Imágenes para la Entrevista con Emiliano Cotelo via Zoom

radiomundo 1170 am
ENPERSPECTIVA®

Jueves 7 de mayo 2020

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Positive Pressure Ventilation - Fundamentals

Air is forced in, either through dialing the applied pressure (**pressure control**) or the supplied volume (**volume control**).

Patients can vary between being deeply comatose to alert and interactive.

The ventilator can provide

- a **mandatory breath**,
- **assist** a patient who can initiate a breath,
- or a **combination** of the above.

The Harms of Positive Pressure Ventilation- the Evil "**V**"s

- Ventilator-induced lung injury (**VILI**)
  - Volutrauma
  - Atelectotrauma
  - Biotrauma
- Ventilator-associated pneumonia (**VAP**)
- Ventilator-induced diaphragmatic dysfunction (**VIDD**)

Ventilator-Induced Diaphragmatic Dysfunction

VIDD

- "a **loss** of diaphragmatic force-generating capacity that is **specifically related to the use of mechanical ventilation**."

- Work in multiple animal models showed a significant reduction of diaphragmatic force-generating capacity that was proportional to **duration** of mechanical ventilation.

Vassilakopoulos et al. Am J Respir Crit Care Med 2004
Haistma, Curr Opin Anesth 2011

VIDD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2008 VOL. 358 NO. 13

Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans

Cited by 1142 to-date

Sanford Levine, M.D., Taitan Nguyen, B.S.E., Nyali Taylor, M.D., M.P.H., Michael E. Friscia, M.D., Murat T. Budak, M.D., Ph.D., Pamela Rothenberg, B.A., Jianliang Zhu, M.D., Rajeev Sachdeva, M.D., Seema Sonnad, Ph.D., Larry R. Kaiser, M.D., Neal A. Rubinstein, M.D., Ph.D., Scott K. Powers, Ph.D., Ed.D., and Joseph B. Shrager, M.D.

Results

Diaphragm Muscle Fiber Cross Section Reduction

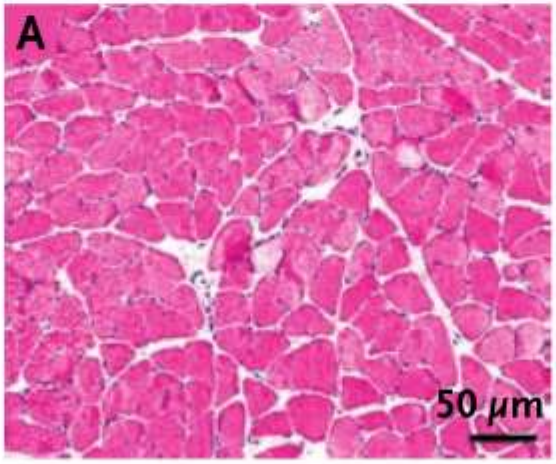
Slow Twitch (Type I): ↓ **57%**

Fast Twitch (Type II): ↓ **53%**

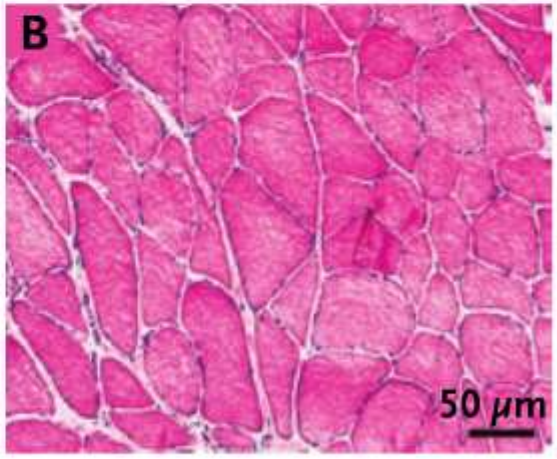
Timeframe

18-69 Hours

Case Histology



Control Histology



Diaphragm muscle fiber atrophy in brain dead donors kept on MV for 18-69 hours (case subjects) vs. surgery patients kept on MV for only 2-3 h (control subjects). H&E staining showed neither inflammation nor necrosis. - Images from Levine et al. 2008

Can VIDD be Prevented?

* The standard teaching is to encourage voluntary modes of ventilation as soon as is feasible.

"daily vacation from sedation"

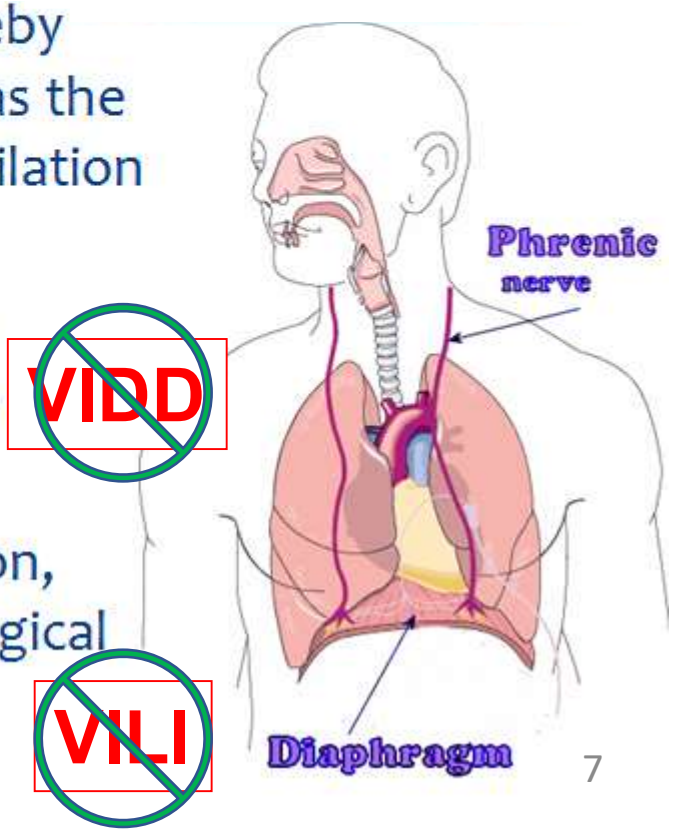
* There is some evidence that despite patients being on a voluntary mode of ventilation (pressure support or PSV) they continue to have a decay in diaphragmatic force.

* Essentially we have no clinically available way to avoid VIDD.

Hermans et al. Crit Care 2010

Could VIDD be Prevented by Pacing the Phrenic Nerves?

* Activating the phrenic nerves and thereby inducing diaphragmatic contractions has the potential to impact on mechanical ventilation in a variety of ways:
  1. Maintain diaphragmatic endurance
  2. Provide exercise and strengthen an already weakened diaphragm
  3. Provide negative pressure ventilation, thereby replicating a more physiological respiratory pattern



Provisional Patent Application

Date: **26 January 2007**

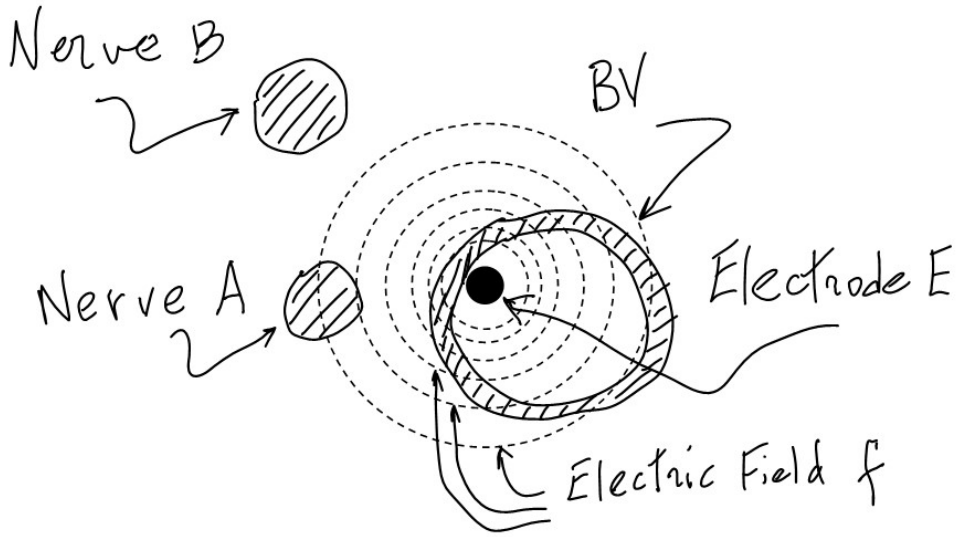
Title: **Minimally Invasive Nerve Stimulation Method and Apparatus**

Inventor: **Joaquin Andres Hoffer**

Nationality: Canadian

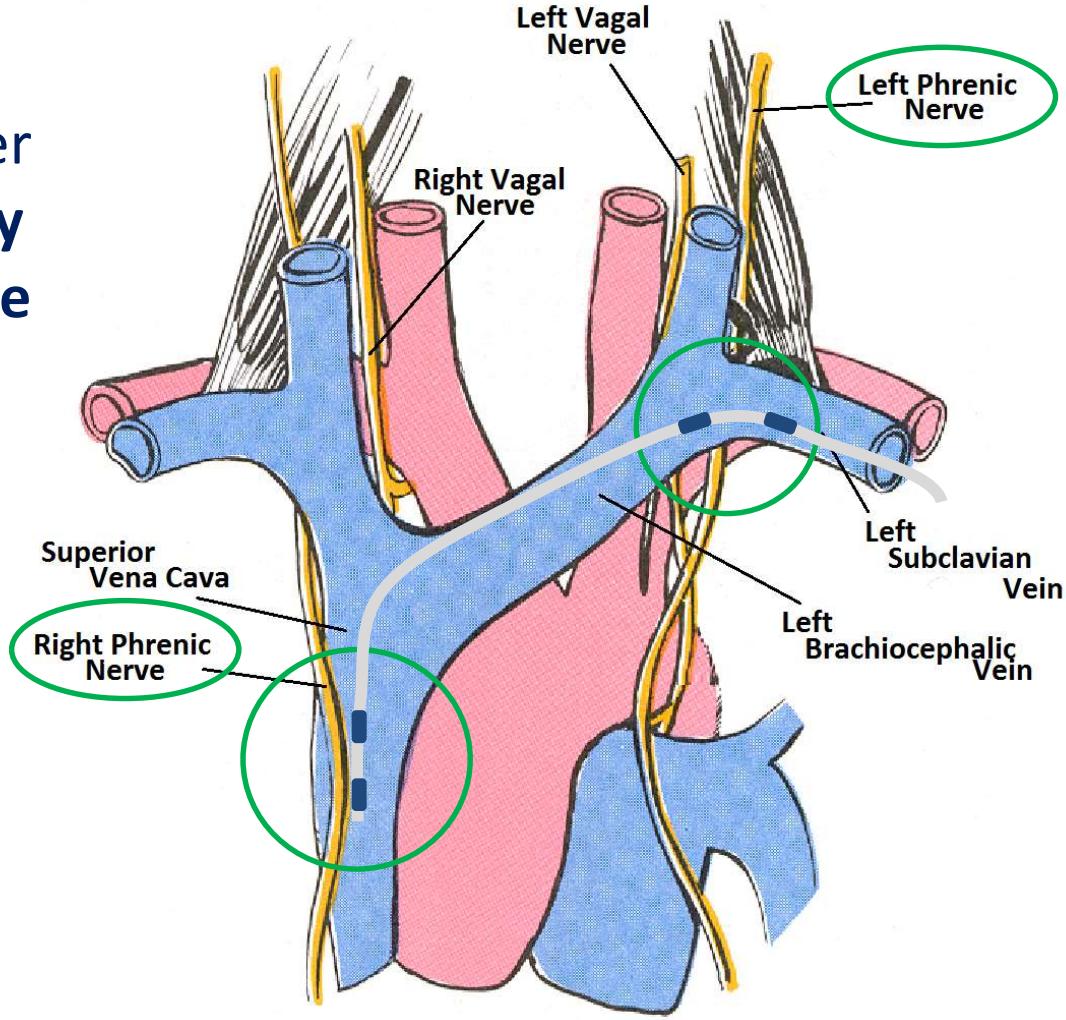
Address: 241 Strong Road
Anmore, British Columbia V3H 5E9
Canada

