

Treatment of asthmatic bronchoconstriction by percutaneous low voltage vagal nerve stimulation: case report.

P Sepulveda, G Bohill, T Hoffmann

Citation

P Sepulveda, G Bohill, T Hoffmann. *Treatment of asthmatic bronchoconstriction by percutaneous low voltage vagal nerve stimulation: case report.* The Internet Journal of Asthma, Allergy and Immunology. 2008 Volume 7 Number 2.

Abstract

Background: A 34 year old Hispanic male patient presented himself in the emergency room with recurring severe asthma that was unresponsive to b-adrenergic and steroid therapy. Spirometry demonstrated significant airflow obstruction. Objective: We sought to test the ability of low voltage vagus nerve stimulation to induce bronchodilation and improve airflow. Method: A percutaneous electrode was inserted into the patient's neck and positioned to lie in the vicinity of the carotid sheath. Following placement, stimulation was administered and the signal amplitude slowly increased until muscle twitching or discomfort was reported by the patient then reduced to a comfortable level. Results: Within minutes of stimulation, the patient reported reduced dyspnea that was confirmed by spirometry fifteen minutes later (FEV₁ increased from 2.70 L to 3.18 L). The FEV₁ remained elevated during the 180min treatment (3.29 ± 0.04 L) and at 30min post stimulation (3.36 L). The FEV₁ then decreased to 2.84 L 60min after stimulation ended. Conclusion: This finding indicates that low voltage vagus nerve stimulation could be a useful critical care treatment to alleviate smooth muscle bronchoconstriction and offer a new therapeutic approach to the treatment of acute asthma.

FINANCIAL SUPPORT

This study was conducted as part of an FDA IDE and sponsored by ElectroCore LLC, Morris Plains, NJ.

ABBREVIATIONS

VNS: Vagal nerve stimulation FEV₁ - forced expiratory volume in 1 second

INTRODUCTION

Asthma is a common chronic lung disease characterized by pulmonary inflammation and bronchoconstriction resulting in dyspnea. When severe, asthma can be life threatening and require emergency medical treatment and hospitalization. In a recent American Lung Association report, there were 1.8 million emergency department visits and 3,816 deaths per year attributable to asthma¹. Medical treatment may include supplemental oxygen to treat the hypoxemia, and pharmacologic agents such as β-agonists to relieve the bronchoconstriction, anticholinergics to treat the vagal reflex component of bronchoconstriction, and corticosteroids to treat inflammation. Here we report on the first patient to be treated with a new pulsed electrical vagal nerve stimulation

device that may open a new therapeutic approach for the temporary treatment of acute asthma. This study was conducted as part of an FDA IDE, and was completed under IRB supervision.

CASE PRESENTATION

A 34 year-old Hispanic male patient with a four year history of severe asthma and a former smoker was admitted to the emergency department with an acute asthma attack. He reported self treatment with albuterol without success. Upon admission, the patient was alert and calm but demonstrated bilateral wheezing, elevated blood pressure (BP) (163/92 mmHg) related to chronic hypertension, acute bronchitis, and mild throat hyperemia. All other vital signs were normal. The patient was administered conventional pharmacologic therapy over a 9 hour period without benefit. Treatment included albuterol (2.5mg), prednisone (60mg PO), and zithromax (500mg PO). At five hours, spirometry assessment of the lung function revealed a Forced Expiratory Volume in 1 second (FEV₁) of 2.68 L or 69% of predicted². After eight hours, the patient was provided information on this study, was consented, and entered a 90 minute

Treatment of asthmatic bronchoconstriction by percutaneous low voltage vagal nerve stimulation: case report.

observation period. During this time, the patient continued to receive pharmacologic therapy (2.5mg albuterol) and began supplemental oxygen (2 L/min). The patient then underwent placement of a percutaneous, bipolar electrode to stimulate the right vagus nerve (figure 1).

The patient was prepped and draped and, using anatomical landmarks and ultrasound guidance, the electrode lead was inserted to a position parallel to the right vagus nerve in the vicinity of the carotid sheath. The patient remained fully conscious and responsive during the procedure and received only local anesthesia at the insertion site. The electrode insertion was uneventful and a sub-threshold test confirmed the device was functioning. Spirometry was repeated and FEV₁ remained impaired at 2.70 L. Stimulation strength was gradually increased until the patient felt a mild muscle twitch at 7.5 volts (25Hz, 200µs pulse width signal) then reduced to 7 volts. This setting achieved therapeutic levels without discomfort and the patient was able to repeat the FEV₁ test without difficulty. At the 15min test point, FEV₁ had improved to 3.18 L and stabilized during 180 minutes of testing (3.29 ± 0.04 L, 85% predicted). Benefit remained during the first thirty minutes after terminating treatment (3.38 L) then decreased. At 60 minutes post stimulation, FEV₁ was only modestly elevated above pre-stimulation levels (2.84 L, 73% predicted) (figure 2). The patient remained under observation overnight to monitor the concomitant hypertension and then discharged. At the 1-week follow-up visit, the exam showed complete healing of the insertion site, and the patient reported no after effects from the treatment.

