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Multimodal Measurement and Stimulation System to Investigate the Effects of Non-invasive Electrical Stimulation of the Phrenic Nerve

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Abstract: Mechanical ventilation, as performed daily in intensive care units, can lead to ventilator-induced diaphragmatic dysfunction. A reduction in diaphragmatic force generation can occur within the first 24 h. Electrical stimulation of the phrenic nerve can mitigate this effect, but optimal stimulation parameters are largely unexplored. The aim of this work is to build a multimodal measurement and stimulation setup allowing for the test of a wide range of stimulation parameters. Ultrasound, breathing belt, electromyogram, and electrocardiogram measurements are performed simultaneously. The results demonstrate the feasibility of transcutaneous electrical phrenic nerve stimulation, showing observable responses in diaphragmatic movement and breathing belts. The developed system provides a platform for further investigations into the effects of phrenic nerve stimulation.

Keywords: artificial respiration, ventilator weaning, electric stimulation therapy, peripheral nerves

1 Introduction

Mechanical ventilation is used daily in intensive care units worldwide. In the United States alone, it is estimated that over 750,000 people are mechanically ventilated every year [1]. Within the first day of invasive ventilation, a decrease in the fibre cross-section of the diaphragmatic myofibrils can be observed, which is associated with a reduction in the force generation of the diaphragm. The ventilator-induced diaphragmatic dysfunction (VIDD) considerably increases morbidity, mortality, and hospitalisation costs [2] and prolongs the weaning process. Studies have shown that the effects of VIDD can be reduced by electrical stimulation of the phrenic nerve, which innervates the diaphragm [3].

Our aim is to investigate phrenic nerve stimulation, transcutaneously applied via surface electrodes, to induce a diaphragm muscle contraction. We aim at a setup, which can generate arbitrary stimulation waveforms with a wide range of stimulation repetition rates, wave patterns and enables a multimodal effect evaluation.

2 Material and Methods

We developed a multimodal measurement and stimulation system to investigate the effects of non-invasive electrical stimulation of the phrenic nerve. An overview of the hardware setup is given in Figure 1. The stimulation part of the setup (Figure 1A) is controlled by an in-house developed application in LabVIEW 2023 (National Instruments, Austin, USA). The user outlines the stimulation parameters and controls the stimulation with a graphical user interface. The underlying software architecture is implemented as a Queued Message Handler. The user defines a single stimulus by an arbitrary waveform which is repeated by a specified pulse rate. This signal is transferred via USB to the multifunction input/output device (DAQ device) USB-6361 (National Instruments, Austin, USA). This DAQ device generates the analogue stimulation signal scaled to a range of +/- 10 V with a sampling frequency of 2 MHz which is then transferred to the Terminal Block BNC-2120 (National Instruments, Austin, USA) and the DS5 Isolated Bipolar Constant Current Stimulator (Digitimer, Welwyn Garden City, UK). The

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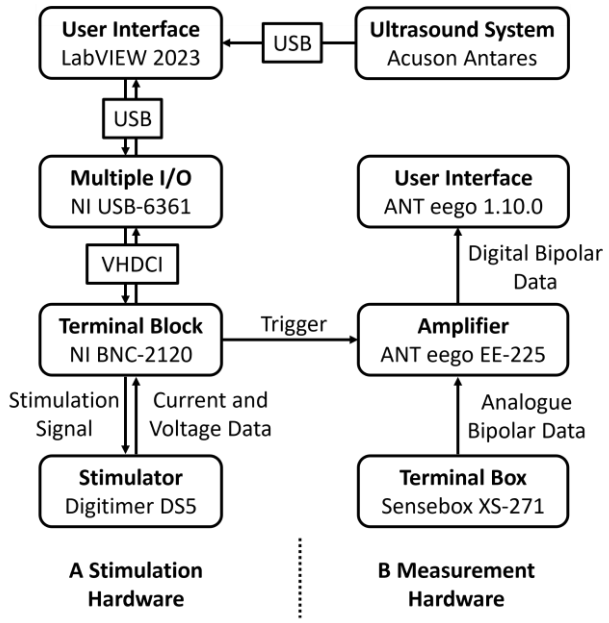

Fig. 1: Experimental setup for phrenic nerve stimulation. The direction of data flow is indicated by arrows. **A** shows the devices used for stimulation, **B** displays the measurement equipment.

stimulator generates current-driven stimulation signals with a maximum amplitude of +/- 50 mA. The input-to-output ratio is 10 V : 50 mA. The stimulation signal is described by a wide range of parameters. Figure 2 illustrates the relationship between different intensities, stimulation durations, and pause intervals across various time scales.

