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MUDr. Michal Soták, DESA

Czech Technical University in Prague
Faculty of Biomedical Engineering
Department of Biomedical Technology

PERCUATENEOUS ELECTRICAL PHRENIC NERVE STIMULATION (PEPNS) SYSTEM IN PATIENTS ON MECHANICAL VENTILATION

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MUDr. Michal Soták, DESA

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Supervisor: prof. Ing. Karel Roubík, Ph.D.
Supervisor-Specialist: MUDr. Tomáš Tyll, Ph.D.

Statement of authorship

I declare, that I conducted the research described in the submitted doctoral thesis entitled “Percuateneous electrical phrenic nerve stimulation (PEPNS) system in patients on mechanical ventilation” myself. All used sources of information are acknowledged in the attached list of references. I do not have a compelling reason against the use of the thesis within the meaning of Section 60 of the Act No.121 / 2000 Coll., on copyright, rights related to copyright and amending some laws (Copyright Act).

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In Prague, _____ 2022

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Michal Soták

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Abstract

The diaphragm atrophy and dysfunction is a major problem among critically ill patients on mechanical ventilation. Ventilator induced diaphragmatic dysfunction is thought to play a major role in this process resulting in a failure of successful weaning. Stimulation of the phrenic nerves leading to the diaphragm contraction could prevent or treat this atrophy. The subject of this study is to determine the feasibility of temporary Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) and its effectiveness on change in the diaphragm thickness.

A total of 12 patients in the intervention group, of which 10 were stimulated bilaterally, and 10 patients in the control group were enrolled. Stimulation was used for six, two-hour sessions at eight-hour intervals over 48 hours. Data collected included lead deployment technique and its success, ventilation parameters, vital signs, work of breathing, electrical stimulation parameters and stimulation-breath synchrony. The thickness of the diaphragm was measured by ultrasound in both groups at the beginning of the study enrollment (hour 0), after 24 hours and after 48 hours. The obtained data were then statistically analyzed and both groups were compared.

The modified procedure of electrode insertion using ultrasound navigation has proven to be suitable and safe with high success rate. The PEPNS System was able to capture both the left and right phrenic nerve at voltages within defined limits with excellent patients' tolerance. The analyzis of measured diaphragm thickness demonstrate that in contrast to the non-interventional group, where the thickness of the diaphragm decreases during both 24 and 48 hours, stimulation of the diaphragm via the phrenic nerve leads to its significant increase.

The study demonstrated the ability to safely and successfully place stimulation electrodes and proofed feasibility of using this approach to synchronize electrical stimulation with patient's inspiration while maintaining work of breathing within defined limits which led to a significant increase in its thickness as the main determinant of muscle strength required for spontaneous ventilation and weaning from mechanical ventilation. Percutaneous electrical phrenic nerve stimulation offers a future option for preventing or even treating ventilator induced diaphragm dysfunction.

Abstrakt

Jedním z hlavních problémů kriticky nemocných pacientů vyžadujících umělou plicní ventilaci je rychle progredující atrofie bránice vedoucí k její dysfunkci. Předpokládá se, že v tomto procesu hraje hlavní roli jednotka zvaná ventilátorem indukovaná dysfunkce bránice. Kontrakce bránice pomocí stimulace bráničních nervů by mohla této atrofii zabránit nebo ji dokonce léčit. Předmětem této práce je zjistit proveditelnost dočasné, perkutánní, elektrické stimulace bráničního nervu a ověřit její efekt na změnu šíře bránice.

Do studie bylo zařazeno 12 pacientů v intervenční skupině, z nichž 10 bylo stimulováno oboustranně a 10 pacientů v kontrolní skupině. Stimulace byla aplikována v šesti dvouhodinových sezeních v osmihodinových intervalech po dobu 48 hodin. Sledovaná data zahrnovala techniku zavedení elektrod a její úspěšnost, parametry ventilace, vitální funkce, dechovou práci, parametry elektrické stimulace a synchronizaci stimulace s pacientovým dechovým úsilím. Tloušťka bránice byla měřena ultrazvukem v obou skupinách na začátku experimentu, tj. v 0 hodině, po 24 a po 48 hodinách. Získaná data byla poté statisticky zpracována a obě skupiny porovnány.

Modifikovaný postup inzerce elektrod pomocí ultrazvukové navigace se ukázal jako vhodný a bezpečný s vysokou úspěšností zavedení. Systém PEPNS dokázal stimulovat jak levý, tak i pravý brániční nerv při použití stimulačních proudů v definovaných mezích s vynikající tolerancí pacientů. Analýza měřené tloušťky bránice ukazala, že na rozdíl od neintervenční skupiny, kde se tloušťka bránice zmenšila během 24 i 48 hodin, vede stimulace bránice k jejímu významnému nárůstu.

Studie prokázala nejen schopnost bezpečně a úspěšně zavést stimulační elektrody, ale i celkovou použitelnost tohoto přístupu k synchronizaci elektrické stimulace s inspiračním úsilím pacienta při zachování dechové práce v definovaných mezích, což vedlo k významnému nárůstu její tloušťky jako hlavní determinanty svalové síly nutné pro spontánní ventilaci při odvykání pacienta od umělé plicní ventilace. Perkutánní elektrická stimulace bráničních nervů nabízí budoucí možnost prevence i léčby ventilátorem indukované dysfunkce bránice.

Table of content

List of symbols and abbreviations

ACV	Assist-control Ventilation
AMI	Acute Myocardial Infarction
ASM	Anterior scalene muscle
ASB	Assisted Spontaneous Breathing
BMI	Body mass index
CA	Carotid artery
CMAP	Compound Muscle Action Potential
CPAP	Continuos Positive Airway Pressure
CPOT	Critical Care Pain Observation Tool
EC	Ethics Committee
ERS	European Respiratory Society
Fr	The French size is three times the diameter in millimeters
ICD	Implantabile Cardioverter Defibrilator
ICU	Intensive care unit
IJV	Internal jugular vein
LOS	Length of stay
LVEF	Left ventricular ejection fraction
MSM	Medial scalene muscle
MV	Mechanical ventilation
PC-SIMV	Pressure Control - SIMV
PEEP	Positive End Expiratory Pressure
PEPNS	Percutaneous Electrical Phrenic Nerve Stimulation
PRVC	Pressure Regulated Volume Control
PSV	Pressure Support Ventilation
RASS	Richmond Agitation and Sedation Scale

SD	Standard Deviation
SBT	Spontaneous Breathing Trial
SIMV	Synchronized Intermittent Mandatory Ventilation
SCM	Sternocleidomastoid muscle
TPNS	Transvenous phrenic nerve stimulation
TTVDP	Temporary transvenous diaphragm pacing
US	Utrasound
VC-SIMV	Volume Control - SIMV
VIDD	Ventilator-induced Diaphragm Dysfunction
WOB	Work of breathing

Definitions

Assist Breath

A breath initiated by the patient but terminated by the ventilator. PRVC-SIMV, VC-SIMV and PC-SIMV could be assist breaths if initiated by the patient.

Capture

Diaphragmatic movement as a direct consequence of electrical phrenic nerve stimulation.

Difficult to Wean

According to the European Respiratory Society (ERS) Task Force, difficult-to-wean patients are those requiring more than 7 days of weaning after the first spontaneous breathing trial (SBT) [1]. SBT assesses the patient's ability to breathe while receiving minimal or no ventilator support [2].

Mandatory Breath

A breath initiated and terminated by the ventilator. PRVC-SIMV, VC-SIMV and PC-SIMV could be mandatory breaths if initiated by the ventilator.

Spontaneous Breath

A breath initiated and terminated by the patient. PSV, ASB and CPAP are spontaneous breaths.

Weaning failure

It is defined as either the failure of SBT or the need for reintubation within 48 hours following extubation [3, 4].

Work of Breathing

The energy expended to inhale a breathing gas. It is usually expressed as work per unit volume (usually joules/litre).

1 Introduction

The following thesis deals with the feasibility of a system developed to stimulate the diaphragm using electrodes inserted transcutaneously near the phrenic nerve in patients on mechanical ventilation. It describes the current state of the art, the main aims of the study, describes the experimental part with individual results and puts them together for a final discussion with a proposal for further research steps in this field to put the system into clinical practice.

Mechanical ventilation (MV) is one of the most common organ support routinely administered in intensive care units (ICUs) with proportion of patients required MV up to 40% [5-7]. The time required to wean patients from MV is directly proportional to ICU length of stay (LOS) which increases morbidity, mortality, and healthcare costs [8-10]. Almost half of the patients have difficult or prolonged weaning from MV [11]. Mechanical ventilation has a number of side effects such as infections called ventilator-associated pneumonia [12], lung injury [13, 14], and a recently widely studied pathophysiological unit called ventilator-induced diaphragmatic dysfunction (VIDD) [15, 16].

General muscle weakness is a common problem in patients hospitalized in ICUs [17]. While wasting striated muscle of the limbs is rather a gradual process with development over weeks [18], diaphragmatic atrophy and dysfunction appear more rapidly [19, 20]. VIDD is thought to be a complex process caused not only by muscle inactivity during MV, but associated with many other risk factors such as malnutrition [21], sepsis or other systemic infections [22], and a number of intravenous drugs commonly used in intensive care such as neuromuscular blockers [23] and/or glucocorticoids [24]. Diaphragmatic muscle thinning is an essential part of VIDD [25, 26]. Ventilator induced diaphragm dysfunction is considered a major determinant of the ability to successfully wean patients from mechanical ventilation [27], with delayed liberation from MV and longer ICU stays with all of its consequences [28]. More than 50% reduction in cross-sectional areas of diaphragm myofibers quickly develops, between 18-69 hours, after onset of mechanical ventilation [25]. This leeds to reduction of diaphragmatic force and patient’s ability to wean from the ventilator [29].

It has been hypothesized that electrically pacing the diaphragm during mechanical ventilation may theoretically prevent VIDD or at least reduce diaphragm dysfunction resulting in faster weaning and shortens the time on mechanical ventilation [30, 31].

The phrenic nerve, as a main inspiratory nerve, activates contraction of the diaphragm that expands the lungs and thereby draws air into them [32]. To evaluate the effect of phrenic nerve pacing on VIDD, animal studies have been performed and demonstrated that the diaphragm strength is maintained in paced animals versus non-paced [33-35]. Thus, it is assumed that pacing the diaphragm by stimulating the phrenic nerve could be an ideal solution to the development of VIDD by maintaining the muscular strength of the diaphragm and thus its function and lead to a reduction in time spent on MV [36-38]. The subject of this thesis was to verify that this approach is safe and usable in the human population.

2 State of the Art

Surgically implanted systems for pacing the phrenic nerves and diaphragm are used for patients with amyotrophic lateral sclerosis or patients with high-level spinal cord injury for years [39-41], but this high specific, invasive, surgical procedure is not suitable for critically ill patients in common intesive care unit settings.

Less invasive aproach of diaphagm stimulation could be done via transvenous phrenic nerve stimulation (TPNS) system [42]. The phrenic nerve passes along the wall of the thoracic cavity adjacent to several veins, which allows transvenous electrode stimulation of the nerve. To stimulate phrenic nerve within the thoracic cavity, a transvenous approach is anatomically feasible [43]. Transvenous phrenic stimulation which could be achived in humans on a permanent basis to treat central sleep apnea [44]. Although this system is referred to as minimally invasive, it still requires subcutaneous implantation of the stimulator with all of its possible consequences. A promising approach in this field seems to be the newly investigated pacing system using a central venous catheter equipped with pacing poles [45]. The Lungpacer RESCUE 2 study tests if temporary transvenous diaphragm pacing (TTVDP) used in ICU patients who are difficult to wean from MV will improve the weaning outcome. Although the study is still ongoing and the preliminary results are not yet known, after studying the clinical trial protocol, I have a few critical comments on this method. Transvenous stimulation with a central venous catheter inserted through the left subclavian vein seems to be an excelent idea as almost all critically ill patients usually require this type of venous access to the vascular system, however the catheter size used in this study is relatively large-9.5 French and allows only one lumen for administration of fluids and drugs. However, most critically ill patients require the use of a multi–lumen catheter, not only for use of a variety of drugs during the day, but also for drugs where unwanted bolus administration can endanger the patient's life as it is in a case of catecholamines. Therefore, these patients will almost always require to insert another central venous catheter. The period of inserted catheter with stimulation in a study protocol is planned for 30 days. In the case of transcutaneously left „artificial material" in a vein, the risk of blood flow infection increases enormously for such a long time. If this occurs and leads to the catheter extraction, the pacing session ends. Catheter insertion/reinsertion itself is associated with all potential risks associated with central venous catheterization.

However, these are just my thoughts, for the final conclusions we have to wait for the evaluation of the study.

Another possibility currently being explored is a use of transcutaneous magnetic stimulation [46]. Bilateral phrenic nerve stimulation is achieved using the repetitive cervical magnetic stimulation approach on the neck. Although this would be a suitable solution because magnetic stimulation is not painful, this approach has so far only been studied in healthy, spontaneously ventilating volunteers and its feasibility among critically ill patients on MV in unknown. In addition, the stimulation procedure in this form seems a bit cumbersome.

Transcutaneous electrical stimulation of phrenic nerves is often used for diagnostic purposes in humans [47]. Commonly, stimulation is performed with hand–held electrodes, however, these are unsuitable for therapeutic purposes requiring repeated stimulations where recruitment of rib cage and neck muscles may shift the probes in relation to the nerves [48]. Moreover, in patients with higher body mass index (BMI), stimulation is possible only at the expense of higher currents that would require deepening of the patient's sedation [49].

Stimdia Medical Inc., has developed a novel Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System, which uses trascutaneous stimulation lead insertion close to the phrenic nerve in the neck region using utrasound navigation. It is minimally invasive aproach enabling temporary pacing of phrenic nerve for stimulation of diaphragm. The PEPNS System has been evaluated extensively in several animal studies [50] and the system pre-clinical testing demonstrated that the device is safe and effective for its intended use. The feasibility of this system in human population is unknown and is the subject of this study. The Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System is a device used in conjunction with a standard respiratory ventilator to stimulate the patient diaphragm to exert effort when the patient is on mechanical ventilation, regardless on ventilation mode used. The wiring diagram of the PEPNS system is shown in Fig. 1. Stimulation is delivered during inspiration. The PEPNS system recognizes the onset of inspiration using the wye flow sensor when inspired flow exceeds a defined flow velocity and bilaterally stimulates the phrenic nerves, using deployed multipolar leads. Stimulation is ceased when the patient starts to exhaling as determined again by the flow sensor.

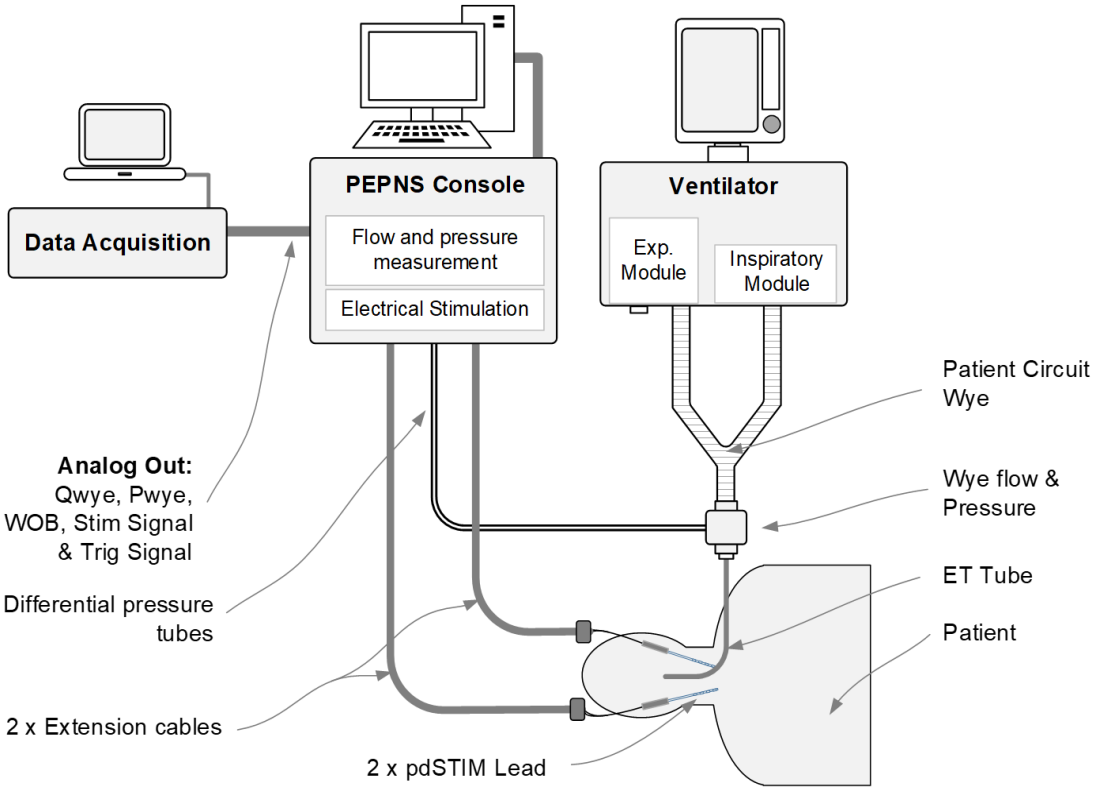

Figure 1. PEPNS system [51]

PEPNS Console setup - stimulation leads (left and right) inserted near the phrenic nerves in the neck area and Wye flow and pressure sensors connected to console. Data acquisition system connected to PEPNS console.

The PEPNS System delivers stimulation waveforms in terms of the set current and the resultant voltage is a function of the resistance the current driver experiences. This voltage is limited to a maximum of 12.5 volts. Bipolar constant current generator is used to follow the desired current waveform output by the waveform generator, which is a commercially available medical device used for electrical stimulation of peripheral nerves. Time duration settings of pulses ranges from 100 to 300 μs, in rate 5 to 25 Hz and current setting from 0.5 to 25 mA.

The physician-anesthetist has been trying to avoid the phrenic nerve, so far, because its unwanted blockade during the use of regional anesthesia techniques, specifically when applying a local anesthetic close to the brachial plexus, could lead to acute respiratory insufficiency, especially in patients with chronic respiratory disease [52]. Now, in a case

of the intended stimulation of the phrenic nerve for active respiratory rehabilitation, which could theoretically reduce the time required for mechanical ventilation, we are trying not only to visualize the phrenic nerve, but even to insert an electrode close to it to allow stimulation and thereby active diaphragm muscle contraction, even in a fully sedated patient.

3 Aims of the study

3.1 Safe and succesful eletrode insertion

The goal is to find a way, how to safely and easily place the three-french, flexibile, multipolar, stimulation electrode using the ultrasound navigation in the neck region with successful pacing of the phrenic nerve. In order to insert electrodes to phrenic nerves it is necessary to first verify the feasibility of the insertion set, then to orientate the ultrasound guidance and to test the overall proposed insertion technique. Last but not least, to find out how to easily and safely fix the electrodes to the skin.

3.2 Ability to contract the diaphagm by stimulation of the phrenic nerve

After solving the electrode insertion technique, it is necessary to verify that we are able to stimulate the diaphragm. Successful pacing of the phrenic nerve means the diaphragm contraction in synchrony with mechanical ventilation without collateral brachial plexus pacing. The goal is defined as the ability to capture of the left and/or right phrenic nerve in > 80% of patients with an output parameter of < 10.5 volts.

3.3 Patient's stimulation tolerance and safety endpoints

The following goals of the thesis focus on the interaction between the stimulation system and the patient. First, the ability to synchronize electrical stimulation with inspiration to mobilize the diaphragm and keep WOB (Work of Breathing) between 0.2 and 2.0 joules/L for 80% of stimulated breaths. Second, to assess the interaction between the PEPNS system and the patient's tolerance, and if possible, to determine level of the „painless" pacing current required to successfull stimulate the nerve. Due to the close proximity of the vagus nerve, it is essential to determine if the electrical stimulation has any impact on changing the patient's echocardiogram. The safety of the procedure will be monitored and percentage of patients who experience serious device/procedure-related adverse events will be reported.

3.4 Influence of diaphragm contraction on its thickness

The final aim of the thesis is to verify whether the diaphragm contraction as a response to phrenic nerve stimulation has any impact on a change in its thickness compared to nonstimulated, control group.

4 Experimental part of a research

This chapter is divided into several separate chapters with a description, methodology, results and resulting conclusions, which will be summarized in the final discussion section.

This thesis describes the first-in-human, multi-center (Military University Hospital in Prague, Czech Republic and Beaumont Hospital in Dublin, Ireland), non-blinded, non-randomized study to evaluate the safety and performance of the PEPNS System in hospitalized ICU patients requiring MV. A maximum of 20 subjects were planed to be enrolled in the study at two sites with up to 10 subjects per site.

All study documentation was reviewed and approved by the appropriate regulatory bodies, at each of the investigational sites, including the Ethics Committees (App. A) and SÚKL (App. B), prior to subject screening and enrollment. This was followed by electrode insertion in patients who met inclusion/exclusion criteria, listed in Tab. 1, and authorized representative (usually family member) was informed in detail about the course of the study, including all risks and potential benefits and was willing to sign informed consent (App. C). The study was registered with ClinicalTrials.gov (App. D).