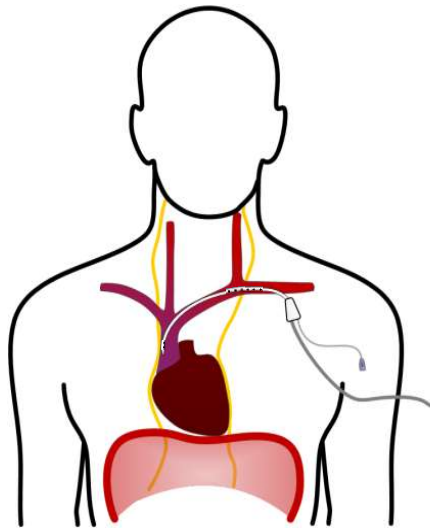
Figure 3. Cross-sectional view showing an Electrode E disposed inside blood vessel BV, and the Electric Field f created by Electrode E which propagates radially outward from the Electrode E. When the distance from target Nerve A to Electrode E is less than the distance from second Nerve B to Electrode E, it is possible to select stimulation strength parameters that will stimulate target Nerve A in isolation, without causing stimulation of more distant nerves such as Nerve B.



IntraVenous Catheter with Stimulation Electrodes

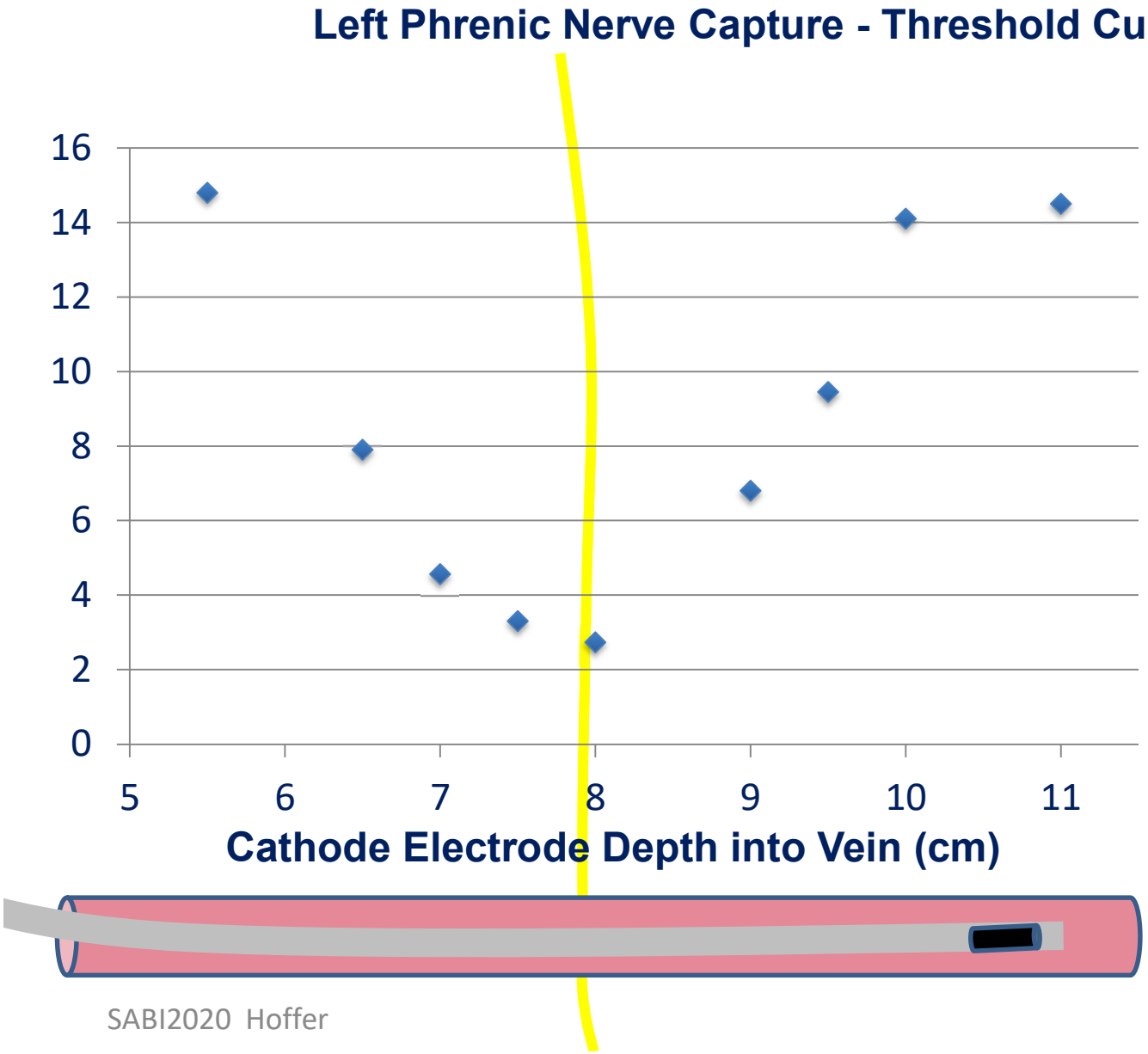
The SFU Hoffer Lab **Minimally Invasive Nerve Stimulation (MINS)** approach to diaphragm pacing





Transvascular Nerve Stimulation Apparatus and Methods. Hoffer, Joaquín Andrés.
U.S. provisional patent filed **January 29, 2007** *(priority date);*
P.C.T. application No. WO2008/092246, published August 7, 2008.

Stimulation Efficacy vs Location in Vein (Chronic Pig 1)



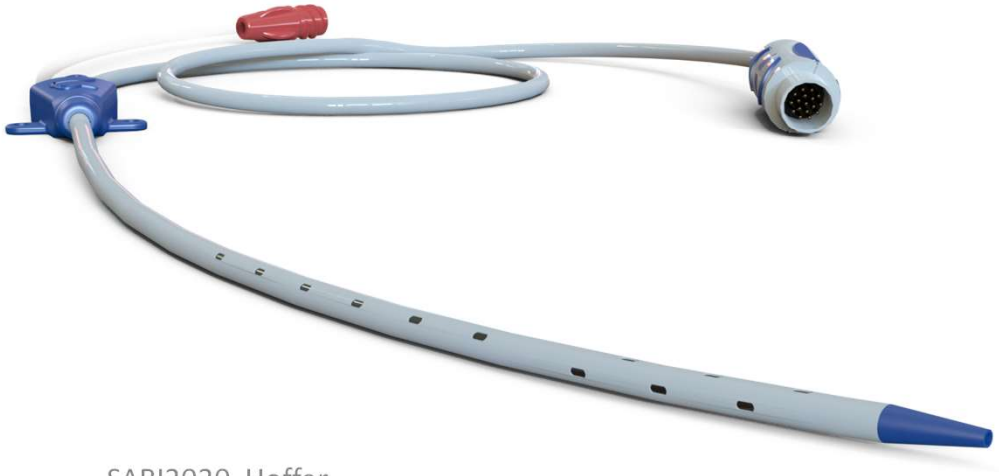
James Saunders, MD

Vancouver CoastalHealth
Promoting wellness. Ensuring care.

SFU MINS Team, April 2009

Lungpacer Medical Inc.

- Company founded in May, 2009
- Spun out from the SFU Neurokinesiology Lab
- Developing a proprietary electrical stimulation technology with the potential to:
  - Improve clinical outcomes for patients in the Intensive Care Unit (**ICU**)
  - Shorten the hospital stay, and
  - Significantly reduce healthcare costs



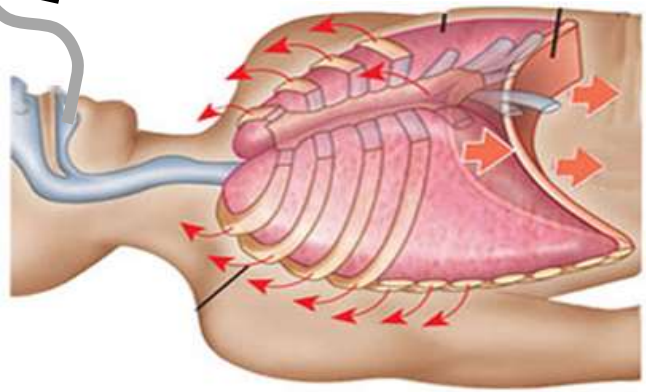
- Simple to place
- Easy to use
- Temporary & easily removable

