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EDITORIAL

The Israeli Trial to Treat Heart Failure. From Science to Politics.

The stupid neither forgive nor forget;
the naive forgive and forget;
the wise forgive but do not forget.
Thomas Szasz, *The Second Sin (1973) (1)*

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The recent advances in the treatment of heart failure (HF) with the introduction of new drugs as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (2-4), and new pacemaker-like devices to reduce tachycardia-induced arrhythmias and to improve LV-remodeling (5), showed a limited improvement in morbidity and mortality without halting the progress of HF.

Many previous clinical and basic studies have demonstrated that the abnormal activation of the sympathetic nervous system (SNS) leads to further worsening of heart failure. It is well known that the effect of SNS stimulation will lead to a wide variety of cardiovascular actions, including heart rate acceleration, increase in cardiac contractility, reduction of venous capacitance, and constriction of resistance vessels (6, 7).

On the other hand, parasympathetic or vagal activation affects the cardiovascular system by slowing heart rate (8). In heart failure the observed SNS hyperactivity is related to abnormalities in cardiovascular reflexes (6, 7). The sympathoinhibitory cardiovascular reflexes such as the arterial baroreceptor reflex are significantly suppressed.

The central nervous system receives inputs from a variety of sources in the body and activates mechanisms that play a major role in progressive cardiac remodeling and dysfunction (8).

The autonomic imbalance with the combination of sympathetic up-regulation and parasympathetic withdrawal is associated with progressive ventricular remodeling, arrhythmia generation and disease progression.

The use of beta-blockers as the second generation, with higher affinity for the beta1-than for the beta2-receptor (atenolol, metoprolol, bisoprolol); and third generation as carvedilol, which has a vasodilation effect mediated via alpha1-receptor blockade are almost universally approved for the treatment of chronic heart failure (9-14), the ability of these drugs to influence parasympathetic function is limited (15), although digoxin may have some effect (16, 17).

Parasympathatic stimulation seems to have a beneficial effect on the failing heart with limitation of the notorious exaggerated SNS hyperactivity.

Vagus Nerve

The vagus nerves or tenth cranial nerves are the main parasympathetic nervous supply to the heart. It extends through the jugular foramen, and then passes into the carotid sheath between the internal carotid artery and the internal jugular vein down below the head, to the neck, chest and abdomen (18). The vagus nerve is responsible for important tasks as heart rate, gastrointestinal peristalsis, sweating, and muscle movements in the mouth, including speech and keeping the larynx open for breathing (19). They give recurrent laryngeal nerves and contribute to cardiac, pulmonary, and esophageal plexuses (20).

Vagus nerve stimulation (VNS) can be achieved by holding breath, dipping the face in cold water, coughing, or tensing the stomach muscles. Other methods leading to VNS include carotid sinus massage, Valsalva maneuver, or pain from any cause leading to vasovagal syncope.

Parasympathetic activation showed not only slowing of the heart but also many proved beneficial effects mainly for its anti-inflammatory effects (21) (Table 1).

Vagus nerve stimulation was used to treat epilepsy when other treatments haven't worked. Vagus nerve stimulation is also a treatment for depression, and it's being studied for conditions such as multiple sclerosis, migraine and Alzheimer's disease (22-26).

Abbreviations and Acronyms	
SNS	: Sympathetic Nervous System
VNS	: Vagus Nerve Stimulation
INOVATE-HF	: INcrease Of VAgal TonE in CHF

Table 1: Potential cellular and electrophysiological benefits of parasympathetic activation (21):

Anti-inflammatory effects
Change in nitric oxide expression
Change in cytokine expression
Inhibition of the renin-angiotensin system
Improved baroreflex sensitivity
Reduced heart rate
Increased heart rate variability
Direct anti-arrhythmic effects

INOVATE-HF Trial

The INcrease Of VAgal TonE in CHF (INOVATE-HF), is an international multi-center randomized clinical trial to assess safety and efficacy of VNS in symptomatic patients with heart failure on optimal medical therapy using the CardioFit System. The study is sponsored by BioControl Medical, Yehud, Israel (27).

The trial started on February, 2011, and the estimated study completion in June 2015. It will recruit 650 patients with chronic heart failure functional class III. This will be from 80 different sites, mainly from USA, Germany and Israel.

CardioFit System (BioControlMedical, Yehud, Israel); it is a sort of a pacemaker device with 2 leads; a standard intracardiac sensing electrode in the right ventricular apex and a stimulation lead with cuff placed surgically over the right vagus nerve (Figure 1, 2) (28).

