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A PATIENT CARE & INNOVATION COMPANY

Neuromodulation for COVID-19 Cytokine Storm

The potential of non-invasive Vagus Nerve Stimulation (nVNS) therapy

May 2020

Eric Grigsby, MD, MBA

CEO and Founder of Neurovations
A Patient Care and Innovation Company

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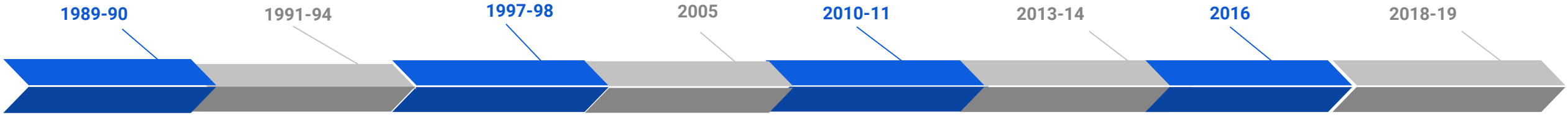
Neurovations is a national leader in medical device and pharmaceutical innovation, clinical research, pain and neuroscience education, and community health through our non-profit



1989-90 — Inaugural Napa Pain Conference

Dr Grigsby starts one of the first university pain management clinics in the US at UC Davis.

1991-94 — Napa Pain Institute

Dr. Grigsby is certified in first cohort of pain management by the Board of Anesthesiology.

1997-98 — Clinical Research

Leveraging Mayo Clinic training, Dr. Grigsby becomes Principal Investigator in early stage trials with active involvement in clinical and translational patient care

2005 — Neurovations!

Research and education combine to become Neurovations-a patient care and innovation company .

2010-11 — N3 Laboratories

Neuromodulation: The Science debuts focused on science and innovation of neuromodulation. Napa Pain Institute earns conference accrediting rights for continued medical education which at multiple conferences and events. N3 Laboratories is established.

2013-14 — Spine and Pain Center of Kaua'i

The Kauai Clinic is established in part to handle an underserved clientele. Kauai Pain Conference debuts to an international audience.

2016 — Redwood Pain Institute

Redwood Pain Institute opens in partnership with St. Joseph's Health.

2018-19 — Neurovations Center for Hope

The Neurovations Center for Hope begins research and development phase with 5 patients.

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Peter Staats, MD, MBA

Chief Medical Officer, National Spine and Pain

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Today's Agenda

- A little Background on Covid-19 for non-virologists
- nVNS and it's potential effect on Covid-19 cytokine storm
- Questions and Hopefully Some Answers

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Covid Disease Progression

- Viral load of patients with COVID-19 seems to peak in the early stages of illness
- A subset of patients deteriorate later at around days 10–14

Haigh et al, Hyperinflammation with COVID-19: The key to patient deterioration?, Clinical Infection in Practice, May 24, 2020.

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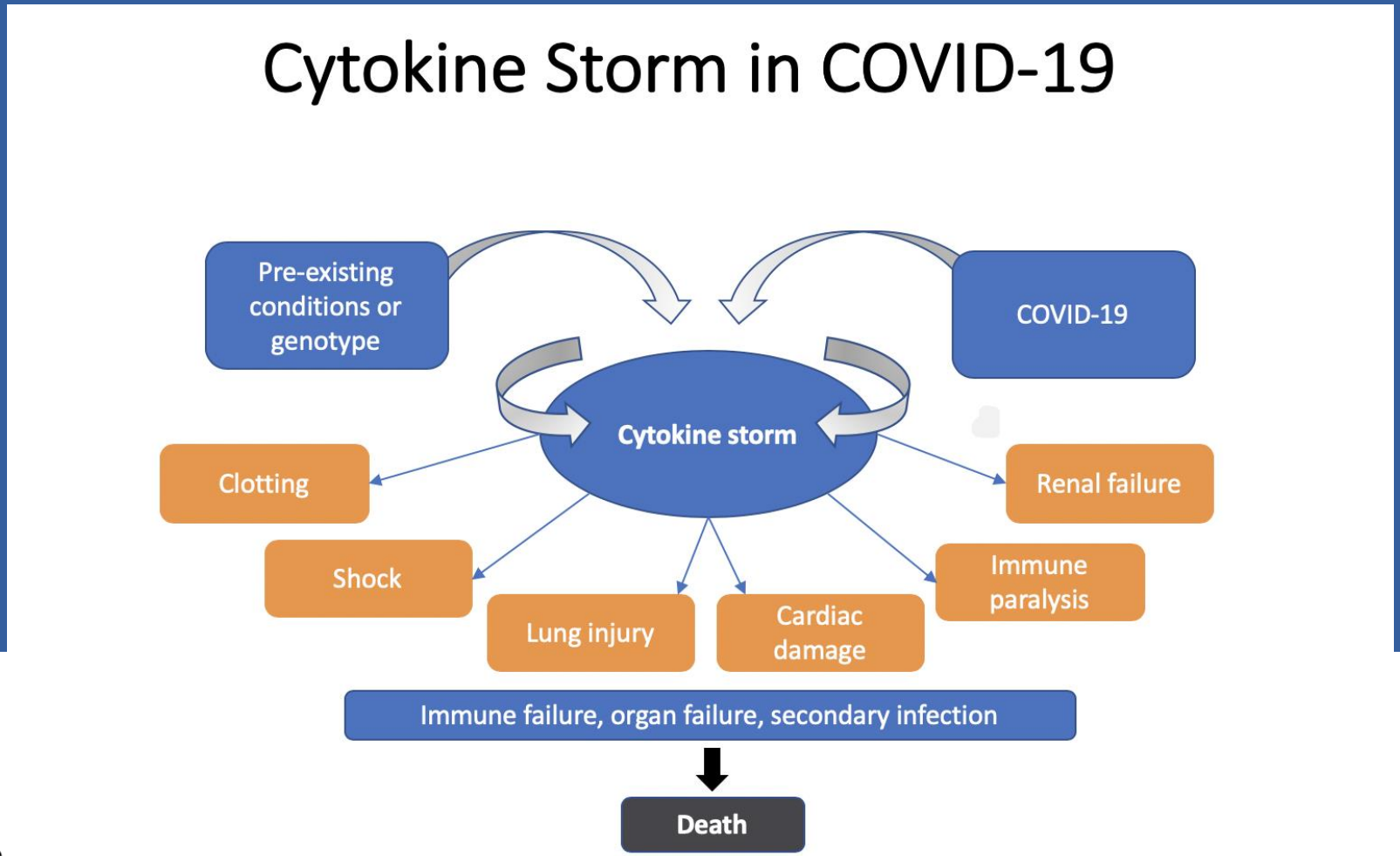
Covid Disease Progression

Stage 1	Pre-symptomatic phase which may lead to fever, cough, and generalized malaise, high viral loads
Stage 2	7-10 Days, viral pneumonia that involves the lower respiratory tract while viral loads in the upper respiratory tract decrease exponentially. A vast majority show clinical improvement as protective humoral responses are developed at this stage of the disease.
Stage 3	A minor proportion develop symptoms of hypercytokinemia (“cytokine storm”) characterized by exaggerated levels of pro-inflammatory cytokines
Stage 4	Onset of acute respiratory distress syndrome (ARDS) and multi-organ failure (70-90 % mortality)

Girija eta al, Could SARS-CoV-2-Induced Hyperinflammation Magnify the Severity of Coronavirus Disease (CoViD-19) Leading to Acute Respiratory Distress Syndrome?, Front. Immunol., 27 May 2020.

What is Cytokine Storm?



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Which Inflammatory Cytokines Which Are Released?

- IL-6
- IL-1β
- TNF-α
- IL-8

Girija eta al, Could SARS-CoV-2-Induced Hyperinflammation Magnify the Severity of Coronavirus Disease (CoViD-19) Leading to Acute Respiratory Distress Syndrome?, *Front. Immunol*., 27 May 2020.

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Dr. Bruce Beutler
Nobel Prize in Medicine 2011

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Can We Determine Who is at Risk for Cytokine Storm?

Kuo et al, APOE E4 GENOTYPE PREDICTS SEVERE COVID-19 IN THE UK BIOBANK COMMUNITY COHORT,
Journal of the Gerontological Society of America, May 25, 2020.

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APOE

- *APOE* gene provides instructions for making the protein apolipoprotein E. This protein combines with lipids to form lipoproteins.

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A Genetic Basis for Cytokine Storm?

Circumstantial Evidence!

- UK Biobank is a community cohort currently aged 48 to 86- approximately 500,000 individuals
- Hospitalized Covid patients March 16 to April 26, 2020 cross referenced to the UKB genotypes
- ApoE e4e4 homozygotes were more likely to be COVID-19 test positives compared to normal e3e3 homozygotes

- ApoE e4e4 moderates macrophage pro-/anti-inflammatory phenotypes

- The novel coronavirus SARS- CoV-2 causing COVID-19 uses the ACE2 receptor for cell entry.
- ACE2 is highly expressed in type II alveolar cells in the lung
- ApoE is one of the highly co-expressed genes in lung alveoli

Kuo et al, APOE E4 GENOTYPE PREDICTS SEVERE COVID-19 IN THE UK BIOBANK COMMUNITY COHORT, *Journal of the Gerontological Society of America,* May 25, 2020.

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Methods to Mitigate Hypercytokinemia

Can Neuromodulation Play a Role?