Diaphragm Pacing Assists Ventilator

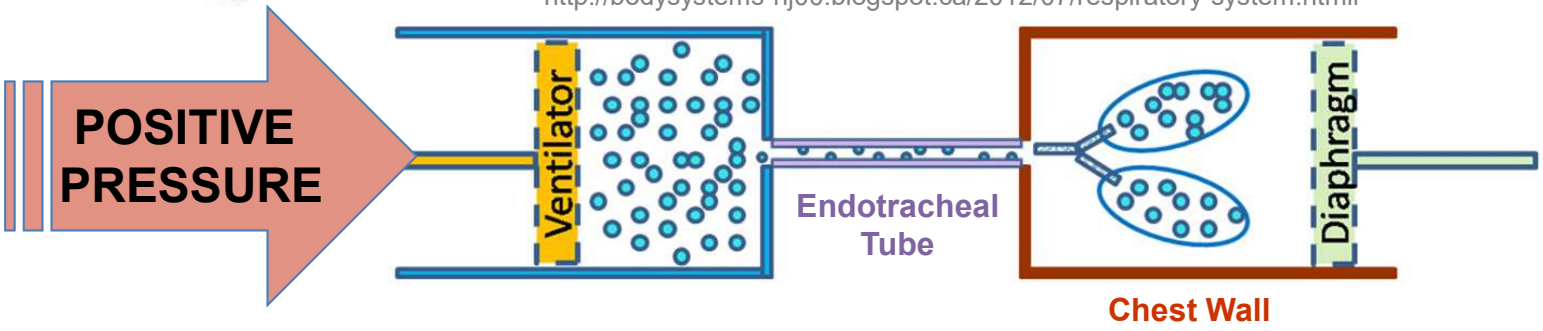
Lungpacer®

Mechanical ventilators use positive pressure; cause lung injury

www.leistungbrasil.com/eng/mechanical-ventilator-luft1g.php



http://bodysystems-rlj00.blogspot.ca/2012/07/respiratory-system.htmll

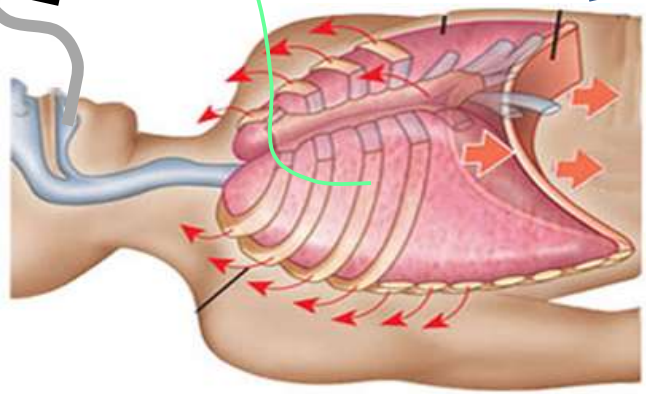


Diaphragm Pacing Assists Ventilator

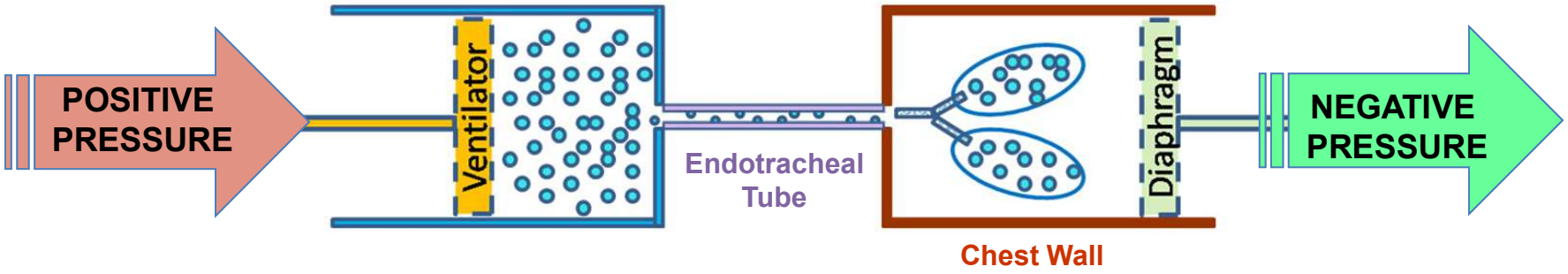
Mechanical ventilators use positive pressure; cause lung injury

Diaphragm pacing provides negative pressure to inflate lungs more normally

www.leistungbrasil.com/eng/mechanical-ventilator-luft1g.php



http://bodysystems-rlj00.blogspot.ca/2012/07/respiratory-system.htmll



Immediate Therapeutic Benefit During Pacing

(Acute Pig #11 17 May 2011)

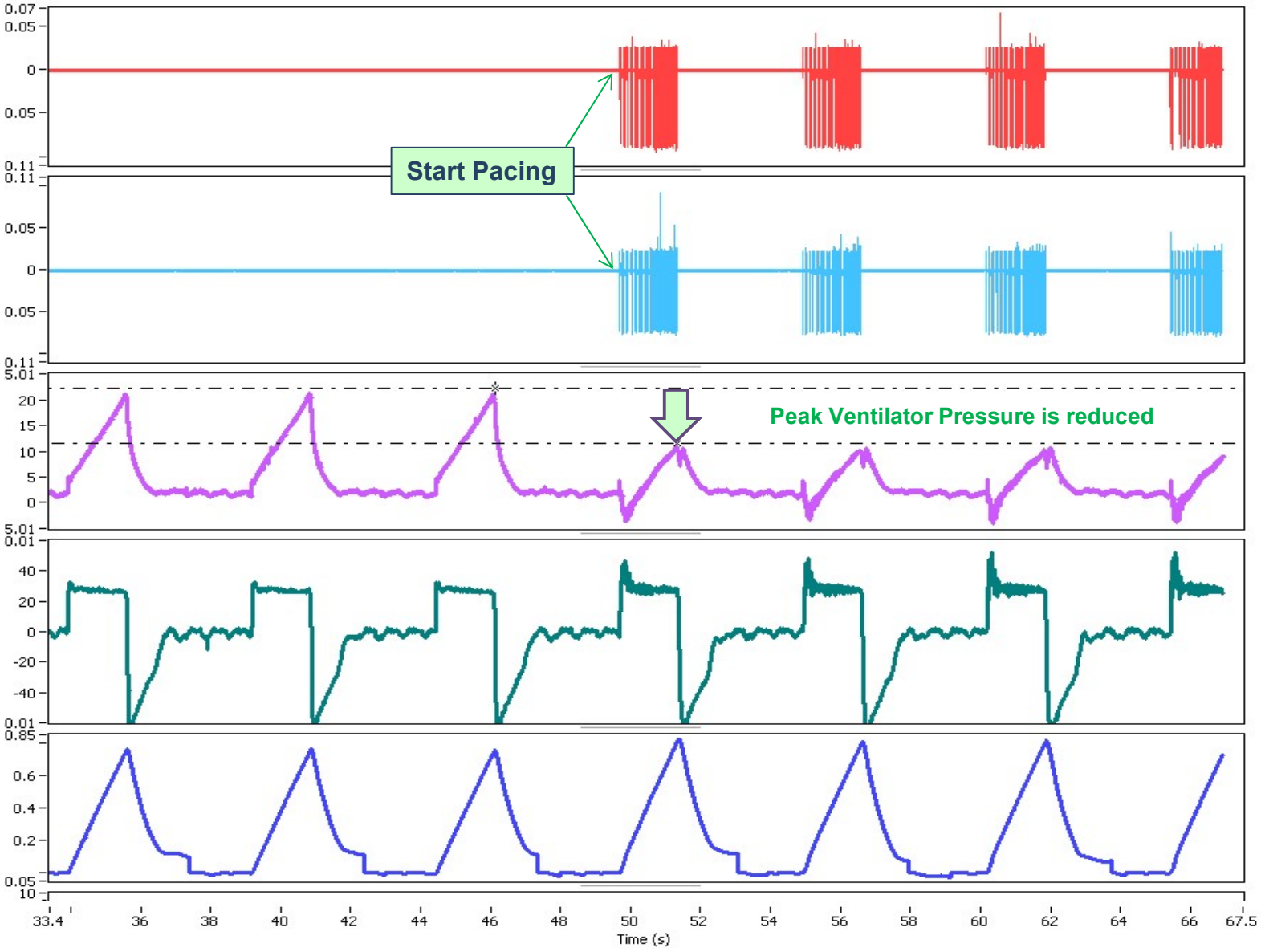
Left phrenic pacing

Right phrenic pacing

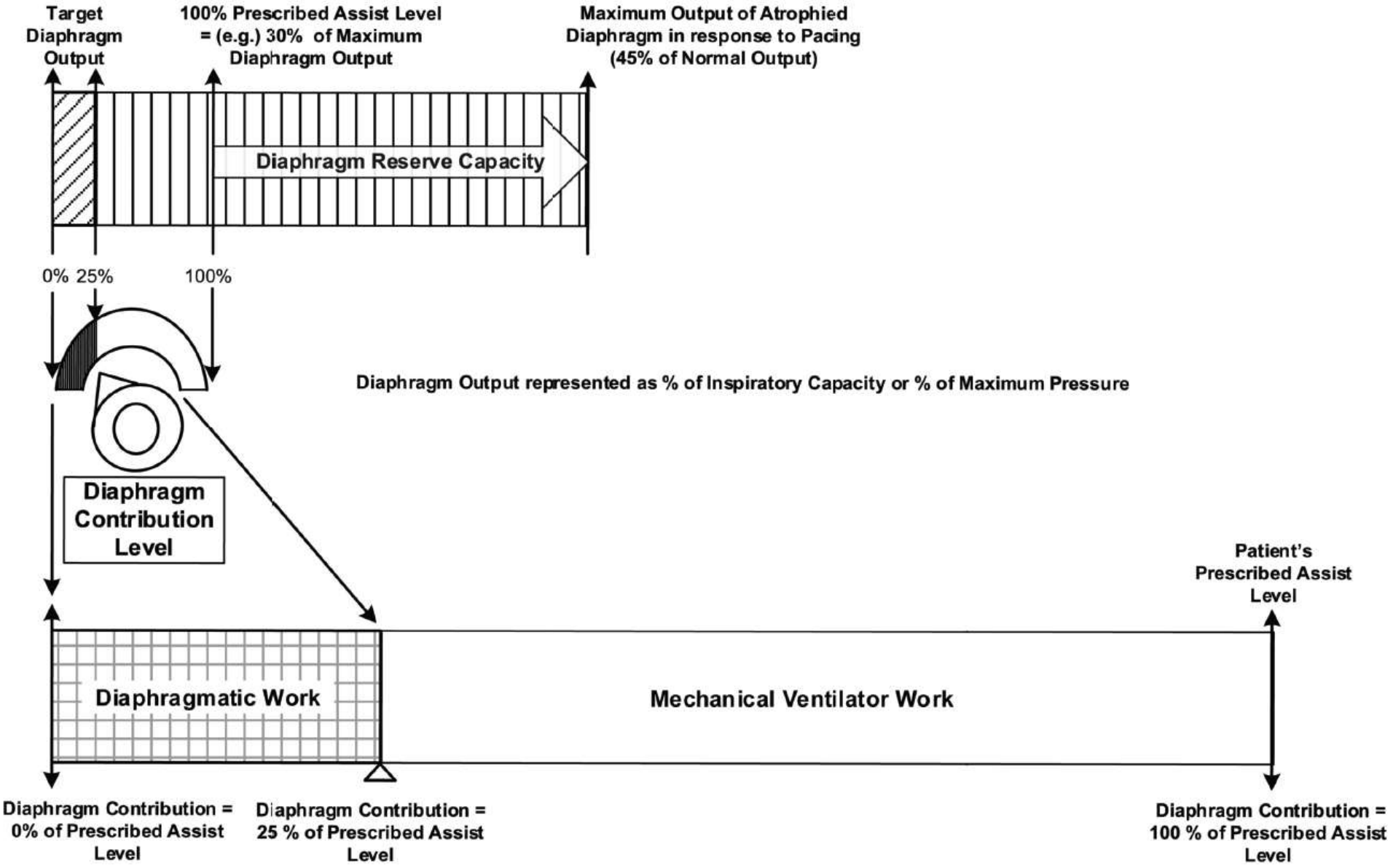
Airway pressure (cm H_2O)

Airway flow (L/min)

Required tidal volume (L)



