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DOI

[10.1109/NER.2019.8717064](https://doi.org/10.1109/NER.2019.8717064)

Publication date

2019

Document Version

Accepted author manuscript

Published in

2019 9th International IEEE/EMBS Conference on Neural Engineering

Citation (APA)

Kawasaki, S., Giagka, V., de Haas, M., Louwerse, M., Henneken, V., van Heesch, C., & Dekker, R. (2019). Pressure measurement of geometrically curved ultrasound transducer array for spatially specific stimulation of the vagus nerve. In *2019 9th International IEEE/EMBS Conference on Neural Engineering* (pp. 1239-1242). IEEE. <https://doi.org/10.1109/NER.2019.8717064>

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Pressure measurement of geometrically curved ultrasound transducer array for spatially specific stimulation of the vagus nerve

S. Kawasaki, V. Giagka, M. de Haas, M. Louwerse, V. Henneken, C. van Heesch, and R. Dekker

Abstract— Vagus nerve stimulators currently on the market can treat epilepsy and depression. Recent clinical trials show the potential for vagus nerve stimulation (VNS) to treat epilepsy, autoimmune disease, and traumatic brain injury. As we explore the benefits of VNS, it is expected that more possibilities for a new treatment will emerge in the future. However, existing VNS relies on electrical stimulation, whose limited selectivity (due to its poor spatial resolution) does not allow for any control over which therapeutic effect to induce. We hypothesize that by localizing the stimulation to fascicular level within the vagus nerve with focused ultrasound (US), it is possible to induce selective therapeutic effects with less side effects.

A geometrically curved US transducer array that is small enough to wrap around the vagus nerve was fabricated. An experiment was conducted in water, with 48 US elements curved in a 1 mm radius and excited at 15 MHz to test the focusing capabilities of the device. The results show that the geometrical curvature focused the US to an area with a width and height of 110 μm and 550 μm . This will be equivalent to only 2.1% of the cross section of the vagus nerve, showing the potential of focused US to stimulate individual neuronal fibers within the vagus nerve selectively.

I. INTRODUCTION

Currently marketed vagus nerve stimulators are used to treat epilepsy and depression [1] by stimulating the vagus nerve. Vagus nerve stimulation (VNS) works by implanting a cuff electrode directly onto the vagus nerve located at the neck. Since the vagus nerve is a bundle of nerves that includes efferent nerves connecting to many organs other than the brain (i.e. heart, lung, spleen, stomach etc.) recent clinical trials have begun to explore VNS as a method to modulate these other organs for therapeutic benefits. Some examples of these clinical trials target chronic heart failure [2] or autoimmune diseases [3] such as Crohn's disease or rheumatoid arthritis. However, the side effects of these therapies still remain; these include neck pain, coughing, voice alteration, and dyspnea [4]. Therefore, the goal of this paper is to explore a new stimulation technique, which has the potential to induce therapeutic effect that targets only one of the previously mentioned diseases, while reducing the side effects by localizing the stimulation to individual fascicles within the nerve.

One option that was explored by T. Stieglitz et al. was to mechanically pierce through a peripheral nerve and distribute highly selective electrode contacts over the cross section of the nerve, which can create localized activation at the fascicular level [5]. This method was proven to work for motor nerves.

Nonetheless, to our knowledge this concept has not been applied to the vagus nerve, most likely because the vagus nerve has vital functions and is too risky to penetrate with such a device. Another option investigated was to use multiple electrodes along the inner walls of a cuff that can be excited independently (i.e. multi-contact electrode [4], [6]). For this method, additional advancement must be made to increase the number of electrodes to achieve better spatial resolution.

As an alternative approach, we propose focused ultrasound (US) to stimulate individual fascicles within the vagus nerve. It has already been shown that US can stimulate neurons [7]. The stimulation mechanism remains to be unclear, but one possible explanation is that the acoustic force from the US deforms the cell membrane and stimulates the mechano-sensitive ion channels [8]. Transcranial US neurostimulation has been studied extensively over the past decade due to its compelling characteristic to stimulate certain regions deep within the brain but without invasively penetrating the brain [9]. Similarly, we hypothesize that if US transducers are wrapped around the vagus nerve, individual fascicles within the vagus nerve can be stimulated without penetrating the nerve.