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Peter Staats, MD, MBA

Chief Medical Officer, National Spine and Pain

President-Elect World Institute of Pain

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CoVid 19 and Vagus Nerve Stimulation

Scientific and Clinical Basis for the Treatment

Presented By: Peter Staats: MD, MBA, FIPP

- President-Elect World Institute of Pain
- Co-Founder and Chief Medical Officer electroCore
- Chief Medical Officer National Spine and Pain
- Committee one Pain Task Force HHS
- Founder and Director Division of Pain Medicine- Johns Hopkins University 1993-2004
- Past President. American Society of Interventional Pain Physicians, North American Neuromodulation Society, New Jersey Society of Interventional Pain Physicians, Southern Pain Society
- Co Inventor Qutenza Patch

How should we think about Neuromodulation in CoVid 19?

A Scientific discussion

CoVid 19 is not killing people… it is the Cytokine Storm

Vagus nerve review…The science of how this could all work

Cervical non-invasive vagus nerve stimulator (nVNS)

History of development of nVNS device

..... Bronchodilation/anaphylaxis/shock

Medical Hypothesis and early clinical experience

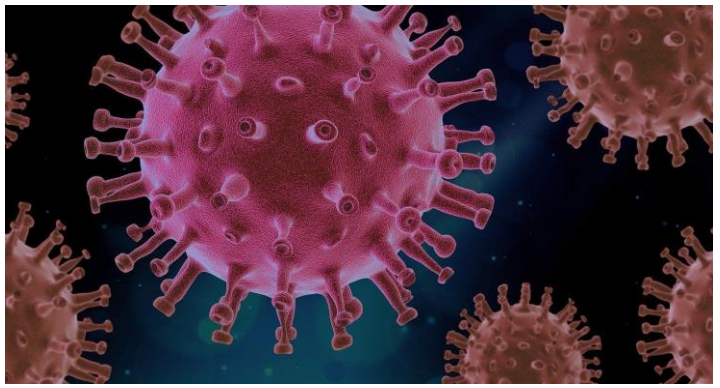
EUA application

Need for randomized controlled trials and real world data

(Savior 1, Savior 2) Vangard, Convert

Can Medical Devices be effective in treating the cytokine storm?

What is COVID-19?



- The coronavirus has genetic material similar to the deadly SARS virus
- First identified in the Wuhan district of China
- Technical name is SARS-CoV-2 which is a coronavirus
  - **Coronaviruses are typically mild (30% of common colds are coronaviruses)**
- This disease was discovered in December 2019 was named COVID-19 (coronavirus disease 2019)
- A small percentage of patients develop a “Cytokine Storm”
- Has created an unprecedented pandemic that has spread throughout the world

More than 200 countries have reported the disease

Hallmarks of COVID-19

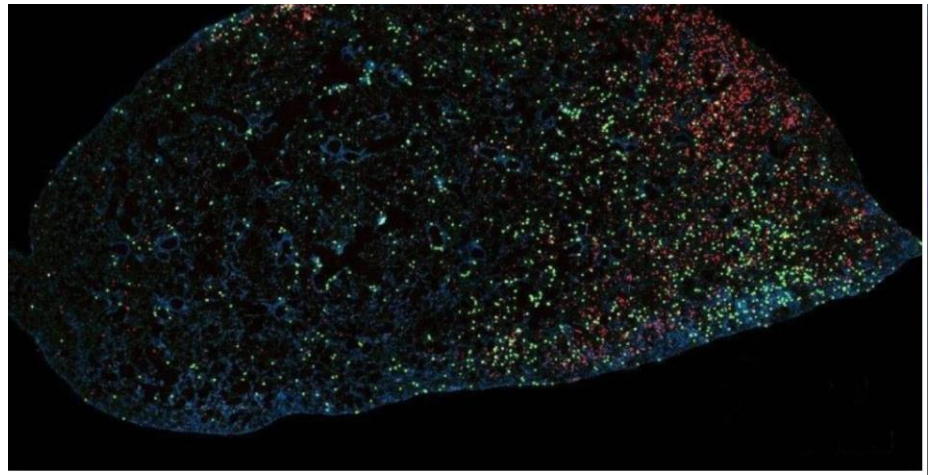
88% of patients
have mild symptoms

Small percentage of patients
have more severe symptoms requiring hospitalization

Respiratory symptoms
can rapidly progress to ARDS, requiring mechanical ventilation

70–90% percent mortality
for those who require ventilation

More ventilators
are not the answer



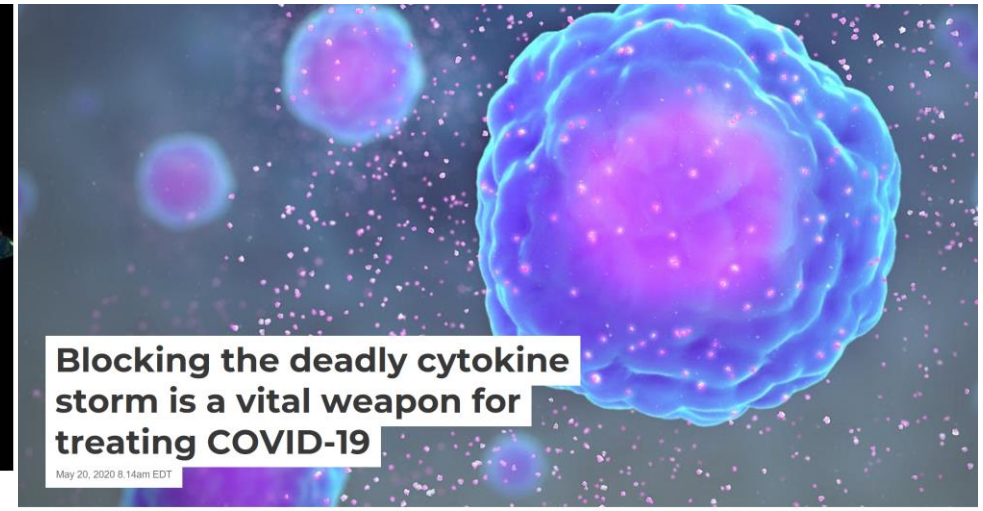
mmune system cells produced by a cytokine storm appear as green and red dots in a microscopic mage of lung tissue infected with influenza.

PHOTOGRAPHY COURTESY HUGH ROSEN AND MICHAEL OLDSTONE, SCRIPPS RESEARCH INSTITUTE

SCIENCE | CORONAVIRUS COVERAGE

How quieting 'blood storms' could be key to treating severe COVID-19

n some coronavirus patients, the body turns its attacks on itself. Anti-nflammatory drugs may be able to help stop this friendly fire.



Immune cells release proteins called cytokines which alert the rest of the immune system that a virus is present. www.scientificanimations.com, CC BY-SA

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The killer is not the virus but the immune response.

The current pandemic is unique not just because it is caused by a new virus that puts everyone at risk, but also because the range of innate immune responses is diverse and unpredictable. In

Author

Alexander (Sasha) Poltorak
Professor of Immunology, Tufts University

Science News *from research organizations*

Preventing 'cytokine storm' may ease severe COVID-19 symptoms

Date: May 21, 2020

Source: Howard Hughes Medical Institute

Summary: A clinical trial in people with the new coronavirus is testing a drug that may halt an overactive immune response before it ramps up.

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FULL STORY

For some COVID-19 patients, the body's immune response may be as destructive as the virus that causes the disease. The persistent high fevers, severe respiratory distress, and lung damage seen in some critically ill patients are all signs of an immune system in overdrive.

Now, a new clinical trial will test a treatment that targets this overactive immune response, says Howard Hughes Medical Investigator Bert Vogelstein. He and his team at the Johns Hopkins University School of Medicine are currently recruiting

What is killing everyone? The Cytokine storm

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao*

Lancet 2020; 395: 1054–62

Published Online March 9, 2020 https://doi.org/10.1016/S0140-6736(20)30566-3

See Comment page 1014

This online publication has been corrected. The corrected version first appeared at thelancet.com on March 12, 2020

*Contributed equally

Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China (F Zhou MD, G Fan MS, Z Liu MD, Y Wang MD, X Gu PhD, H Li MD, Y Zhang MD, Prof B Cao MD); Department of Tuberculosis and

Summary

Background Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed clinical course of illness, including viral shedding, have not been well described.

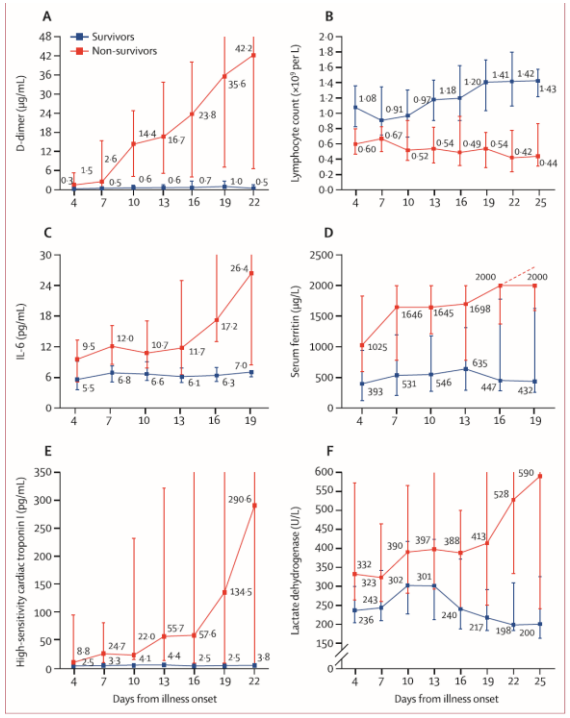
Methods In this retrospective, multicentre cohort study, we included all adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors. We used univariable and multivariable logistic regression methods to explore the risk factors associated with in-hospital death.