Therapist specifies desired diaphragm output



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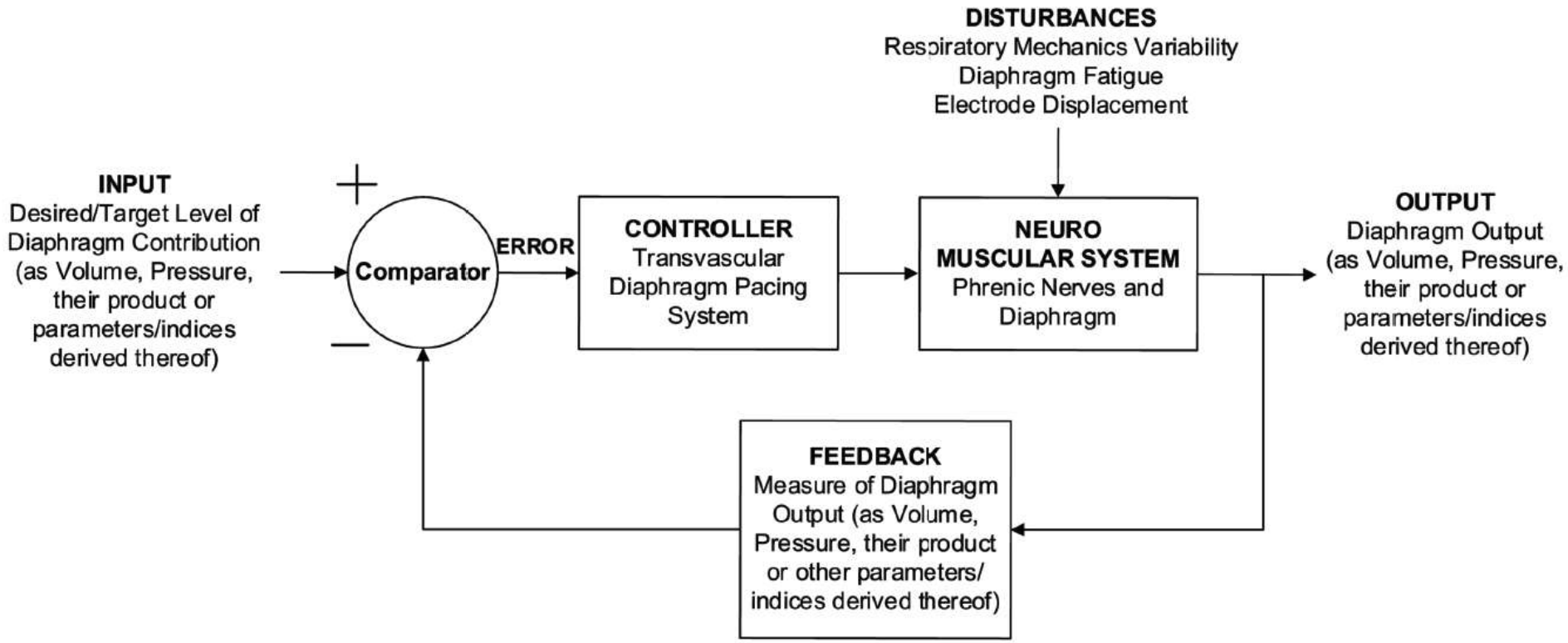
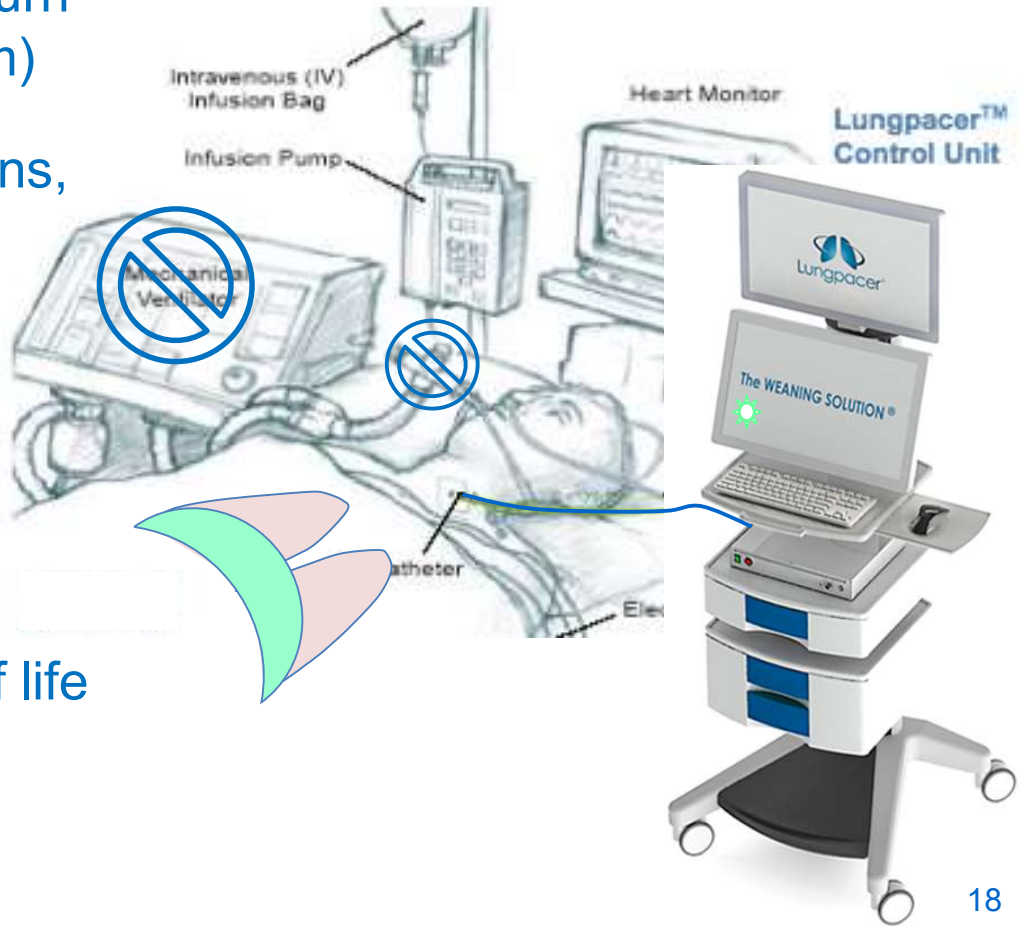
Therapist specifies desired diaphragm contribution; Control Unit monitors output and titrates pacing level



Expected Therapeutic Benefits

1. Protect the diaphragm
2. Protect the lungs
3. Assist the heart (venous return is pumped by the diaphragm)
4. Reduce nosocomial infections, pneumonia
5. Accelerate weaning
6. Liberate patients from MV
7. Reduce mortality rates
8. Improve survivor's quality of life



9 Grants and 11 Industry Awards received

SFU **Innovation Office**
2008, 2010
Prototype Development Funding

new ventures BC competition 2009
3rd Prize Winner

NSERC CRSNG 2008-9 Phase I
2010-13 Phase II
Idea-to-Innovation Grants

BRITISH COLUMBIA INNOVATION COUNCIL 2009
Emerging Technology Award

NRC·IRAP
Canada 2010-2016
Industry Contribution Programs

LifeSciences British Columbia 2010
Innovation and Achievement Award
www.youtube.com/watch?v=_XaE8XM5zpY

wbt™ Innovation Marketplace
2012
Silver Award
San Diego

READY TO ROCKET
2012 2013 2014
2015 2016 2017

bctia british columbia technology industry association
2012
Most Promising Pre-Commercial Technology

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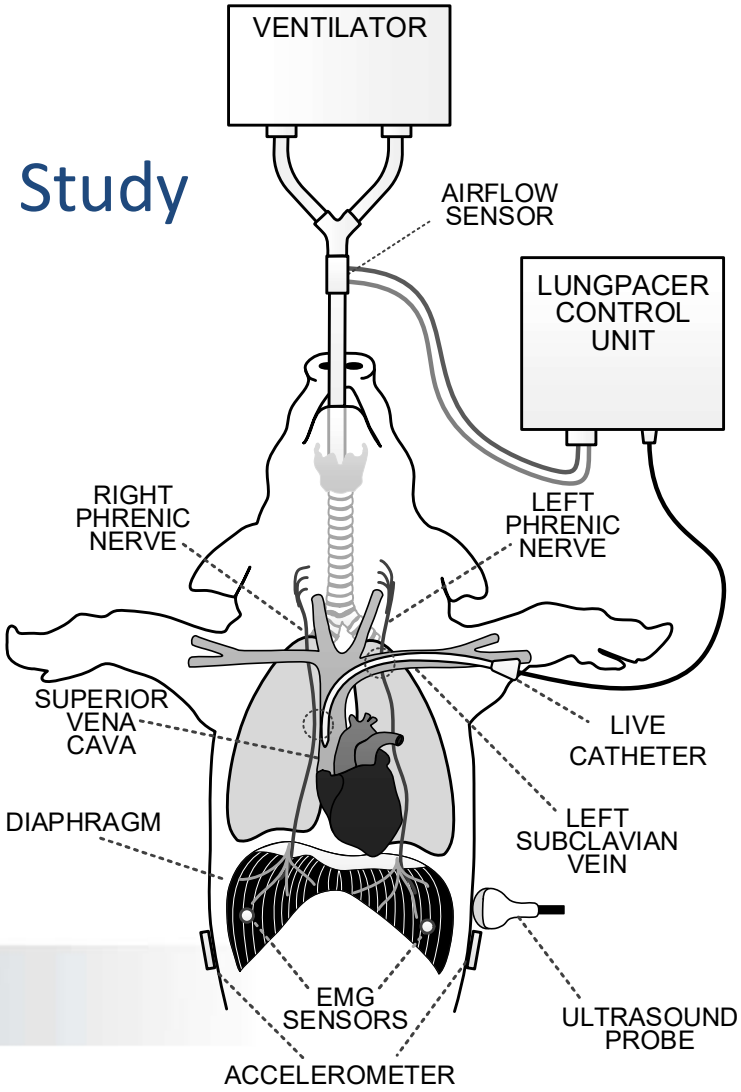
Preclinical Proof of Concept Study

Preclinical Objectives

1. Pace phrenic nerves in synchrony with MV
2. Protect diaphragm from disuse atrophy
3. Preserve diaphragm endurance



Am. J. Respir. Crit. Care Med., Feb. 2017
195(3):339-348.