Table 1. List of inclusion/exclusion criteria

Inclusion criteria
18 years or older (Adult)
Male or Female
Able and willing to give informed consent or whose legally authorized representative is able and willing to give informed consent
Patient who in the opinion of the admitting consultant/intensivist is likely to be ventilated for > 48 hours from time of recruitment

Exclusion criteria
Subject has a left ventricular ejection fraction (LVEF) < 20%.
Subject unlikely to survive 72 hours due to coexisting medical conditions.
Subject has an implanted pulse generator or implanted electronic device: Examples: Cardiac pacemaker, Defibrillator, ICD, Watchman, Vagus nerve stimulator, Spinal cord stimulator, Gastric stimulator or Diaphragmatic stimulator.

Subject has experienced an Acute Myocardial Infarction (AMI) within 72 hours prior to this screening or patient is on high dose inotropic support or patient is deemed to be in cardiogenic shock.

Subject has significant bleeding diathesis, or is at risk of significant hemorrhage, patient is receiving full dose systemic anticoagulation.

Subject has a known or suspected phrenic nerve paralysis or neuromuscular or inflammatory muscle diseases where the diaphragm itself may not be functional.

Subject has an active systemic infection or local infection at or around the insertion site. Patient is neutropenic or has signs of significant immunocompromise.

Subject is known or suspected to be pregnant or is lactating.

Subject will be unavailable for, or is unwilling to comply with, follow up requirements of the protocol.

Subject is currently enrolled or is expected to be enrolled in any other study of an investigational drug or device who has received treatment under that protocol with the investigational product during the 30 days prior to screening.

Subject has undergone a surgery or interventional procedure within the neck region aside from placement of an internal jugular (IJ) vein catheter.

Subject has been diagnosed and has been treated for neck cancer within the past 5 years.

Subject is known to have a demonstrated intra cardiac thrombus on echocardiography.

Subject has uncontrolled hyperthyroidism, hypertension.

Subject has had any cerebral ischemic event in the 6–month.

4.1 Safe and succesful eletrode insertion

Introduction

The phrenic nerve descends obliquely with the internal jugular vein under the sternocleidomastoid muscle (SCM) across the anterior scalene muscle (ASM). The ideal position of the electrode appeared logically parallel to the assumed course of the phenic nerve "line A" as shown in Fig. 2 and 3.

The lead insertion point should be clinically determined by anatomical landmarks and review by the ultrasound images with the goal of placing the lead electrode poles on both sides of the phrenic nerve while also taking into account respective anatomical landmarks.

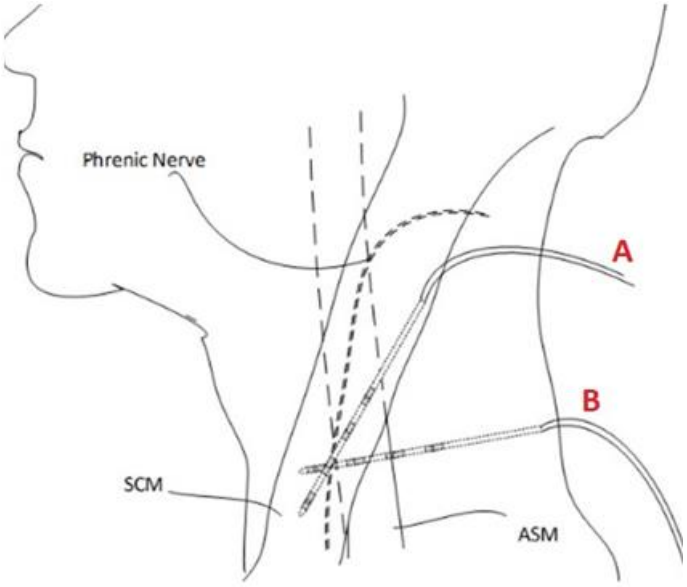

Figure 2. Location of phrenic nerve with possible insertion lines A and B [50].

Intended „ideal line A“ – vertical with the introduction of an electrode under the SCM parallel to the presumed curse of the phrenic nerve. Alternative „line B“ – horizontal with the introduction of the electrode between the SCM and the ASM, crossing the presumed course of phrenic nerve.

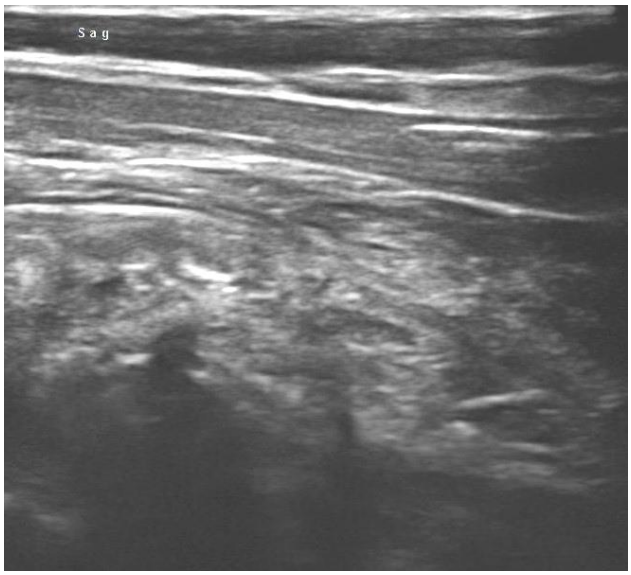

Figure 3. Ultrasoud view of A-line
(linear probe, 10 MHz)

Methods/Procedure

Once the anatomical landmarks associated with the phrenic nerves are identified, preparation of the access area with desinfection liquid follows with placement of sterile drape over the access site. Using a scalpel to make a small 1 to 2 mm skin incision at the designated access site. For deployment an electrode the sponsor decided to use commercial set using Tuohy echogenic, blind tip needle (StimuLong Sono II, PAJUNK, Germany) commonly used in regional anaesthesia techniques (Fig. 4).

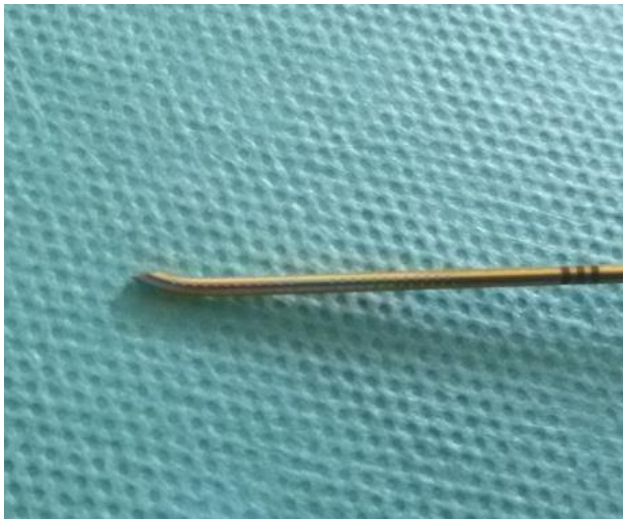

Figure 4. Tuohy, 18G, needle blind tip.

Subsequently, with utrasound (US) navigation using "in-plane" technique (long axis view of the probe, out-of-plane means short axis view to the course of the probe), Tuohy needle is inserted close to the curse of the phrenic nerve and connected to the nerve stimulator. After verifying the correct position of the needle by visible contractions of the diaphragm, disconnection the needle from the stimulator and insertion the stimulation electrode using through-the-needle technique is followed. This is followed by removing the needle and leaving the electrode in place. In order to avoid unwanted pulling of the flexible electrode together with the Tuohy needle, a tool called Lead Deployment Device (LDD) has been developed. The LDD scheme is shown in Fig. 5. It features a slide clamp on the side that helps to keep the lead in position. After connecting the multipolar electrode to the PEPNS console and verifying the success of the stimulation, the injection site cleaned and the electrode is fixed to the skin using tissue glue and transparent foil. The complete, assembled lead insertion set is shown in Fig. 6.

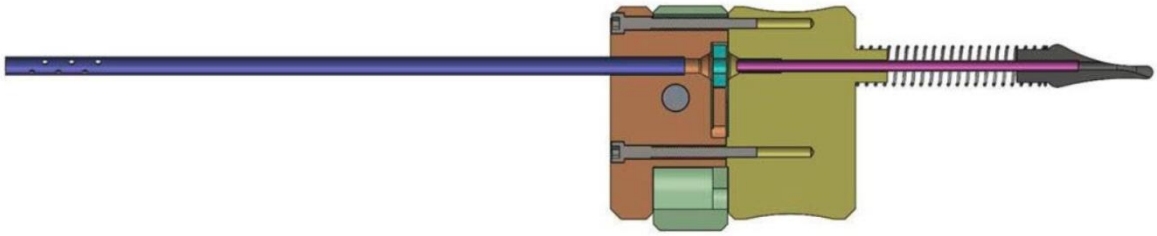

Figure 5. Lead Deployment Device [50].

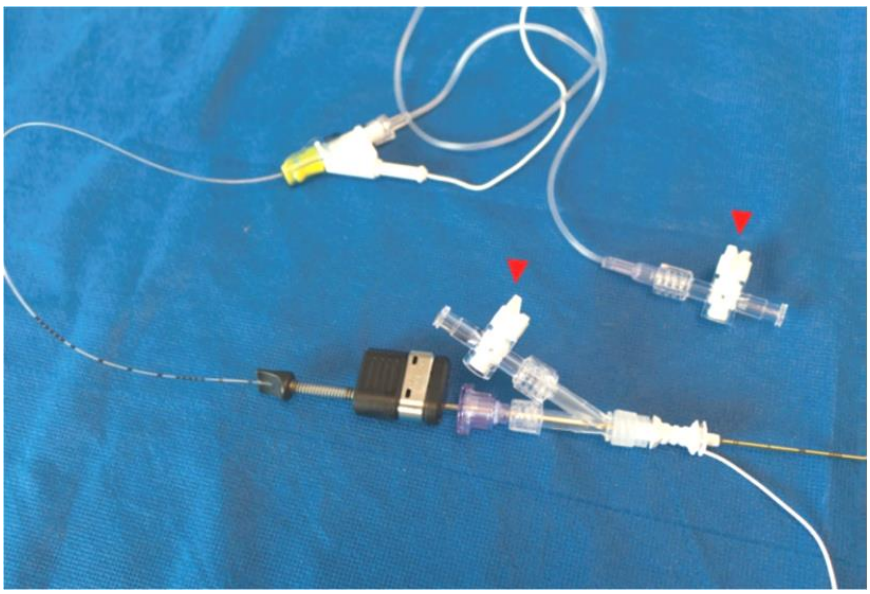

Figure 6. Complete set for lead insertion [50].

After the first two bilaterally stimulated patients, I have encountered several problems. To complete the whole insertion set, due to a lot of parts, took quite a long time. Compelling nerve visualization difficult, needle insertion in the theoretically proposed A-line almost impossible, as well as an attempt to directly stimulate the phrenic nerve during insertion failed. The use of a B-line (Fig. 2 and 7), where the "usual US view" for physicians well known from regional anesthesia, forces the dorsal–ventral insertion, which unfortunately became difficult due to the length of the entire set. Finally, an electrode with difficulty was introduced at 35 and 60 minutes to the left and right respectively, with the necessity of repeated insertion on the right side. This approach was eventually abandoned in the other patients.

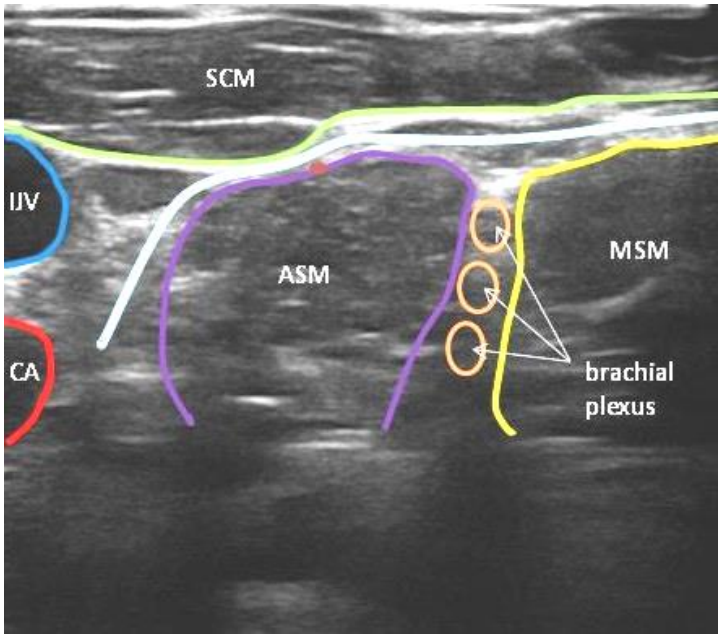

Figure 7. Ultrasound view of B-line

(linear probe, 10 MHz)

Red dot – phrenic nerve, SCM – sternocleidomastoid muscle, ASM – anterior scalene muscle, MSM – medial scalene muscle, IJV – internal jugular vein, CA – carotid artery, Blue line – position of electrode).

To improve the usability of the procedure, I have abandoned the need for direct visualization and nerve stimulation. Despite studies supporting the claim of simplicity of visualization of the phrenic nerve, with more than 93% success rate [53], I was not able to confirm this in our patient group. In addition, good visualization, even with successful nerve stimulation during insertion, still does not guarantee an optimal

placement of the stimulation electrode. Unlike the insertion of a catheter for continuous application of local anesthetics in the case of regional analgesia, where the plexus or nerve is stimulated and the tip of the inserted catheter is left at the best stimulation response, the stimulation electrode design can lead to a substantial migration from the optimal location of the electrode and the inability to effectively stimulate the phrenic nerve. In addition, when choosing the initially intended A-line, the physician loses the orientation between the various structures well known from routine use of ultrasound during interscalene blockade (Fig. 2 versus Fig. 7).

Using a linear ultrasound probe (in our site - Ultrasonix, Linear probe 14-5, in the 10 MHz setting), I begun by locating the subclavian artery midclavicularly where lateral brachial plexus divisions are located, then pointed the probe cranially up to approximately 5-6 cervical vertebrae level. Thus, I offered a standard US projection during interscalene blockade (Fig. 7). It is well known that the phrenic nerve at this point runs under the sternocleidomastoid muscle and over the anterior scalene muscle. Then, laterally from the ultrasound probe, I made an injection (I also decided not to make an incision for a higher risk of bleeding around the insertion site) and pointed the Tuohy needle by in-plane technique (Fig. 8) with bolus administration of fluid (up to 10 ml of 0,9% saline) – called hydrodissection technique (Fig. 9, 10), which makes a gap between the subcutaneous structures to create a space for safe entry of the needle and thereby reduce the risk of unwanted nerve injury, up to the place between the internal jugular vein (IJV) and carotid artery (CA). At this point I applied another fluid bolus of 3–5 ml followed by insertion of the stimulation electrode itself. Due to the concave shape of the Tuohy tip (Fig. 4) and the shape of the electrode ending, despite the use of LDD, the insertion of the electrode remained difficult, in two cases with dislocation during removal of the needle with the necessity of reinsertion.

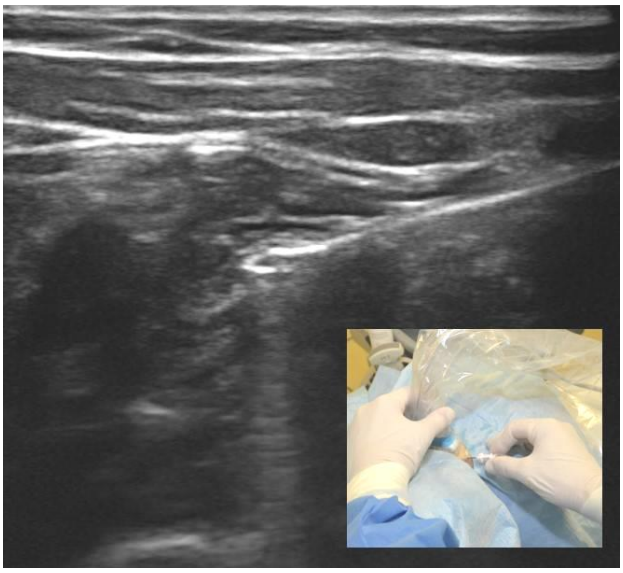

Figure 8. Visualization of the needle end using an in-plane technique.

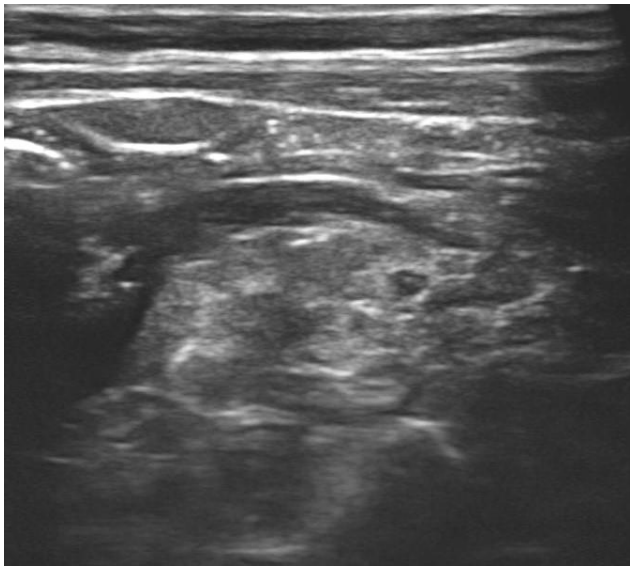

Figure 9. Hydrodissection with 0,9% saline between SCM and ASM.

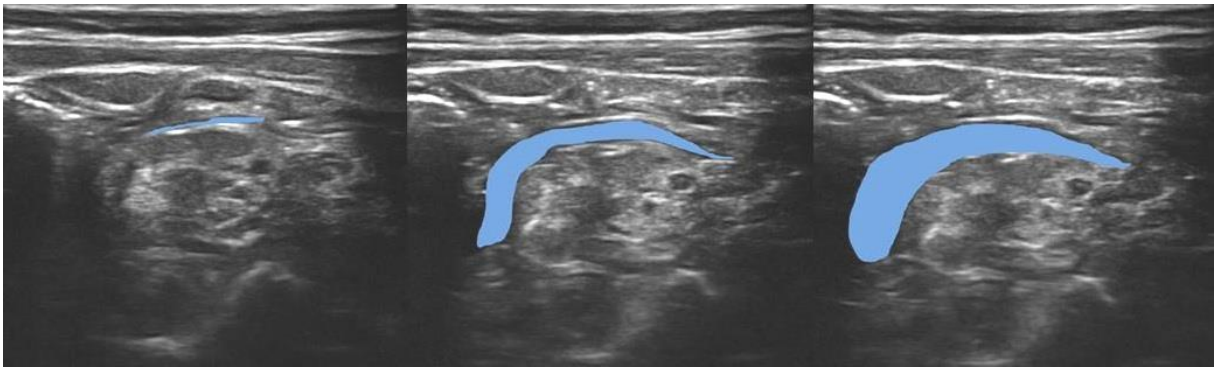

Figure 10. Highlighting the use of hydrodissection over time.

In the next step in the following patients, therefore, I have left using LDD and the rest of the originally intended set (Fig.6). This modification, shown in Fig. 11-13, i.e. Tuohy needle connected only to the extension tube with a syringe for the use of hydrodissection and LDD replaced by a T-piece connector, a device used to insert the epidural catheter, made much easier and faster to assemble the whole set and led to more agile handling when advertising a Tuohy needle to the desired location (Fig. 14, 15). All of this not only speeded up the whole procedure significantly, but also got cheaper.

Figure 11. Modified insertion set.

Figure 12. T-piece connector.

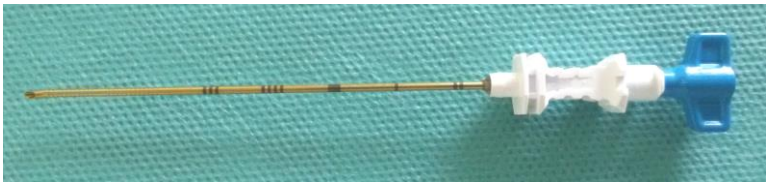

Figure 13. T-piece connected to Pajunk needle**.**

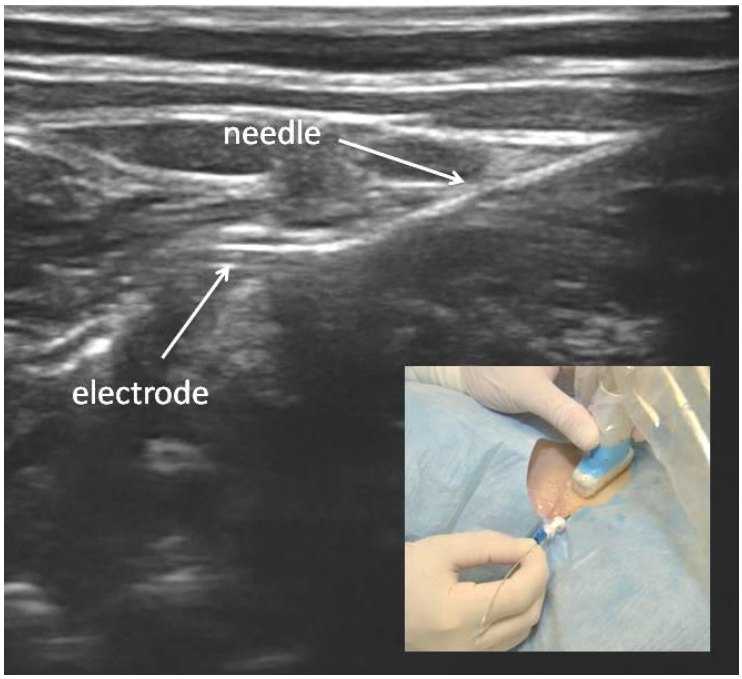

Figure 14. Insertion of the lead.