Findings 191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included in this study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart disease (15 [8%] patients). Multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1·10, 95% CI 1·03–1·17, per year increase; p=0·0043), higher Sequential Organ Failure Assessment (SOFA) score (5·65, 2·61–12·23; p<0·0001), and d-dimer greater than 1 μg/mL (18·42, 2·64–128·55; p=0·0033) on admission. Median duration of viral shedding was 20·0 days (IQR 17·0–24·0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.

191 patients admitted two hospitals in China

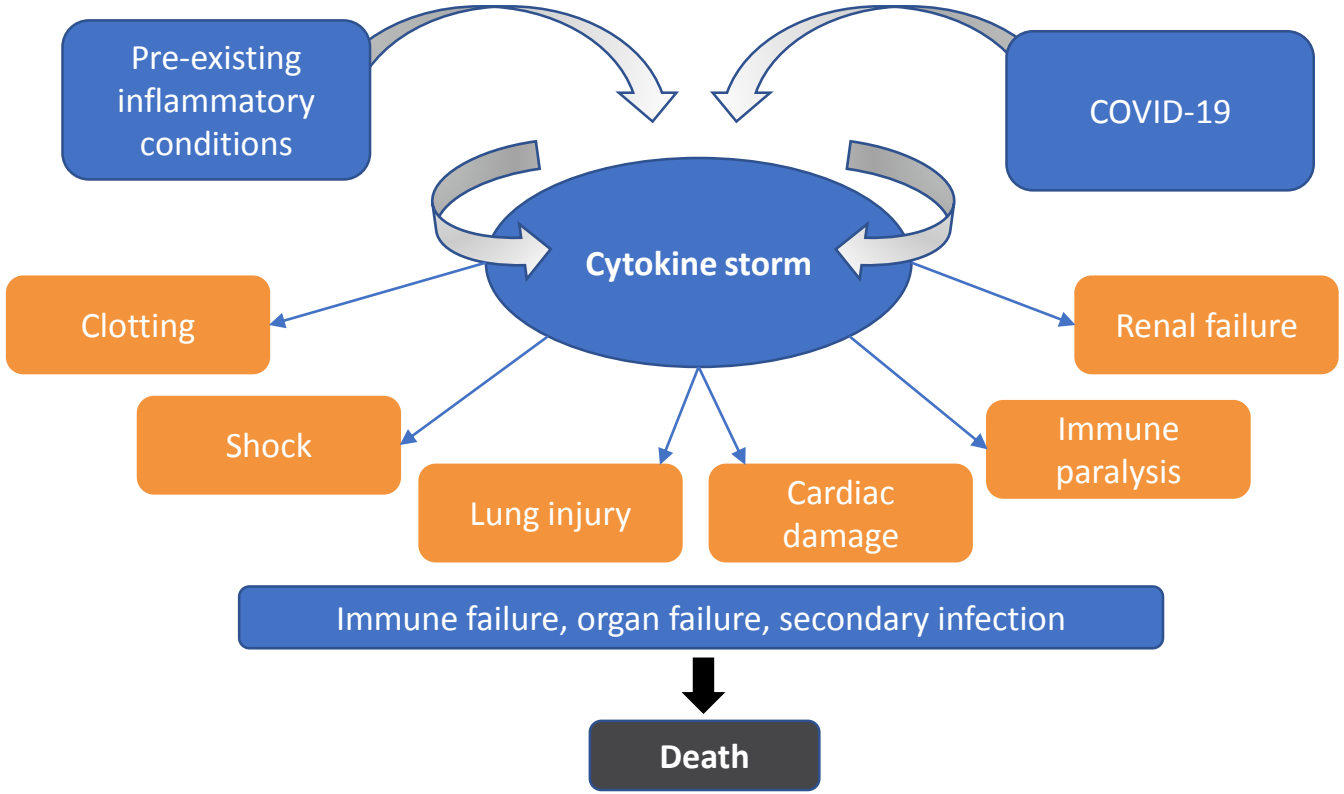
\+ 137 were discharged

\+ 54 died



Zhao, et al. *Lancet.* March 9, 2020.

Inflammatory Storm in COVID-19



COVID-19, coronavirus disease 2019.

Covid and treating the cytokine storm

Covid 19 and interleukin (81 studies listed on Clintrials.gov May27)

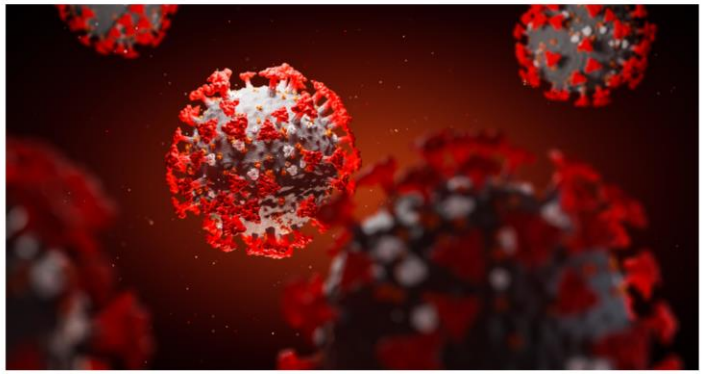
- Tocilizumab *Actemra* (IL 6 6 receptor antagonist)
- Anakinra *Kineret* (IL 1 Receptor antagonist)
- Baricitinib *Olumiant* Inhibits Janus Kinase (JAk)
- Recombinant Interleukin 7 (CYT107)
- Anti IL 8 (BMS -986253)
- Siltuximab *Sylvant* (Anti IL 6 monoclonal antibody..Binds to IL 6
- Clasakizumab (Anti IL 6)
- Low dose IL 2 (ILT 101)
- Leronlimab (CCR5 receptor antibody on t lymphocytes) keeps c from being activated in inflammatory cascade
- Methylprednisolone
- Convalescent plasma
- Plasma filtration
- Ecmo with cytosorb (Cytokine absorber)

- (Others being studied…Kevzara(anti IL 6) Nivolumab,emapalumab sarilumab,N803, Allogeneic HB-adMSC, clarithromycin , low dose anti inflammatory radiotherapy, colchicine

Pharma

Are IL-6 inhibitors one key to COVID-19? EUSA Pharma joins Sanofi, Regeneron in rolling out trials

by Kyle Blankenship | Mar 18, 2020 9:43am



EUSA's Sylvant is being tested to treat COVID-19 in an observational trial in Italy. (Getty)

Autoimmunity Revi

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journal homepage: www.elsevier.com/locate/autrev

Review

The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease

Dennis McGonagle[a,b,*], Kassem Sharif[a,c], Anthony O'Regan[d], Charlie Bridgewood[a]

[a] Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), University of Leeds, Leeds, UK
[b] National Institute for Health Research (NIHR) Leeds Biomedical Research Centre (BRC), Leeds Teaching Hospitals, Leeds, UK
[c] Sheba Medical Center, Tel Aviv, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[d] National University of Ireland, Saolta University Healthcare Group, Galway, Ireland

ABSTRACT

Severe COVID-19 associated pneumonia patients may exhibit features of systemic hyper-inflammation designated under the umbrella term of macrophage activation syndrome (MAS) or cytokine storm, also known as secondary haemophagocytic lymphohistocytosis (sHLH). This is distinct from HLH associated with immunodeficiency states termed primary HLH -with radically different therapy strategies in both situations. COVID-19 infection with MAS typically occurs in subjects with adult respiratory distress syndrome (ARDS) and historically, non-i classification of MAS to stratify the MAS-like presentation in COVID- potential impact of timing of anti-cytokine therapy on viral clearance pulmonary vascular disease.

Montefiore and Einstein Test a New Drug Combination to Conquer COVID-19

Montefiore

Researchers Hope Giving Remdesivir Along with a Powerful Anti-Inflammatory Could be the Key to Treating the Most Severe COVID-19 Cases

NEWS PROVIDED BY
Montefiore Health System; Albert Einstein College of Medicine →
May 26, 2020, 10:00 ET