Figure 1

Figure 1. Patient with a percutaneous VNS electrode

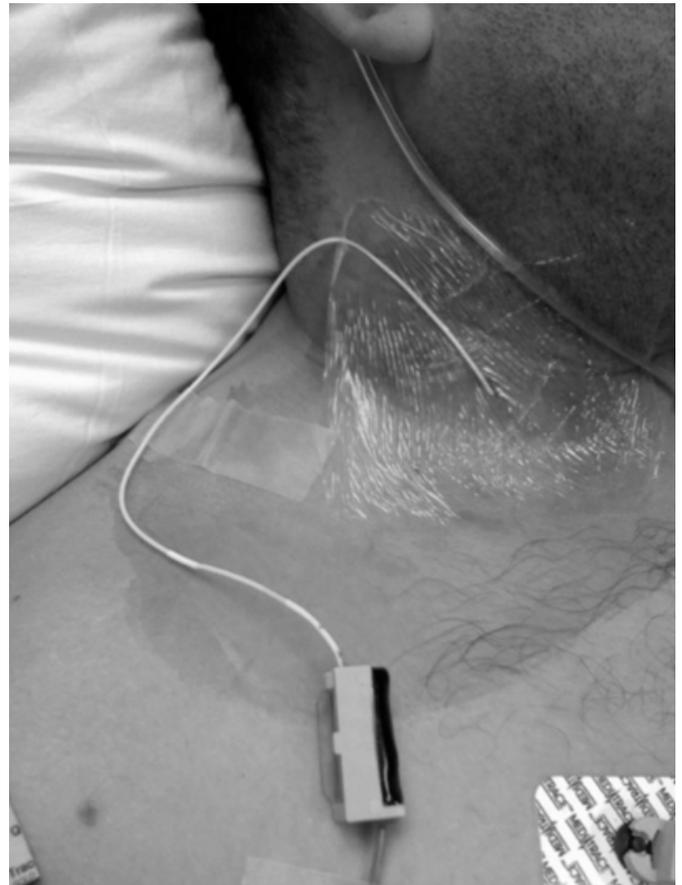
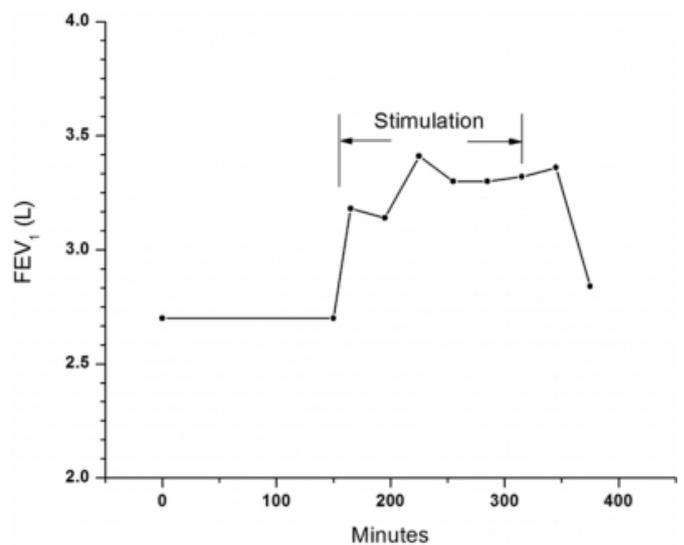


Figure 2

Figure 2. The effect of VNS on FEV



DISCUSSION

Here, we report on the first use of vagus nerve stimulation (VNS) in a human asthma patient to treat

bronchoconstriction. Although a form of VNS has been in clinical use for over ten years³ for the non-pharmacologic treatment of seizure disorders and depression, until now, VNS has not been applicable for the treatment for asthma. Indeed in one report on a patient with intractable seizures, VNS Therapy™ was associated with dyspnea although this was easily remedied after reprogramming the stimulation signal⁴. A further limitation of VNS Therapy™ is that the procedure requires direct visualization and manipulation of the vagus nerve in order to attach an electrode array. In the treatment report here, invasive surgery was not required. Instead a minimally invasive, percutaneous approach was used to position an electrode in close proximity to the nerve. This was a relatively simple and rapid procedure that was performed in the emergency department and completed in approximately 10 minutes without evidence of bleeding or scarring.

The neural pathways of the parasympathetic nervous system are the primary regulators of pulmonary smooth muscle tone. Postganglionic parasympathetic nerves mediate both cholinergic contractions and inhibitory nonadrenergic noncholinergic (iNANC) relaxations. It is the close balance between these two that ultimately determines airway caliber. Electrophysiological studies suggest that these relaxation and contraction responses are through anatomical and physiological distinct vagus nerve pathways⁵.