ORIGINAL ARTICLE

Mitigation of Ventilator-induced Diaphragm Atrophy by Transvenous Phrenic Nerve Stimulation

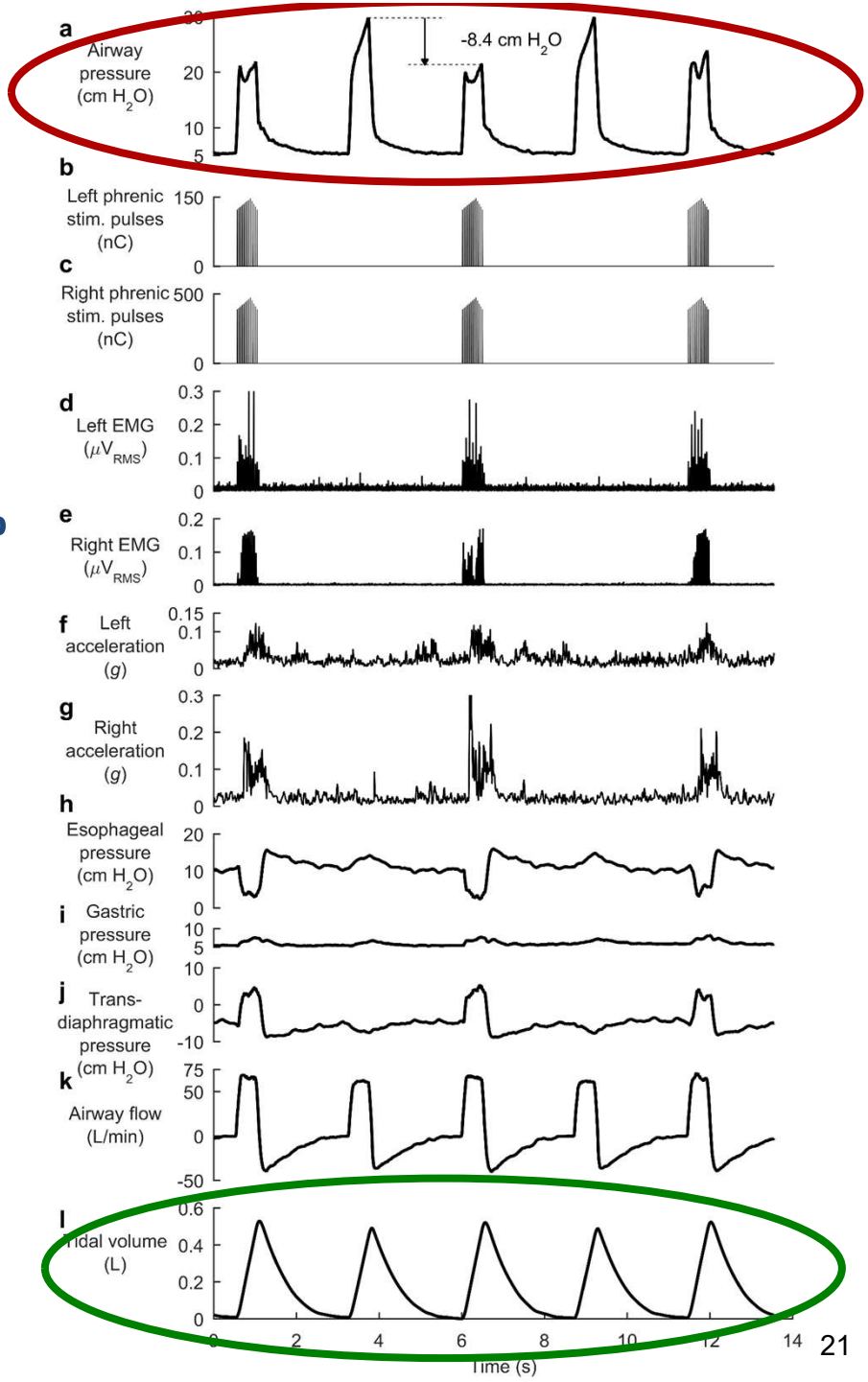
Steven C. Reynolds[1,2,3], Ramasamy Meyyappan[4], Viral Thakkar[4], Bao D. Tran[4], Marc-André Nolette[4], Gautam Sadarangani[4], Rodrigo A. Sandoval[4], Laura Bruulsema[4,5], Brett Hannigan[4,5], Jason W. Li[5], Elizabeth Rohrs[2], Jason Zurba[2], and Joaquín Andrés Hoffer[4,5*]

Preclinical study: Pressure reduction

Test the ability to reduce positive pressure

- Paced every 2nd ventilated breath
- **Airway pressure was reduced 20-30%**
- Tidal Volumes were unchanged

Demonstrated the ability to reduce positive pressure while maintaining tidal volumes, which has been documented to reduce the risk of lung injury[1,2,3]



1. Neto, Lancet Respir Med; March 2016
2. Slutsky et al., N Engl J Med 2013;369:2126-36
3. Fan et al. BMC Medicine 2013, 11:85

Pre-Clinical Study: Ventilated vs. Paced Breaths

Video shows 7 ventilated breaths:

1 Unpaced
2 Paced
3 Unpaced
4 Paced
5 Unpaced
6 Unpaced
7 Paced

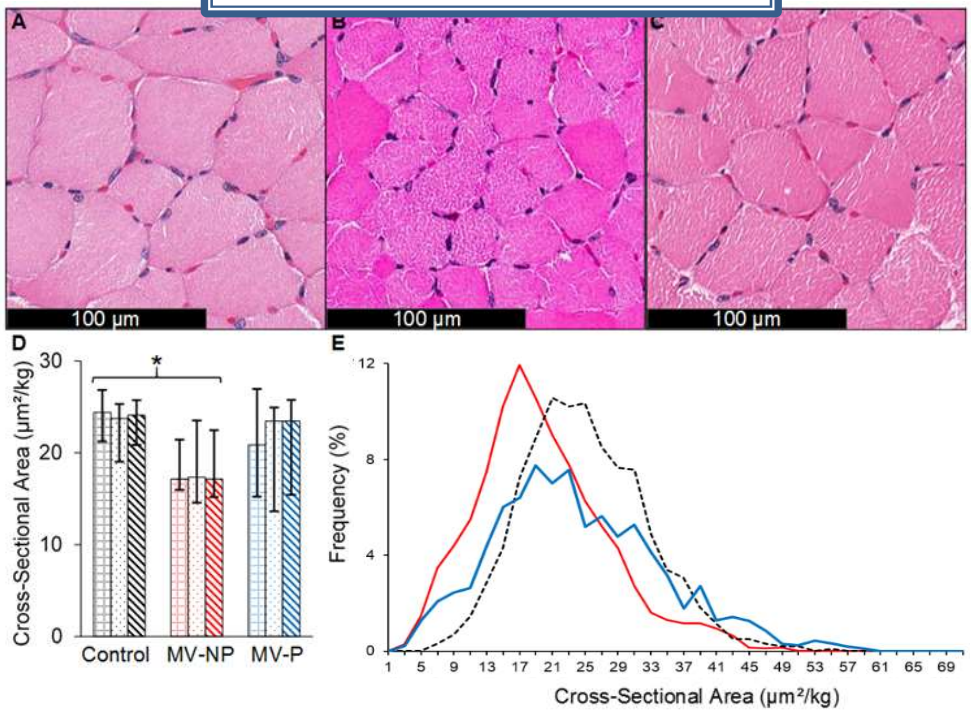
- The distal lungs were better ventilated during paced breaths

Preclinical study: Pacing reduces muscle atrophy

- 60 Hours of IMV caused >25% Atrophy of Diaphragm Muscle Fibers ($p < 0.05$).

✓ **Pacing reduced ventilator-induced muscle fiber atrophy.**

Histological comparison



A: Control; B: MV-NP; C: MV-P

D: Grid = Left side; Dotted white = Right side; Diagonal lines = both sides; *P < 0.05

E: Black dotted = Control; Red solid = MV-NP; Blue solid = MV-P.

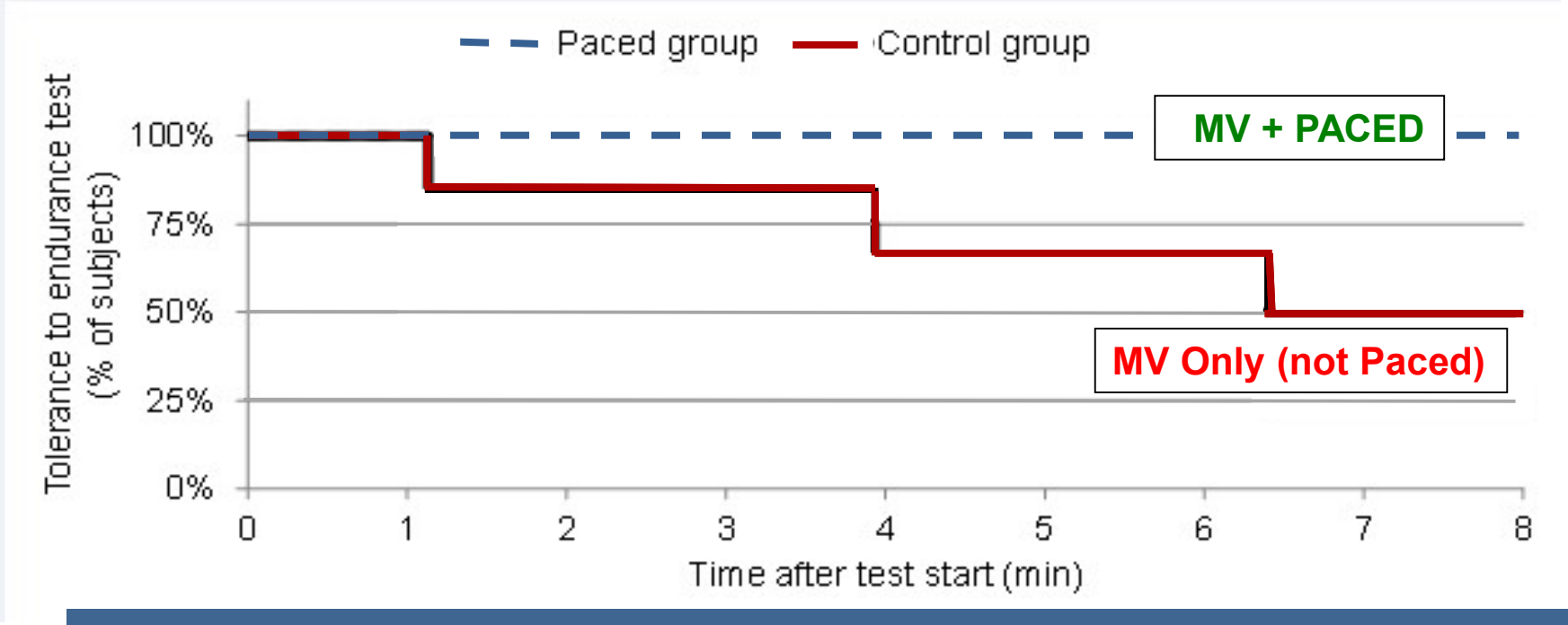
Demonstrated the ability to reduce muscle atrophy, which has been documented to extend MV, ICU, weaning and hospital stay time[1,2,3]

1. Berger et al., Journal of Cachexia, Sarcopenia and Muscle; 2016
2. Slutsky et al., N Engl J Med 2013;369:2126-36
3. Fan et al. BMC Medicine 2013, 11:85

Preclinical study: Respiratory muscle endurance

Tolerance of endurance test

Kaplan-Meier representation of the proportions of the 6 Paced and 6 Control group pigs that were able to tolerate endurance testing for 8 minutes and their time characteristics.



All MV + Paced pigs endured the 8-minute test. 50% of the MV Only pigs failed, due to low O_2 saturation, high CO_2 levels resulting from diaphragm fatigue.