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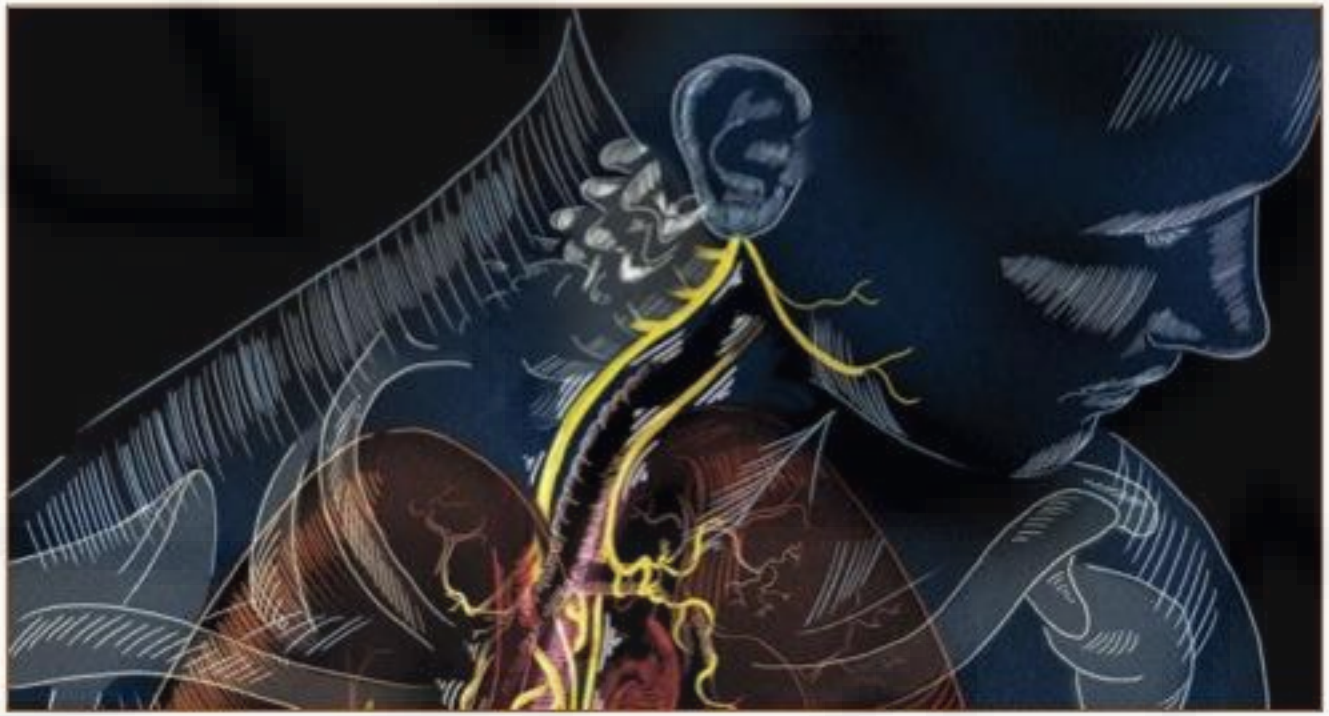
BRONX, N.Y., May 26, 2020 /PRNewswire/ -- Montefiore Health System and Albert Einstein College of Medicine have begun the next stage of the Adaptive COVID-19 Treatment Trial (ACTT), to evaluate treatment options for people hospitalized with severe COVID-19 infection. The new iteration of the trial, known as ACTT 2, is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

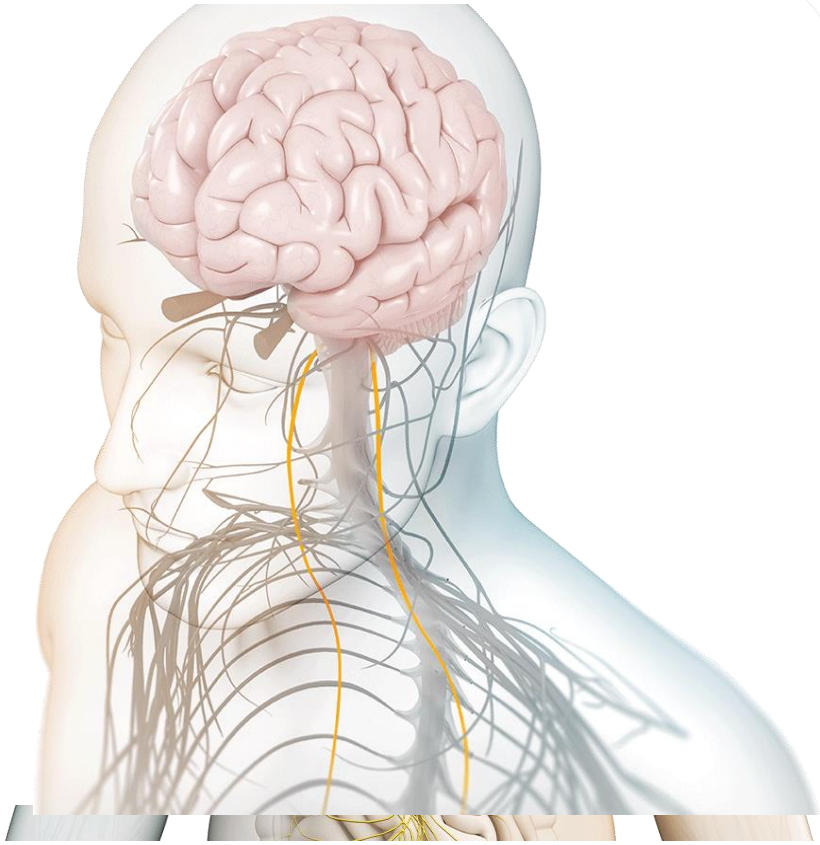
Vagus Nerve Basics

An Old Wanderer … or a New Wonder?



Vagus Nerve Basics

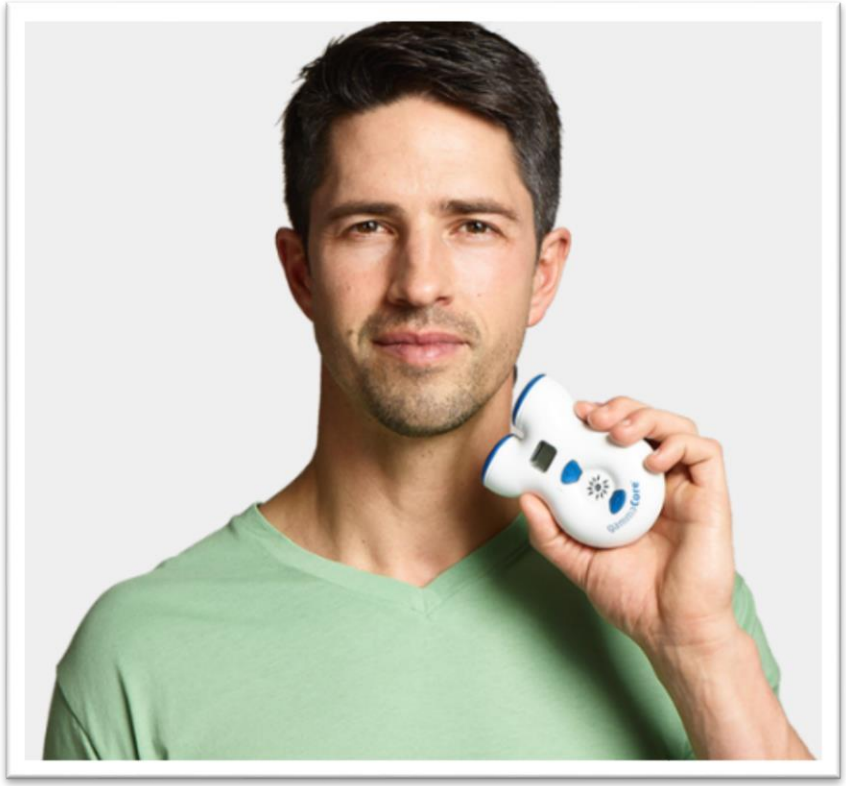
- Longest cranial nerve
- Right and left branches
- Contains both afferent and efferent fibers
- Initially enters the CNS via the trigeminal nucleus caudalis (TNC) and projects into the periaqueductal gray (PAG) area
- Innervates structures of head, neck, thorax, and abdomen
- Efferent Branch controls cholinergic anti inflammatory pathway or CAP



Yuan H, et al. *Headache*. 2016;56:71-78.
Sadler RM, Purdy RA, Rahey S.*Cephalagia*. 2002.22;482-484.

History of Vagus Nerve Stimulation (VNS)

- 1997—FDA approves implanted VNS (iVNS) for refractory epilepsy[1,2]
- 2000 Tracey publish in *Nature* CAP
- 2002—iVNS first reported to abort or reduce migraine pain[3]
- 2005—approval of iVNS for chronic treatment-resistant depression[1,2]
- 2010- Airway reactivity
- 2017—nVNS released for acute treatment of eCH[4]
- Early 2018—nVNS cleared for acute treatment of migraine headache[4]
- Late 2018—nVNS cleared as adjunctive treatment for the prevention of cluster headache[4]
- March 2020 gammaCore approved for prevention of headache[4]
- Lerman, Tarn, Ng Bremner study cytokine modulation



eCH, episodic cluster headache.

1. Howland RH. *Curr Behav Neurosci Rep.* 2014;1(2):64-73.
2. Yuan H, et al. *Headache*. 2016;56(2):259-266.
3. Sadler RM, et al. *Cephalagia*. 2002.22;482-484.
4. gammaCore Instructions for Use. Basking Ridge, NJ: electroCore, Inc; 2018

Dual Mechanisms of Action by which vagus nerve stimulation could help

- Inhibit airway constriction through parasympathetic-sympathetic reflex arc

- Activation of the Cholinergic Anti-Inflammatory Pathway (CAP) to regulate the immune response to COVID-19