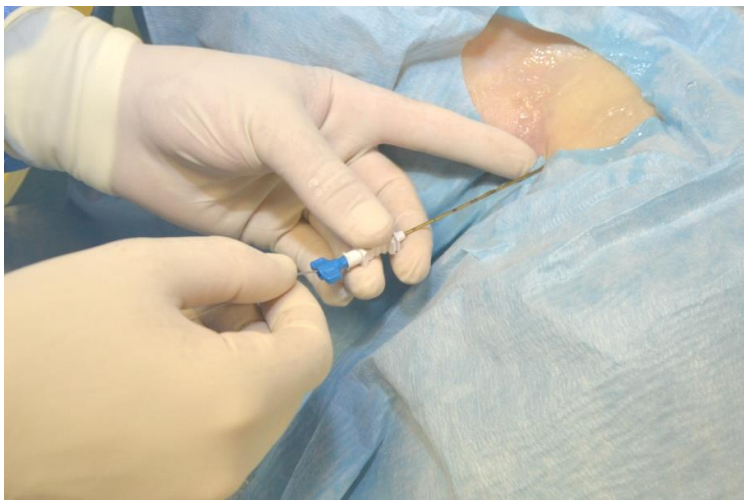

Figure 15. Extraction of Tuohy needle with leaving lead in place.

The stimulation lead was inserted deeper than originally intended to create a reserve for eventual withdrawal during needle extraction. The 3Fr lead design shown in Fig. 16, consists of four stimulable portions allows pacing pulses variable between any portions.

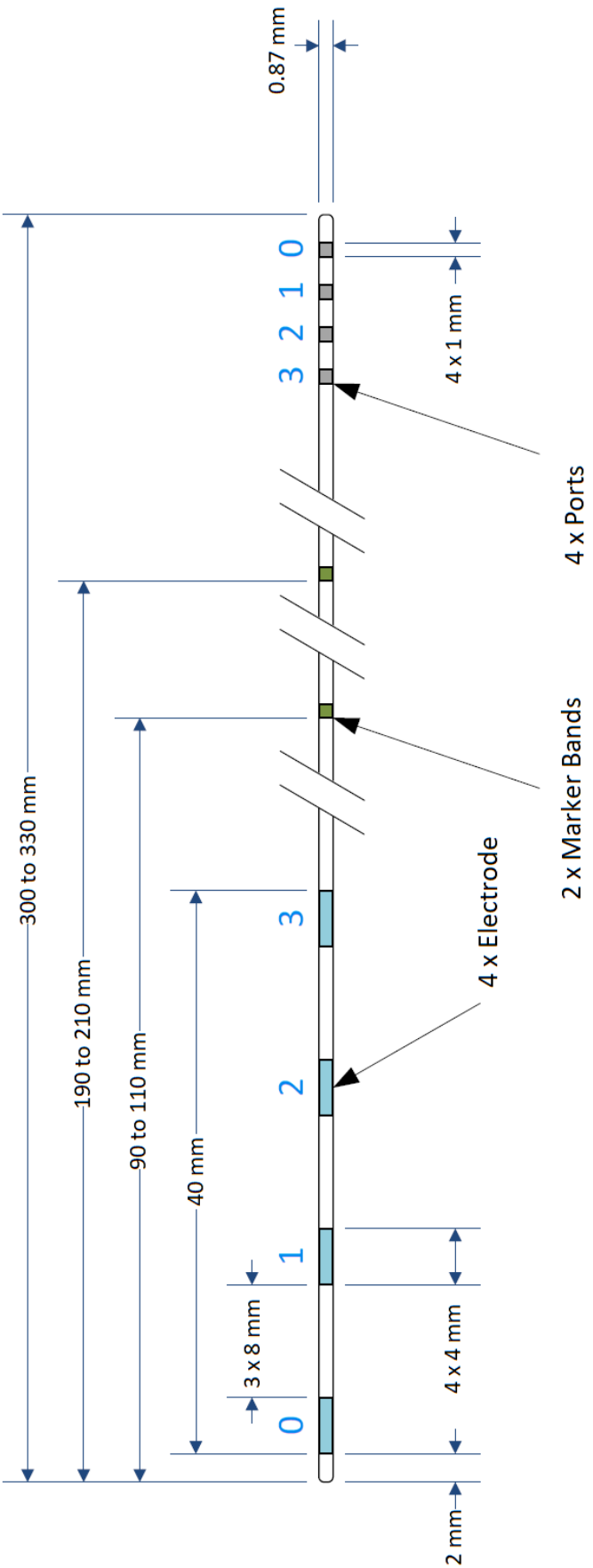

Figure 16. Diagram of the four pole eletrode [50].

After connecting to the PEPNS console, I verified the correctness of the lead position by starting stimulation between the most proximal portions, i.e. 2-3, and gradually extracted the lead out until a stimulatory response was obtained by contracting the brachial plexus muscles. At this point, I left the lead in place and started stimulating between distal points 0-1 or 1-2. After receiving a response to stimulation of the diaphragm contractions, I left the electrode in place and fixed. Due to the abandonment of the incision at the beginning of insertion, I didn´t need to use tissue glue for treating the insertion site and fixed the catheter with a grip-lock system (commonly used for epidural catheter fixation), then I looped and fixed the lead with transparent foil (3M Tegaderm^{TM}) which enable monitor the injection site for following days (Fig.17). In contrast to the fixation of the epidural catheter, where the catheter passes through the relatively rigid structures of the intervertebral ligaments, maintaining the stimulation lead in place for several days at the site of generally soft structures, in the neck area, was real challange. The final position of the two electrodes imaged by the chest radiograph is shown in Fig. 18.

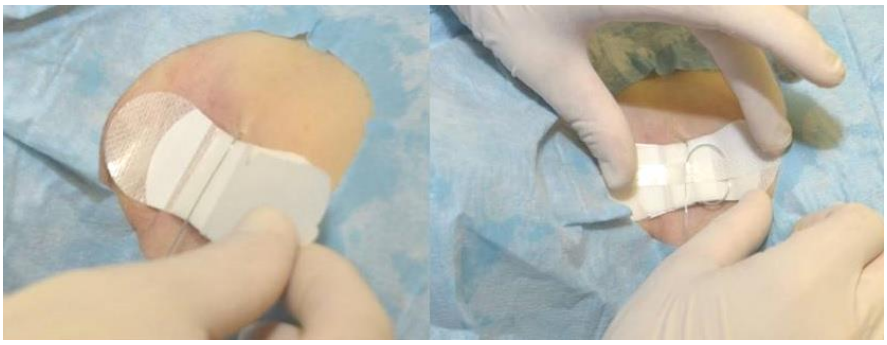

Figure 17. Fixation of the lead using Grip-lock system.

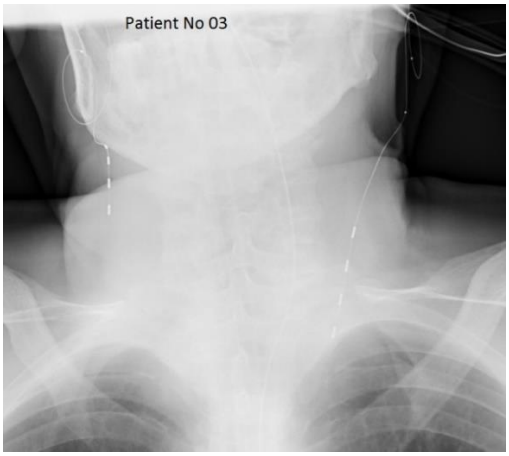

Figure 18. Chest radiograph shows the position of bilateral electrodes in the neck area. An alternative way how to verify the position. Unfortunately not usable for clinical use.

Results

The lead insertion procedure was examined only subjectively and was very much dependent on the anatomical conditions of the particular patient, especially on the neck circumference. Not suprisingly, as the width of neck area increased and the deeper landmark structures used to guide the needle insertion were, the difficulty of deployment rapidly increased.

Time taken for lead insertion was also examined including the time to view the anatomy of the neck (Tab.2, Fig.19). As the operators became more familiar with the procedure, the lead insertion times decreased with less puncture attempts. It is interesting that left lead insertion has alway been easier than the right side, which can be explaned by a more ergonomic approach from the left side for right-handend operators.

Table 2. Time of lead insertion and insertion device used

Patient	Right phrenic nerve (min)	No of attempts	Left phrenic nerve (min)	No of attempts	Insertion device
P01S02	not inserted	not inserted	80	2	Pajunk + LDD
P02S02	not inserted	not inserted	80	2	Pajunk + LDD
P03S01	62	2	54	1	Pajunk + LDD
P04S01	30	1	33	3	Pajunk + LDD
P05S02	119	2	81	2	Pajunk + LDD
P06S02	47	1	31	2	Pajunk + T-piece
P07S02	22	1	13	1	Pajunk + T-piece
P08S01	35	1	26	1	Pajunk + T-piece
P09S02	60	1	30	1	Pajunk + T-piece
P10S02	27	1	20	1	Pajunk + T-piece
P11S01	19	1	11	1	Pajunk + T-piece
P12S01	46	2	11	1	Pajunk + T-piece

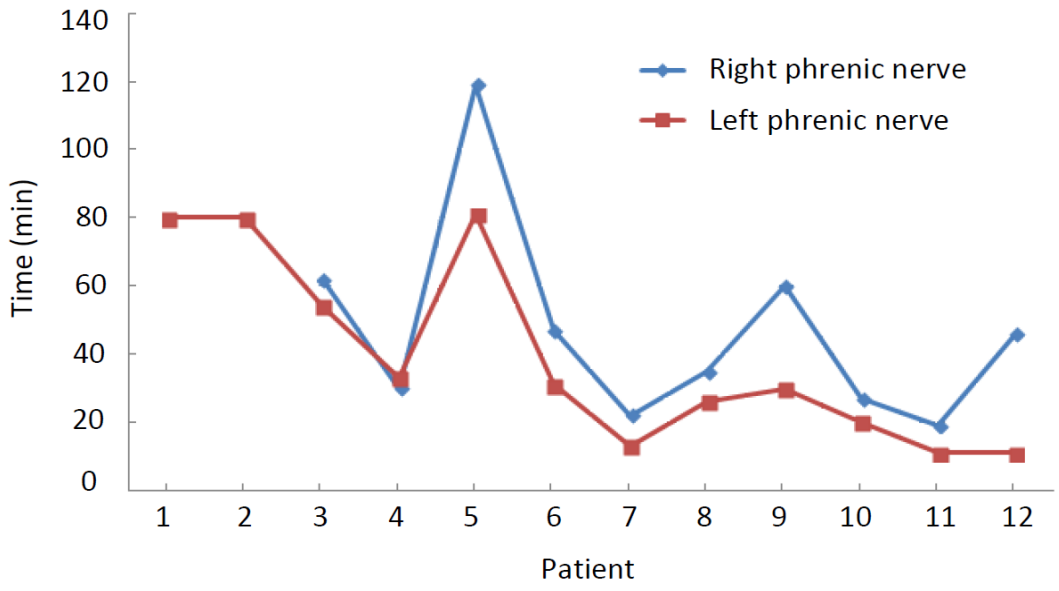

Figure 19. Twelve right and ten left lead insertion times

Discussion

Improved ultrasonographic orientation in the neck area and using the insertion approach in „B-line“ has been shown to be appropriate and clear in all enrolled patients. Despite the impossibility of direct visualization of the phrenic nerve, I was able to insert the electrode using hydrodissection technique to the desired location without any signs of a nerve injury. Since I have never visualized the nerve, I did not have to try to stimulate the nerve during lead insertion. Due to the modification of the insertion set, I was always able to successfully insert the electrode in less time and without the need for repeated advertising. After choosing the puncture technique, instead of incision, I did not have to use a tissue glue in any way and fixation with the set Grip-lock + loop + tegaderm proved to be usable. In five bilaterally stimulated patients in our department, i.e. ten leads inserted, during the whole therapy (48 hours duration), I did not experience any significant dislocation of the stimulation lead even during standard patient 3–hour, regular repositioning. In addition, the last patient enrolled was fully conscious during the pacing periods, was able to sit in a chair and move freely during rehabilitation with excellent pacing tolerance.

Conclusion

By modifying the insertion set and adapting the ultrasound navigation in the neck area, it was verified that the electrodes could be safely and relatively quickly inserted. The proposed system of fixation of the electrodes to the skin does not restrict the normal nursing care of the patient and does not lead to their unintentional dislocation.

4.2 Ability to contract the diaphagm by stimulation of the phrenic nerve

Introduction

Once the issue of electrode insertion was resolved, it was necessary to determine whether stimulation of the phrenic nerves leads to contraction of the diaphragm. Successful pacing of the phrenic nerve was defined as diaphragm contraction without collateral brachial plexus pacing. The goal was the ability to capture of the left and/or right phrenic nerve in > 80% of stimulated patients with an output parameter of < 10.5 volts.

Methods

After the lead placement with succesful contraction of a diphragm, electrical stimulation parameters were recorded (detail in App.E). The custom PEPNS Console output balanced current biphasic pulses (Fig.20) bilaterally at the user specified current level with the resultant voltage generated being a function of the resistance and impedance of the tissue between the electrodes. This „compliace“ voltage was limited in hardvare to 12.5 volts. Configuration parametres set on pulse generator with pulse duration time with a range of 100 to 300 μs, pulse frequency has setting range of 5-25 Hz during operation in increments of 1 Hz and maximum current left/right with a range of 0.5 to 25 mA. Stimulation parametres in terms of pulse width, current and frequency were set on PEPNS console based upon achieving a desired range of work of breathing. During therapy the PEPNS console was connected to disposable multi pole, platinum iridium electrode leads which have four poles equally spaced along the lead facilitating a number of stimulation combinations between the various electrodes and allow easy optimization of electrode placement and enhances the user’s ability to maintain stimulation if the patient is moved. The lead is symmetrical in design and is of consistent diameter over its entire length (Fig.16).

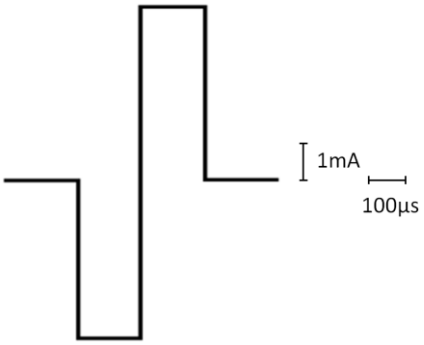

Figure 20. The electric current pulse shape.

Results

Twelve subjects were enrolled in the study with the initial two patients having leads placed and assessed on the left side only. Five patients were stimulated bilaterally in both investigation sites, so in total 22 leads were succesfully inserted.

First two pilot paties with left side stimulation only (P01S02 and P02S02) were excluded from analysis. The final analysis (10 bilaterally stimulated patients) of capture of the left and/or right phrenic nerve in > 80% of stimulated breaths with an output parameter of less than 10.5 volts using a generalized linear mixed model yielded a capture rate of 96.56%, with a 1-sided lower 98.75% confidence bound of 93.15%. The lower confidence bound was greater than the performance goal of 80%, therefore the null hypothesis was rejected and this endpoint was considered met (Tab.3). The combined tissue and lead resistance encountered by the leads varied between 723 ohms on the right lead to 1079 ohms on the left lead. This implies that the maximum stimulation current the therapy can deliver without exceeding 10.5 volts in 14.5 mA (Fig. 21).

Table 3: Proportion of Phrenic Nerve Capture

Capture Rate	Standard Error	1-sided Lower 98.75% Confidence Bound
0.9656	0.0152	0.9315

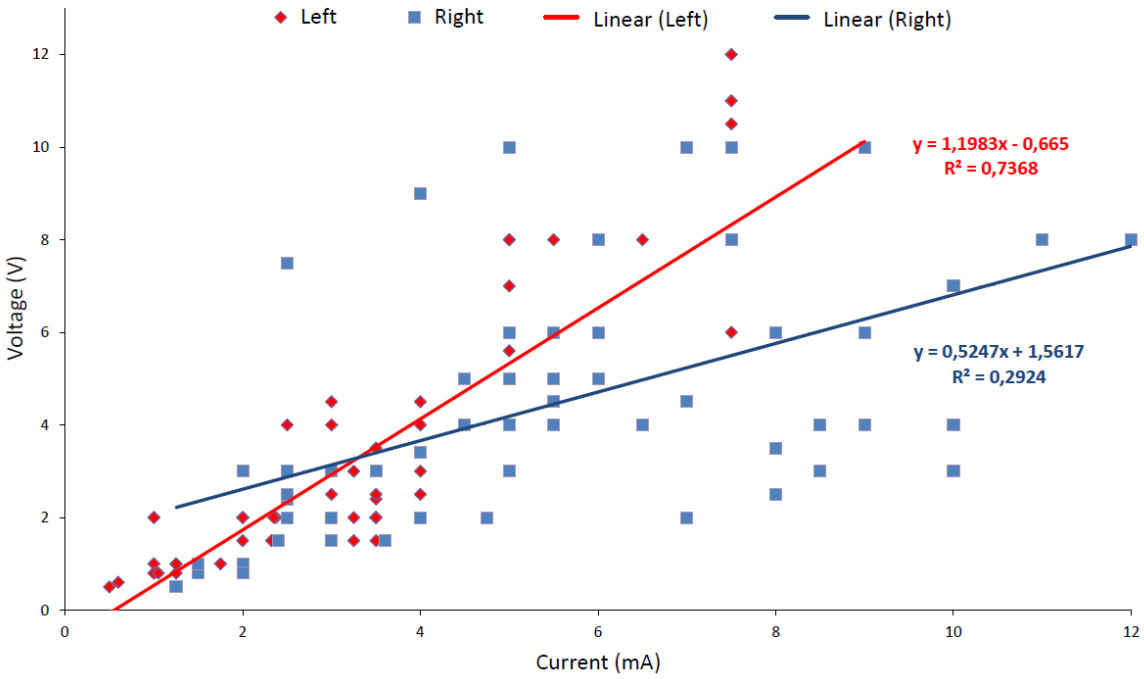

Figure 21: Left and Right Leads P01—P12. Required stimulation currents and voltages to capture the phrenic nerves. The slope of line depicts the best fit lead resistance.

Discussion

After analyzing the data from all stimulation sessions, I was able to demonstrate the high effectiveness of pacing both phrenic nerves with an adequate response of the diaphragm by its contraction. Because the electrodes were placed in close proximity to the nerves, I was able to induce diaphragm contraction at voltages less than 10.5 volts and charge densities less than 25 μC/cm^2 per phase. The final current pulse width used was 150 μs which was effective in all patients.

Conclusion

If the stimulating electrodes are placed precisely in the immediate vicinity of the phrenic nerves, we are able to effectively contract the diaphragm using low stimulation currents.

4.3 Patient's stimulation tolerance and safety endpoints

Introduction

In the first two patients, only the one side (left) phrenic nerve stimulation was performed with conducted CMAP tests (Compound Muscle Action Potential) [54] and nerve conduction test on both phrenic nerves prior to and at least 3 weeks after the stimulation. Followed by a 30–day follow up to confirm safety of this method of stimulation of the phrenic nerve before enrolling the remaining patients. First two, left-sided stimulations were done in Beaumont Hospital, Dublin.

After optimizing the electrode insertion procedure and ensuring the ability to succesfully contract the diaphragm by pacing a phrenic nerve, it was necessary to verify the patient's tolerance to stimulation. This part of thesis is focused on painfulness of stimulation, the ability to synchronize pacing with mechanical ventilation, keeping work of breathing during stimulated breaths in the physiological values, monitoring of the patient's vital signs and evaluation of pacing safety.

Methods

After the lead placement with succesful capture of diaphragm contraction, six periods of two hours of stimulation treating sessions over 48 hours were done with measurement of stimulation breath synchrony, ventilation parameters, 12–lead ECG, chest radiograph, blood gasses, vital signs and calculated work of breathing (WOB).

The interaction between the PEPNS system and the patient's tolerance

The following scoring systems were chosen to assess the interaction between the PEPNS system and the patient's tolerance. The Critical Care Pain Observation Tool (CPOT) [55, 56] and Richmond Agitation & Sedation Scale (RASS) [57] assessments were taken at baseline and approximately every 6 hours during the 48–hour study period. These assessments were used to objectively determine if any signs of discomfort and/or need to deepen sedation, was caused by electrical stimulation therapy. The pain assessment tool CPOT is based on four domains (details in Table 4): the patient's facial expressions, body movements, compliance with ventilator (or voice use for non-intubated patients), and muscle tension. Each domain has a possible score of 0 to 2.