For transcranial applications, the US frequency is commonly below 5 MHz, as higher frequency US will not penetrate through the skull. This limits the spatial resolution of the therapy to several millimeters. Unfortunately, this is already too coarse for VNS, as the vagus nerve has a diameter of about 2 to 4 mm at the site of stimulation. However, this resolution can be increased if higher frequencies and a larger number of US transducers are employed. Luckily, operating at higher frequencies is not a limitation for our proposed solution, as the US transducers will be wrapped directly around the vagus nerve.

Only a handful of researchers have conducted in-vivo tests at these frequencies. M. Menz et al. stimulated retinal ganglion cells with US at a frequency of 43 MHz for retinal prosthetic application [10]. This was possible because the retinal cells are directly accessible through the surface of the eye without penetrating the skull. These results indicate that neurons can indeed be activated at higher US frequencies, strengthening our hypothesis that stimulation of neurons within the vagus nerve with such high frequencies should be feasible.

In the past, creating a cuff with US transducers so small that could be wrapped around the vagus nerve would be

*Research supported by ULIMPIA

S. Kawasaki and V. Giagka are with the Microelectronics Department, Delft University of Technology, Delft, The Netherlands (corresponding author e-mail: shinnosuke.kawasaki@philips.com). V. Giagka is also with Fraunhofer Institute for Reliability and Microintegration IZM, Berlin,

Germany. M. Louwerse, V. Henneken, C. van Heesch, R. Dekker is with Philips Research, Eindhoven, The Netherlands. M. de Haas is with Philips Innovation Services, Eindhoven, The Netherlands.

unthinkable. Due to the advent of mechanical and electrical micro systems (MEMS) it is now possible to fabricate thousands of US transducers in a few millimeter square area. This allows for a high-resolution US cuff at a size comparable to conventional VNS cuff electrodes.

In this paper, we propose a new high-resolution vagus nerve stimulator. A flexible array of US transducers that can be wrapped around the vagus nerve. This device will have the potential to achieve single fascicle stimulation along with the ability to control the stimulation region by applying a phase delay to each US transducer. Finally, the concept can be extended to all peripheral nerves. Thinner nerves can also be targeted if a suitable spacer with an acoustic impedance similar to water is used between the nerve and the US transducers because US will propagate through the spacer.

The rest of this paper illustrates the focusing capabilities of such a proof-of-concept high-resolution cuff, in a proof-of-concept experiment. A device with 48 US transducer elements (each element consisting of 24 US transducers) was fabricated and positioned in a half-cylinder with 1 mm radius inside the water medium. The array of transducers were excited and the pressure profile in the volume within and above the half-cylinder (where the nerve would be positioned) was measured. To verify measured results, simulations of the US pressure field were also conducted, using the same geometry.

II. MATERIAL AND METHOD

A. Sample preparation

Capacitive Micromachined Ultrasonic Transducers (CMUTs) consist of two circular parallel plates with the bottom plate on the silicon substrate and the top plate suspended over the bottom one, with an insulating layer and a vacuum gap in between. By applying an AC signal to the two plates, the distance between them changes generating US. An additional DC voltage can be applied either to tune the center frequency or to increase the amplitude of the US [11].

The CMUT devices were fabricated through MEMS microfabrication. Each features with a diameter of 25 μm and 24 of them were aligned on a single silicon island with 2 μm spacing between two adjacent CMUT devices. This silicon

island will be referred to as a CMUT element. On the same wafer, 112 of these CMUT elements were aligned next to each other with 2 μm spacing. The Flex-to-rigid process [12], [13] was employed to use polyimide as a flexible layer that connects all elements, thus creating a flexible device which can curve.

The array of CMUT elements was fixed in a curvature along the inner wall of a half-cylinder with an inner radius of 1 mm. This was placed on top of a PCB and was wire bonded to connect to external connectors. Subsequently, the device was coated with 20 μm of PDMS and 5 μm of Parylene. The PDMS served as an acoustic matching layer between the CMUT and water. The parylene on top of it prevented PDMS from absorbing water and avoided short circuits at the electrical connectors. Fig. 1a shows an overview of the prepared sample before it was coated with PDMS and Parylene. Fig. 1b is a close up image of the CMUTs.

