendritic shape with microscopic pores.

The mechanical strength test of the polyimide vagus nerve electrode was performed. The setup and result were shown in Fig. S1 in Supplementary material. Furthermore, the electrical connection property was tested under 1000 stretching cycles, the resistance change of the electrode was less than 2%. Details was described in supplementary text (Fig. S2).

2.2. Electrochemical measurements

To study the signal recording capability and charge transport property of the cuff electrode neural device, electrochemical impedance spectroscopy (EIS) measurement and cyclic voltammetry (CV)