The total score can vary between 0 and 8, where 0 indicates no pain behavior and 8 indicates clear signs of pain behavior.

Table 4: The Critical Care Pain Observation Tool [58]

The Critical Care Pain Observation Tool (CPOT)		
Indicator	**Description**	**Score**
Facial expression	No muscular tension observed Presence of frowning, brow lowering, orbit tightening and levator contraction All of above facial movements plus eyelid tightly closed	Relaxed, neutral 0 Tense 1 Grimacing 2
Body movements	Does not move at all (does not necessarily mean absence of pain) Slow, caution movements, touching or rubbing the pain site, seeking attention through movements Pulling tube, attempting to sit up, moving limbs/thrashing, not following comnnands, striking at staff, trying to clim out of bed	Absence of movenents 0 Protection 1 Restlessness 2
Muscle tension (Evaluation by passive flexion and extension of upper extremities)	No resistance to passive movements Resistance to passive movements Strong resistance to passive movements, inability to complete them	Relaxed 0 Tense, rigid 1 Very tense or rigid 2
Compliance with the ventilator (intubated patients) or Vocalization (extubated patients)	Alarms not achived, easy ventilation Allarms stop spontaneously Asynchrony: blocking ventilation, alarms frequently activated Talking in normal tone or no sound Sighing, moaning Crying out, sobbing	Tolerating ventilator or movement 0 Coughing but tolerating 1 Fighting ventilator 2 Talking in normal tone or sound 0 Sighing, moaning 1 Crying out, sobbing 2
Total/range		**0-8**

The RASS measures agitation and sedation level, the score ranging from +4 to -5 (details in Table 5), where a score of 0 indicates an awake and fully cooperating patient. Scores from -1 to -5 indicate an increasingly sedated patient, and scores from +1 to +4 indicate an increasingly irritable and agitated patient.

Table 5: The Richmond Agitation/Sedation scale [59]

The Richmond Agitation–Sedation Scale		
Score	**Term**	**Description**
+ 4	Combative	Overtly combative or violent; immediate danger to staff
+ 3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+ 2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+ 1	Restless	Anxious or apprehensive but movements not aggressive or vigorous

0	Alert and calm	Spontaneously pays attention to caregiver
- 1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
- 2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
- 3	Deep sedation	Any movement (but no eye contact) to voice
- 4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Any changes in pacing threshold settings were monitored to verify whether the proposed electrode fixation did not lead to severe dislocation of the inserted electrodes and its applicability in routine clinical practice, where it is necessary to change the patient's bed position at regular intervals to prevent pressure ulcers − decubitus.

ECG monitoring, chest radiograph, vital signs

Due to the immediate proximity of the inserted electrodes to the carotid sinus and vagal nerve, whose collateral stimulation would potentially lead to several arrythmias or even an asystolic event, standard vital signs were monitored and recorded throughout the stimulation procedure. In addition, 12–lead ECG was taken at baseline, during one of the six electrical stimulation sessions and after the completion of electrical stimulation therapy. Routine chest radiographs were taken prior to initiation of stimulation and at or before the 30–day follow up. Chest radiographs was used to ensure the diaphragm had not been damaged or paralyzed due to participation in the study.

Patient's breath synchrony and WOB

For optimal "rehabilitation" of the diaphragm with good pacing tolerance, it is essential to properly synchronize the patient's breathing effort (unless Controled Mechanical Ventilation−CMV mode is used, i.e. fully controlled ventilation) with the phrenic nerve stimulation with subsequent diaphragm contraction. The ability of the stimulation pulse to capture the diaphragm was assessed using a logistic regression model that included repeated measurements within a subject. Capture was defined as synchrony of the stimulated breath with the output parameter <10.5 volts and WOB between 0.2 and 2.0 J/L. The PEPNS Console outputs independent balanced current biphasic pulses bilaterally at user specified current levels. The resultant voltages generated is a function of the resistance and impedance of the tissue between the electrodes. This voltage was

limited in hardware to 12.5 volts. Synchrony was considered successful if the lag time between start of inspiration and start of stimulation was less than 88 ms which should be fast enough for inspiratory breath detection (Fig. 22). Among commonly used ventilators, the inspiratory triggering delay is around 125 ms with expiratory triggering delay similiar or even longer [50].

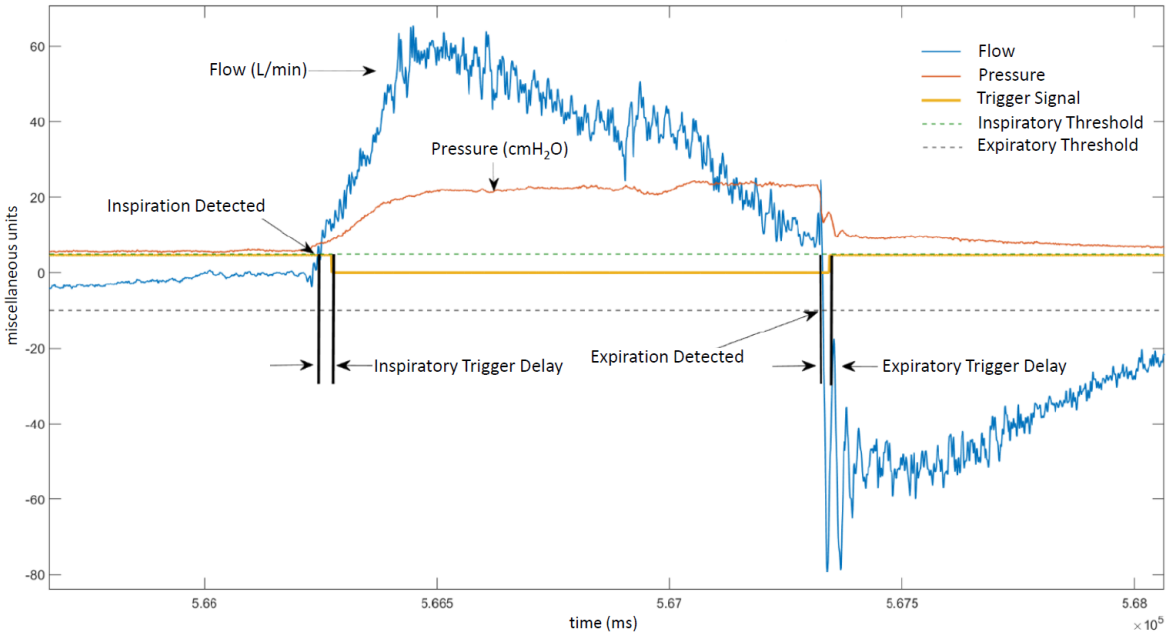

Figure 22. Inspiratory and expiratory trigger delay [50].

Qwye - blueline, flow in L/min[1], Pwye - redline, pressure in cmH_20, Trigger Signal - orangeline, Inspiratory Treshold - green dash line, Expiratory Treshlod - grey dash line.

PEPNS System parameters, including the stimulation electrode setup, inspired/expired flow trigger sensitivities, pulse width and rate, stimulation current, breath stimulation rate, and other relevant values were recorded for all stimulation sessions. LabChart (ADInstruments, Colorado Spring, CO, USA) was used to record Flow, Pressure, WOB, Stimulation signal (pulse rate) and Trigger signal (for detection of start of inspiration and expiration) at 1 KHz sample rate (Fig. 23). To perform data extraction for WOB, Inspiratory and expiratory trigger times MATLAB 9.5.0.1049112 Update 3´ was used.

[1] I deliberately used the symbol "L" used and preferred in foreign literature in the field of respiratory care, because the symbol "l" (small letter L) can be easily confused with 1 (digit one), which reduces the readability of the text and there is a risk of unintentional confusion.

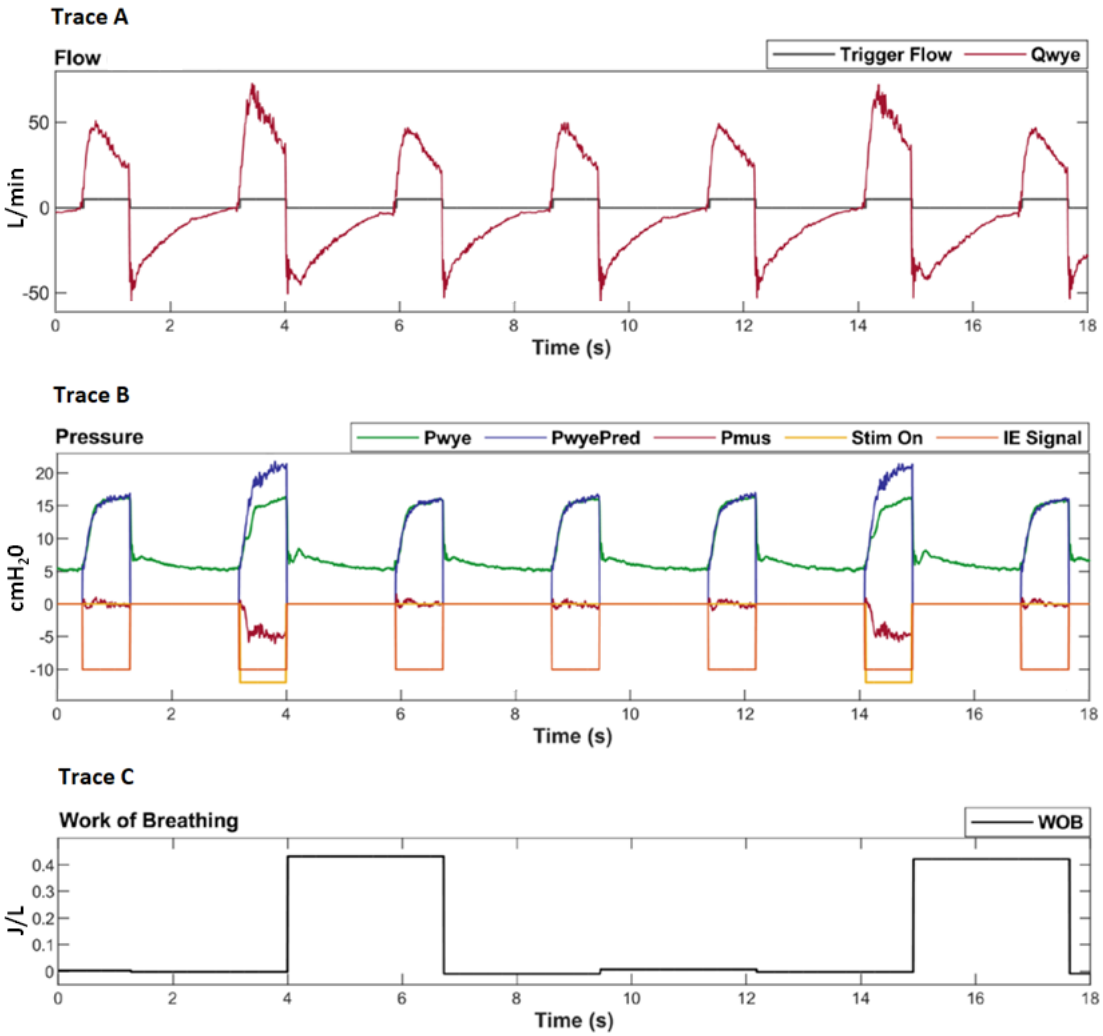

Figure 23. Example of data acquired by ADInstruments Labchart at 1 kHz sample rate [50].

Trace A: Qwye - redline, flow in L/min, Trigger flow - greyline in L/min, **Trace B**: Pwye - greenline, measured pressure in cmH_2O, PwyePred - blueline, predicted pressure based upon the equation of motion in cmH_2O, Pmus - redline, diaphragm pressure as a result of stimulation or patients voluntary effort in cmH_20, StimOn - yellowline, stimulation active, IE Signal - orangeline where - 10 is an inspiration and 0 means expiration, **Trace C**: WOB - blackline, Work of Breathing in J/L.

Patient WOB was calculated in real time during the inspiratory period of each breath using the equation of motion and the ventilator calculated static compliance (C_{STAT}) and resistance (R_{STAT}).

$$PwyePredicted = (1/C_{STAT} \cdot \int_0^t Qwye \, dt) + (R_{STAT} \cdot Qwye) + PEEP$$

$$P_{mus} = PwyePredicted - Pwye$$

Where PEEP is Positive End Expiratory Pressure, PwyePredicted is predicted wye pressure, P_{mus} is diaphragm muscle effort exerted by patient, all in cmH_2O. If C_{STAT} and R_{STAT} values were unavailable, dynamic compliance and resistance values were used as initial estimates and adjusted manually such that PwyePredicted equaled the measured Pwye on breaths where no patient effort (P_{mus}) was present.

WOB was normalized to J/L and displayed to user at the end of each breath.

$$W = \int_{t0}^{t1} Pmus \cdot Qwye \, dt$$

$$WOB = W / \int_0^{Ti} Qwye \, dt$$

Where *W* is work in *J*; *WOB* is its normalized value in *J/L*.

In pressure regulated modes no discernable difference in the Pwye pressure waveforms were visible between stimulated and unstimulated pressure waveforms. Flow and volume curves were affected and show an increase in peak flow and inspired volume. To minimize the potential for collateral stimulation, the lowest possible stimulation parameters were used while achieving the defined WOB limits.

Safety endpoints

The percentage of patients who experience one or more serious device/procedure-related adverse events during the study have been reported.

Results

The interaction between the PEPNS system and the patient's tolerance

There were no signs of pain during stimulation and non-stimulation periods. The mean CPOT during electrical stimulation was 0,51±0,44 versus 0,91±0,86 without electrical stimulation as shown in Tab. 6.

Table 6. Mean CPOT assesment scores

Patient	Mean CPOT Scores	
	During stimulation	Without stimulation
P03S01	0.5	2.2
P04S01	0.8	1.4
P05S02	0.8	0.3
P06S02	0.0	0.0
P07S02	0.0	0.0
P08S01	1.2	2.2
P09S02	1.0	1.2
P10S02	0.0	0.0
P11S01	0.8	1.6
P12S01	0.0	0.3
Means	0.51	0.92
St. Deviation	0.45	0.86

On average, most of our patients were moderately to highly sedated during stimulation and non-stimulation periods. The exception was patient P12S01, who required sedation only for the lead insertion procedure, then she was fully awake for the rest of the stimulation period. The RASS assesment scores are presented in Tab 7.

Patients were repositioned approximately every 2 to 4 hours per hospital protocol and disease management requirements. Leads were disconnected from the electrical stimulator using the extension lead when not stimmulating. Reestablishing stimulation after reconnection typically took 5 to 10 minutes. One patient P12S01 was able to sit in a chair and adjust body position autonomously while on CPAP and still maintained

effective electrical stimulation. None of our patients lost stimulation capture after repositioning.

Table 7. Mean RASS assesment scores

Patient	Mean RASS Scores	
	During stimulation	Without stimulation
P03S01	-3.5	-3.4
P04S01	-3.3	-2.7
P05S02	-5.0	-5.0
P06S02	-2.0	-2.5
P07S02	NA	-4.0
P08S01	-2.8	-1.2
P09S02	-2.0	-2.0
P10S02	-5.0	-4.6
P11S01	-4.5	-3.0
P12S01	-0.8	-0.4
Means	-3.21	-2.88
St. Deviation	1.56	1.46

ECG monitoring, chest radiograph, vital signs

All vital signs data, including heart rate, blood pressure, oxygen saturation and temperature was reviewed to determine if the stimulation had any impact on them. There were no major changes during stimulation and non-stimulation periods. Analysis of 12–lead ECGs of all our patients showed no cardiac pacing, no stimulation of the carotid sinus, no change in ECG morphology, nor stimulation of the vagus nerve, which could potentialy cause asystole or arrythmias, or any other effects caused by PEPNS system. Chest radiograph analysis concluded that there were no obvious changes in lung volume, degree of atelectasis, or status of elevated hemidiaphragm in any patients due to electrical stimulation.

Patient's breath synchrony and WOB

Excluding the pilot patients (P01 and P02), overall N=36 059 stimulated breaths have been analyzed. For analysis of lag time in 4 breaths the inspiratory trigger data were

missing so a lag time could not be calculated. Therefore N=36 055 stimulated breaths were used for analysis.

The analysis of phrenic nerve stimulation in synchrony with MV breaths yielded a mean inspiratory lag of 23.66 ms and a mean expiratory lag of 15.48 ms. With the null hypothesis defined as the mean Lag > 88ms and a p-value of <0.0001, the null hypothesis was rejected and this endpoint was considered met (Tab. 8).

Table 8: Inspiratory and Expiratory Lag Time

Mean Inspiratory Lag (ms)	N	95% Confidence Limits (ms)	P-value H0: Mean Lag > 88 ms
23.66	36055	[23.52, 23.80]	<.0001
Mean Expiratory Lag (ms)	**N**	**95% Confidence Limits (ms)**	**P-value H0: Mean Lag > 88 ms**
15.48	36045	[15.29, 15.67]	<.0001

The analysis of WOB kept between 0.2 joules/L and 2 joules/L yielded that 96.77% of samples were kept between the exclusive limits. The 95% confidence interval spans from 96.58% to 95.95%. Since the lower bound of this confidence interval exceeded the 80% target, this endpoint was met (Tab. 9).

Table 9: Work of Breathing

Proportion Between 0.2 and 2.0 Joules/L	N	95% Confidence Limits
0.9677	36059	[0.9658, 0.9695]

Patient's safety

No adverse events were reported related to the study. Four patient deaths were reported during the follow up period and were reviewed by the hospital, investigators and Clinical Events Committee. These were critically ill patients and none of the deaths were related to study participation. There were no signs of clinical infection at the lead insertion site. Leads were easy to remove in the end of stimulation session and wound closure by suture was never necessary. There were no signs of bleeding or tissue adhesion to the electrode lead after its removal.

Discussion

Phrenic nerve stimulation was vell tolerated by all endrolled patients. None of them showed any signs of pain and there was never necessary to deepen the existing depth of sedation. The last enrolled patient did not require any sedation during stimulation sessions, and was able to sit in a chair and actively rehabilitate. This opens an unexpected possibility of diaphragm rehabilitation even in patients already at an advanced stage of weaning. It was possible to continue with standard nursing care of the patients, including changes in the patient's position at regular intervals and daily hygienic procedures. An important finding was that stimulation of phrenic nerves in the neck region, where the vagal nerve also passes nearby, does not adversely affect cardiac electrical activity, nor does it affect other vital functions and is therefore safe for the patient. Extremely short inspiration and expiration lag times allowed excellent synchronization of stimulation with mechanical ventilation and did not cause interference with the ventilator. This also applies when the ventilatory support is initiated by the patient's own respiratory effort. Work of breathing during this active rehabiliation of the diaphragm was maintained in physiological values throughout the stimulation sessions.

Conclusion

Bilateral phrenic nerve stimulation has been proven to be a painless and safe procedure. The ability to synchronize the stimulation with the patient, regardless of the ventilation mode used, and the ability to keep the WOB within the physiological values contributes to excellent patient tolerance of the stimulation sessions.

4.4 Influence of diaphragm contraction on its thickness

Introduction

It has been demonstrated that the electrodes can be easily and safely inserted near the phrenic nerves in the neck. Further, that a contraction of the diaphragm can be elicited in response to stimulation and synchronized with the patient's inspiration during mechanical ventilation. It has been verified that the stimulation is very well tolerated by the patient, does not affect the patient's cardiac electrical activity, and is safe. It remains to be determined whether active contraction of the diaphragm leads to an increase in its thickness as a major determinant of muscle strength.

Methods

To evaluate the effect of stimulation on diaphragm thickness, we have decided to use the ultrasonographic method again. Diaphragm muscle thickness was measured using a standardized technique [60-62]. Imaging was performed using the B-mode with linear probe on 10-15MHz frequency at the zone of apposition between the eighth or ninth intercostal spaces on the both sides in the midaxillary line (Fig. 24).