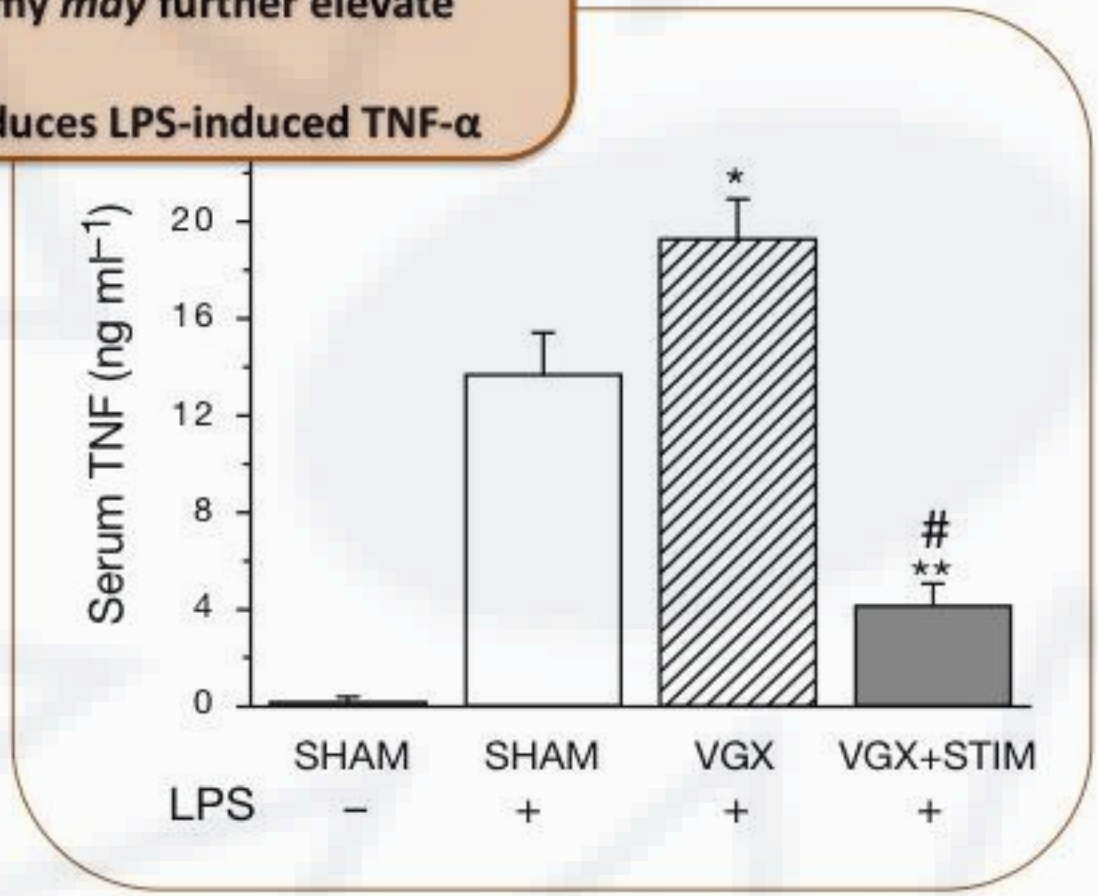
VNS Blocks Inflammation

Circulating levels of TNF-α are typically minimal

Exposure to LPS results in elevated TNF-α

Vagotomy *may* further elevate TNF-α

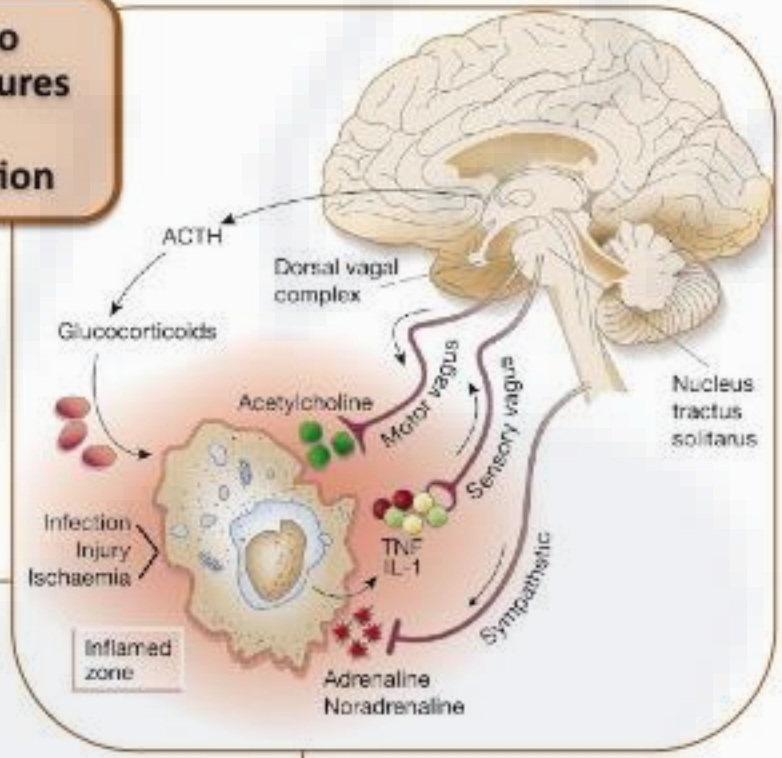
VNS reduces LPS-induced TNF-α

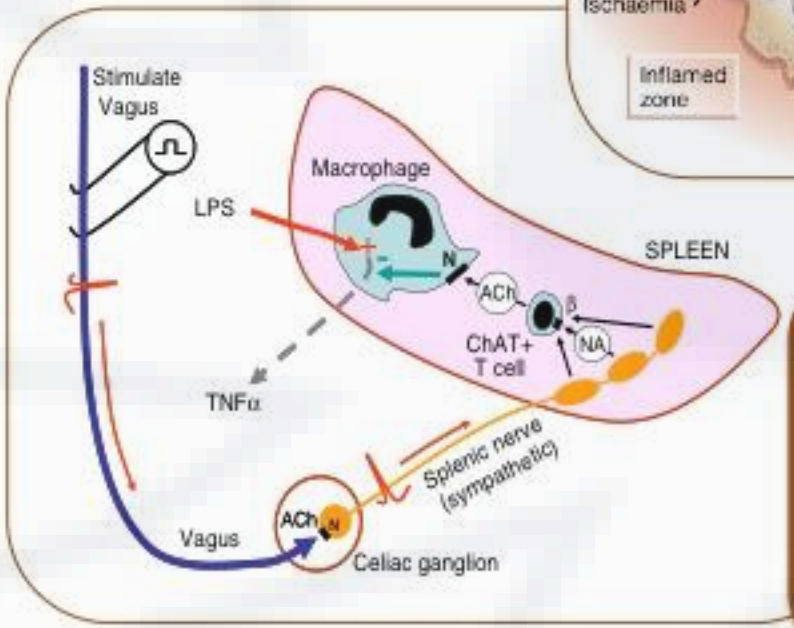


Borovikova, et al. , Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin, *Nature* 2000

VNS Initiates a CAP

The CNS has multiple ways to monitor the chemical signatures of inflammation, and to modulate immune cell function





VNS triggers sympathetic neurons to release norepinephrine, causing ACh release from ChAT⁺ cells that activates α7nAChRs on macrophages, suppressing cytokine production

Martelli, et al. , The cholinergic anti-inflammatory pathway: A critical review, *Autonomic Neuroscience: Basic and Clinical* 2014

Clinical Data in Reduction of Inflammatory Cytokines

Table 2. Summary of Inflammatory nVNS trials relevant to COVID-19

Study	Design	N	Findings relevant to COVID-19
nVNS decreases whole blood culture–derived cytokines and chemokines[20]	Randomized, blinded, pilot trial in healthy controls	20	24 hours after treatment, the nVNS group had a greater (vs the sham group) percentage decrease in levels of IL-1β, TNF, IL-6, IL-8, MIP-1α, and MCP-1
Effects of nVNS on fatigue and immune responses in patients with primary Sjögren's syndrome[21]	Prospective, single-center, open-label study	15	90 minutes after nVNS, levels of MIP-1α, IL-1β, TNF-α, IL-6, and IP-10 were significantly reduced on days 0, 7, and 28 of the study 12 participants had an improvement in their fatigue scores, 7 of whom had a ≥30% reduction in fatigue within 28 days

Abbreviations: IL, interleukin; IP, interferon γ–induced protein; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; nVNS, non-invasive vagus nerve stimulation; TNF, tumor necrosis factor; VAS, visual analog scale.

Decrease of Cytokines and Chemokines in Healthy Subjects

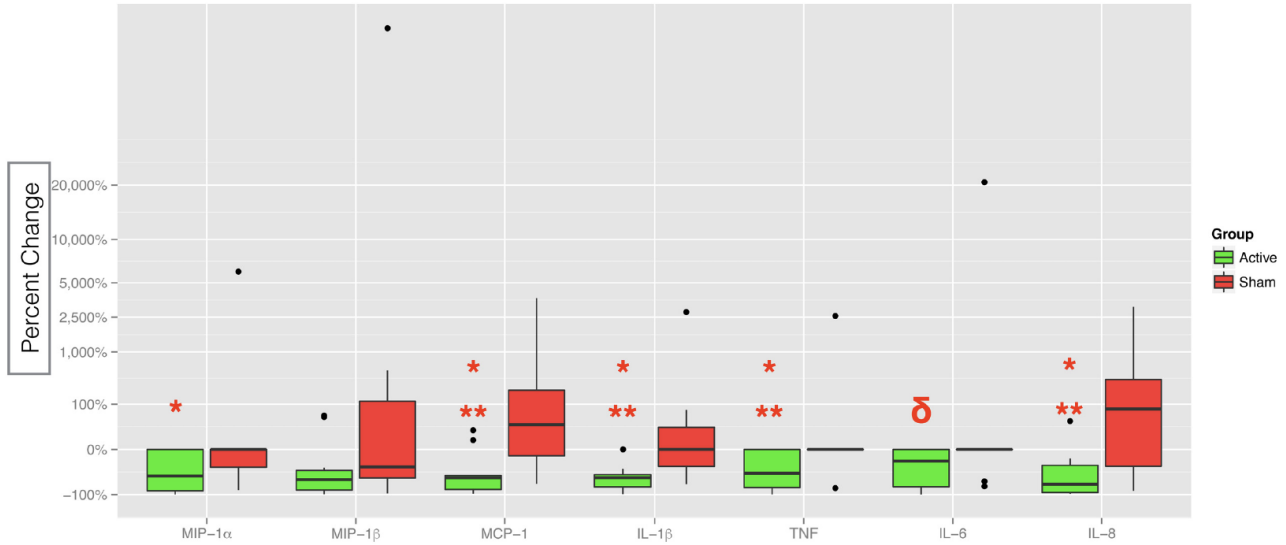


Figure 3. Within the nVNS group, non-LPS-stimulated whole blood culture (n-WBCx) demonstrated a significant percent decrease in cytokine (TNF, IL-1β) and chemokine (MCP-1 and IL-8) levels at the 24-hour time point (* = < 0.05). In the nVNS group, IL-6 approached a significant decrease at the 24-hour time point as well (δ = < 0.06). Compared with the SST group, the nVNS group had a significantly greater percent decrease in cytokine (IL-1β, TNF) and chemokine (MCP-1 and IL-8) levels at 24 hours (** = < 0.05).