B. Experimental setup

Fig. 2a shows the experimental circuit. A 5 V DC bias was connected to all of the CMUTs through a 100 k Ω resistor. The 48 CMUT elements at the center of the device were connected in parallel and were excited simultaneously. An US tone burst of 15 MHz at a pulse repetition frequency (PRF) of 1 kHz with 30 cycle was generated with a function generator (Keysight Model 3621A). This signal was amplified through an amplifier up to 17 V peak-to-peak voltage to excite the CMUT elements via a decoupling capacitor (47 nF). This input RF signal was measured across a 100:1 voltage divider. The acoustic pressure was measured with an optical fiber pressure sensor along with the fiber optic hydrophone (Precision Acoustics).

Fig. 2b is a side view of the CMUT immersed inside water during the measurement. The optical fiber pressure sensor with a tip diameter of 0.1 mm was positioned from the top. Water was used as the acoustic medium to mimic the acoustic property of a nerve, since sound velocity is relatively similar for water (1500 m/s) and nerve (1630 m/s). Using water also confirms that the device is watertight and can be extended to in-vitro experiments in the future.

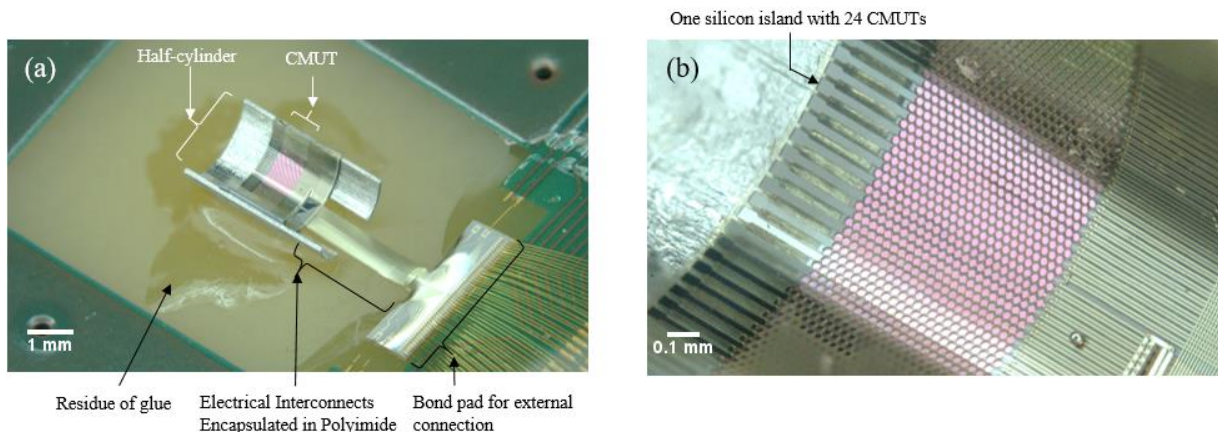


Figure 1. (a) Overview of curved CMUT wire bonded to a PCB before coating of PDMS and Parylene. The CMUT elements were glued to the half-cylinder which was then glued to the PCB. The electrical interconnects are encapsulated in polyimide which is further connected to the bondpad for external connection. (b) a close up image of the CMUTs with 24 CMUTs in one column and 112 CMUT elements (not shown entirely) in a row. The transparent yellow film encapsulating the islands is the polyimide.

