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Chronic Vagal Stimulation in Patients with Congestive Heart Failure

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Abstract—**Increased sympathetic and reduced vagal activity predict increased mortality in patients with congestive heart failure (CHF). Experimentally, vagal stimulation (VS) is protective both during acute myocardial ischemia and in chronic heart failure. In man, VS is used in refractory epilepsy but has never been used in cardiovascular diseases.**

Thus, there is a strong rationale to investigate the effects of chronic VS in patients with CHF.

We assesses the feasibility and safety of chronic VS with CardioFit (BioControl Medical), a VS implantable system delivering pulses synchronous with heart beats to the right cervical vagus nerve in a preliminary pilot study in eight advanced CHF patients with favorable results, and subsequently in a larger multicenter study. Overall, 32 patients have been successfully implanted (mostly in NYHA Class III; mean age 56 years, ischemic etiology in 69%; prior implantable cardioverter-defibrillator (ICD) in 63%; concomitant beta blocker and angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) in 100%). Preliminary results confirm feasibility of the study, an acceptable side effect profile and promising preliminary efficacy data. Several mechanisms may contribute to the beneficial effect observed in patients with heart failure.

Should these results be confirmed in larger controlled studies, chronic vagal stimulation could be a further treatment option for CHF patients, possibly integrated with defibrillator and resynchronization therapies.

Congestive Heart Failure (CHF) is a progressive disease in which a decreased cardiac function produces an imbalance between metabolic demand of peripheral tissues and cardiac output. Most commonly CHF is associated to progressive cardiac dilation following cardiac remodeling, a complex process that involves structural, biochemical, neurohormonal, and electrophysiologic factors. Ventricular remodeling in CHF is facilitated by the activation of compensatory mechanisms, such as the sympathoadrenal and renin-angiotensin-aldosterone systems, that act to increase cardiac output. Neurohormonal activation exerts beneficial effects in the short term but contributes to deterioration of long-term cardiac function.

Autonomic imbalance with increased sympathetic and decreased parasympathetic activity is an important feature of CHF and is associated with increased mortality both after myocardial infarction and in heart failure[1]-[4]; additionally in this latter condition further vagal withdrawal has been documented to precede acute decompensation[5].

In agreement with the concept that sympathetic as well as renin-angiotensin activation play a significant role in ventricular remodeling, it has been demonstrated that pharmacological antagonists of the neurohormal cascade exert a beneficial effect in the progression of the disease and in the prognosis of CHF patients. Notably, beta adrenergic receptors antagonists counteract the autonomic, imbalance with sympathetic dominance and reduce morbidity and mortality[6].

Direct parasympathetic activation (pharmacologic or electric) was also demonstrated to induce positive effects, albeit at experimental level[7], [8]. It has been shown that vagal stimulation decreases the likelihood of ventricular fibrillation in a chronic canine model for sudden cardiac death[8] and that it significantly improves survival in a post-ischemic model of heart failure in the rat[9].

In a canine model of intracoronary microembolization-induced heart failure chronic vagal stimulation was shown to exert positive effects on left ventricular function that were found to be additive to those conferred by beta-blockers therapy[10].

Altogether, these findings provide a strong rationale toward the evaluation of the potential benefit of chronic vagal stimulation in patients with heart failure. Chronic vagus nerve stimulation has been approved and is being frequently used for the treatment of drug-refractory epilepsy[11], [12] and more recently also for depression[13].

So far a single-center pilot safety and feasibility study has been concluded in 8 patients[14]. Subjects aged 18 to 75 years, with left ventricular ejection fraction <35% and a history of chronic heart failure in NYHA class II–III were eligible for the study.

Exclusion criteria included the presence of acute coronary syndrome, myocardial revascularization or acute decompensation in the previous 3 months, a previous stroke, severe valvular heart disease, insulin-dependent diabetes mellitus, active peptic disease, asthma or severe chronic obstructive pulmonary disease, glaucoma. Finally, patients with left bundle branch block and/or with an indication for cardiac resynchronization therapy were excluded.

The patients underwent implantation of CardioFit 5000 (BioControl Medical Ltd.), an implantable neuro-stimulator

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system designed to sense the heart rate (via an intracardiac electrode) and deliver one or more pulses at a adjustable delay from the R wave (Fig. 1). The stimulator microprocessor responds to the sensed heart rate and can adjust the stimulation accordingly.

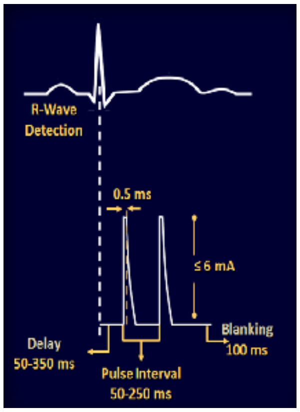

Fig. 1. Characteristics of the delivered impulse synchronization waveform, and amplitude.