Effect on Immune Responses in Patients with Sjögren's Syndrome

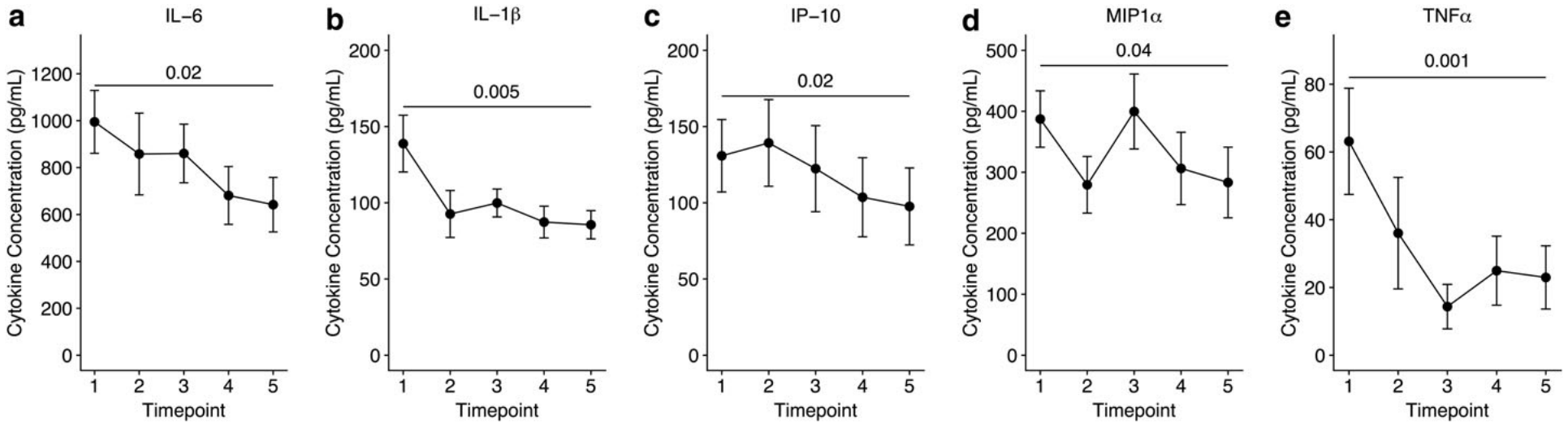


Figure 3. a–e. Supernatant cytokine levels (pg/mL) upon stimulation with 2 ng/mL LPS. Points showing mean values standard error at each TP for each of five cytokines IL-6, IL-1β, IP-10, MIP-1α, and TNFα. Labels 1–5 represent TPs 1–5. The time profiles of all five cytokines show a significant reduction across the five TPs determined by repeated measures ANOVA.

A second mechanism of action

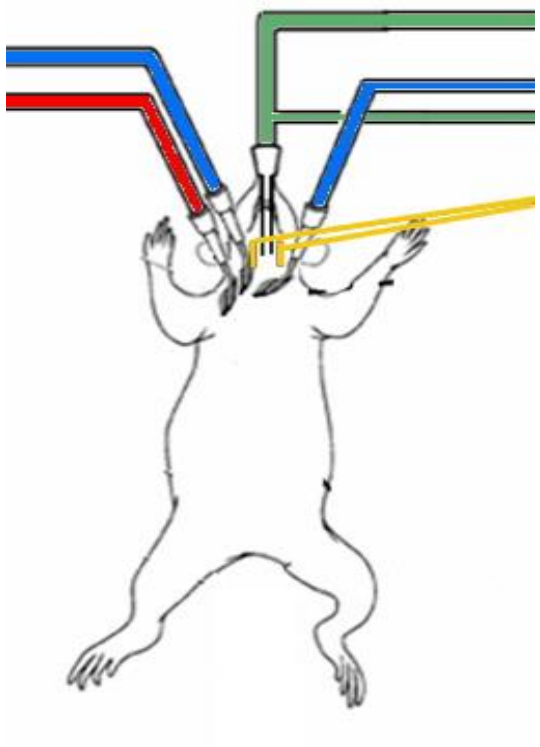
Acute Airway Reactivity

A second mechanism of action

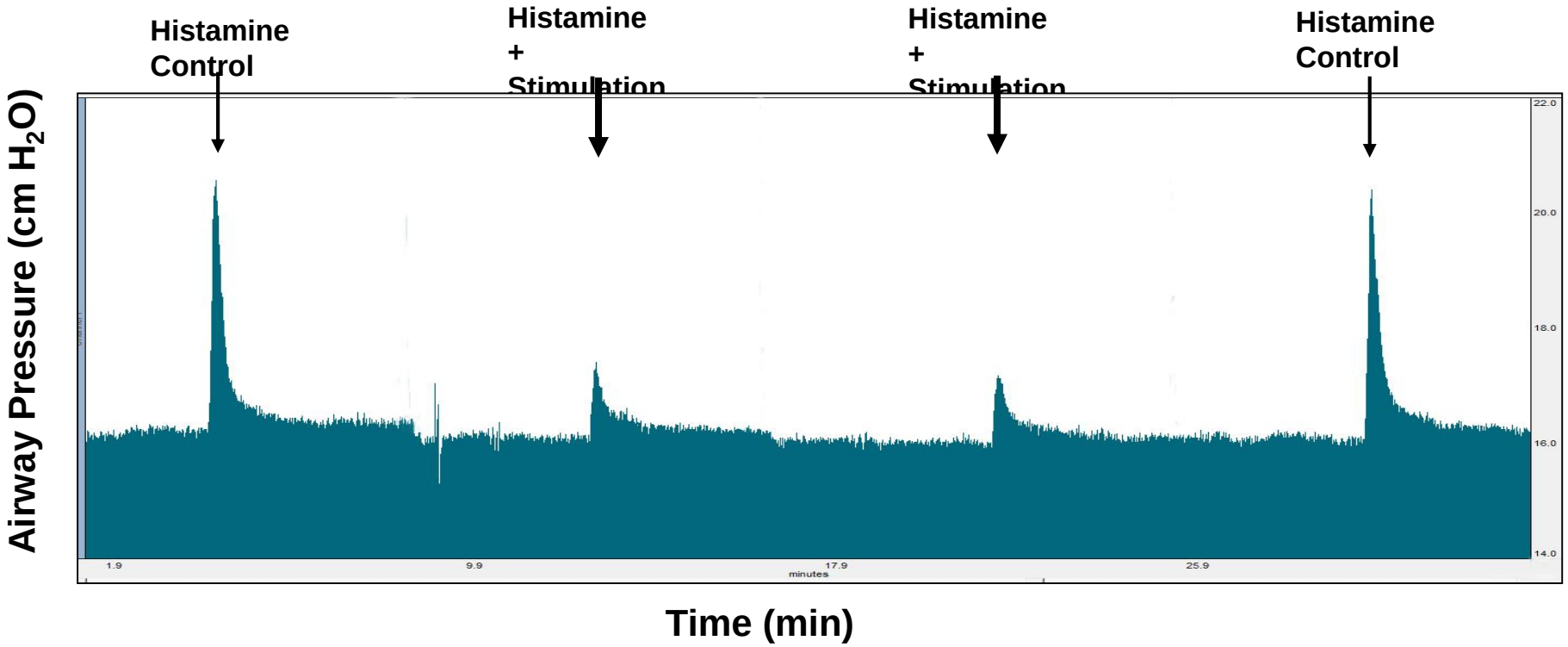
- Worked with leading airway reactivity researcher, Dr. Charles Emala, of Columbia University to develop a treatment for relief of bronchoconstriction
- Used a well-established *Histamine Model* for inducing and measuring airway pressure changes with direct nerve control of airway “tone”
- Used a standard model for *Naturally Induced Anaphylaxis*
- In 4 guinea pig studies, Electrical Stimulation showed significant effectiveness in reducing bronchoconstriction by 40% (and avoiding a fatal drop in blood pressure)
- Swine studies confirm effects with the same signal, and indicate alternate (safer and more effective) lead placement possible

Materials and Methods

- Used a Standard Guinea Pig Model for Measuring Airway Pressure Changes and Vagal Nerve Control of Airway Tone for Over 30 Years