In animal studies, relatively high levels of direct vagal nerve stimulation have been used to induce bronchoconstriction^{6,7}. Recently, our group has found that similarly applied low voltage stimulation could be used to reduce histamine induced bronchoconstriction in two animal models⁸. This has led to the development of a new percutaneous proximity neurostimulator for stimulating the cervical vagus nerve that was used in this study.

In animal models, VNS is frequently used to investigate the neural pathways and receptors involved in controlling the airways and their association with asthma. Electrical stimulation of the vagus nerve can result in the release of acetylcholine from its pulmonary endings to activate muscarinic acetylcholine receptors on airway smooth muscle cells and induce bronchoconstriction. In contrast, we have demonstrated previously in animal models⁸ and now in a human patient that VNS can be used to reduce bronchoconstriction associated with asthma. Although the mechanism has not been fully established, iNANC nerves constitute a likely neural pathway since they can be activated

by electrical stimulation and are known to mediate relaxation in human airways⁹.

In this patient, normal pharmacological therapy with β_2 -agonist inhalation was ineffective. It is possible that the airway limitations and reduced inhalation volume created inefficiencies in airflow dynamics. Therapeutic aerosol delivery involves impaction, sedimentation, and diffusion¹⁰. During an acute asthma episode, the air flow changes from what is largely laminar under normal circumstances to a pattern with increasing velocities and turbulence. This makes delivery of the pharmacological inhalation agents to the distal lungs difficult, both by reducing transport and by depleting the concentration through impact and absorption in the upper respiratory tract. The application of this new VNS treatment bypasses airflow limitations to bring immediate bronchodilation. The resulting improvement in airflow dynamics provided by VNS can then facilitate the delivery of standard inhalation therapies to achieve prolonged remission of asthma symptoms.

CONCLUSION

The specific VNS signal applied in this study suggests that stimulation can safely reduce bronchoconstriction. This offers an exciting new opportunity to provide a non-pharmacological and non-airflow dependent treatment modality to emergency department practice for acute asthma as well as a potential new rescue treatment in critical care settings.

References

1. American Lung Association, Epidemiology & Statistics Unit. Trends in asthma morbidity and mortality. November 2007. Available at http://breathehealthy.org/uploads/2007_Asthma_Trend_Report.pdf. Accessed February 12, 2009.
2. Crapo RO, Jensen RL, Lockey JE, Aldrich V, Elliott CG. Normal spirometric values in healthy Hispanic Americans. *Chest*. 1990; 98:1435-9.
3. Cyberonics, Inc. Corporate profile. Houston, Texas U.S.A. 77058, Available at: <http://www.cyberonics.com/corporateprofile>. Accessed January 19, 2008.
4. Bijwadia, JS, Hoch RC, Dexter DD. Identification and treatment of bronchoconstriction induced by a vagus nerve stimulator employed for management of seizure disorder. *Chest* 2005; 127:401-402
5. Mazzone SB, Canning BJ. Evidence for differential reflex regulation of cholinergic and noncholinergic parasympathetic nerves innervating the airways. *Am J Respir Crit Care Med* 2002; 165:1076-1083
6. Jooste E, Zhang Y, Emala CW. Neuromuscular blocking agents' differential bronchoconstrictive potential in Guinea pig airways. *Anesthesiology*. 2007; 106:763-72.
7. Blaber LC, Fryer AD, MacLagan J. Neuronal muscarinic receptors attenuate vagally-induced contraction of feline

Treatment of asthmatic bronchoconstriction by percutaneous low voltage vagal nerve stimulation: case report.

bronchial smooth muscle. *Br J Pharmacol.* 1985; 86:723-8.
8. Hoffmann TJ, Mendez S, Staats P, Emala CW, Guo P. Inhibition of Histamine-Induced Bronchoconstriction in Guinea Pig and Swine by Pulsed Electrical Vagus Nerve Stimulation. *Neuromodulation.* in press
9. Maarsingh H, Leusink J, Bos TS, Zaagsma J, Meurs H. Arginase strongly impairs neuronal nitric oxide-mediated

airway smooth muscle relaxation in allergic asthma. *Respir Res.* 2006; 7:6 .
<http://respiratory-research.com/content/7/1/6>. Accessed February 2, 2009.
10. Newhouse MT, Dolovich M. Aerosol therapy of reversible airflow obstruction. *Concepts and clinical applications.* *Chest.* 1987; 91: 58S-64S.

Author Information

Pedro Sepulveda, MD

Director, Alamo Clinical Research Center, San Antonio, TX

Gorav Bohill, MD

Emergency Department Director, Christua Santa Rosa Hospital, San Antonio, TX

Thomas J. Hoffmann, BS

ElectroCore LLC, Morris Plains, NJ