The Acuson Antares ultrasound system (Siemens, Berlin/Munich, Germany) is used to assess the respiratory activity in real time by observing the movement of the diaphragm. The analogue video output of the system is digitalized with a frame rate of 25 frames per second and is saved during stimulation. In addition to the stimulation duration, three seconds of pre- and post-stimulation are saved, to compare diaphragm movement in non-stimulation periods.

The second part of the measurement setup (Figure 1B) is the ANT eego EE-225 amplifier (ANT Neuro, Hengelo, Netherlands) which measures output from breathing belts, the electromyogram (EMG), and the electrocardiogram (ECG). The belts and the electrodes are connected via the sensebox XS-271 bipolar terminal box (ANT Neuro, Hengelo, Netherlands). The belts use piezoelectric sensors that convert the extension of the belt into an electrical voltage. The signals are acquired with a sampling rate of 2048 Hz. In addition to the biosignal measurements, the current and voltage data of the stimulator output are recorded by the DAQ device with a sampling rate of 150 kHz.

Synchronisation of stimulation signal generation and measurement data acquisition is done with a binary sequence which is used as a trigger. After the first rising edge, the binary sequence decodes a stimulation counter and the stimulation date. Stimulation data is stored in a custom file format for later analysis. The raw data of the amplifier are exported in a separate file. Scripts for importing and synchronising the various data sets are developed for Python 3 (Python Software Foundation, Delaware, USA).