Reduction in Acute Airway Resistance in a Guinea Pig Histamine Model

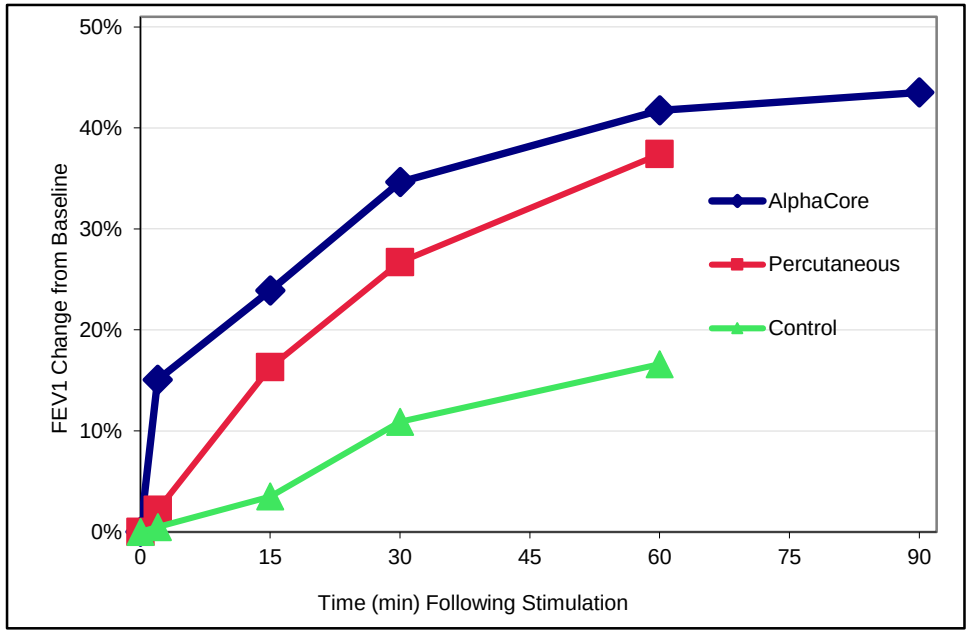


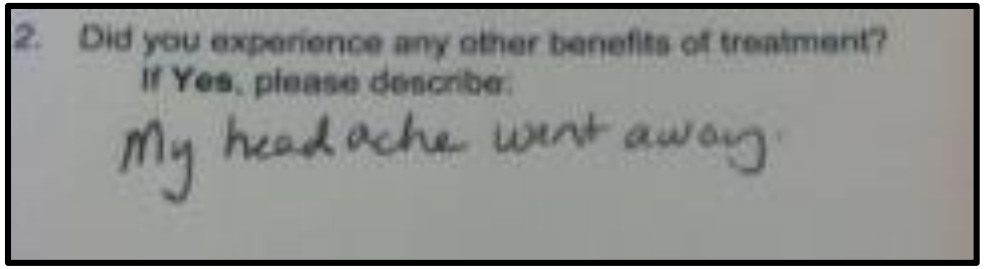
Clinical Data in Respiratory Distress

Study	Design	N	Findings relevant to COVID-19
nVNS for the treatment of acute asthma exacerbations	Prospective, multicenter, open-label study	4	90 minutes after acute nVNS treatment, FEV_1 improved from baseline by a mean of 73%, and mean VAS dyspnea score decreased from 8 (at baseline) to 1
nVNS for the relief of acute bronchoconstriction due to asthma	Prospective, multicenter, open-label study	30	90 minutes after acute nVNS treatment, 93% of patients reported improvement in VAS dyspnea score, and 86% had improvements in FEV_1
nVNS for the prophylactic treatment of COPD	Prospective, single-center, randomized, controlled trial	54	After 8 weeks of daily treatment, the nVNS group had a significant increase from baseline in distance walked (9.9-meter greater improvement than the sham group) on the 6MWT

6MWT, 6-minute walk test; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; FEV_1, forced expiratory volume in 1 second; nVNS, non-invasive vagus nerve stimulation; TNF, tumor necrosis factor; VAS, visual analog scale.
Staats MD, et al. *Neuromodulation*. Online ahead of print.

Transition of nVNS: Acute Bronchoconstriction to Headache





Confirmation of the effect of the nVNS device in humans through a small pilot in South Africa.

US and South African study patients reported spontaneous relief of headache symptoms.

A quick check of the literature showed that asthma and migraine are very closely associated with one another (ie, highly co-prevalent).

Two presumed mechanisms of action

Direct bronchodilatation and blockade of the cytokine storm

CHAPTER

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Neurostimulation for Asthma

Peter Staats[1], *Charles Emala*[2], *Bruce Simon*[3], *J.P. Errico*[3]

[1]Premier Pain Centers, Shrewsbury, NJ, United States; [2]Columbia University, New York, NY, United States; [3]electroCore, LLC, Basking Ridge, NJ, United States

OUTLINE

INTRODUCTION

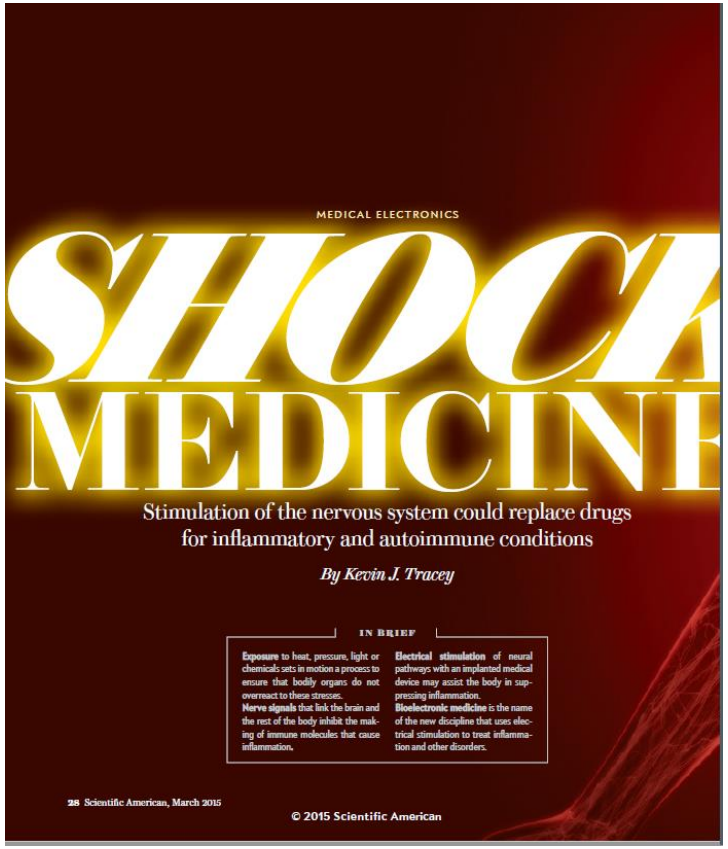
When one considers electricity a *digital drug*, it becomes evident that any innervated organ should be amenable to neuromodulation. The field of neuromodulation is expanding greatly, with novel targets constantly being explored, from cardiac disease to urinary incontinence. Spinal cord stimulation (SCS) for pain and deep brain stimulation (DBS) for motor dysfunction, such as Parkinson's disease, are considered mainstream therapies for those disorders. Novel neuromodulatory targets that include the pulmonary system, previously not thought to be amenable to neuromodulation interventions, are under study.

Vagus nerve stimulation (VNS), which has been used to treat epilepsy since the 1990s, is being considered for people with a variety of disorders such as headaches, inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease, neurologic disorders including anxiety, depression, and posttraumatic stress disorder, sleep disorders, fibromyalgia, stroke, bleeding diatheses, metabolic disorders such as diabetes mellitus, and airway reactivity. Historically, disorders associated with these diseases have not been considered amenable to neurostimulation.

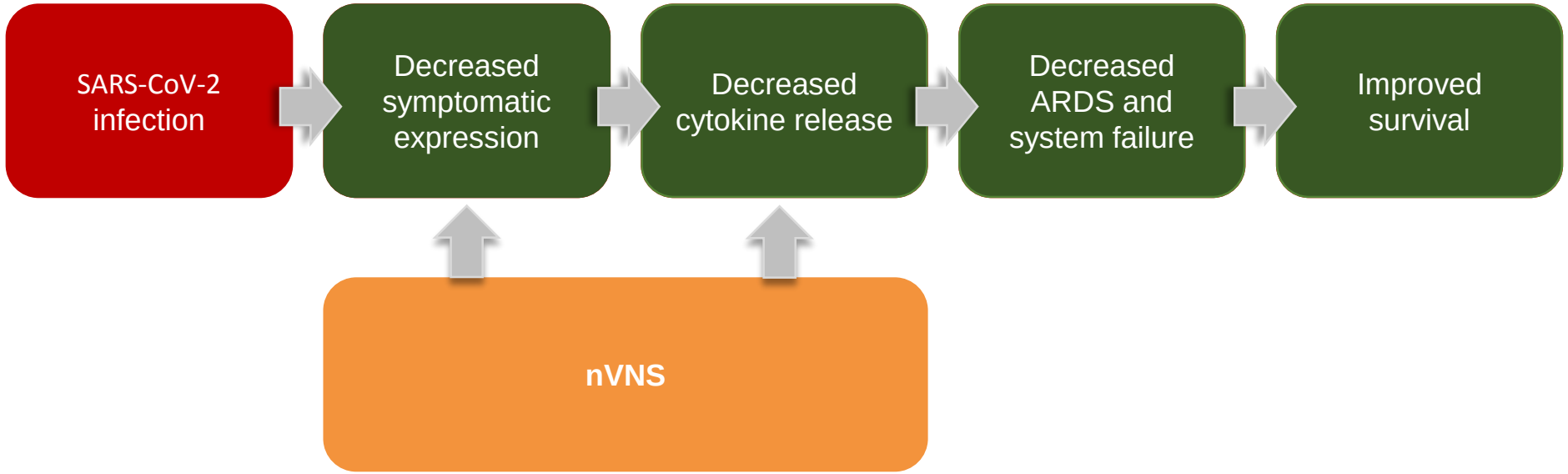
ASTHMA: THE SCOPE OF THE PROBLEM

Asthma is a chronic, long lasting, inflammatory disease of the lung and airways, characterized by reversible bronchoconstriction in response to noxious stimuli. This is mediated by airway smooth muscle contraction and the release of mucus, which leads to airway narrowing. Asthma is classically considered to have both an inflammatory and a neural component. In stress-induced asthma for example, an anxiety attack will trigger the release of histamine and leukotrienes, which can trigger the narrowing of airways (Rietveld et al., 2000). Local anesthetics can be used to blunt airway reactivity, when administered either locally or systemically (Groeben and Peters, 2007).