The CardioFit system is designed to provide vagus nerve stimulation to patients with heart failure based on sensed ventricular impulses via R wave measurement using the sensing lead.

The patient inclusion criteria are; sinus rhythm and a QRS duration of less than 120 milliseconds, on optimal medical therapy, LVEF ≤40%, left ventricular end diastolic diameter between 50 and 80mm, and subjects with CRT devices may be included in the trial provided they have had CRT for at least 12 months (27, 28).

Figure 1: The CardioFit system. The CardioFit system consists of a stimulator, nerve stimulation lead with cuff and right ventricular sensing lead (28).

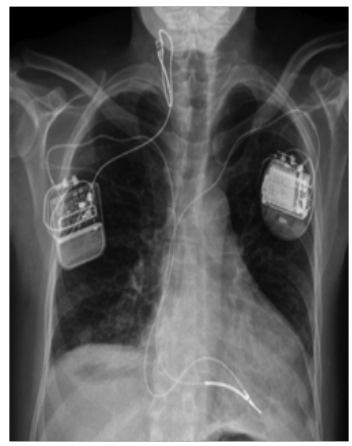

Figure 2: Radiograph of an implanted CardioFit System, showing the CardioFit implant on the patient's right and a previously implanted defibrillator on the left. Two leads are in the RV apex: one is the sensing lead from the CardioFit device (28).

The exclusion criteria is a long list including acute coronary syndrome, history of stroke or TIA within the previous 3 months, acute myocarditis, restrictive cardiomyopathy, constrictive pericarditis, significant aortic valve disease, creatinine level >3mg/dL, total bilirubin level >1.8mmol/dL, uncontrolled diabetes, systolic blood pressure below 80mmHg, 2nd or 3rd degree AV block or other pacemaker indication, atrial fibrillation or flutter in the previous 3 months, use of unipolar sensing, long QT syndrome, the subject must not have received inotropic therapy within 2 months or be considered a possible candidate for inotropic therapy within the next 1 month (27).

Results from a small multi center European trial on 32 patients have been recently reported (29). There were improvements in 6-minute hall walk distance, NYHA class and Quality of Life measurements were achieved. Left ventricular ejection fraction increased significantly from a mean of 22.3±6.9 to 28.7±8.4 at 6 months, as a result of a reduction in end systolic volume index. The positive effect of vagus nerve stimulation was sustained in the patients who were followed for 12 months.

The major limitation of the trial is that, it randomizes patients with heart failure within a narrow spectrum as mentioned before in the exclusion criteria. Those with chronic advanced heart failure of grade >3/4 (AHA) fulfilling the inclusion criteria may be less than one third of their total population. The technical aspects of device implantation, seems more difficult than any other technique used for pacemaker implantation specially on applying the vagus nerve stimulator cuff over the nerve in the carotid sheath.

The vagus nerve does not only supply the heart but also other different important organs. The possible

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side effects of VNS reported before may be sleep apnea (30, 31), hoarseness of voice,, coughing, pharyngitis and throat pain (32), with other nonspecific symptoms such as headache, nausea, vomiting, dyspepsia (33), dyspnea and paresthesia (34).

The final results of this large trial will not appear before the year 2015. Nevertheless, this pilot study sponsored by an Israeli medical company represents a novel approach for correction of the autonomic imbalance commonly seen in heart failure. It also gives us an idea about the advanced technology and background wealth of the sponsoring company (BioControlMedical, Yehud, Israel).

Editor Opinion

The quotation in the beginning of the article looks like an equation composed of two variables; forgive and forget, and ends with 3 conclusions; stupid, naïve and wise. We think that it is neither applicable in our situation, nor in theirs. It failed to mention the prevailing distrust, which is very prominent between us in spite of the fragile political peace treaty.

In the case of the INOVATE-trial, if it proved to be truly reducing the mortality and morbidity with minimal complications, and for the fact that the trial was carried out in 80 international centers (27, 28). This will give it its widespread legibility. The Arab doctors will accept the Yehud, Israel stimulator if its wrapping carries a label indicating its origin from outside Israel.

The two arms of the quotation; forgive and forget will have a third limb, which is "ignore or overlook", simply for the fact that "money has no smell".

It is wise that the hostile attitude between neighboring countries should come by all means to an end. We should remember that our area can be the summit of civilization as history told us.