The stimulation lead is an asymmetric bipolar multi-contact cuff electrode specifically designed for cathodic induction of action potentials in the vagus nerve, while simultaneously applying asymmetrical anodal blocks which are expected to lead to preferential, but not exclusive, activation of efferent fibers. The electrode size can be specifically adjusted for each patient, with a selection of 7 different sizes and an internal diameter ranging between 2.0 and 3.5 mm. During the positioning of the vagal cuff electrode, performed under general anesthesia a brief stimulation test is performed to document adequate heart rate reduction, and consequently appropriate positioning around the vagus nerve.

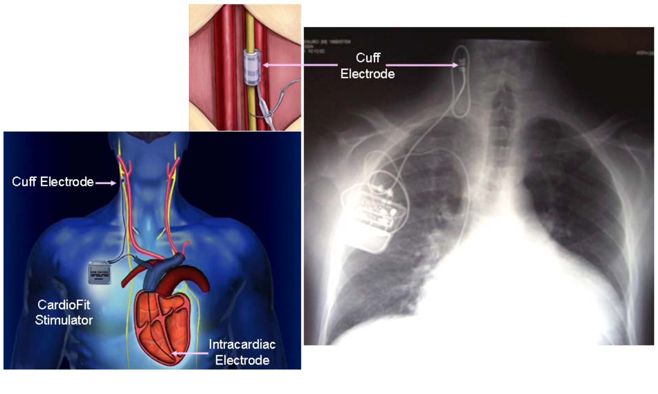

Fig. 2. Schematic representation of implanted system with an expanded view of the cuff electrode (left side) and chest X-ray of an implanted patient.

Three weeks after implantation, a 3-week phase of current up-titration begun. Stimulation was started with 1 ms pulse per beat delivered 70 ms after the R wave and an amplitude of 1 mAmp progressively increasing until the obtainment of either 6 mAmp, a heart rate (HR) reduction of 5-10 beats or the development of important side effects. Patients were then followed for a 6-month period.

The surgical procedure was uneventful in all patients. Side effects that were related to the stimulation included: cough in 4 patients, pain at stimulation site in 4 patients, mandibular pain in 3 patients, voice alteration in 2 patients. These side effects were resolved after either patient adaptation or fine current down-titration. Also, we showed the absence of interaction between high intensity vagal stimulation with CardioFit and ICD sensing in two patients who had ICD implanted either before or during the follow-up.

During the study resting heart rate, was progressively slightly but significantly reduced, NYHA class was reduced, particularly at month 1 and 3 and quality of life markedly improved already at month 1 and remained significantly better throughout the study (see Table 1).

TABLE 1
CLINICAL RESULTS IN THE FIRST EIGHT PATIENTS.

Variable	Baseline	1 m	3 m	6 m	*p*
HR (beats/min)	87±13	78±13	79±13	83±12	0.01
NYHA class (I/II/III/IV)	0/1/7/0	0/7/1/0	0/8/0/0	1/3/4/0	<0.01
Minnesota QoL	52±14	21±9	25±10	31±18	0.001
6MWT (m)	405±43	462±87	480±95	446±99	0.04
LVEDV (ml)	273±81	242±66	248±73	250±82	0.13
LVESV (ml)	208±71	174±60	184±75	190±83	0.03
LVEF (%)	24±5	29±10	27±12	26±10	0.2

m=months; HR=heart rate; NYHA=New York Heart Association; Minnesota QoL= Quality of Life by Minnesota Living with Heat Failure® Questionnaire; 6MWT= six-minute walk test; LVEDV=left ventricular end diastolic volume; LVESV=left ventricular end systolic volume; LVEF=left ventricular ejection fraction.
Modified from Reference[14].

Following this preliminary experience, a multi-center international trial has been conducted. Overall, 32 patients have been successfully implanted with a mean age 56 years (range 30-75); ischemic etiology in 69%; prior ICD in 63%; concomitant beta blocker and ACE-I or ARB in 100%. Preliminary results[15] have been presented confirming the favorable trend observed in the single-center study; 6-month follow up will be soon completed for all patients.

This preliminary finding raises the intriguing possibility that careful modulation of cardiac autonomic activity may play a contributory role in the management of selected high risk patients with cardiovascular disease, especially those with advanced heart failure but possibly also those at risk for recurrent ventricular fibrillation.

Several mechanisms may contribute to the beneficial effect observed in patients with heart failure[16]. These may include anti-adrenergic effects anti-apoptotic effects, anti-inflammatory effects[17] and increase in nitric oxide.

Should these favorable results be confirmed in larger controlled studies, chronic vagal stimulation could be a further treatment option for CHF patients, possibly integrated with defibrillator and resynchronization therapies.

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