Asthma and airway reactivity is an enormous problem. In recent decades, both asthma prevalence and incidence have been increasing worldwide. According to the World Health Organization, asthma affects over 334 million people worldwide. In the United States, per the National Health Interview Survey (NHIS)-2012, about 26 million people (8%) suffer from current asthma. It is the most common chronic disease in childhood, affecting an estimated 7 million children. Asthma is a significant public health problem, which often requires the use of emergency care, sometimes including hospital admission, and



Possible Role for nVNS



ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; nVNS, non-invasive vagus nerve stimulation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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The Use of Non-invasive Vagus Nerve Stimulation to Treat Respiratory Symptoms Associated With COVID-19: A Theoretical Hypothesis and Early Clinical Experience

Peter Staats, MD*; Georgios Giannakopoulos, DO†; Justyna Blake*; Eric Liebler*; Robert M. Levy, MD, PhD‡

ABSTRACT

Objectives: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a pandemic with no specific therapeutic agents and substantial mortality, and finding new treatments is critical. Most cases are mild, but a significant minority of patients develop moderate to severe respiratory symptoms, with the most severe cases requiring intensive care and/or ventilator support. This respiratory compromise appears to be due to a hyperimmune reaction, often called a cytokine storm. Vagus nerve stimulation has been demonstrated to block production of cytokines in sepsis and other medical conditions. We hypothesize that non-invasive vagus nerve stimulation (nVNS) might provide clinical benefits in patients with respiratory symptoms similar to those associated with COVID-19.

Materials and Methods: Information on two case reports was obtained via email correspondence and phone interviews with the patients.

Results: Both patients reported clinically meaningful benefits from nVNS therapy. In case 1, the patient used nVNS to expedite symptomatic recovery at home after hospital discharge and was able to discontinue use of opioid and cough suppressant medications. In case 2, the patient experienced immediate and consistent relief from symptoms of chest tightness and shortness of breath, as well as an improved ability to clear his lungs.

Conclusions: Preliminary observations and a strong scientific foundation suggest that nVNS might provide clinical benefits in patients with COVID-19 via multiple mechanisms.

Subjective Feedback: Patients with RAD

- Not wheezing as much
- Less shortness of breath, less tightening
- My lungs felt much clearer and my breathing improved
- Calm and relaxed feeling

Need for Controlled Studies and real world experience

Medical Hypothesis and early clinical experience (2 patients)

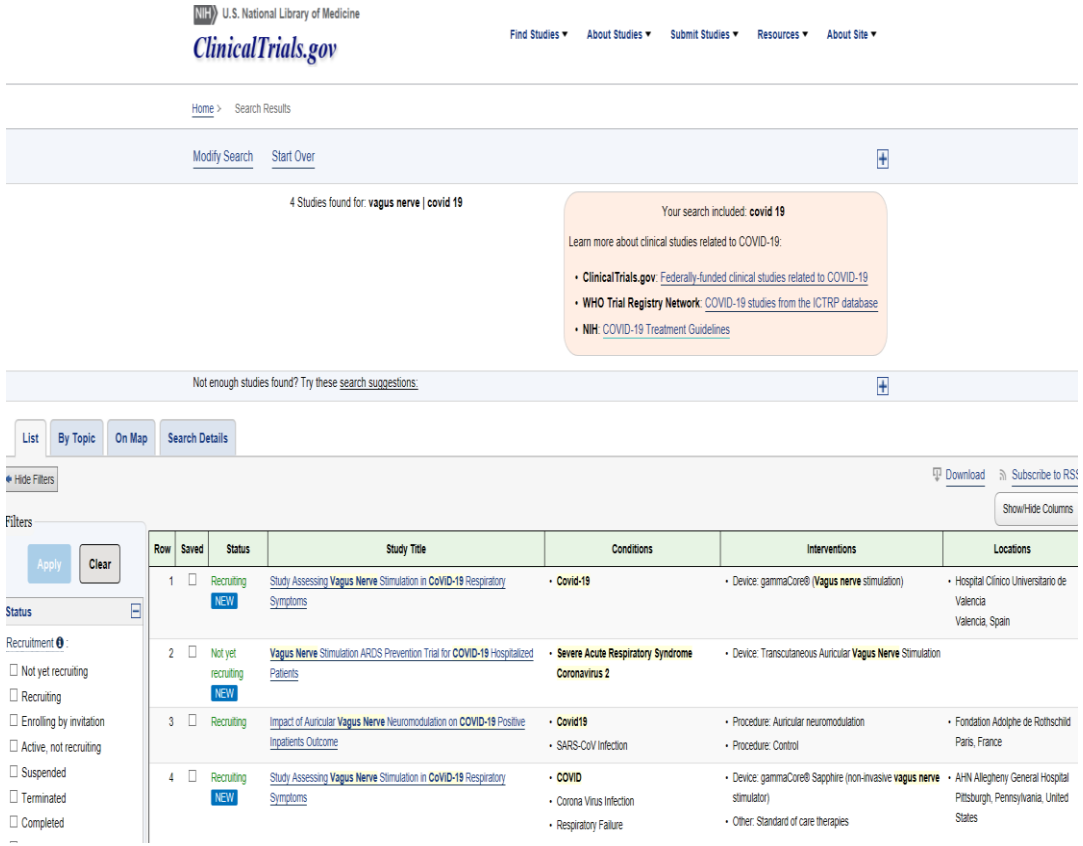
Savior 1 Valencia Spain PI Carlos Tornero 90 Patients Improvement in Respiratory function in inpatients

Savior 2 Allergheny Health systems PI Tarqi Cheema, 60 patients Improvement in respiratory function inpatient

CONVERT Srdj Nedelkovic Brigham and Womans

Auricular vagus nerve stimulator (France)

Vangard VA outpatient study under review



nVNS COVID-19 Clinical Trial Program

Study	Location	Format	Sites/Patients	Status
Respiratory Symptoms (SAVIOR 1)	Valencia, Spain	DB, SoC: RCT	1/90	Enrolling (6)
Respiratory Symptoms (SAVIOR 2)	AHN, PA	DB, SoC: RCT	1/60	Enrolling (2)
Cytokine Reduction (CONVERT)	B&W, MA	DB, SoC: RCT	1/60	IRB
Early Out-patient Treatment (VANGARD)	VA System	Real World Evidence	TBD	Planning

Vagus Nerve Stimulation and Cytokines and the Cytokine storm? Or Respiratory function

Expanding interest

ICNC (International Consortium on neuromodulation in Covid 19)

- Chris Czura*
- Elliott Krames*
- Jared Huston*
- Peder Olofsson*
- Jiande Chen*
- Kristyl Vonck*
- Yaakov Levine*
- Lawrence Poree*
- Navid Khodaparast*
- Manfred Francke*
- Marom Bickson*
- Eric Grigsby*
- Samuel Hamner*
- Mark Lambert*
- Jo Jo Platt*
- Dan Powell*
- Peter Staats*
- Kevin Tracey
- JP Errico
- Eric Liebler
- Bruce Simon*
- Justyna Blake
- Serena Chase
- Paul Bremner
- Fai Ng
- Jessica Tarn
- Imanuel Lerman
- Ricardo Vallejo*
- Georgios Giannokoplis
- Chas Emala
- Rob Levy
- Carlos Tornero
- Boyle Cheng
- Tariq Cheema
- Srdj Nedlkovic

electroCore, Set Point, Spark Biomedical, ICNC*

A medical device in CoVid 19?

- 1662 studies on covid 19
- 81 list drugs studies for Interleuken and CoVID 19
- (four on vagus nerve, 2 enrolling)

- Medical devices are effective in medical disorders
  - Pacemakers
  - Spinal Cord stimulators
  - Movement disorders
  - Epilepsy
  - Incontinence

- Cervical nVNS has FDA cleared device with four indications
- Great safety profile
- Studied in over a thousand patients in a variety of medical conditions
- Commercially available in the US since 2017 and Europe 2011
- Sound clinical rationale

Conclusion

- COVID-19 is not specifically a reactive airway disease, but frequently causes acute respiratory distress and is responsible for severe exacerbations of pre-existing respiratory conditions.
- There are no treatments that currently target the underlying mechanism of COVID-19.
- nVNS may address the symptoms and progression of COVID-19 through two distinct mechanisms of action
- nVNS offers a safe, convenient, and potentially effective acute symptomatic treatment for patients with respiratory symptoms secondary to COVID-19.
- gammaCore can potentially:
  - Provide rapid acute symptomatic relief
  - Reduce the need for standard of care medications for respiratory distress and contribute to efforts to minimize virus transmission.

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Questions?

Thank you for attending!

NEUROVATIONS