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REFERENCES

1. http://www.brainyquote.com/quotes/quotes/t/thomasszas138710.html.
2. Savarese G, Costanzo P, Cleland JGF, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. J Am Coll Cardiol 2013; 61(2):131-42.
3. Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: Recent advances in basic science. Lancet 2011; 378(9792):704-12.
4. Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: A report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular. J Am Coll Cardiol 2013; 61(12):1318-68.
5. Triposkiadis F, Karayannis G, Giamouzis G, et al. The sympathetic nervous system in heart failure. Physiology, pathophysiology and clinical implications. J Am Coll Cardiol 2009; 54(19):1747-62.
6. Floras JS. Sympathetic nervous system activation in human heart failure. Clinical implications of an updated model. J Am Coll Cardiol 2009; 54(5):375-85.
7. Schwartz PJ. Vagal stimulation for heart diseases: From animals to men - an example of translational cardiology. Circ J 2011; 75(1): 20-7.
8. Leenen FHH. Brain mechanisms contributing to sympathetic hyperactivity and heart failure. Circ Res 2007; 101(3):221-3.
9. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. Circulation 2005; 112(12):e154-235.
10. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353(9169):2001-7.
11. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. Lancet 2001; 357(9266):1385-90.
12. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002; 106(17):2194-9.
13. Poole Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): Randomised controlled trial. Lancet 2003; 362(9377): 7-13.
14. Willenheimer R, Van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 2005; 112(16):2624-35.
15. Desai MY, Watanabe MA, Laddu AA, et al. Pharmacologic modulation of parasympathetic activity in heart failure. Heart Failure Rev 2011; 16(2):179-93.

16. Van Veldhuisen DJ, De Graeff PA, Remme WJ, et al. Value of digoxin in heart failure and sinus rhythm: New features of an old drug? J Am Coll Cardiol 1996; 28(4):813-9.
17. Hauptman PJ, Kelly RA. Digitalis. Circulation 1999; 99(9): 1265-70.
18. Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. Autonom Neurosci Basic Clin 2000; 85(1-3):1-17.
19. Brown OE. Structure and function of the upper airway. In: Wetmore RF, Muntz HR, McGill TJ, editors. Pediatric otolaryngology: Principles and practice pathwaysNew York: Thieme; 2000. p. 679-88.
20. Agur AMR, Dalley AE. The cranial nerves. In: Agur AMR, Dalley AE, editors. Grant's atlas of anatomyBaltimore, MD: Lippincott Williams & Wilkins; 2004. p. 793-824.
21. Olshansky B, Sabbah HN, Hauptman PJ, et al. Parasympathetic nervous system and heart failure pathophysiology and potential implications for therapy. Circulation 2008; 118(8):863-71.
22. Beekwilder JP, Beems T. Overview of the clinical applications of vagus nerve stimulation. J Clin Neurophysiol 2010; 27(2):130-8.
23. Krahl SE. Vagus nerve stimulation for epilepsy: A review of the peripheral mechanisms. Surg Neurol Int 2012; 3(Suppl. 1):S47.
24. Buchhalter JR, Jarrar RG. Therapeutics in pediatric epilepsy, Part 2: Epilepsy surgery and vagus nerve stimulation. Mayo Clin Proc 2003; 78(3):371-8.
25. Schachter SC. Vagus nerve stimulation therapy summary: Five years after FDA approval. Neurology 2002; 59(6 Suppl. 4):S15-20.
26. Martin JLR, Martín Sánchez E. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: Variable results based on study designs. Eur Psychiatry 2012; 27(3):147-55.
27. http://www.clinicaltrials.gov/ct2/show/NCT01303718?term=INOVATE-HF&rank=1.
28. Hauptman PJ, Schwartz PJ, Gold MR, et al. Rationale and study design of the INcrease of Vagal TonE in Heart Failure study: INOVATE-HF. Am Heart J 2012; 163(6):954-62.
29. De Ferrari GM, Crijns HJGM, Borggrefe M, et al. Chronic vagus nerve stimulation: A new and promising therapeutic approach for chronic heart failure. Eur Heart J 2011; 32(7):847-55.
30. Malow BA, Edwards J, Marzec M, et al. Effects of vagus nerve stimulation on respiration during sleep: A pilot study. Neurology 2000; 55(10):1450-4.
31. Marzec M, Edwards J, Sagher O, et al. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. Epilepsia 2003; 44(7):930-5.
32. Hsieh T, Chen M, McAfee A, et al. Sleep-related breathing disorder in children with vagal nerve stimulators. Pediatr Neurol 2008; 38(2):99-103.
33. Hatton KW, McLarney JT, Pittman T, et al. Vagal nerve stimulation: Overview and implications for anesthesiologists. Anesth Analg 2006; 103(5):1241-9.
34. George MS, Sackeim HA, Rush AJ, et al. Vagus nerve stimulation: A new tool for brain research and therapy. Biol Psychiatry 2000; 47(4):287-95.