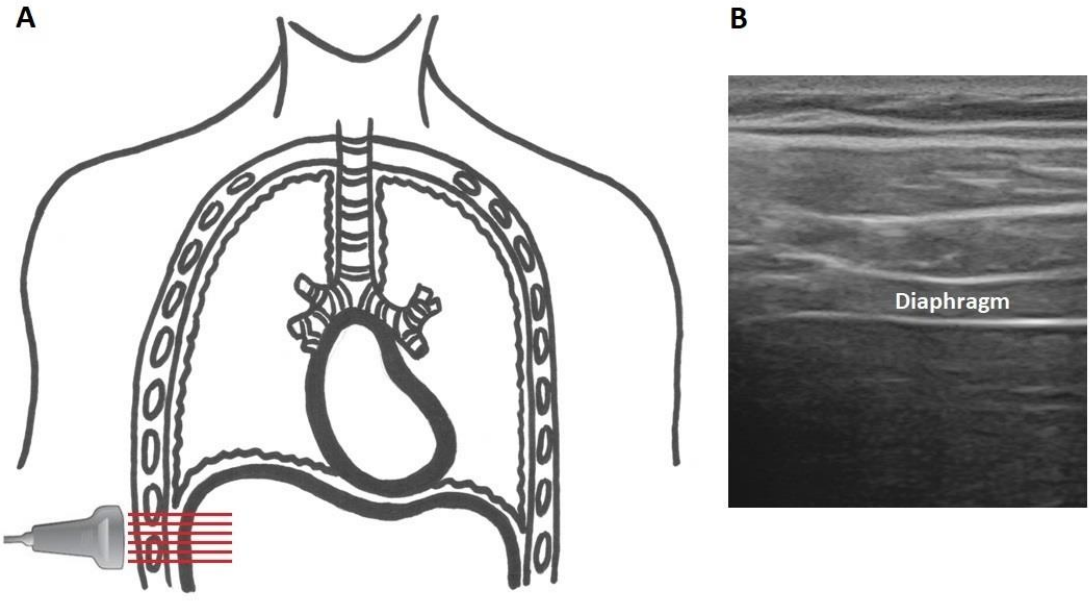

Figure 24. Ultrasound linear probe orientation **(a)** and a view of diaphragm **(b)** identified as a 3–layer comprising two hyperechoic lines representing the pleural and peritoneal membranes and a middle hypoechoic layer representing the diaphragmatic muscle itself.

The sponsor's planned study design included diaphragm thickness measurement only as additional data within the feasibility study, but due to the fact that changing the diaphragm thicknesss is the only way how to verify the effect of active diaphragm rehabilitation by phrenic nerve pacing, I decided to create a control, non-interventional group of patients. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram as a standard way of transparent reporting of clinical findings is presentend in App. F.

The interventional group (N=12), consisted of two unilaterally and ten bilaterally stimulated patients, four were predominantly ventilated on spontaneous modes such as pressure support ventilation (PSV), while the remaining eight patients were on assist-control ventilation (ACV) or some combination of ACV a PSV during stimulation days. Before starting the stimulation, at the time of the first measurement of the thickness of the diaphragm, patients had spent an average of 165 hours on mechanical ventilation. The majority of patients had trauma as the leading diagnosis (nine out of twelve), seven of whom had traumatic brain injury (TBI), the remaining patients had sepsis, rupture of the arteriovenous malformation, and lung infection (details in App. G).

The control group (N=10) of nonstimulated patients, nine were on ACV during the measured days and one was exclusively on PSV mode. The average time spent on mechanical ventilation before enrollment in the study was 159 hours. As with in the stimulated group, the majority of patients had a traumatic and/or neurosurgical diagnoses (seven out of ten) the others were after extensive, complicated abdominal surgery, and one patient was treated for respiratory infection (details in App. G). The comparison of demographic characteristics of the interventional and control groups is shown in Tab.10.

Table 10: The demographic characteristics of the interventional and control study groups.

Parameter	Intervention group	Control group	p
N	12	10	—
Sex (Male : Female)	11:1	6:4	—
Age (years)	61.9 ± 7.5	60.2 ± 9.9	0.65
Weight (kg)	89.3 ± 24.4	82.5 ± 12.8	0.43
Height (cm)	174.7 ± 6.7	173.9 ± 7.3	0.80
BMI ($kg \cdot m^{-2}$)	29.1 ± 6.6	27.3 ± 3.8	0.46
Time on ventilator before the study (hours)	165 ± 67	159 ± 37	0.82

The values are presented as mean ± standard deviation.

Measurement

Diaphragm thickness was measured once daily at the end of expiration on three separate breaths with three thickness measurements attempted on each breath where possible, as the diaphragm relaxes prior to the initiation of a new breath at baseline, 24 ± 4 hours, and at 48 ± 4 hours.

To increase accuracy, the measurement was performed in three different ways. At the end of the expiration, the ultrasound image was frozen and a total of three values were measured in different parts of the diaphragm (Fig.25). This was done in a total of three different breath cycles. The calculated average diameter of the diaphragm thickness was then recorded. The image documentation of the entire measurement was then saved to disk for further analysis. This consisted of a manual control measurement in the locations originally marked by the electronic calliper of the ultrasound device followed by measurement of other locations along the course of the diaphragm using the acquired images from the scan. These measurements were performed by a different physician than the one who performed the original ultrasound (detail in App. H, I).

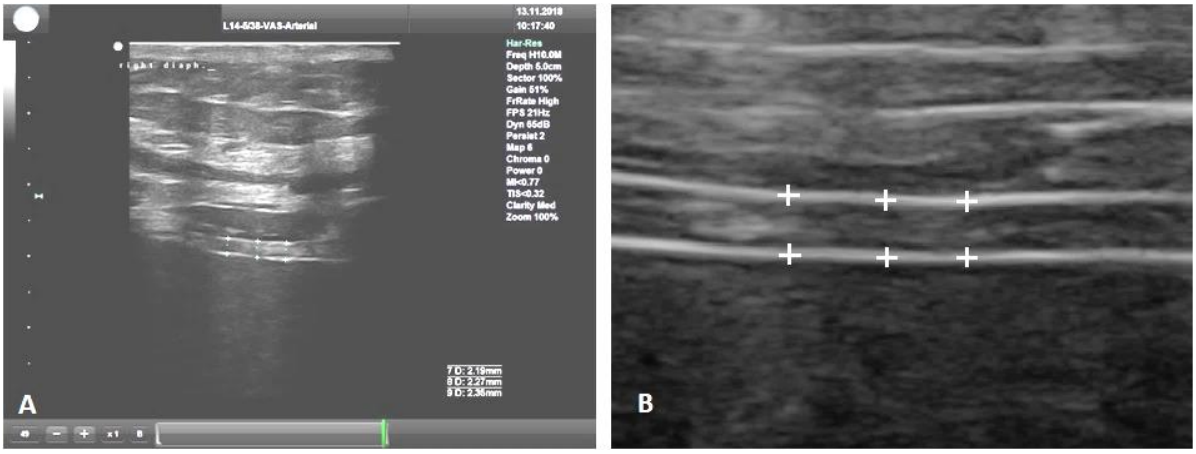

Figure 25. Ultrasound measurement of right side diaphragm, linear probe, 10 MHz **(a)**, measurement is made from the middle of the pleural line to the middle of the peritoneal line **(b)** in detail.

Statistical analysis

Results are presented as mean ± standard deviation (SD). Normal distribution of data was confirmed using the Shapiro-Wilk test (Statistica v7.1, StatSoft, Inc., Tulsa, OK, USA). The statistical significance of the diaphragm thickness in time within the study groups was tested using the ANOVA for repeated measures followed by Fisher's least significant difference post-hoc tests (Statistica v7.1). A paired T-test was used for testing of the statistical significance of the overall diaphragm thickness before and after the whole experiment. Statistical differences with p values less than 0.05 by two-tailed tests were considered significant.

Results

Diaphragm thickness was analyzed in terms of % change in thickness from baseline (hour 0), then at 24 ± 4 hours, and at 48 ± 4 hours. Using this approach allowed comparison of the effect of electrical stimulation between patients minimizing the influence of natural variability in diaphragm thickness between patients.

From the interventional group, first two, pilot patients with only left sided measurements were not included in the analysis. Among bilaterally stimulated group, patient 05 was measured only on the left side since right side was not stimulated after

electrode dislocation and patient 06 was excluded from the analysis due to difficulty to acquire the ultrasound image due to extensive pleural effusion and body habitus.

During the experiment, the original diaphragm thickness (i.e. the baseline) in the interventional group was (1.98 ± 0.52) mm and after 48 hours of phrenic nerve stimulation increased to (2.20 ± 0.45) mm (p=0.001). In the control the original diaphragm thickness of (2.00 ± 0.33) mm decreased after 48 hours of mechanical ventilation to (1.72 ± 0.20) mm (p<0.001).

The details of changes in diaphragm thickness during the experiment are presented in Fig. 26 for the interventional group and in Fig. 27 for the control group. The results are presented for the right and left side separately.

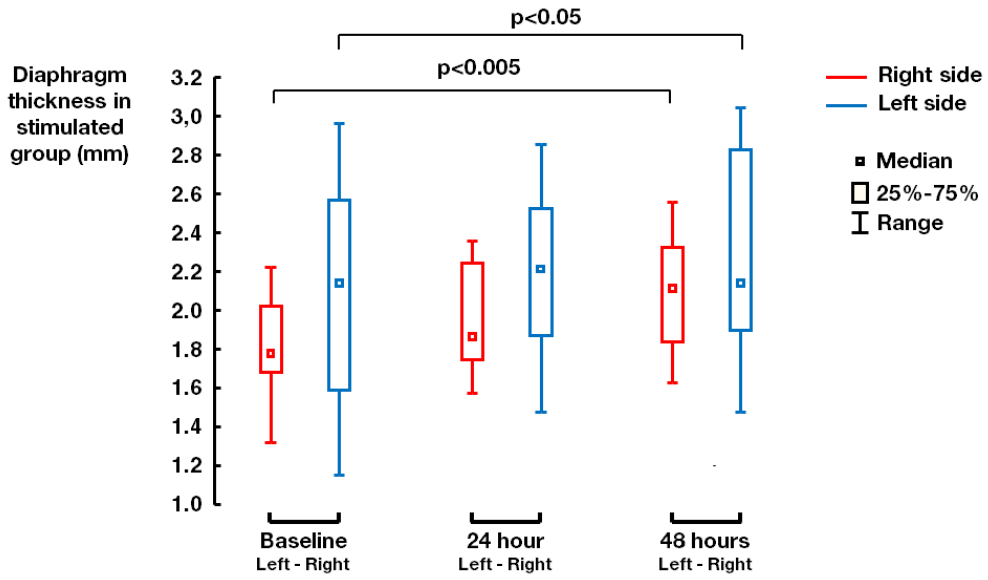

Figure 26: Increase in diaphragm thickness during the phrenic nerve stimulation.

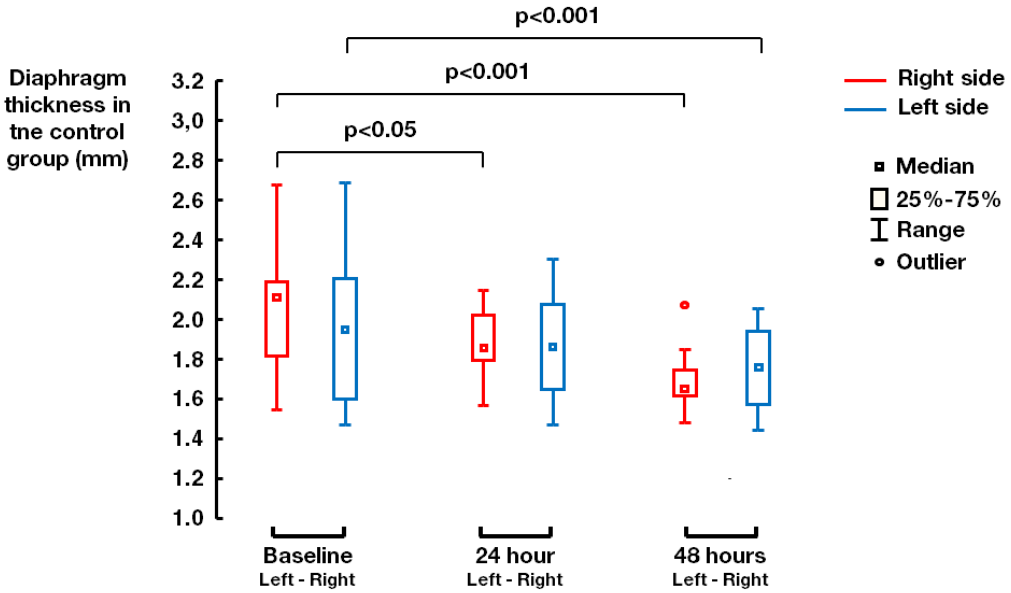

Figure 27: Decrease in diaphragm thickness in the control group.

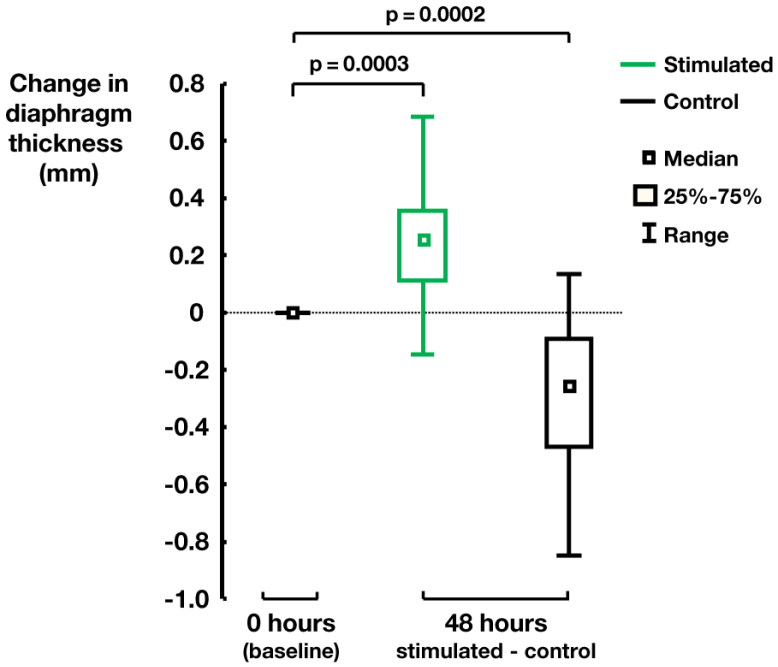

Figure 28: Increase in diaphragm thickness after 48 hours stimulation and its corresponding decrease after 48 hours in the control group (without stimulation) compared to baseline at hour 0.

Fig. 28 shows the overall increase (right and left together) in diaphragm thickness in the interventional group after 48 hours. This increase was statistically significant (p=0.0003). By 48 hours, the diaphragm thickness was on average almost 15% thicker

than at baseline in the interventional group and 12% thinner than at baseline in the control group (p=0.0002).

Discussion

The principal finding in this part of thesis was that ICU patients who recieved phrenic nerve stimulation during mechanical ventilation experienced an increase in diaphragm muscle thickness, whereas similar ventilated patients who did not recieved stimulation experienced a corresponding decrease in thickness. This effect was observed on both sides of the diaphragm with nearly 15% increase in diaphragm thickness seen in the stimulated group and more than 12% decrease in thickness seen in the control group.

I have performed multiple measurements of the diaphragm thickness. The reason was to exclude the subjective variability in the measurement and the relative error of the US device measurement, which, however, is very low (± 0.36%) when using a linear probe with a frequency of 10 Hz measuring in the axillary plane [63]. Thus, I was able to demonstrate very low inter and intraindividual variability of measured values, so this method is suitable for assessing changes in the thickness of the diaphragm.

The thickness of the diaphragm progressively decreases during assist-control ventilation (ACV) modes and, conversely, increases during pressure support ventilation (PSV), when all breaths are initiated by the patient's spontaneous respiratory activity [62]. Francis et al. observed a reduction in diaphragm thickness in patients on ACV of approximately 5-6% per day, which is consistent with previous findings by Grosu et al. [64] and gradual increase among patients who started on ACV during the study and continued on PSV. Another interesting variable is the level of Positive End Expiratory Pressure (PEEP) used. It has been hypothesised that lung volume at the end of expiration with the use of PEEP puts the passive diaphragm in a contracted position, so it is possible that the diaphragm atrophied at a relatively faster rate than in patients not on PEEP [62]. However, because the use of PEEP for prevention of lung atelectasis [62] is standard practice in ICU, it is not possible to investigate its effect to a rate of diaphragm atrophy. In this study, it should be noted that in both groups, the patients were predominantly on ACV mode, but some were irregularly switched to PSV during the day/night, so it is not possible to precisely quantify the effect of ventilation mode on the change in diaphragm thickness. In addition, some patients on PSV in the control

group in contrast to the findings of previous studies still experianced a reduction in diaphragm thickness. In addition, one patient from the intervention group, who had been on PSV for many days prior to enrollment in the study, nevertheless responded to 48 hours of stimulation with a significant increase in diaphragm thickness. Thus there is likely an effect not only of the selected ventilation mode (ACV or PSV), but also of the intensity of ventilation support itself as well as the selected PEEP level. In addition, I believe that "external" stimulation of the phrenic nerve allows the involvement of much larger muscular units of the diaphragm leading to more effective contraction than when the stimulus is induced spontaneously (i.e. physiologically from the brain center). This assumption allows for the possibility of use of phrenic nerve stimulation for active rehabilitation of the diaphragm even in patients who are exclusively on PSV, i.e. those who are already in the advanced phase of weaning. The possibility of using low stimulation current allows for tolerance of stimulation even in fully conscious patient. However, precise insertion of the stimulation electrodes in the immediate vicinity of the phrenic nerve is required to achieve this. Although the increase in diaphragm thickness in the stimulated group was significant, as was the decrease in the control group, it would be appropriate to verify this in a larger sample of patients.

Conclusion

Contraction of the diaphragm, i.e. its active rehabilitation by pacing the phrenic nerve not only reduces the rate of its atrophy during mechanical ventilation, but on the contrary leads to an increase in its thickness as the main determinant of muscle strength required for spontaneous ventilation and weaning a patient from the ventilator.

5 Discussion

The main results of the thesis can be summarized as follows. The first task was to verify the applicability of the proposed procedure for insertion pacing electrodes for the first time in the human population. In standard practice, physicians approach the pheric nerve using ultrasound-guided regional blocking of the brachial plexus, but have never attempted to insert and stimulate the phrenic nerve. After the first few bilaterally stimulated patients, the theoretically proposed procedure of ultrasound imaging and lead electrode insertion seemed unsuitable for clinical practice. The procedure of electrode insertion during ultrasound navigation was modified using anatomical landmarks, namely the anterior scalene muscle, sternocleidomastoid, brachial plexus and internal jugular vein. After identifying these landmarks, the needle was inserted using a hydrodisection technique with saline to the target electrode placement site, which was then inserted through the needle and left in situ. This was followed by stimulation between individual portions of the electrodes until an effect in the form of visible contraction of the diaphragm was achieved, without collateral stimulation of brachial plexus. The electrode was then fixed to the skin with a grip lock and loop and covered with a transparent foil to monitor the injection site. Despite the variability of the body habitus of our patients, it was possible to successfully insert electrodes in all cases. My proposed modification of the ultrasound view, insertion approach and modification of the entire insertion set, including the final fixation of the electrode, have proved to be easy and safe to perform in a functional manner.

Once the issue of electrode insertion has been resolved, the ability to stimulate the diaphragm nerve to achieve effective contractions of the diaphragm and synchronition the stimulation with mechanical ventilation, followed. The PEPNS System was able to capture both the left and right phrenic nerve at voltages less than 10.5 volts. Although almost all patients in the intervention group were sedated during stimulation sessions and were regularly scored for possible signs of pain using CPOT scoring system, with no signs of pain recorded, only one patient was fully conscious. Therefore, to find a safe painless stimulation current limit, it would be necessary to enroll more unsedated patients. Passive rehabilitation care and regular positioning of patients were not affected by stimulation and, conversely, changes in the patient’s position did not lead to dislocation of the electrodes. All vital signs data, including 12–lead ECG a chest

radiograph were reviewed to determine if the stimulation had any impact on them. There were no major changes in ECGs or chest radiographs during stimulation and non-stimulation periods, as well as all other observed vital signs during the 48 hour period showed no extreme deviations. The PEPNS system was able to safely deliver electrical stimulation with excellent synchronization with mechanical ventilation. Breath detection and electrical stimulation worked well in all modes of ventilation tested. Work of breathing during stimulation breaths was possible to keep in physiological values even for spontaneously breathing patiens. Detailed analysis of diaphragm thickness data in the intervention and control groups led to the conclusion that electrical stimulation of the diaphragm nerve can prevent or even treat diaphragm atrophy.

The study stimulation timing protocol was designed to pace a diaphragm every fourth breath, in two-hour sessions after eight hours, for 48 hours. It would be appropriate to try other time protocols and to estimate how long the stimulation period would be suitable for a particular patient. It is very likely that even with the current stimulation schedule, most patients would require a much longer stimulation time to achieve a clinically significant effect.

It would certainly be interesting to compare individual subgroups of stimulated patients with each other, according to the presence or absence of primary pulmonary pathology. It can be assumed that patients with lung disease could benefit from stimulation more than those without it. Unfortunately, our group of patients is too small to draw these conclusions.

My previous experience with diaphragmatic stimulation led me to the idea of using this method in patients with respiratory failure on the background of chronic lung disease such as Chronic Obstructive Pulmonary Disease (COPD). Exacerbation of this disease due to infection, according to the causative agent, usually needs targeted antibiotic / antifungal therapy, which requires at least several days to achieve clinical effect. Unfortunately, this time necessarily spent on MV leading to an acceleration of the diaphragmatic atrophy and therefore may prolong or completely prevent successful ventilator weaning. Hospital mortality in mechanically ventilated patients with COPD is almost 25%, 1–year mortality approached 40%, and 5–year mortality exceeded 70% [65]. These patients often eventually require a tracheostomy, becoming patients for long-term intensive care dependent on ventilatory support for weeks or more. If such

patients were stimulated at the initiation of MV, we could gain time for pharmacological therapy of the infection to take effect without an increased risk of prolonged weaning due to diaphragm atrophy and long-term MV with all of its possible consequences. I believe that there are a number of other diseases where stimulation of the diaphragm in sedated patients on MV would be appropriate. The aim of further research should therefore be to look for indications for individual diseases and find out which patients could benefit the most from this method.