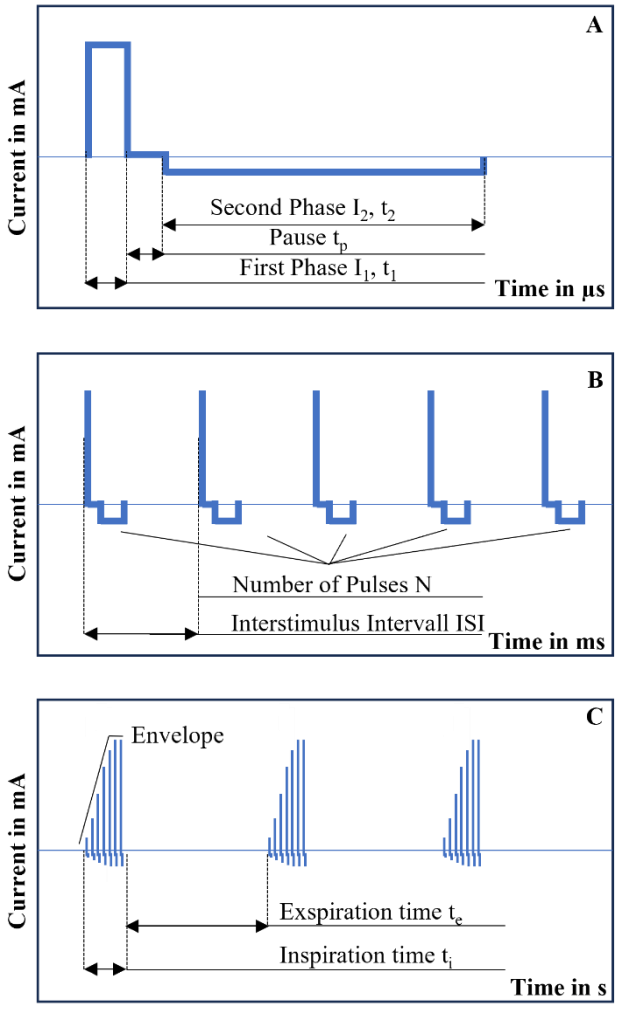

Fig. 2: Stimulation signals. **A** shows a single biphasic rectangular pulse. The first phase of the pulse triggers the stimulation. The second phase balances the charge of the first phase to avoid electrolysis by charge accumulation. Intensity I_1 and duration t_1 of the first phase are connected by the strength duration curve. The pause time between these phases has the duration t_p. **B** shows a stimulation train that consists of *N* pulses. The time between the onset of two consecutive pulses is given by the interstimulus interval *ISI*. **C** shows the stimulation train. They are defined by the inspiration (expiration) time t_i (t_e). Stimulation trains can be modulated by envelopes. A linear ascending envelope is showed here.

3 Experimental Paradigm

We use hydrogel electrodes for surface stimulation, following the electrode geometry and arrangement proposed by Keogh et al. [7]. Their design consists of six 1 cm × 1 cm cathodes, spaced 2 mm apart, surrounded by an anode. The distance between a cathode and the inner anode edge is 5 mm. In contrast to Keogh et al., we use the electrode array at a lower position on the neck as described in [8]. We position the upper edge of the surrounding anode at the level of the cricoid cartilage. The palpable sternocleidomastoid muscle is close to the course of the phrenic nerve.

Breathing belts are placed on the chest and the abdomen of the subject. The chest belt provides information about the thoracic respiration and the belt around the belly about the abdominal respiration.

The ultrasound probe is placed on the anterior axillary line and is adjusted between the 6th to 8th intercostal space until the diaphragmatic movement is clearly visible and stable. Motion mode is used to compare the diaphragmatic movement over time.

The EMG can be used to analyse the activity of the different muscles involved in the breathing process. Therefore, we measure the diaphragmatic EMG between the midclavicular lines at the height of the 8th intercostal space (Figure 3, Pos. 1) [4] and distal to the midclavicular line at the 8th intercostal space of the stimulation side (Figure 3, Pos. 2) [5]. Additionally, we measure the EMG of the external intercostal muscles on the anterior axillary line on the height of the mamma (Figure 3, Pos. 3) [6] on the stimulation side. ECG is measured on the forearm. The EMG and ECG measurements are done bipolar with adhesive electrodes.

A grounding strap is moistened with sodium chloride solution and placed around the chest through the armpits to electrically separate stimulation and measurement. Figure 3 shows the positioning of the stimulation and measurement components systematically and on a test subject.

For the first assessment, we incrementally increase the intensity I_1 of the first phase until a stimulation response is visible in the diaphragm. Durations t_1 and t_p are set to 150 µs. The second phase depends on the first phase and is selected as described by equation 1. These parameters were chosen according to the findings of Wegert et al. [9].

$$t_2 : t_1 = I_1 : I_2 = 10 : 1 \qquad (1)$$

We use an *ISI* of 67 ms for the stimulation, which is equivalent to 15 pulses per second. Stimulation was performed with N = 15 pulses (t_i = 1000 ms). Single pulse trains without envelopes are used in the validation of our setup. Validation is done by stimulation of one healthy subject.

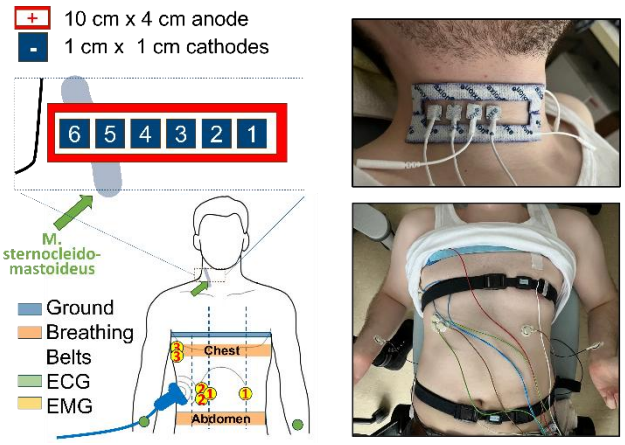

Fig. 3: Positioning of the stimulating electrode array, the ultrasound probe, measurement electrodes, the breathing belts, and the grounding strap on a volunteer. The upper edge of the electrode array is placed at the level of the cricoid cartilage. Cathodes 1 – 6 (blue) are surrounded by an anode (red). The course of the M. sternocleidomastoideus is marked with a green arrow. The yellow dots indicate EMG electrode pairs, green dots indicate the ECG electrodes. The positions of the electrodes are described in the text.