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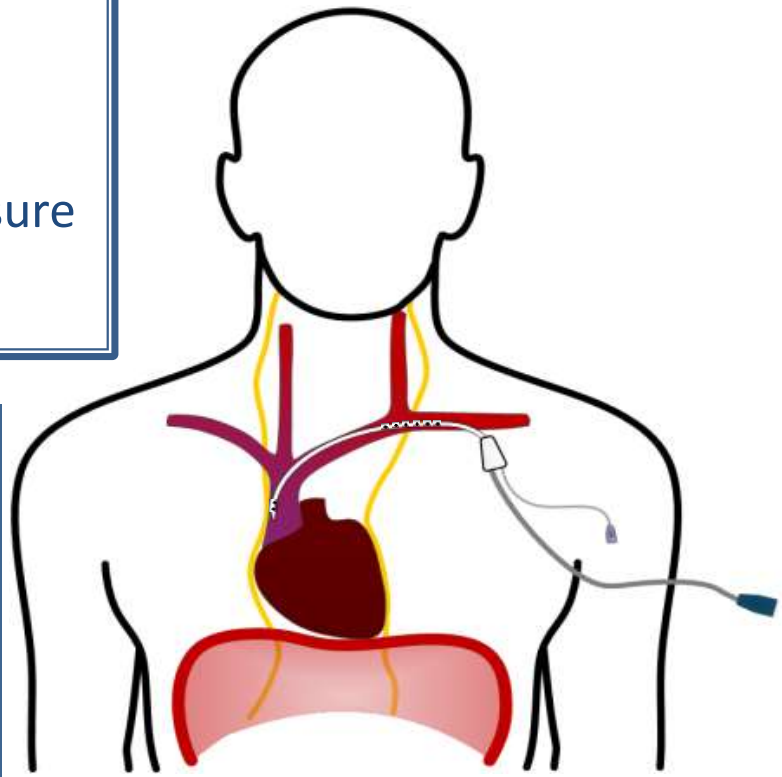
First-in-Human Clinical Studies
Oct 2015 through April 2016

Patient Population: 24 anesthetized, intubated, adult patients on mechanical ventilation.

Study Objectives

1. Place LIVE Catheter, map nerve locations
2. Pace phrenic nerves in synchrony with IMV
3. Demonstrate that Pacing reduces airway pressure
4. Total procedure time < 2 hours



Diaphragm Activation in Ventilated Patients using a Novel Transvenous Phrenic Nerve Pacing Catheter.

Reynolds S; Ebner A; Meffen T; Thakkar V; Gani M; Taylor K; Clark L; Meyyappan R; Sadarangani G; Sandoval R; Rohrs E; Hoffer JA.

Critical Care Medicine, July 2017

45(7):e691-e694.

Human safety assessment

Summary: First-in-Human studies, October 2015-April 2016

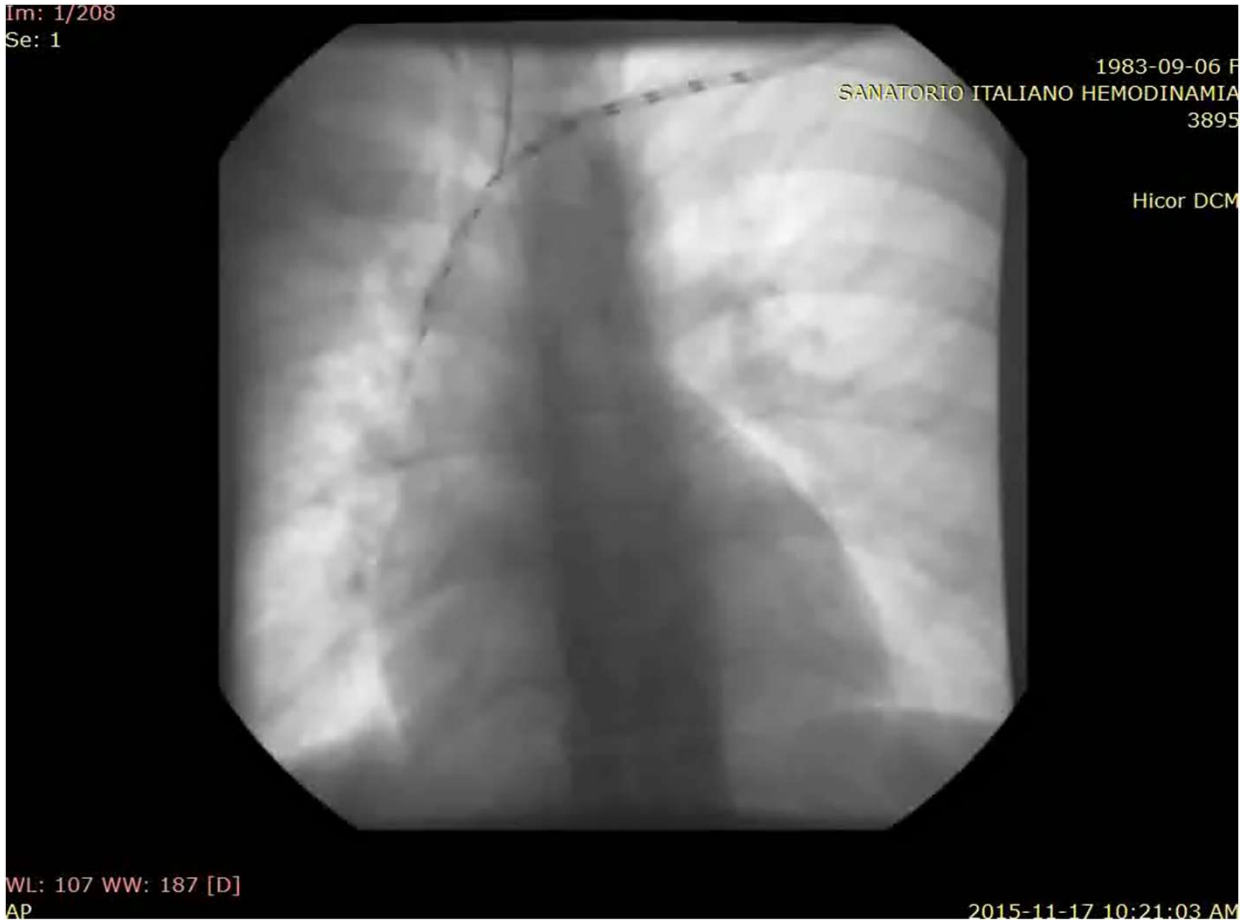
		Successful N/ Total N
Primary Endpoints	**Successful LIVE** Catheter Insertion and Placement	**24/24**
	Absence of device- or procedure-related **adverse events**	**24/24**
Secondary Endpoints	**Bilateral** phrenic **nerve stimulation**	**20[1,3]/23[2]**
	Diaphragm contraction in synchrony with IMV	**22/22[2,3]**
	Reduction of airway **pressure**	**22/22**

1 In two patients, only one phrenic nerve could be stimulated.

2 One patient was excluded from the procedure after LIVE Catheter insertion but prior to nerve stimulation, due to unstable blood pressure that was unrelated to the Lungpacer System.

3 In one patient, neither phrenic nerve could be stimulated.

Fluoroscopy of Diaphragm Pacing

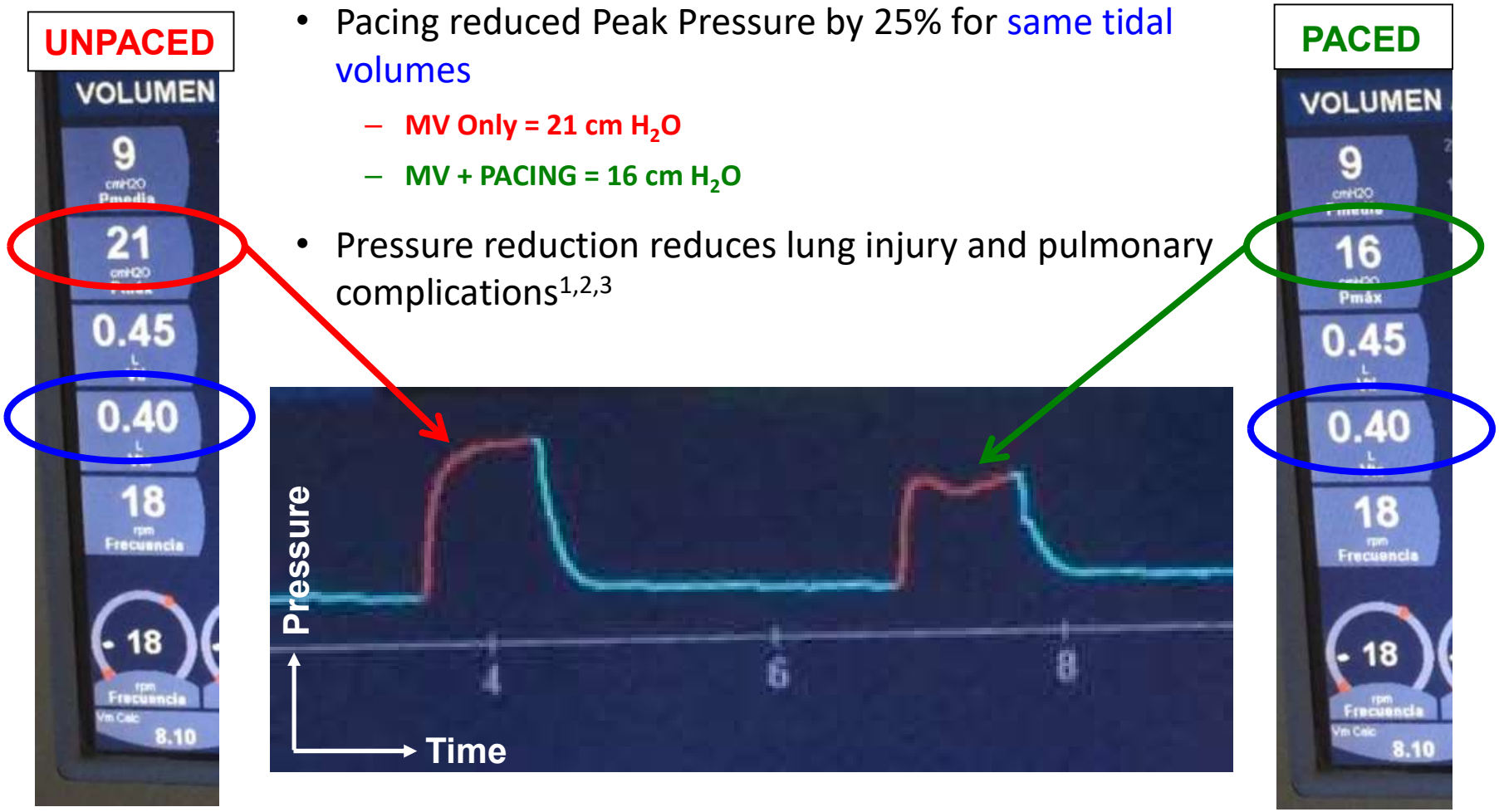


First breath: mechanical ventilation only.

Second breath: mechanical ventilation **PLUS** phrenic pacing.

Human clinical data
Pacing reduces pressure

- Pacing reduced Peak Pressure by 25% for same tidal volumes
  - **MV Only = 21 cm H_2O**
  - **MV + PACING = 16 cm H_2O**
- Pressure reduction reduces lung injury and pulmonary complications[1,2,3]



[1]Slutsky AS, Ranieri VM. **Ventilator-induced lung injury**. *N Engl J Med*. 2013;269:2126-36. PubMed PMID: 24283226.

[2]Neto S, Let al., "***Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anesthesia***", Lancet Respir Med (March 2016).