6 Conclusion

The study sponsor have conducted extensive preclinical testing of its system, which was applicable to the animal model. In collaboration with medical experts, they have suggested a possible use in the human population. It has been demonstrated that this method is both applicable and safe in humans as well.

This study with further data analysis contributed to the robustness of the preliminary results and support the feasibility of this method allowing further investigation in this field for introduction into clinical practice. Percutaneous electrical phrenic nerve stimulation has the potential to prevent or treat the diaphragm atrophy and represents a promising new approach to maintaining diaphragm work and may offer a future option for preventing or even treating ventilator induced diaphragm dysfunction. However, it is not yet possible to say whether it has any impact on weaning time. These results should lead to a randomized clinical study focusing on weaning time in patients on mechanical ventilation.

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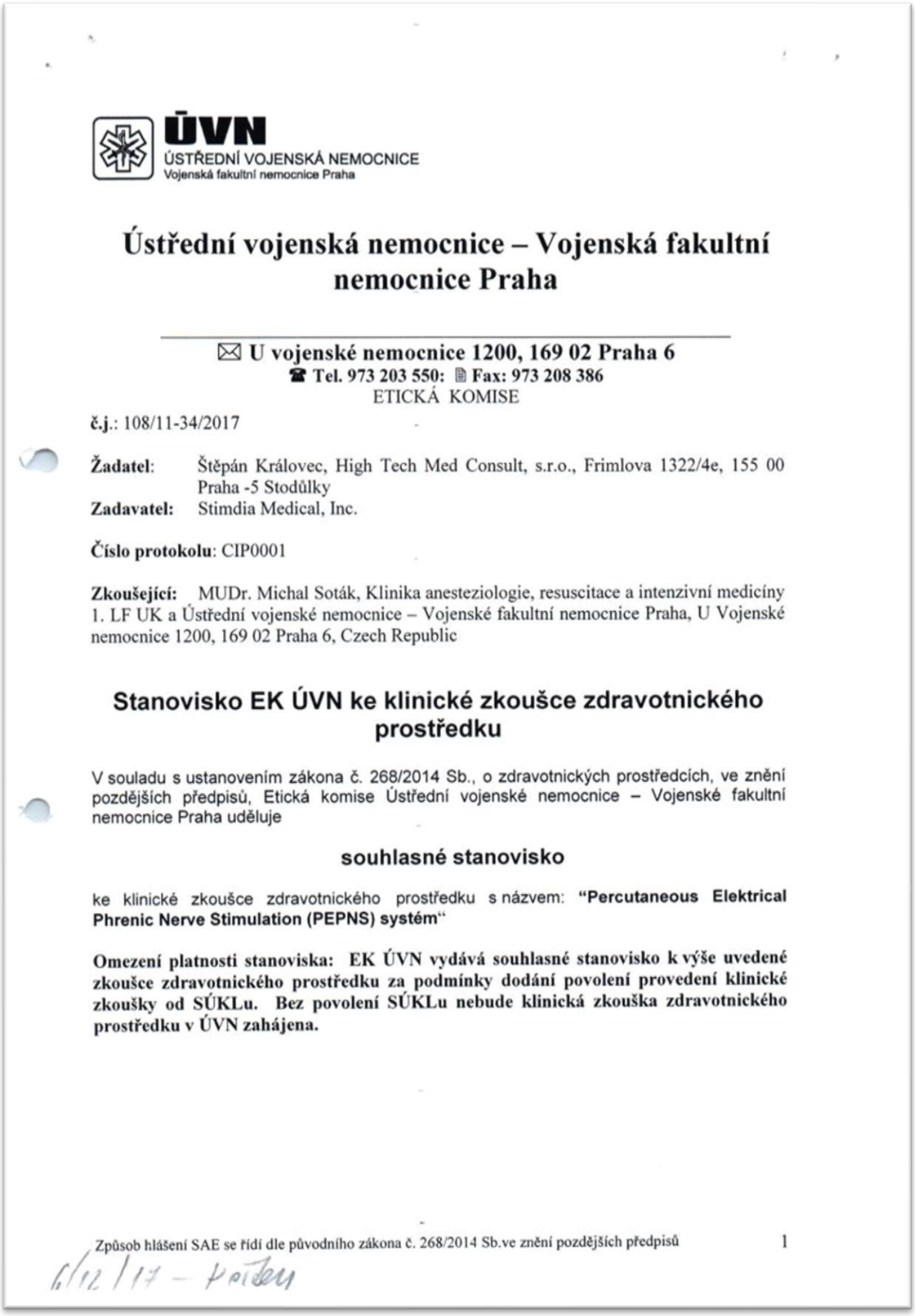
Appendices

Appendix A: Military University Hospital in Prague and Beaumont Hospital Ethics Commitee statements



ÚVN
ÚSTŘEDNÍ VOJENSKÁ NEMOCNICE
Vojenská fakultní nemocnice Praha

Ústřední vojenská nemocnice – Vojenská fakultní nemocnice Praha

U vojenské nemocnice 1200, 169 02 Praha 6
Tel. 973 203 550: Fax: 973 208 386
ETICKÁ KOMISE

č.j.: 108/11-34/2017

Žadatel: Štěpán Královec, High Tech Med Consult, s.r.o., Frimlova 1322/4e, 155 00 Praha -5 Stodůlky
Zadavatel: Stimdia Medical, Inc.

Číslo protokolu: CIP0001

Zkoušející: MUDr. Michal Soták, Klinika anesteziologie, resuscitace a intenzivní medicíny 1. LF UK a Ústřední vojenské nemocnice – Vojenské fakultní nemocnice Praha, U Vojenské nemocnice 1200, 169 02 Praha 6, Czech Republic

Stanovisko EK ÚVN ke klinické zkoušce zdravotnického prostředku

V souladu s ustanovením zákona č. 268/2014 Sb., o zdravotnických prostředcích, ve znění pozdějších předpisů, Etická komise Ústřední vojenské nemocnice – Vojenské fakultní nemocnice Praha uděluje

souhlasné stanovisko

ke klinické zkoušce zdravotnického prostředku s názvem: **"Percutaneous Elektrical Phrenic Nerve Stimulation (PEPNS) systém"**

Omezení platnosti stanoviska: EK ÚVN vydává souhlasné stanovisko k výše uvedené zkoušce zdravotnického prostředku za podmínky dodání povolení provedení klinické zkoušky od SÚKLu. Bez povolení SÚKLu nebude klinická zkouška zdravotnického prostředku v ÚVN zahájena.

Způsob hlášení SAE se řídí dle původního zákona č. 268/2014 Sb.ve znění pozdějších předpisů 1

6/12/17 – Kotěra

Seznam hodnocených dokumentů: název, verze, datum / *List of all submitted documents: Document title, version, date*

Seznam hodnocených dokumentů: název, verze, datum *List of all submitted documents: Document title, version, date*	Schváleno *Approved*		Na vědomí *Due notice*	
	Ano *Yes*	Ne *No*	Ano *Yes*	Ne *No*
Žádost o schválení klinické zkoušky ZP ze dne 11.05.2017	☐	☐	☒	☐
CIP0001 Rev 1 PEPNS Systém Feasibility Study CIP April 7.2017 – Protokol KZ	☒	☐	☐	☐
CIP0001 Rev 1 PEPNS Systém Feasibility Study CIP April 7.2017 Summary CZ – souhrn protokolu	☒	☐	☐	☐
IB0001 Rev. PENPS System Investigators Brochure April 10.2017- příručka pro zkoušejícího zkoušejícího 10 april. 2017	☒	☐	☐	☐
Životopis zkoušejícího, MUDr. Michal Soták	☐	☐	☒	☐
Dotazník EK k předkládaným dokůmentům 10/05/2017	☐	☐	☒	☐
Předběžný souhlas s prováděním studie 03/05/2017	☐	☐	☒	☐
Návrh smlouvy o provedení klinického hodnocení	☐	☐	☒	☐
Pojistná smlouva	☐	☐	☒	☐
Potvrzení o pojištění /Certificate of insurance č. C0006995	☐	☐	☒	☐
Dokument kvalifikace zkoušejícího podepsaný MUDr. Sotákem a MUDr. Tyllem ze dne 14.11.2017	☐	☐	☒	☐
ICF0001 Formulář informovaného souhlasu ze dne 14 listopadu 2017	☒	☐	☐	☐
ICF0001 Rev B Potential Risk Reference Source Document	☐	☐	☒	☐
Prohlášení zadavatele o pojištění klinické zkoušky May 3.2017	☐	☐	☒	☐

20.11.2017
Datum / *Date*

Ústřední vojenská nemocnice -
Předseda EK / *Chairman of the EC*
Etická komise
Prof.MUDr. Přemysl FRIČ, Dr.Sc
- 1 -

Podpis předsedy EK / *Signature of Chairman the EC*

Způsob hlášení SAE se řídí dle původního zákona č. 268/2014 Sb.ve znění pozdějších předpisů 2

Seznam členů Etické komise / *List of the IEC members*

Jméno a příjmení *Name and Sumame*	Muž / Žena *Male / Female*	Odbornost *Occupation*	Závislost *Liability*	Hlasoval *Voted*
prof. MUDr. Přemysl Frič, DrSc.	M	Gastroenterologie	☒	☒
Mgr. Matyáš Monhart	M	Právo a právní věda	☒	☒
MUDr. Petr Hrabal	M	Patologická anatomie	☒	☒
MUDr. Zdeněk Šňupárek	M	Soudní lékařství	☒	☐
MUDr. Luboš Zach	M	Anesteziologie a intenzivní medicína	☒	☒
MUDr. Svatopluk Solař	M	Diabetologie	☒	☐
MUDr. Libor Kameník, Ph.D.	M	Kardiologie	☒	☒
mjr. Mgr. Jan Blažek	M	Teologie	☒	☐
Mgr. Martina Němečková	F	Pedagogika a ošetřovatelství	☒	☒
plk. PhDr. Jiří Klose, Ph.D.	M	Klinická psychologie	☒	☒
prof. MUDr. Mojmír Kasalický, CSc.	M	Chirurgie	☒	☒
MUDr. Petr Výborný, CSc. FEBO	M	Oftalmologie	☐	☐
doc. MUDr. Bohumil Seifert, Ph.D.	M	Všeobecné praktické lékařství	☐	☒
MUDr. Tomáš Hnátek	M	Kardiologie	☒	☒
doc. MUDr. Ing. Jaroslav Plas	M	Neurochirurgie	☒	☒

20.11.2017
Datum / *Date*

Ústřední vojenská nemocnice -
Vojenská fakultní nemocnice Praha
Předseda EK / *Chairman of the EC*
Prof.MUDr. Přemysl FRIČ, Dr.Sc.
- 1 -

Přemysl Frič
Podpis předsedy EK / *Signature of Chairman the EC*

Způsob hlášení SAE se řídí dle původního zákona č. 268/2014 Sb.ve znění pozdějších předpisů 3

Beaumont Hospital
Ethics (Medical Research) Committee

26th March 2018

REC reference: 17/47 Your Ref: PPENS System Feasiblity Study Protocol: CIP0001

Dr. James O'Rourke
Consultant in Intensive Care Medicine
Anaesthesia and Intensive Care Medicine
Beaumont Hospital
Dublin 9

To: jamesorourke2@beaumont.ie
cc: gercurley@rcsi.ie; laurie.lynch@centurylink.net

Dear Dr O'Rourke

RE: 17/47 - Dr. James O'Rourke - Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System Feasibility Study

Consultant Co-investigator: Professor G. Curley

Thank you for your correspondence dated 26th February 2018 enclosing Amendment #1 to this study.

I can advise that the Ethics committee is now happy to approve this amendment.

Kind regards

Yours sincerely

Dr. Peter Branagan
Convenor
Ethics (Medical Research) Committee

Appendix B: SÚKL Approval Form

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV
Šrobárova 48
100 41 Praha 10
Telefon: +420 272 185 111
Fax: +420 271 732 377
E-mail: posta@sukl.cz
Web: www.sukl.cz

ADRESÁT
Stimdia Medical, Inc.
400 Spojené státy

ZASTOUPEN
High Tech Med Consult s.r.o.
IČ: 28473221
Štěpán Královec
pověřená osoba

ADRESA PRO DORUČENÍ
Frimlova 1322/4e
Praha
15500

Spisová zn.sukls401258/2017
Č. jedn. sukl132619/2019

Vyřizuje/linka
Kučera/933

Datum
30. 5. 2019

Vypraveno dnem předání k poštovní přepravě vyznačeným na obálce provozovatelem poštovní služby, dnem odeslání datové zprávy z datové schránky Státního ústavu pro kontrolu léčiv, v případě osobního doručení dnem předání adresátovi.

ROZHODNUTÍ

Státní ústav pro kontrolu léčiv, se sídlem v Praze 10, Šrobárova 48 (dále jen „Ústav"), jako orgán příslušný k rozhodnutí podle § 9 písm. h) a § 15 zákona č. 268/2014 Sb., o zdravotnických prostředcích a o změně zákona č. 634/2004 Sb., o správních poplatcích, ve znění pozdějších předpisů (dále jen „zákon o zdravotnických prostředcích"), rozhodl v souladu s tímto zákonem a s § 67 zákona č. 500/2004 Sb., správní řád, ve znění pozdějších předpisů (dále jen „správní řád"),

takto:

Účastníkovi správního řízení, sp. zn. sukls401258/2017, zahájeného dne 3.5.2019 na základě žádosti o povolení změny podmínek klinické zkoušky **Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System Feasibility Study,** společnosti **Stimdia Medical, Inc.,** se sídlem **Vernon Road, 5021, Edina, MN55436, 400 Spojené státy,** zastoupené společností **High Tech Med Consult s.r.o.,** se sídlem **Frimlova 1322/4e, Praha, 15500, IČ: 28473221,** za kterou jedná Štěpán Královec, Ústav tímto v souladu s § 9 písm. h) a § 15 zákona o zdravotnických prostředcích

povoluje

změny podmínek klinické zkoušky:

Změny upravující popis potenciálních rizik výkonu v rámci zkoušky, upřesňují popis hlavního sledovaného parametru WOB a doplnění pravidel GDPR do protokolu.

změny v dokumentaci:

1. Protokol klinické zkoušky CIP0001 verze 4, November 30, 2018

2. Souhrn protokolu CIP0001 verze 4, November 30, 2018

3.Příručka zkoušejícího IB0001 verze 3, July 26, 2018

4. Formulář informovaného souhlasu ICF0001 verze D, 3. prosinec 2018

5. System Operators Manual LM0001 verze 6, November 30, 2018

6. pdSTIM L4300 Lead Instructions for Use verze 8, February 12, 2019

Odůvodnění

V souladu § 68 odst. 4 správního řádu není odůvodnění třeba, jestliže správní orgán prvního stupně všem účastníkům v plném rozsahu vyhoví.

Poučení

Proti tomuto rozhodnutí je možno podat podle § 81 správního řádu u Ústavu odvolání, a to ve lhůtě do 15 dnů ode dne jeho doručení. O odvolání rozhoduje Ministerstvo zdravotnictví ČR. V souladu s § 81 odst. 2 správního řádu se lze vzdát práva na odvolání, a to písemně nebo ústně do protokolu. Rozhodnutí v takovém případě nabývá právní moci v souladu s § 73 odst. 1 správního řádu dnem vzdání se práva na odvolání.

Otisk úředního razítka

Mgr. Karolína Peštová
vedoucí oddělení
klinického hodnocení zdravotnických prostředků a vigilance
Odbor zdravotnických prostředků

Appendix C: Informed consent form

Ústřední Vojenská Nemocnice
Souhlas s účastí ve výzkumné studii

Datum verze formuláře souhlasu: 30. ledna 2018

Název studie:	Studie použitelnosti systému k perkutánní elektrické stimulaci bráničního nervu (PEPNS)
Hlavní zkoušející:	MUDr. Michal Soták
Oddělení:	Klinika anesteziologie, resuscitace a intenzivní medicíny 1. LF UK a ÚVN
Telefonní číslo:	+420 973 202 999
Zadavatel:	Stimdia Medical, Inc.

Vážený paciente / vážená pacientko,

byla Vám nabídnuta účast v klinické zkoušce – výzkumné studii. Studii budou mít na starost výše uvedení zkoušející a další zdravotničtí pracovníci jim mohou pomáhat nebo jednat jejich jménem.

<u>Jaké obecné věci byste měl/a vědět ohledně výzkumných studií?</u>

Výzkumné studie jsou určeny k tomu, aby s jejich pomocí byly získány vědecké poznatky, které v budoucnosti mohou pomoci dalším lidem. Účast ve studii Vám nemusí nutně přinést nějaký přímý prospěch. S účastí ve výzkumných studiích se mohou pojit také rizika.

Účast ve studii je dobrovolná, což znamená, že o tom, zda se jí budete chtít zúčastnit, rozhodujete Vy sám/sama. Účast můžete odmítnout a můžete také kdykoli a z jakéhokoli důvodu zrušit svůj souhlas s účastí v libovolné studii, aniž by to ohrozilo budoucí péči o Vás v tomto zdravotnickém zařízení nebo Vaše vztahy s lékařem. Pokud jste pacient/ka s určitým onemocněním, k tomu, abyste byl/a léčen/a, se studie účastnit nemusíte.

Podrobné informace o této konkrétní studii jsou uvedeny níže. Je důležité, abyste těmto informacím porozuměl/a, abyste se mohl/a na základě získaných informací svobodně rozhodnout, zda se jí chcete zúčastnit. Dostanete kopii tohoto formuláře souhlasu. Zkoušejícím uvedeným výše nebo zdravotnickým pracovníkům, kteří jim budou pomáhat, můžete kdykoli položit jakýkoli dotaz týkající se této studie.

Co je účelem této studie?

Účelem této studie je vyhodnotit bezpečnost a výsledky používání systému k perkutánní (skrz kůži) elektrické stimulaci bráničního nervu (PEPNS) u pacientů, kteří musejí být napojeni na umělou ventilaci (umělé dýchání) na jednotce intenzivní péče (JIP). Zařízení PEPNS se bude u pacientů používat na JIP po dobu 48 hodin.

Bránice je sval, který umožňuje, aby byl do plic nasát vzduch. Odpovídá za Vaši schopnost dýchat a je elektricky ovládán bráničním nervem, který vede od mozku k bránici. Nedostatečná funkce bránice je závažným faktorem u pacientů, kteří mají problém začít samostatně dýchat po použití umělé ventilace.

Výzkum se bude zabývat otázkou, zda elektrická stimulace bránice povede ke zkrácení doby, kterou musejí pacienti zůstat na ventilátoru.

V průběhu Vašeho pobytu nebo pobytu Vašeho rodinného příslušníka na JIP se bude zaznamenávat čas, který je nutný k odstavení ventilátoru po elektrické stimulaci pobíhající v souladu s ventilací. Po kompletním ukončení používání ventilátoru nebo po 48 hodinách elektrické stimulace, podle toho, která z této doby bude kratší, budou odstraněny elektrody používané k elektrické stimulaci.

Účast ve studii Vám byla nabídnuta proto, že jste Vy sám/sama nebo Váš rodinný příslušník považován za vhodného kandidáta na tuto léčbu, která může zkrátit dobu, kdy je nutné používat umělou ventilaci.

Kolik pacientů se bude účastnit této studie?

Studie se na tomto zdravotnickém pracovišti zúčastní 10 pacientů. Celkem se jí bude moci zúčastnit až 20 pacientů až na dvou pracovištích.

Kandidáty na účast ve studii bude nutné vyloučit, pokud se u nich vyskytuje KTERÁKOLI z následujících situací:

1. Pacient má nízký srdeční výdej (tj. srdce má značné potíže s pumpováním krve), prodělal v nedávné době (v posledních 72 hodinách) infarkt nebo užívá vysoké dávky léků, které mění sílu srdečního stahu.
2. Pacient pravděpodobně nepřežije příštích 72 hodin.
3. Pacient má implantován kardiostimulátor nebo jiné elektronický přístroj.
4. Pacient je ohrožen rizikem závažného krvácení nebo užívá maximální dávky systémově podávaných látek na ředění krve.
5. Pacient má poškozený brániční nerv nebo u něj existuje podezření na jeho poškození, což se někdy projevuje zvýšenou polohou bránice.

