Autonomic regulation therapy suppresses quantitative T-wave alternans and improves baroreflex sensitivity in patients with heart failure enrolled in the ANTHEM-HF study

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BACKGROUND Autonomic regulation therapy (ART) with chronic vagus nerve stimulation improves ventricular function in patients with chronic heart failure, but its effects on quantitative T-wave alternans (TWA), ventricular tachycardia (VT), baroreflex sensitivity, and autonomic tone remained unknown.

OBJECTIVE Effects on TWA, a marker of risk of life-threatening arrhythmias; heart rate turbulence (HRT), an indicator of baroreflex sensitivity; heart rate variability; and VT incidence were studied in 25 patients with chronic symptomatic heart failure and reduced ejection fraction enrolled in the ANTHEM-HF study (NCT01823887).

METHODS Twenty-four-hour ambulatory electrocardiographic recordings made before ART system (Cyberonics, Inc., Houston, TX) implantation involving the left or right vagus nerve and after 6 and 12 months of chronic therapy (10-Hz frequency, 250-μs pulse width, maximum tolerable current amplitude after 10 weeks of titration) at low-intensity (<2 mA; n = 10, 40%) or high-intensity (≥ 2 mA; n = 15, 60%) stimulation levels were analyzed.

RESULTS At 12 months, peak TWA levels were reduced by 29% from 71.0 ± 4.6 to 50.5 ± 1.8 μV ($P < .0001$). The number of patients with severely abnormal TWA (≥ 60 μV) was reduced by 76% from 17 to 4 ($P < .0005$), and the number of patients with nonsustained VT decreased by 73% from 11 to 3 ($P < .025$). HRT slope ($P < .025$), high frequency heart rate variability (HRV) ($P = .05$), and square root of the mean squared differences of successive normal-to-normal interval HRV ($P = .013$) increased. The mean heart rate derived from 24-hour Holter electrocardiograms decreased by 10% from 77 ± 2 to 69 ± 2 beats/min ($P = .0002$). HRT onset was unchanged.

CONCLUSION Chronic ART in patients with symptomatic heart failure improves cardiac electrical stability, as reflected by reduced TWA levels and heart rate, suppresses VT, and increases baroreceptor sensitivity. These observations deserve study in a larger population.

KEYWORDS Heart failure; T-wave alternans; Baroreceptor sensitivity; Vagus nerve stimulation; Autonomic regulation therapy; Heart rate turbulence; Ventricular tachycardia; Heart rate variability; Autonomic tone; Autonomic reflexes

ABBREVIATIONS **ANTHEM-HF** = Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure; **ART** = autonomic regulation therapy; **ECG** = electrocardiogram/electrocardiographic; **HF** = high-frequency; **HRT** = heart rate turbulence; **HRV** = heart rate variability; **LF** = low-frequency; **LV** = left ventricular; **LVEF** = left ventricular ejection fraction; **LVESV** = left ventricular end-systolic volume; **MMA** = Modified Moving Average; **NECTAR-HF** = NEural Cardiac TherApy foR Heart Failure; **NYHA** = New York Heart Association; **rMSSD** = square root of the mean squared differences of successive normal-to-normal intervals; **SCD** = sudden cardiac death; **SDNN** = standard deviation of normal-to-normal intervals; **TWA** = T-wave alternans; **VNS** = vagus nerve stimulation; **VT** = ventricular tachycardia

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Introduction

The prognosis of patients with advanced heart failure remains poor despite extensive use of pharmacologic therapy and devices.[1] Because autonomic dysfunction characterized by excessive sympathetic nerve activity and concomitant withdrawal of parasympathetic activation[2] are critically implicated in heart failure morbidity and mortality, there has been strong interest in chronic nerve stimulation strategies to counteract these abnormalities.[3] Autonomic regulation therapy (ART) via chronic vagus nerve stimulation

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(VNS) has been a focus of considerable research because of its multifactorial cardioprotective mechanisms[4–7] and the excellent safety profile established in managing >100,000 patients with epilepsy or depression for >2 decades.[8]

In a pioneering study, Schwartz and De Ferrari[9] conducted a "first-in-man" study of the effects of chronic VNS in a series of 8 patients with advanced heart failure. They demonstrated a significant improvement in left ventricular end-systolic volume (LVESV) and New York Heart Association (NYHA) class, supporting feasibility and safety. This experience was then extended to the multicenter international CardioFit study (NCT00461019), which enrolled a total of 32 patients and confirmed favorable effects on left ventricular ejection fraction (LVEF), LVESV, NYHA class, and quality of life measures.[10]