[3] Grasso F et al. **Negative-Pressure Ventilation: Better Oxygenation and Less Lung Injury.** Am J Respir Crit Care Med (2008) 177:412–418.

Clinical strategy

Initial Focus: 1) Rescue Failed-to-Wean, and then 2) Protection from likely Failure

Rescue failed-to-wean IMV patients

1)"**Rescue"** Restore diaphragm strength and endurance by pacing supported exercise in patients who failed to wean in at least two Spontaneous Breathing Trials (SBTs).

In May, 2016, the FDA granted Lungpacer the Expedited Access Pathway (EAP) designation for this indication.

Protect ICU Patients needing IMV > 96 hrs

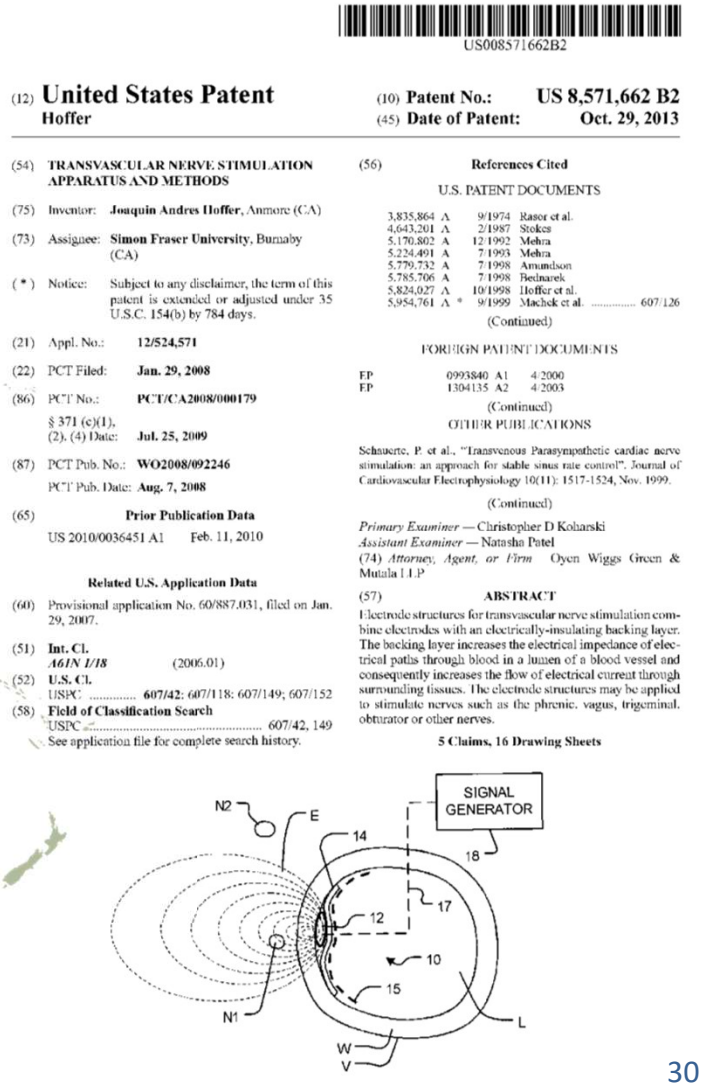
2) "**Protection"** Mitigate diaphragm muscle atrophy and lung injury in adult critical care patients with Acute Respiratory Failure who are expected to require IMV for at least 96 hours and are at high risk of failing to wean.

Lungpacer technology
Intellectual property status

IP Filed in All Key Markets

	Granted / Allowed	In Process
USA	21	15
Canada	-	6
Europe	13	4
Japan	1	4
Hong Kong	1	-
China	-	4
Brazil	-	2
India	-	1
Australia	-	4
TOTALS	36	39

First Issued US Patent - 2013



US008571662B2

(12) **United States Patent**
Hoffer

(10) **Patent No.: US 8,571,662 B2**
(45) **Date of Patent: Oct. 29, 2013**

(54) **TRANSVASCULAR NERVE STIMULATION APPARATUS AND METHODS**

(75) Inventor: **Joaquin Andres Hoffer**, Anmore (CA)

(73) Assignee: **Simon Fraser University**, Burnaby (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 784 days.

(21) Appl. No.: **12/524,571**

(22) PCT Filed: **Jan. 29, 2008**

(86) PCT No.: **PCT/CA2008/000179**
§ 371 (c)(1),
(2), (4) Date: **Jul. 25, 2009**

(87) PCT Pub. No.: **WO2008/092246**
PCT Pub. Date: **Aug. 7, 2008**

(65) **Prior Publication Data**
US 2010/0036451 A1 Feb. 11, 2010

Related U.S. Application Data
(60) Provisional application No. 60/887,031, filed on Jan. 29, 2007.

(51) **Int. Cl.**
A61N 1/18 (2006.01)

(52) **U.S. Cl.**
USPC **607/42**; 607/118; 607/149; 607/152

(58) **Field of Classification Search**
USPC 607/42, 149
See application file for complete search history.

(56) **References Cited**
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3,835,864 A 9/1974 Rasor et al.
4,643,201 A 2/1987 Stokes
5,170,802 A 12/1992 Mehra
5,224,491 A 7/1993 Mehra
5,779,732 A 7/1998 Amundson
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5,824,027 A 10/1998 Hoffer et al.
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EP 1304135 A2 4/2003

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Schauerte, P. et al., "Transvenous Parasympathetic cardiac nerve stimulation: an approach for stable sinus rate control", Journal of Cardiovascular Electrophysiology 10(11): 1517-1524, Nov. 1999.

(Continued)

Primary Examiner — Christopher D Koharski
Assistant Examiner — Natasha Patel
(74) *Attorney, Agent, or Firm* Oyen Wiggs Green & Mutala LLP

(57) **ABSTRACT**

Electrode structures for transvascular nerve stimulation combine electrodes with an electrically-insulating backing layer. The backing layer increases the electrical impedance of electrical paths through blood in a lumen of a blood vessel and consequently increases the flow of electrical current through surrounding tissues. The electrode structures may be applied to stimulate nerves such as the phrenic, vagus, trigeminal, obturator or other nerves.

5 Claims, 16 Drawing Sheets

Patentes Otorgadas en 2019-2020

55. Transvascular Nerve Stimulation Apparatus. **Hoffer, Joaquín Andrés**; Nolette, Marc-André; Thakkar, Viral; Tran, Bao Dung. **European Patent EP 3 228 351 B1** granted June 5, 2019.

56. Systems and related methods for optimization of multi-electrode nerve pacing. **Hoffer, Joaquín Andrés**, Sadarangani, Gautam; Nolette, Marc-Andre; Thakkar, Viral; Tran, Bao Dung. **U.S. Patent 10,391,314** issued August 27, 2019.

57. Transvascular diaphragm pacing systems and methods of use. Meyyappan, Ramasamy; **Hoffer, Joaquín Andrés**; Baru, Marcelo; Coquinco, Bernard; Sandoval, Rodrigo; Tang, Jessica Kit-Sum. **U.S. Patent 10,406,367** issued September 10, 2019.

58. Transvascular Nerve Stimulation Apparatus. **Hoffer, Joaquín Andrés**; Nolette, Marc-André; Thakkar, Viral; Tran, Bao Dung. **European Patent EP 3 556 427 A2** granted October 23, 2019.

59. Transvascular nerve stimulation apparatus and methods. **Hoffer, Joaquín Andrés**; Nolette, Marc-André; Thakkar, Viral; Tran, Bao Dung. **U.S. Patent 10,512,772** issued December 24, 2019.

60. Transvascular nerve stimulation apparatus and methods. **Hoffer, Joaquín Andrés**. **U.S. Patent 10,561,843** issued February 18, 2020.

61. Diaphragm pacing systems and methods of use. Meyyappan, Ramasamy; **Hoffer, Joaquín Andrés**; Baru, Marcelo; Coquinco, Bernard; Sandoval, Rodrigo; Tang, Jessica Kit-Sum. **U.S. Patent 10,561,844** issued February 18, 2020.

Lungpacer Clinical Trials: Current Status

https://clinicaltrials.gov/ct2/results?cond=&term=lungpacer&cntry1=&state1=&recrs=

Row	Saved	Status	Study Title	Conditions	Interventions	Number Enrolled	Last Update
3	☐	Completed	Percutaneous Temporary Placement of a Phrenic Nerve Stimulator for Diaphragm Pacing, a First in Human Trial	• Ventilator Induced Lung Injury	• Device: LIVE Catheter	24	April 15, 2016
		Locations:	• Italian Hospital Asuncion, Casa Zanotti, Paraguay				
5	☐	Completed	Percutaneous Temporary Placement of a Transvenous Phrenic Nerve Stimulator for Diaphragm Pacing Using Jugular Access	• Ventilator-Induced Lung Injury	• Device: LIVE Catheter	13	September 6, 2018
		Locations:	• Italian Hospital Asunción, Casa Zanotti, Paraguay				

Lungpacer Clinical Trials: Current Status

https://clinicaltrials.gov/ct2/results?cond=&term=lungpacer&cntry1=&state1=&recrs=

Row	Saved	Status	Study Title	Conditions	Interventions	Number Enrolled	Last Update
1	☐	Completed	Percutaneous Temporary Placement of a Phrenic Nerve Stimulator for Diaphragm Pacing (RESCUE1)	• Ventilator Induced Diaphragm Dysfunction	• Device: **Lungpacer** DPTS (Diaphragm Pacing Therapy System)	9	May 3, 2018

Locations:

- University of Florida Health Science Center - Shands
  Gainesville, Florida, United States
- New York University Medical Center
  New York, New York, United States
- Temple University Hospital
  Philadelphia, Pennsylvania, United States
- University of Texas Southwestern Medical Center
  Dallas, Texas, United States

Lungpacer Clinical Trials: Current Status

https://clinicaltrials.gov/ct2/results?cond=&term=lungpacer&cntry1=&state1=&recrs=

Row	Saved	Status	Study Title	Conditions	Interventions	Number Enrolled	Last Update
4	☐	Recruiting	Percutaneous Temporary Placement of a Phrenic Nerve Stimulator for Diaphragm Pacing	• Ventilator Induced Diaphragm Dysfunction	• Device: Diaphragmatic Pacing Therapy DPTS	110	May 15, 2019
		Locations:	• CHU Angers, Reanimation Medicale Angers, France • Hopital Louis-Mourier Colombes, France • CHU Montpellier Montpellier, France • (and 18 more...)				