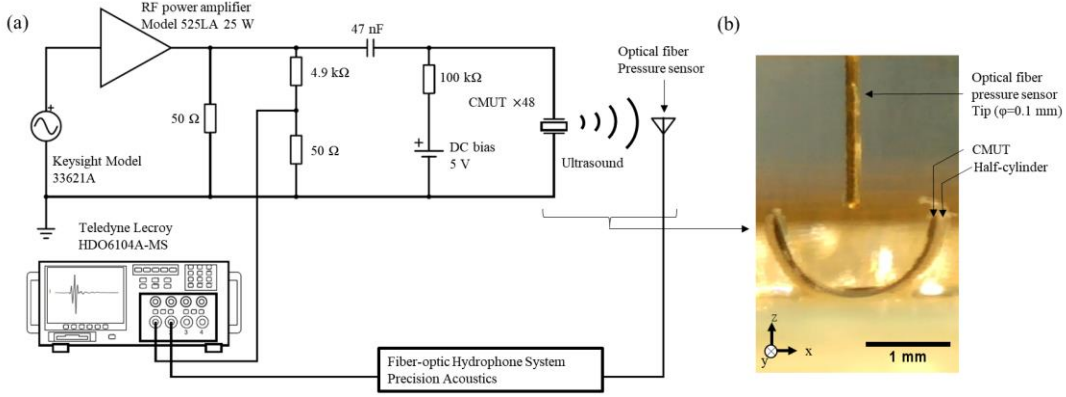


Figure 2. (a) An overview of the experimental circuit. A sine wave with 30 cycles, a center frequency of 15 MHz, and a peak to peak voltage of 17 V at a pulse repetition frequency of 1 kHz, was applied to 48 CMUT connected in parallel via an RF power amplifier and a decoupling capacitance 47 nF. The DC bias voltage was supplied through a 100 k Ω resistor. (b) The sideview of the measurement setup. The CMUT is aligned in a curvature along the half-cylinder and the optical fiber pressure sensor is positioned within the curvature.

The tip of the optical fiber was moved with a motor controlled micromanipulator in 20 μm steps in the x and z direction shown in Fig. 2b. The y-position was adjusted at the x-z plane with maximum pressure by moving the optical fiber tip in the y-direction (in/ out of plane in Fig. 2b).

C. Simulation of the US pressure field

The US pressure field from the CMUT was simulated with an open source software from Michigan State University, Fast Object-Oriented C++ US Simulator (FOCUS) [14]–[16]. In FOCUS, the US field can be simulated by describing the geometry of the US transducer and the medium in which the US propagates. The US transducer geometry was constructed by aligning 48 rectangular transducer elements into a curvature with a radius of 1 mm. Each rectangular element represents a single CMUT element. The width and height of the rectangle element was 25 μm and 0.65 mm respectively. The spacing between each transducer was 2 μm .

The simulation was done in a continuous wave mode and the medium used for the simulation was water. The pressure was simulated on the x-z plane at $y = 0$, which is the center of the US transducer element.

III. RESULTS

Fig. 3a is the measured pressure field. The instantaneous spatial peak pressure (P_{peak}) was 310 kPa. The width and length of the focal area defined by the -3dB level (shown with a black contour) was 110 μm and 570 μm respectively. The experimentally scanned area is relatively small compared to the size of the half-cylinder. This was because a larger measurement area requires a quadratic increase in the experimental time.

To put this result in perspective, Fig. 3b is the simulation result of a larger US field and Fig. 3c is the close up view where the measurement was conducted. The white circle has a radius of 1 mm and represents the vagus nerve. The red dot are where the 48 CMUTs were positioned.

From both the simulations and the experiments, the focal area is elongated in the vertical direction because the 48 CMUT transducers were aligned at the bottom of the half-cylinder. An interference pattern can also be seen, radiating outwards from the US transducer. This is because the US

transducers were stimulated at the same amplitude. The focal area size from the experiment was $6.50 \times 10^4 \mu\text{m}^2$. Assuming that the vagus nerve has a diameter of 2 mm, the ratio between the focal area to the cross section of the vagus nerve was 2.1 % from the experiment. This was larger than the simulation result as can be seen by comparing Fig. 3a and Fig. 3c. One possible reason for this is that the measured sample was tilted.

The spatial peak pulse average intensity (I_{SPPA}) of US can be calculated by the following equation,

$$I_{\text{SPPA}} = \frac{P_{\text{peak}}^2}{2Z_0}$$

where, Z_0 is the acoustic impedance of the medium ($Z_0 \approx 1.5 \times 10^6 \text{ kg/m}^2/\text{s}$ for water). Based on this equation, I_{SPPA} was 3.2 W/cm^2 . The mechanical index (MI) is a figure of merit that describes the acoustic force of the US [17]. This value increases as the pressure increases and decreases with frequency. In this research, MI was 0.078.

IV. DISCUSSION

To our knowledge, in-vivo experiments that uses an acoustic frequency of 15 MHz to stimulate a neuron has not yet been conducted. Furthermore, it is not clear at which intensity or amplitude is required to stimulate a nerve at this frequency. Nonetheless, G. F. Li et al. stimulated a mouse brain at 5 MHz with an intensity of 210 mW/cm^2 [18] and M. Menz et al. stimulated the retinal ganglion cell of a salamander at 43 MHz with an intensity of 20 W/cm^2 [10]. Extrapolating from these results it is expected that an intensity of several W/cm^2 will be required at 15 MHz. Thus, the intensity from this research (3.2 W/cm^2) will likely to be sufficient. This must be verified with additional in-vivo experiments.