However, there is limited information on the effects of VNS on cardiac electrophysiological properties and susceptibility to ventricular arrhythmias in patients with heart failure. Recently, it was demonstrated that VNS reduced T-wave alternans (TWA) and improved heart rate variability (HRV) in patients with drug refractory epilepsy in a dose-dependent manner.[11]

In the present study, we hypothesized that concomitant with the previously demonstrated improvement in left ventricular (LV) function,[10,12,13] VNS would improve autonomic reflexes, reduce VT incidence, and decrease TWA, an established marker of risk of sudden cardiac death (SCD) in patients with diverse cardiovascular diseases including heart failure.[14,15] To address this issue, we investigated the effects of ART using previously established quantitative methods in ambulatory electrocardiographic (ECG) recordings (24-hour duration) from patients with chronic symptomatic heart failure and reduced LVEF enrolled in the Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study (NCT01823887). The autonomic measures included HRV[16] and heart rate turbulence (HRT),[17] which reflect autonomic tone and baroreflex sensitivity, respectively.

Methods

Study design and patient selection

The design and patient selection criteria of the ANTHEM-HF study design have been previously described.[12,13] The study complied with the Declaration of Helsinki. The study protocol was approved by local ethics committees at all sites, and all patients gave written informed consent translated into local languages.

Briefly, individuals in NYHA functional class II/III heart failure, aged ≥18 years, were enrolled at 10 sites. Inclusion criteria included LVEF ≤40%, LV end-diastolic dimension ≥50 and <80 mm, QRS width ≤150 ms, and receiving optimal medical management, including stable β-blocker therapy for heart failure as indicated and tolerated for ≥3 months and all other oral pharmacologic therapies for heart failure, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, loop diuretics, and spironolactone, for ≥1 month. Patients were also required to be capable of performing the 6-minute walk test with a baseline distance of 150–425 meters, as limited by heart failure symptoms. All 25 patients enrolled in the ANTHEM-HF study whose Holter ECG files could be extracted and were available for analysis at all 3 time points (baseline, 6 months, and 12 months) were included in the present analysis.

System implantation and VNS stimulation

Individuals fulfilling the inclusion and exclusion criteria underwent VNS Therapy System implantation (Demipulse Model 103 pulse generator and PerenniaFLEX Model 304 lead; Cyberonics, Inc., Houston, TX) with 1:1 randomized lead placement on either the left (n = 12) or the right (n = 13) cervical vagus nerve. The pulse generator was activated at 15 ± 3 days after implantation. All patients were initially stimulated at a pulse width of 130 μs, a pulse frequency of 10 Hz, and continuous cyclic (14-second active [on] and 66-second inactive [off]; 1080 cycles/day) stimulation.

Stimulation parameters were systematically adjusted during periodic clinic visits over a 10-week titration period to a pulse width of 250 μs, a pulse frequency of 10 Hz, and a target output current amplitude of 1.5–3.0 mA. VNS activation and inactivation periods were unrelated to the cardiac cycle (i.e., open loop), so that no intracardiac sensing lead was used. During titration sessions, VNS intensity was gradually increased in 0.25-mA steps with the use of a radiofrequency programmer (Model 250 programming system, Cyberonics) to levels that produced acute VNS-related adverse effects (tolerance zone boundary), such as activation of the expiratory reflex (mild cough) or moderate heart rate reduction during the VNS-active phase. When the VNS tolerance zone boundary was established by evidence of expiratory reflex activation or heart rate reduction, the output current was reduced by ≥1 output current step (0.25 mA) to ensure that the therapy was well tolerated. During the 10-week titration period, VNS intensity was progressively increased to an average output current of 2.0 ± 0.1 mA (left side: 2.2 ± 0.2 mA; right side: 1.8 ± 0.2 mA). Continuous cyclic stimulation at low-intensity (<2 mA; n = 10) or high-intensity (≥2 mA; n = 15) levels was maintained as tolerated throughout the titration period and the 12-month follow-up period.

Ambulatory ECG recordings and analysis

Twenty-four-hour ambulatory ECG recordings were made (DigiTrak XT, Philips Medical Systems, Best, The Netherlands) at baseline and after 6 and 12 months of chronic therapy. Measurements of TWA, HRT, HRV, ventricular tachycardia (VT) incidence, and heart rate were performed by an investigator (B.D.N.) blinded to clinical status and recording sequence using Food and Drug Administration–cleared commercial software running on the MARS Ambulatory ECG Analysis System (GE Healthcare, Milwaukee, WI).

TWA

The peak TWA level was quantified from standard precordial leads V_1 and V_5 and aVF using the Modified Moving