6. Pacient má aktivní systémovou infekci nebo lokální infekci v místě či kolem vstupu elektrod. Pacient má nízký počet bílých krvinek nebo známky silně oslabeného imunitního systému.
7. Pacientka je těhotná nebo kojí nebo existuje pravděpodobnost, že by mohla být těhotná.
8. Pacient nemůže nebo nechce dodržovat kontrolní návštěvy podle protokolu.
9. Pacient byl v posledních 30 dnech zařazen do jiné klinické studie.
10. U pacienta byl proveden chirurgický nebo jiný intervenční zákrok v oblasti krku vedle místa zavedení katetru do krční žíly (v. jugularis interna).
11. Pacient byl v posledních 5 letech léčen na nádorové onemocnění krku.
12. Pacient má podle ultrazvukového vyšetření v srdci krevní sraženinu.
13. Pacient má neléčené onemocnění štítné žlázy nebo vysoký krevní tlak.
14. Pacient měl v posledních 6 měsících mozkovou mrtvici nebo dočasně zablokovaný průtok krve v mozku.
15. Pacient má progresivní nervové onemocnění.

Jak dlouho bude účast ve studii trvat?

Celková doba zařazování a provádění stimulační terapie v rámci studie může dosáhnout 3 až 4 dny. Doba elektrické stimulace bude činit maximálně 48 hodin v závislosti na době, která je nutná k ukončení umělé ventilace. Po 30 dnech (+- 7 dní) od ukončení období stimulace proběhne kontrolní návštěva, která bude trvat asi 30 minut. Celková doba Vaší účasti ve studii tedy může být až 41 dní.

Co se stane, pokud se studie zúčastníte?

Pokud budete souhlasit s účastí ve studii, bude Vám provedeno rentgenové (RTG), elektrokardiografické (EKG) vyšetření a ultrazvukové vyšetření krku a bránice, což jsou standardní vyšetření. EKG se skládá z přístroje s 12 elektrodami, které se umístí na kůži a jež zaznamenávají elektrickou činnost srdce. Poté Vám budou pod kůži dočasně zavedeny stimulační elektrody, které se použijí k elektrické stimulaci bráničního nervu v průběhu mechanické ventilace. Tyto elektrody budou odstraněny po ukončení stimulačního období, příp. po kompletním ukončení umělé ventilace (maximálně po 48 hodinách). Lékař Vám postup při zavádění stimulačních elektrod pod kůži podrobně vysvětlí a bude Vás informovat také o tom, jak bude probíhat období rekonvalescence. Tento zákrok se provádí za použití nitrožilní sedace (utišující léky) nebo (v případě nutnosti) celkové anestezie.

Kromě toho Vám může být provedeno vyšetření nervové vodivosti, kdy se bude zjišťovat funkce bráničních nervů a bránice před studií a po ní. Jedná se o neinvazivní povrchové vyšetření, kdy se zjišťuje síla a rychlost reakce svalů a nervů podílejících se na dýchání.

Systém PEPNS byl navržen tak, aby na základě stimulace bránice v průběhu ventilace pomáhal u pacientů, kteří jsou uměle ventilováni alespoň 24 hodin a u nichž existuje riziko obtížného ukončení umělé ventilace. Stimulace nutí bránici k tomu, aby se v průběhu umělé ventilace stahovala. Domníváme se, že to zabrání oslabení bráničního svalu.

Nad braniční nerv na krku Vám budou umístěny dvě stimulační elektrody. Jedná se o nervy, které zajišťují stahování dlouhého svalu známého jako bránice. Lékař k zavedení elektrod, použije ultrazvuk, který mu pomůže se zaváděním elektrod pod kůži (viz. popis umístění elektrody níže). Technologie PEPNS se skládá ze dvou stimulačních elektrod na jedno použití, průtokového senzoru a vnějšího elektrického generátoru, který má stimulovat braniční nerv spolu s nádechovým cyklem ventilátoru. Před stimulací a v jejím průběhu budete pomocí standardních nástrojů sledováni, aby se zjistilo, zda je léčba pro Vás vhodná a zda Vám nezpůsobuje bolest nebo nepříjemné pocity.

Budete-li jedním ze dvou prvních pacientů studie, bude Vám stimulován pouze levý braniční nerv a před samotnou stimulací Vám bude proveden test vodivosti bráničního nervu, který na obou bráničních nervech zopakujeme při kontrolním vyšetřením po 30 dnech nebo před ním, abychom zjistili, zda u levého nervu došlo v důsledku stimulace k nějaké změně. Pokud lékař u stimulovaného nervu zjistí nějakou změnu, může Vám být provedena tzv. skiaskopie, tj. RTG video, které zobrazuje pohyby bránice.

Budete sledován/a až po dobu 30 dnů a po 30 dnech proběhne kontrolní návštěva.

Po této návštěvě bude Vaše účast ve studii ukončena. Váš lékař Vás bude dále sledovat obvyklým způsobem.

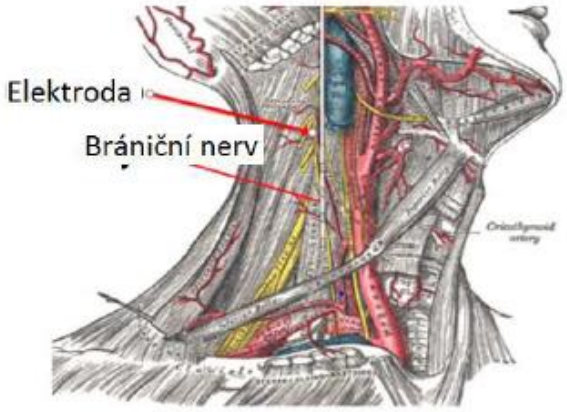
Popis umístění elektrody

Elektrody systému k perkutánní elektrické stimulaci bráničního nervu (PEPNS) jsou zaváděny pod kůži prostřednictvím jehly, podobně jako např. žilní kanyla na ruce. Elektroda je zavedena podél bráničního nervu na krku. Lékař po celou dobu kontroluje průběh zavádění ultrazvukem aby se vyhnul poranění karotického a jugulárního řečiště (žíly a tepny na krku). Jedna elektroda je umístěna na pravou stranu krku a druhá na levou. Elektroda je ohebná plastová hadička vybavená kovovými elektrodami o tloušťce cca 1 milimetr (0.87mm).

Postup zavedení:

1. dezinfekce místa punkce
2. aplikace lokální anestezie (opíchnutí místa zavedení, jako u zubaře)

3. punce kůže v oblasti krční žíly jehlou do hloubky max. cca 2 cm umožňující zavedení elektrody pod kontrolou ultrazvuku na místo stimulace (umístění elektrody viz obrázek níže)
4. kontrola stimulačních parametrů
5. zakrytí místa vstupu (přelepení náplastí)



Jaká jsou možná rizika a nepohodlí?

Možná rizika spojená s použitím systému PEPNS a provedeným zákrokem mohou zahrnovat mj. tato:

Potenciální rizika a komplikace	odhad četnosti
Nemožnost provést stimulaci (z technických nebo anatomických důvodů)	<1%
Barotrauma (poškození plic)	<1%
Ztráta krve (krvácení v místě zavedení elektrody nebo do podkoží)	<1%
Bradyarytmie (pomalý srdeční tep)	<0.01%
popálení	<0.01%
Stimulace okolních nervů (nervy na ruce nebo na krku)	<1%
Úmrtí v důsledku použití PEPNS Systému	<0.01
Únava bránice	<1%
Elektrický výboj	<0.01%
vzduchová embolie	<0.01%
Ohluchnutí	<0.001%
Hematom (modřina, krevní sraženina)	<0.01%
Zánět	<0.1%

Potenciální rizika a komplikace	odhad četnosti
Infekce	<0.1%
Poškození nervu	<0.1%
Bolest	<0.1%
Pneumotorax (kolaps plíce při punkci)	<0.1%
Jizva (v místě punkce)	<0.1%
nekróza tkáně	<0.1%
Alergická reakce	<0.01%
Stimulace bludivého nervu	<0.01%

Tato rizika byla v důsledku dané koncepce studie, detekce chyb, požití standardů, školení a označování minimalizována na přijatelnou míru. Existují také některá potenciální rizika spojená s umělou ventilací a doprovodnými onemocněními pacienta, která zda nejsou uvedena, protože nejsou spojena s použitím systému PEPNS. Použití tohoto přístroje se považuje za poměrně bezpečné, což potvrdily také testy, které se prováděly v rámci preklinických studií.

Jaké jsou možné přínosy této studie?

Tato technologie může zkrátit dobu, po kterou je nutné pacienta ventilovat, nebo tomu tak nemusí být, a pak účast ve studii nebude pro Vás nebo Vašeho rodinného příslušníka žádným přínosem.

Rozhodnete-li se pro neúčast, jaké další možnosti máte?

Můžete se rozhodnout, že se této studie nezúčastníte. Účast či neúčast ve studii nebude mít vůbec žádný vliv na to, jakou léčbu podstoupíte. Alternativou k účasti v této studii je umělá ventilace bez stimulace bránice.

Co se stane, dozvíme-li se v průběhu studie o nových rizicích?

Dostanete veškeré nové informace získané během studie, které by mohly mít vliv na Váš zájem pokračovat ve studii.

Pokud se na základě výsledků získaných během této studie zjistí jakékoli poškození pacienta ve spojitosti s použitím stimulační elektrody, bude tato studie zastavena a Vy budete o těchto zjištěních informován/a. Klinické informace získané v průběhu studie mohou odhalit určitá onemocnění, která vyžadují specifickou léčbu. Veškeré takového informace budou poskytnuty Vašemu ošetřujícímu a praktickému lékaři, kteří zajistí příslušnou léčebnou péči.

Jak bude chráněno Vaše soukromí?

V žádné zprávě nebo publikaci zabývající se touto studií nebude uvedena totožnost pacientů. Přestože se maximálně vynasnažíme zachovat důvěrný charakter záznamů o studii, může se stát, že jejich zveřejnění, včetně osobních informací, bude požadováno zákonem. Je to velmi nepravděpodobné, ale pokud by se tak stalo, nemocnice přijme veškeré kroky, které jí umožňuje zákon, aby ochránila důvěrnost osobních informací pacientů.

Informace získané na základě této studie mohou být předloženy regulačnímu a kontrolnímu orgánu (Státní ústav pro kontrolu léčiv, Etická komise) . Přestože se budeme v co největší míře snažit o zachování důvěrnosti Vašich informací, nemůžeme to stoprocentně zaručit.
Do zdravotnické dokumentace, podle níž se pozná Vaše totožnost, a do formuláře souhlasu, který jste podepsal/a, může nahlížet společnost Stimdia Medical, Inc. nebo regulační orgán. Výsledky této výzkumné studie mohou být prezentovány na seminářích nebo v publikacích, ve kterých však nebude uvedena Vaše totožnost.

Jelikož studie zahrnuje léčbu určitého onemocnění, bude kopie formuláře souhlasu vložena do Vaší zdravotnické dokumentace. To umožní lékařům, kteří Vám poskytují zdravotní péči, získat informace o zákrocích, které u Vás byly rámci studie provedeny, a poskytnout Vám příslušnou léčbu, pokud byste v průběhu studie měl/a zdravotní problémy.

Dostanete za účast ve studii zaplaceno?

Za účast ve studii nebudete nijak odměněni. Mohou Vám být uhrazeny cestovní náklady spojené s návštěvami v rámci studie.

Je účast ve studii spojena s nějakými náklady?

Vaše účast ve studii není spojena s žádnými dalšími poplatky za pobyt v nemocnici nebo za péči lékařů.

Co se stane, pokud Vám bude v průběhu studie způsobena újma na zdraví?

Všechny diagnostické a léčebné postupy, ať už rutinní nebo experimentální, jsou spojeny s určitým rizikem újmy na zdraví. Přes veškerou opatrnost u Vás mohou ve spojitosti se studií vzniknout zdravotní problémy. Dojde-li k tomu, lékaři podílející se na studii Vám pomohou s nalezením vhodné léčby. Podepsáním tohoto formuláře se nevzdáváte žádných svých práv domáhat se odpovědnosti za újmu na zdraví. Zadavatel má uzavřeno zákonem požadované pojištění rizik při provádění této klinické zkoušky.

Co se stane, pokud byste chtěli svou účast ve studii ukončit předčasně?

Vaše účast ve studii je dobrovolná, svůj souhlas proto můžete kdykoli zrušit tím, že to oznámíte lékaři provádějícímu studii. Předčasné ukončení účasti s sebou nenese žádný postih, ani nijak neovlivní výhody, na které máte nárok a které tím neztratíte, a neovlivní Vaši stávající nebo budoucí léčbu.

Rozhodnete-li se svou účast ve výzkumné studii ukončit, měli byste se obrátit na svého lékaře nebo koordinátora studie. Vysvětlí Vám, jaké kroky k tomu musíte podniknout a jaké zdravotní důsledky může předčasné ukončení studie mít. MUDr. Michal Soták má právo kdykoli Vaši účast ve studii ukončit. K tomu může dojít, pokud by se u Vás vyskytla nečekaná reakce, pokud byste nedodržoval/a pokyny či pokud by byla ukončena celá studie.

Co se stane, jestliže studii zadavatel nebo vládní úřad ukončí?

Zadavatel a vládní úřady mají na základě průběžného hodnocení studie právo zastavit zařazování nových pacientů do studie. Jestliže bude studie ukončena před plánovaným datem, bude Vaše další léčba zajištěna.

Co když máte dotazy ohledně této studie?

Máte právo klást ohledně této výzkumné studie jakékoli dotazy, které Vám musejí být zodpovězeny. Budete-li mít další dotazy nebo dojde-li u Vás v souvislosti se studií k újmě na zdraví, obraťte se na MUDr. Michala Sotáka, na tel. čísle: +420 973 202 999. Pokud by nebyl dostupný, zavolá Vám obratem zpět.

Co když máte dotazy ohledně svých práv pacienta?

Tento klinický výzkum bude kontrolován a schvalován etickou komisí (EK) Ústřední vojenské nemocnice – Vojenské fakultní nemocnice Praha.

Souhlas pacienta/rodinného příslušníka/zákonného zástupce:

Výše uvedené informace jsem si přečetl/a. Se svou účastí ve studii dobrovolně souhlasím.

_____ _____

podpis účastníka studie datum

jméno a příjmení účastníka (hůlkovým písmem)

_____ _____

podpis rodinného příslušníka/zákonného zástupce datum

_____

jméno a příjmení rodinného příslušníka/zákonného zástupce (hůlkovým písmem)

_____ _____

podpis osoby, která získala souhlas pacienta datum

_____

jméno a příjmení osoby, která získala souhlas pacienta

Appendix D: Clinical Trials registration Form

NIH U.S. National Library of Medicine

ClinicalTrials.gov

PEPNS System Feasibility Study

ClinicalTrials.gov Identifier: NCT03559933

Recruitment Status : Completed
First Posted : June 18, 2018
Last Update Posted : June 26, 2019

Sponsor:
Stimdia Medical, Inc.

Information provided by (Responsible Party):
Stimdia Medical, Inc.

Study Description

Brief Summary:
The purpose of this feasibility study is to evaluate the safety and performance of the PEPNS System in patients that need to be mechanically ventilated for at least 48 hours and up to 7 days in the Intensive Care Unit (ICU).

Condition or disease	Intervention/treatment	Phase
Ventilator Induced Diaphragmatic Dysfunction (VIDD)	Device: PEPNS System	Not Applicable

Detailed Description:
Mechanical ventilation is a life saving technology but can also cause damage to the lungs and diaphragm such as ventilator induced diaphragmatic dysfunction (VIDD). Research has shown that after being on mandatory mechanical ventilation and sedation the diaphragm begins to atrophy within as little as 18 hours. The PEPNS System consists of a console and disposable lead and will be used to stimulate the patient's diaphragm to contract in synchrony with the inspiratory cycle of the ventilator. The proprietary pdSTIM Lead incorporates multipolar electrodes that align with the left and right phrenic nerves in order to stimulate the nerves to the diaphragm. This feasibility trial will investigate the safety and performance of the PEPNS System as a therapy by stimulating the diaphragm over a 48 hour period to facilitate weaning from the mechanical ventilator. The patient population includes those need to be mechanically ventilated for at least 48 hours and up to 7 days in the ICU.

Study Design

Study Type
Interventional (Clinical Trial)

Actual Enrollment

12 participants

Allocation:

N/A

Intervention Model:

Single Group Assignment

Intervention Model Description:

The pdSTIM Leads are temporarily inserted near the right and left phrenic nerves and connected to the PEPNS System console. Duration of stimulation in PEPNS study is up to 48 hours to allow periodic electrical stimulation in daily sessions until the patients is weaned or 48 hours since initiation of stimulation session has elapsed.

Masking:

None (Open Label)

Primary Purpose:

Treatment

Official Title:

Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) System Feasibility Study

Actual Study Start Date

July 10, 2018

Actual Primary Completion Date

May 29, 2019

Actual Study Completion Date

May 29, 2019

Arms and Interventions

Arm	Intervention/treatment
Experimental: PEPNS System The pdSTIM lead will be temporarily inserted near the right and left phrenic nerves and connected to the PEPNS system console in order to stimulate the phrenic nerves and activate the diaphragm on the patients until extubated/removed from mechanical ventilation or until 48 hours has elapsed, whichever comes first.	Device: PEPNS System PEPNS System therapy will be delivered periodically up to 48 hours or less if patient is no longer being mechanically ventilated. Other Name: pdSTIM

Outcome Measures

Primary Outcome Measures

1. Capture of Phrenic Nerve [Time Frame: Up to 48 hours]

   Capture of the Left and/or Right Phrenic Nerve > 80% with an output parameter of < 10.5 volts.

2. Work of Breathing [Time Frame: Up to 48 hours]

   Work of Breathing (WOB) kept between 0.2 and 2.0 joules/L for 80% of breaths.

Secondary Outcome Measures

1. Safe and successful lead placement [Time Frame: Up to 48 hours]

   The percentage of patients who receive safe and successful placement of the multipolar lead in the left and right phrenic nerve utilizing ultrasound guidance will be determined.

2. Phrenic nerve stimulation effectiveness [Time Frame: Up to 48 hours]

   Phrenic nerve stimulation in synchrony with Mechanical Ventilation breaths will be measured to verify that is occurs with inspiration.

3. Serious device/procedure related adverse events [Time Frame: Up to 48 hours]

   The percentage of patients who experience one or more serious device/procedure-related adverse events during the study will be reported.

Eligibility Criteria

Ages Eligible for Study:

18 Years and older (Adult, Older Adult)

Sexes Eligible for Study:

All

Accepts Healthy Volunteers:

No

Criteria

Inclusion Criteria:

1. 18 years or older (Adult).
2. Able and willing to give informed consent or whose legally authorized representative is able and willing to give informed consent.
3. Subject who in the opinion of the admitting consultant/intensivist is likely to be ventilated for > 48 hours from time of recruitment since study treatment will be for up to 48 hours.

Exclusion Criteria:

1. Subject has a left ventricular ejection fraction (LVEF) < 20%.
2. Subject unlikely to survive 72 hours due to coexisting medical conditions.
3. Subject has an implanted pulse generator or implanted electronic device:
4. Subject has experienced an Acute Myocardial Infarction (AMI) within 72 hours prior to this screening or patient is on high dose inotropic support or subject is deemed to be in cardiogenic shock.
5. Subject has significant bleeding diathesis, or is at risk of significant haemorrhage, patient is receiving full dose systemic anticoagulation
6. Subject has a known or suspected phrenic nerve paralysis or neuromuscular or inflammatory muscle diseases where the diaphragm itself may not be functional.
7. Subject has an active systemic infection or local infection at or around the insertion site. Subject is neutropenic or has signs of significant immunocompromise.
8. Subject is known or suspected to be pregnant or is lactating.
9. Subject will be unavailable for, or is unwilling to comply with, follow up requirements of the protocol.
10. Subject is currently enrolled or is expected to be enrolled in any other study of an investigational drug or device who has received treatment under that protocol with the investigational product during the 30 days prior to screening.
11. Subject has undergone a surgery or interventional procedure within the neck region aside from placement of an internal jugular (IJ) vein catheter.
12. Subject has been diagnosed and has been treated for neck cancer within the past 5 years.
13. Subject is known to have a demonstrated intra cardiac thrombus on echocardiography.
14. Subject has uncontrolled hyperthyroidism, hypertension.
15. Subject has had any cerebral ischemic event (Stroke or Transient Ischemic Attack TIA) in the 6-month interval preceding the screening date.
16. Subject has degenerative nerve disorders such as amyotrophic laterals sclerosis (ALS).
17. Subject has an elevated hemidiaphragm on chest x-ray.
18. Subject written informed consent not obtained.

Contacts and Locations

Locations

Czechia

Military University Hospital (ÚVN)
Prague, Czechia

Ireland

Beaumont Hospital
Dublin, Ireland

Sponsors and Collaborators

Stimdia Medical, Inc.

Investigators

Principal Investigator:	Michal M Soták, MD	Military University I lospital (UVN) Prague
Principal Investigator:	James O'Rourke, PhD	Beaumont Hospital Dublin, Ireland

More Information

Responsible Party:
Stimdia Medical, Inc.

ClinicalTrials.gov Identifier:
NCT03559933

Other Study ID Numbers:
CIP0001

First Posted:
June 18, 2018

Last Update Posted:
June 26, 2019

Last Verified:
June 2019

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD:
No

Plan Description:
There will be no patient identifying information on any of the study case reports forms and all patients will only be identified by a study number.