Lungpacer Clinical Trials: Current Status

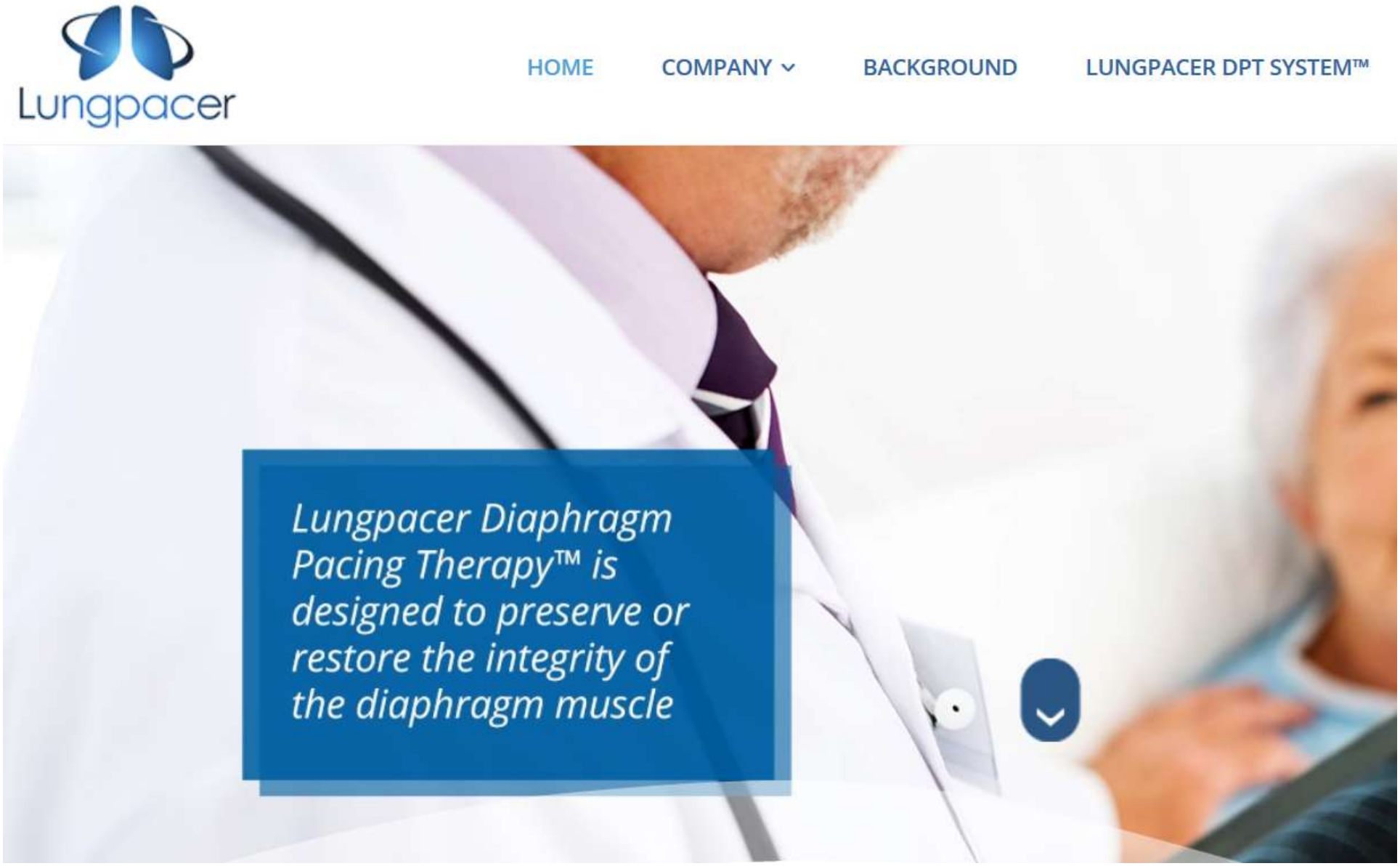
https://clinicaltrials.gov/ct2/results?cond=&term=lungpacer&cntry1=&state1=&recrs=

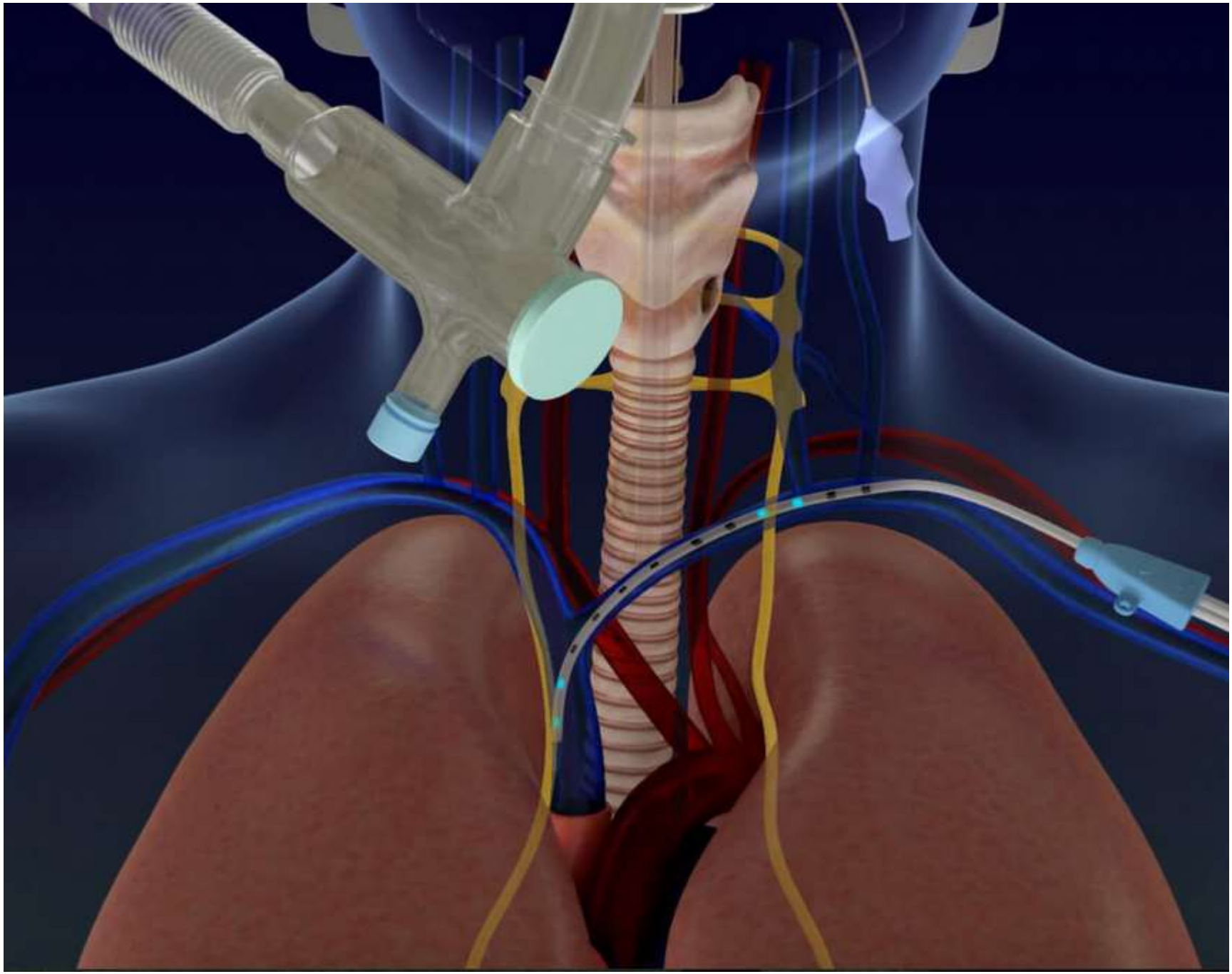
Row	Saved	Status	Study Title	Conditions	Interventions	Number Enrolled	Last Update
2	☐	Recruiting	A Protocol Comparing Temporary Transvenous Diaphragm Pacing to Standard of Care for Weaning From Mechanical Ventilation	• Ventilator Induced Diaphragm Dysfunction	• Device: Diaphragm Pacing Therapy	300	January 7, 2020

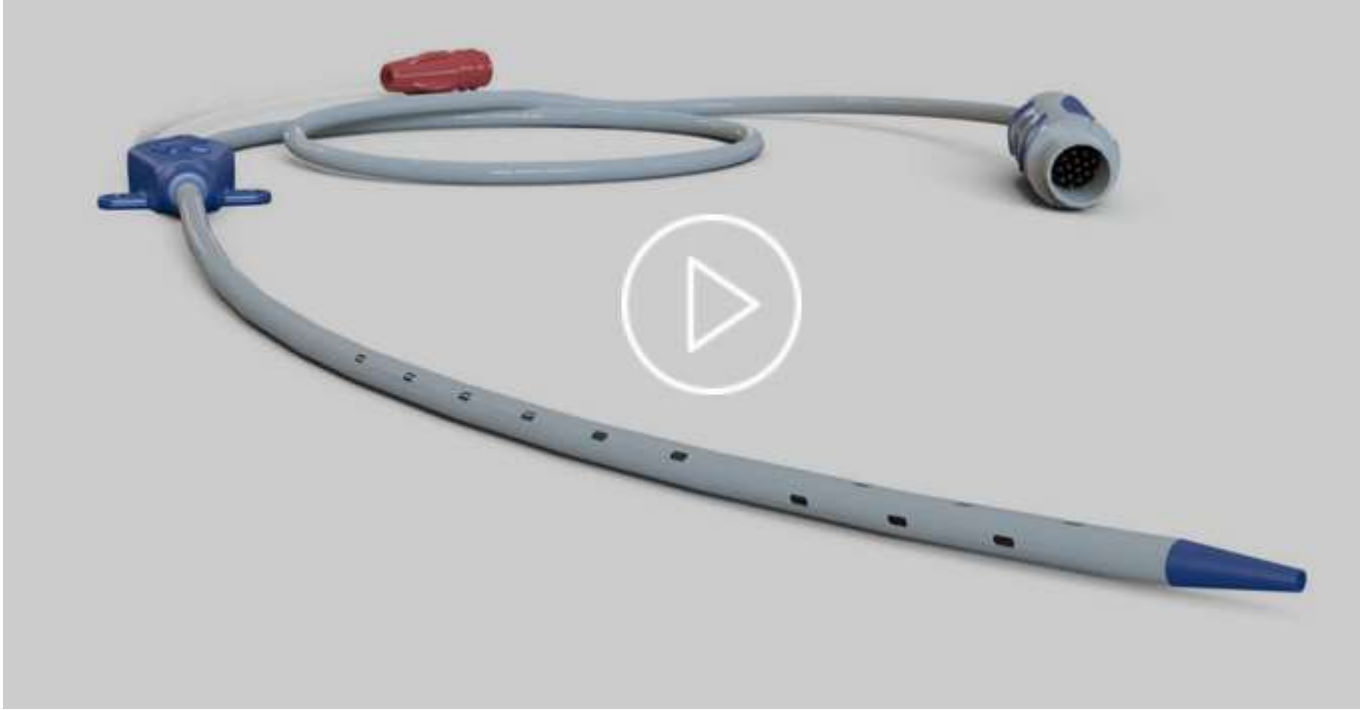
Locations:

- Cedars-Sinai Medical Center
  Los Angeles, California, United States
- UC Davis Medical Center
  Sacramento, California, United States
- Stanford University Medical Center
  Stanford, California, United States
- (and 23 more...)

www.lungpacer.com







The LIVE Catheter is a single-use, disposable device designed to resemble a typical central venous catheter. There are two arrays of electrodes, proximal for targeting the left phrenic nerve and distal for targeting the right phrenic nerve. The LIVE catheter is placed over the wire. The LIVE Catheter is available in three different lengths, 19 cm, 21 cm and 23 cm.