4 Results

Real time observations of the ultrasound data exhibit clear and similar response to stimulation at currents of 15 mA or higher, applied by the two most lateral cathodes. Further increasing the current beyond 15 mA does not appear to enhance the ultrasound response. The maximum voltage applied is 41 V, for stimulations using up to 25 mA. Figure 4 compares the described stimulation effect in the ultrasound data and the two breathing belts. Stimulation is visible in the ultrasound for 26 frames (1040 ms) which is equivalent to the stimulation duration.

The diaphragmatic deflection measured by ultrasound during stimulation reaches up to 3.5 cm, compared to 1.7 cm during normal inspiration. The results differ between the breathing belts. Taking the normal physiological inspiratory process as reference for 100% extension, the abdominal belt shows a change of up to 55% with stimulation, whereas the chest belt exhibits no extension.

The volunteer describes the perception of the stimulation as prickly, but not painful. Co-innervation of shoulder and breast muscles is observable.

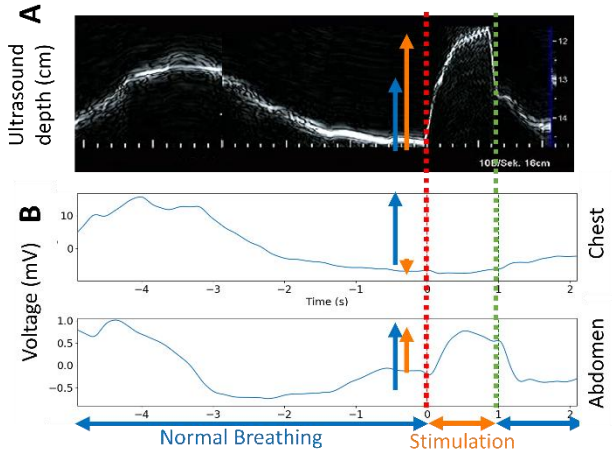

Fig. 4: Recorded ultrasound and belt data after stimulation with 15 mA. Stimulation start is marked with a red dotted line, stimulation end with a green dotted line. Blue arrows indicate deflection in normal breathing, orange arrows deflection after stimulation. A rising signal course indicates inhalation and a falling course exhalation.
A Motion-mode ultrasound of diaphragmatic movement response after stimulation. Ultrasound indicated diaphragmatic deflection of 1.7 cm with normal breathing, and up to 3.5 cm with stimulation. **B** Data of the chest and abdomen belt. While the chest belt indicates almost no extension, the extension of the abdominal belt is up to 55% compared to normal breathing (100%).

5 Discussion

Responses to the stimulation are observable in the diaphragmatic movement of the ultrasound and the extension of the breathing belts. We estimate that the course of the phrenic nerve for this volunteer goes between cathode five and six because stimulation responses are strong and reproducible on both electrodes.

Our results in the ultrasound are comparable to the ones described by Keogh et al. [7], who reported a clear response at 20 mA with a similar stimulation train. These findings are further confirmed by data from the breathing belts. The differences between the chest and abdominal belts can be attributed to diaphragmatic breathing primarily corresponding to abdominal breathing. The smaller relative amplitudes result from our one-sided stimulation, which affects only one side of the diaphragm.

In contrast to Geddes et al. [10], we use stimulation at the neck for our setup, as performed by Sarnoff et al. [11]. Our results show that our setup is suitable for transcutaneous electrical stimulation of the phrenic nerve. Arbitrary waveform generation and the multimodal measurements with our setup open possibilities for further investigation.

Author Statement
The author received funding from the Federal Ministry of Education and Research with the grant *eVent* (13GW0591B). Authors state no conflict of interest. Informed consent has been obtained from all individuals included in this study. The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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