Studies a U.S. FDA-regulated Drug Product:
No

Studies a U.S. FDA-regulated Device Product:
Yes

Device Product Not Approved or Cleared by U.S. FDA:
Yes

Product Manufactured in and Exported from the U.S.:
Yes

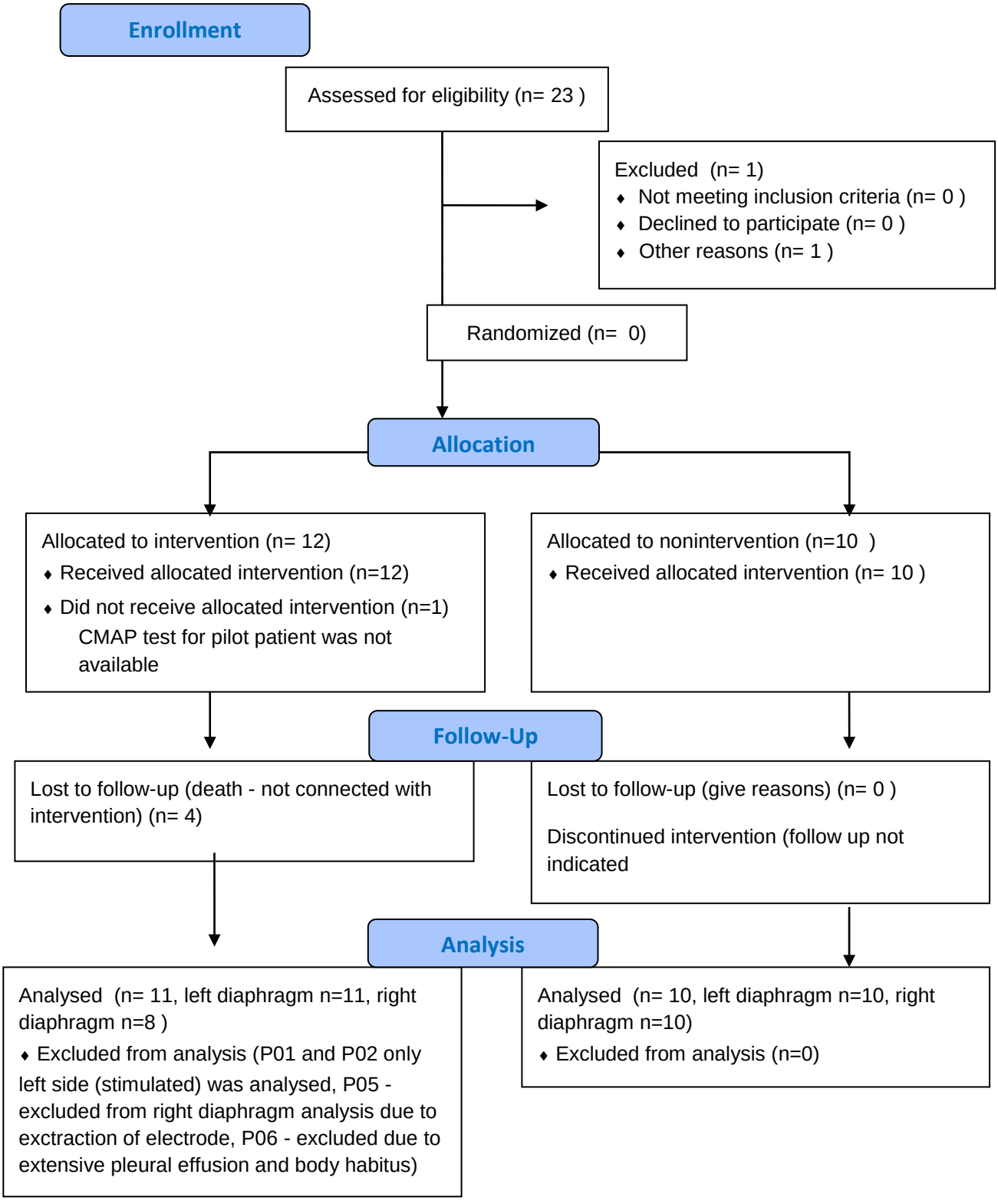
Appendix E: Stimulation Voltages (taken at the begining, in the middle and at the end of every stimmulation session)

	Stimulation No.1			**Stimulation No.2**			**Stimulation No.3**			**Stimulation No.4**			**Stimulation No.5**			**Stimulation No.6**		
P01 L Current (mA)	9	9	9	3	1,5	1,5	2	2	2	2	2	2	3,5	3,5	3,5	1	1	1
P01 L Voltage (V)	4	4	4	1,5	1	1	1	1	1	1	1	1	1,5	1,5	1,5	1	1	1
P02 L Current (mA)	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	8,5	8,5
P02 L Voltage (V)	12	12	12	12	12	12	12	12	12	11	11	11	10,5	10,5	10,5	10	10	10
P03 L Current (mA)	4	4	4	3	3	3	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5
P03 L Voltage (V)	4	4	4	3	3	3	2,4	2,4	2,4	3	3	3	2	2	2	2,5	2,5	2,5
P03 R Current (mA)	5	5	5	2	2	2	2,5	2,5	2,5	2,5	2,5	2,5	2,5	2,5	2,5	2,5	2,5	2,5
P03 R Voltage (V)	6	6	6	3	3	2,4	2,4	2,4	3	3	3	2,5	2,5	2,5	2,5	2,5	2,5	2,5
P04 L Current (mA)	1,5	1,5	1,5	1,5	1,5	1,5	1	1	1	1,5	1,5	2	2	2	2	4	4	4
P04 L Voltage (V)	1	1	1	1	1	1	0,8	0,8	0,8	0,8	0,8	1,5	1,5	1,5	1,5	3	3	3
P04 R Current (mA)	2	2	2	2	2	2	1,5	1,5	1,5	2	2	2,5	1,5	1,5	1,5	1,25	1,25	1,25
P04 R Voltage (V)	1	1	1	1	1	1	0,8	0,8	0,8	0,8	0,8	2	1	1	1	0,5	0,5	0,5
P05 L Current (mA)	5	5	5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	7,5	5	5
P05 L Voltage (V)	5	8	8	6	6	6	8	8	8	8	8	8	8	8	8	8	4	4
P05 R Current (mA)	5	5	5															
P05 R Voltage (V)	4	4	4							Lead removed								
P06 L Current (mA)	5	5	5	5	3,5	3,5	5	5	5	5	5	5	3	3	3	2,5	2,5	2,5
P06 L Voltage (V)	8	8	8	7	3,5	3,5	6	6	6	5,6	5,6	5,6	4	4	4	3	3	3
P06 R Current (mA)	4	4	4	3	3	3	6	6	6	4,5	4,5	4,5	5,5	5	4,5	2,5	2,5	2,5
P06 R Voltage (V)	3,4	3,4	3,4	3	3	3	5	5	5	4	4	4	6	5	5	2	2	2
P07 L Current (mA)	3	3	3	1,5	1,5	1,5	1,5	1,5	1,5	1,25	1,25	1,25	1,25	1,25	1,25	1	1,05	1,05
P07 L Voltage (V)	2	2	2	1	1	1	1	1	1	1	1	1	0,8	0,8	0,8	0,8	0,8	0,8
P07 R Current (mA)	9	9	9	12	11	11	7,5	7,5	7,5	8	8	8	8	8	8	8	10	10
P07 R Voltage (V)	6	6	6	8	8	8	10	10	10	6	6	6	6	6	6	6	7	7
P08 L Current (mA)	6,5	6,5	6,5	3	3	3	2,5	2,5	2,5	4	5	5	5,5	5,5	5,5	5,5	2	2
P08 L Voltage (V)	8	8	8	4,5	4,5	4,5	4	4	4	4,5	4,5	4,5	8	8	8	6	2	2
P08 R Current (mA)	7,5	7,5	7,5	5	5	5	2,5	2,5	2,5	9	7	7	7	7	7	7	6	6
P08 R Voltage (V)	8	8	8	10	10	10	7,5	7,5	7,5	10	10	10	10	10	10	10	8	8
P09 L Current (mA)	1	1	1	0,5	0,5	0,5	2,5	2,5	2,5	1	1	1	0,5	0,5	0,5	0,6	0,6	0,6
P09 L Voltage (V)	2	2	2	0,5	0,5	0,5	3	3	3	2	2	2	0,5	0,5	0,5	0,6	0,6	0,6
P09 R Current (mA)	6,5	6,5	6,5	7	7	7	5,5	5,5	5,5	5,5	5,5	5,5	5,5	5,5	5,5	6	6	6
P09 R Voltage (V)	4	4	4	4,5	4,5	4,5	6	6	6	4	5	5	4,5	4,5	4,5	6	6	6
P10 L Current (mA)	3	3	3	3,25	3,25	3,25	2	2	2	2	2	2	2,375	2,375	2,5	2,25	2,25	2,25
P10 L Voltage (V)	2	2	2	3	3	3	2	2	2	2	2	2	2	2	2,5	2	2	2
P10 R Current (mA)	10	10	10	10	10	10	8	8	8	8	8	8	7	7	7	8,5	8,5	8,5
P10 R Voltage (V)	4	4	4	3	3	3	3,5	3,5	3,5	2,5	2,5	2,5	2	2	2	3	3	3
P11 L Current (mA)	1,25	1,25	1,25	1,25	1,25	1,25	3	3	3	3	3	3	1,75	1,75	1,75	2,325	2,33	2,325
P11 L Voltage (V)	1	1	1	1	1	1	2,5	2,5	2,5	2	2	2	1	1	1	1,5	1,5	1,5
P11 R Current (mA)	5	5	5	5	5	5	9	9	9	8,5	8,5	8,5	3	3	3	2,4	2,4	2,4
P11 R Voltage (V)	3	3	3	3	3	3	4	4	4	4	4	4	2	2	2	1,5	1,5	1,5
P12 L Current (mA)	3,25	3,25	3,25	4	4	4	4	3,5	3,5	3,25	3,25	3,25	3,5	3,5	3,5	3,5	3,5	3,5
P12 L Voltage (V)	1,5	1,5	1,5	2,5	2,5	2,5	2,5	2	2	2	2	2	2	2	2	2	2	2
P12 R Current (mA)	9	9	9	4	4	4	4	4	4	3	3	3	3,6	3,6	3,6	4,75	4,75	4,75
P12 R Voltage (V)	4	4	4	2	2	2	2	2	2	2	1,5	1,5	1,5	1,5	1,5	2	2	2

Appendix F: Consort 2010 Flow Diagram

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



Appendix G: Detailed patient demographics

Patient ID	Mode of Ventilation	Time on vent before Stimulation (hours)	Sex	Age	Weight (kg)	Height (cm)	BMI	Diagnosis
P01S02	PSV/CPAP	89	MALE	70	60	168	21.3	TBI, COPD, Chronic alcohol abuse
P02S02	PSV	163	MALE	56	100	171	34.2	Fall, Evacuation of subdural hematoma
P03S01	BIPAP, SIMV	139	MALE	74	85	180	26.2	Rupture of AV malformation
P04S01	BIPAP, SIMV, PSV	132	MALE	58	90	175	29.4	Pneumonia, Trauma, TBI
P05S02	PRVC-SIMV,PSV	144	MALE	64	127	185	37.1	TBI
P06S02	PSV	218	MALE	64	97	180	29.9	Trauma, postoperative
P07S02	SIMV, PRVC	173	MALE	51	65	173	21.7	TBI, Pneumonia
P08201	SIMV, PSV	142	MALE	61	90	180	28.0	Trauma, TBI
P09202	PSV	269	MALE	56	140	178	44.2	COPD, ARF, CRF, sepsis
P10S02	SIMV, PSV	101	MALE	56	70	171	23.9	Trauma
P11S01	SIMV, PSV	103	MALE	59	80	175	26.1	TBI, Pneumonia, COPD
P12201	PSV	307	FEMALE	74	68	160	26.6	COPD, ARF, Pneumonia, aspiration
P01C	SIMV	112	MALE	62	82	168	29.1	TBI
P02C	SIMV, PSV	96	MALE	55	91	182	27.5	TBI
P03C	SIMV	156	FEMALE	58	100	173	33.4	Multiple tauma, TBI
P04C	PRVC-SIMV	188	FEMALE	77	65	164	24.2	Abdominal surgery, sepsis
P05C	SIMV, PSV	123	MALE	45	73	174	24.1	COPD, pneumonia
P06C	SIMV, PSV	172	MALE	62	85	178	26.8	Subarachnoideal haemorhage
P07C	PSV	202	MALE	67	94	185	27.5	TBI
P08C	SIMV	166	FEMALE	72	86	164	32.0	TBI
P09C	SIMV, PRVC, PSV	179	FEMALE	49	60	171	20.5	Abdominal surgery, sepsis
P10C	SIMV, PSV	201	MALE	55	89	180	27.5	TBI, trauma

Abbreviation: P01-P10 - patient 01-10, S01 - site 01 (Military University Hospital Prague, Czech republic), S02 - site 02 (Beaumont Hospital, Dublin, Ireland), P01C - P10C - patient 01-10 control group, COPD - chronic obstructive pulmonary disease, TBI - trauma brain injury, ARF/CRF - acute/chronic renal failure

Appendix H: Diaphragm Thickness Measurements

Patient ID	Side	Mean Thickness (mm)			Fractional change	
		Baseline	24 Hours	48 Hours	0-24 Hours	0-48 Hours
P01S02	L	2.333	2.220	2.133	–0.0571	–0.0857
	R	2.100	2.133	2.233	+0.0159	+0.0635
P02S02	L	2.567	2.767	2.567	+0.0779	+0.0000
	R	2.567	2.633	2.800	+0.0260	+0.0909
P03S01	L	2.530	2.410	2.917	–0.0474	+0.1528
	R	1.770	1.867	1.943	+0.0546	+0.0979
P04S01	L	2.167	2.010	2.157	–0.0723	–0.0046
	R	2.170	2.110	2.270	–0.0276	+0.0461
P05S02	L	2.933	2.844	3.044	–0.0303	+0.0379
	R	2.867	2.700	2.633	–0.0581	–0.0814
P07S02	L	1.422	1.689	1.667	+0.1875	+0.1719
	R	1.622	1.556	2.022	–0.0411	+0.2466
P08S01	L	1.768	1.803	1.902	+0.0201	+0.0761
	R	1.784	1.753	2.233	–0.0174	+0.2516
P09S02	L	2.978	2.511	2.811	–0.1567	–0.0560
	R	1.867	2.367	2.578	+0.2679	+0.3810
P10S02	L	1.144	1.456	1.456	+0.2718	+0.2718
	R	1.311	1.744	1.622	+0.3305	+0.2373
P11201	L	1.730	2.203	2.343	+0.2736	+0.3545
	R	2.263	2.370	2.408	+0.0471	+0.0638
P12S01	L	1.567	1.873	1.952	+0.1957	+0.2461
	R	1.790	1.926	1.766	+0.0757	–0.0137
P01C	L	1.943	1.667	1.424	–0.1420	–0.2671
	R	2.083	1.807	1.467	–0.1325	–0.2957
P02C	L	1.890	1.990	2.020	+0.0529	+0.0688
	R	2.160	1.943	1.763	–0.1005	–0.1977
P03C	L	1.940	1.823	1.650	–0.0603	–0.1495
	R	2.160	1.860	1.670	–0.1389	–0.2269
P04C	L	2.193	2.050	2.047	–0.0652	–0.0666
	R	2.227	2.133	2.050	–0.0422	–0.0795
P05C	L	1.463	1.467	1.520	+0.0027	+0.0389
	R	1.537	1.553	1.600	+0.0104	+0.0410
P06C	L	1.927	1.863	1.823	–0.0332	–0.0540
	R	1.783	1.727	1.607	–0.0314	–0.0987
P07C	L	2.667	2.080	1.890	–0.2201	–0.2913
	R	2.670	2.093	1.880	–0.2161	–0.2959
P08C	L	2.280	2.297	1.970	+0.0075	–0.1360
	R	2.170	2.007	1.707	–0.0751	–0.2040
P09C	L	1.587	1.577	1.553	–0.0063	–0.0214
	R	1.803	1.773	1.480	–0.0166	–0.1791
P10C	L	1.600	1.633	1.597	+0.0206	–0.0019
	R	1.833	1.820	1.593	–0.0071	–0.1309

Abbreviations: P01–P10—patient 01–10, S01—site 01 (Military University Hospital Prague, Czech Republic), S02—site 02 (Beaumont Hospital, Dublin, Ireland), P01C–P10C—patient 01–10 control group.

Appendix I: Diaphragm Thickness Fractional Change

Pacient ID	Side	Fractional change 0-24h			Fractional change 0-48h		
		Utrasound	Ultrasound - Manual	Manual	Ultrasound	Ultrasound - Manual	Manual
P01S02	Left	–0.0571	–0.0405	–0.0579	–0.0857	–0.0853	–0.1006
	Right (NS)	+0.0159	+0.0238	+0.0094	+0.0635	+0.0730	+0.0546
P02S02	Left	+0.0779	+0.0812	+0.0914	+0.0000	+0.0012	+0.0224
	Right (NS)	+0.0260	+0.0211	+0.0274	+0.0909	+0.0858	+0.1018
P03S01	Left	–0.0474	–0.0410	–0.0808	+0.1528	+0.1324	+0.1307
	Right	+0.0546	+0.0582	+0.0274	+0.0979	+0.0939	+0.0894
P04S01	Left	–0.0723	–0.0280	–0.0377	–0.0046	–0.0079	–0.0641
	Right	–0.0276	–0.0180	+0.0028	+0.0461	+0.0258	+0.0107
P05S02	Left	–0.0307	–0.0238	–0.0138	+0.0389	+0.0306	+0.0530
	Right (NS)	–0.0582	+0.0332	+0.0314	–0.0802	+0.0076	+0.0184
P07S02	Left	+0.1901	+0.1890	+0.1912	+0.1739	+0.1911	+0.1911
	Right	–0.0407	–0.0327	–0.0105	+0.2465	+0.2451	+0.2325
P08S01	Left	+0.0201	+0.0665	+0.1236	+0.0761	+0.0750	+0.1044
	Right	–0.0174	–0.0130	+0.0131	+0.2516	+0.2717	+0.2658
P09202	Left	–0.1567	–0.1461	–0.1346	–0.0560	–0.0439	–0.1070
	Right	+0.2679	+0.2658	+0.2337	+0.3810	+0.3690	+0.3582
P10S02	Left	+0.2718	+0.2809	+0.2904	+0.2718	+0.2669	+0.3025
	Right	+0.3305	+0.3311	+0.3263	+0.2373	+0.2399	+0.2306
P11S01	Left	+0.2736	+0.2831	+0.2944	+0.3545	+0.3550	+0.3686
	Right	+0.0471	+0.0653	+0.0738	+0.0638	+0.0773	+0.1246
P12201	Left	+0.1957	+0.1854	+0.1637	+0.2461	+0.2297	+0.2151
	Right	+0.0757	+0.0783	+0.0488	–0.0137	–0.0039	–0.0017
P01C	Left	–0.1420	–0.1438	–0.1266	–0.2671	–0.2589	–0.2573
	Right	–0.1325	–0.1220	–0.1124	–0.2957	–0.2909	–0.2755
P02C	Left	+0.0529	+0.0683	+0.0534	+0.0688	+0.0806	+0.0840
	Right	–0.1005	–0.0944	–0.0427	–0.1977	–0.1967	–0.1633
P03C	Left	–0.0603	–0.0597	–0.0440	–0.1495	–0.1287	–0.1244
	Right	–0.1389	–0.0138	–0.1189	–0.2269	–0.2208	–0.2059
P04C	Left	–0.0652	–0.0575	–0.0542	–0.0666	–0.0638	–0.0768
	Right	–0.0422	–0.0347	–0.0473	–0.0795	–0.0554	–0.0878
P05C	Left	+0.0027	–0.0136	+0.0158	+0.0389	+0.0361	+0.0459
	Right	+0.0104	+0.1948	+0.0103	+0.0410	+0.0362	+0.0472
P06C	Left	–0.0332	–0.0427	–0.0390	–0.0540	–0.0531	–0.0850
	Right	–0.0314	–0.0410	–0.0520	–0.0987	–0.1026	+0.1022
P07C	Left	–0.2201	–0.2175	–0.2257	–0.2913	–0.2812	–0.2777
	Right	–0.2161	–0.2106	–0.2088	–0.2959	–0.3229	–0.3139
P08C	Left	+0.0075	+0.0176	+0.0044	–0.1360	–0.1423	–0.1728
	Right	–0.0751	–0.0720	–0.0786	–0.2040	–0.2064	–0.2032
P09C	Left	–0.0063	+0.0000	–0.0062	–0.0214	–0.0108	–0.0272
	Right	–0.0166	–0.0111	–0.0132	–0.1791	–0.1775	–0.1651
P10C	Left	+0.0206	+0.0419	+0.0269	–0.0019	+0.0082	–0.0063
	Right	–0.0071	–0.0055	+0.0125	–0.1309	–0.1202	–0.1234

Abbreviations: P01–P10—patient 01–10, S01—site 01 (Military University Hospital Prague, Czech Republic), S02—site 02 (Beaumont Hospital, Dublin, Ireland), P01C–P10C—patient 01–10 control group, NS–non stimulated.