Considering the safety of US stimulation, the U.S. Food and Drug Administration (FDA) allows $I_{\text{SPPA}} < 190 \text{ W/cm}^2$ for diagnostic US imaging [17]. This threshold intensity is relatively high and is higher than what was observed during our experiment. Meanwhile, the average intensity needs to be limited to 720 mW/cm^2 ; also defined by the FDA, to avoid temperature induced tissue damage. Both conditions can be met by using an US waveform with an appropriate duty cycle. Another mechanism that may cause damage is cavitation. Cavitation is a phenomenon when the US forms a gaseous

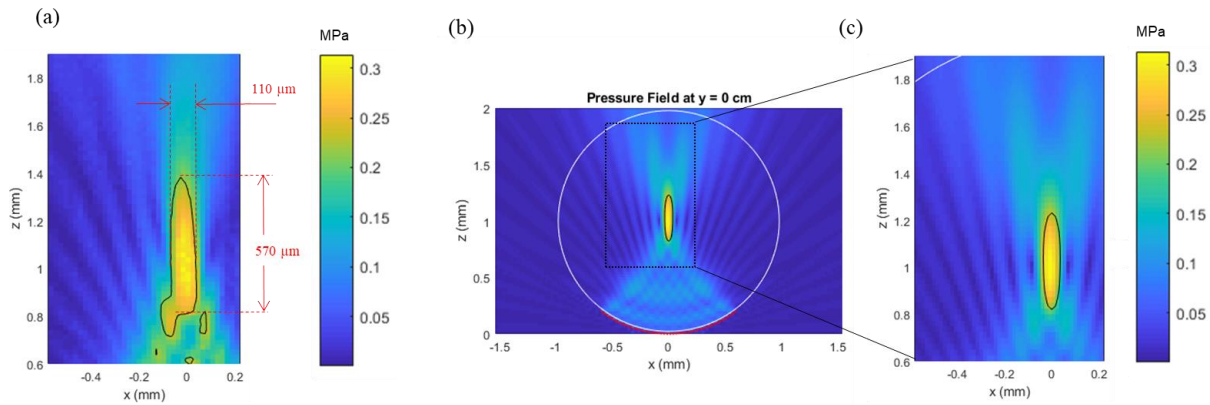


Figure 3. Comparison of the experiment and the simulation. (a) The pressure profile measured using an optical fiber needle. (b) The simulation result of the pressure profile. The white line shows the contour of the vagus nerve ($\phi = 2$ mm) and the black contour line represents the -3 dB level. The color bar shows the positive peak value of the pressure profile. The red dots represent the position of each CMUT element. (c) A close up image of (b) also corresponding to the same location in (a).

body within the tissue and then collapses, creating a shock wave that damages the surrounding tissues. FDA defines that the MI should be less than 1.9 to avoid this effect. The MI observed in this research was 0.078, which is much lower than the safety limit. For the safe application of US nerve stimulation, the amplitude and the intensity of the US that was observed in this research should not be dangerous.

Considering the encapsulation of the device, an US stimulator has a clear advantage over an electrical stimulator. An US stimulator can be entirely encapsulated with a coating, while an electrical stimulator have electrodes that need to be exposed to the body fluid. This creates a complex interface near the electrode that is prone to failure. However, this advantage for an US stimulator has a disadvantage that an US stimulator cannot record any electrical activity from the nerve. Therefore, these devices should complement each other.

Finally, we simplified a nerve by representing it with water. The sound velocity of a nerve is slightly higher than water so we can expect the focal area to become slightly larger. That being said, in reality the nerve will have capillary blood vessels, myelin sheath and other structures which will create multiple boundaries with different acoustic properties, hence, overall a more complex response is expected. This will be investigated in the next step.

ACKNOWLEDGMENT

The authors acknowledge the contribution of researchers working at Philips Research such as S. Shulepov and P. Dirksen for their precious input on CMUTs and the simulation result. This project is funded by ULIMPIA. ULIMPIA is labelled as a PENTA project endorsed by EUREKA under PENTA cluster number E!9911.

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